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Review

# Biological Potential of Substituted Thiadiazole Compounds

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**Abstract:**
Heterocyclic compounds are present in most biologically active molecules. The chemistry of heterocyclic compounds has been an interesting field of study. Heterocyclic nucleus 1,3,4-thiadiazole constitutes constitutes an important class of compounds for drug development. The novel thiadiazoles and investigation of their chemical and biological behavior have gained more importance in recent decades. There has been intense investigation of different classes of thiadiazole compounds, many of which possess extensive pharmacological 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. The broad and potent activity of thiadiazole and their derivatives has established them as pharmacologically significant scaffolds. 1,3,4-Thiadiazole nucleus exhibited remarkable pharmacological activities Such as antibacterial, antifungal, antitubercular, antiviral, antileishmanial, anti-inflammatory, analgesic, antidepressant, anticonvulsant, anticancer, antioxidant, antidiabetic, molluscicidal, antihypertensive, diuretic. So far, modifications 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; antimicrobial activity; biological activities
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# Introduction

The organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents (Horton et al., 2003). Heterocyclic compounds are receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry. There are numerous biologically active molecules with five membered rings, containing three hetero atoms (Kamal et al., 2011). Heterocyclic compounds are cyclic compound with the ring containing carbon and other element, the component being oxygen, nitrogen and sulphur. Thiadiazole is a heterocyclic compound featuring both two nitrogen atom and one sulfur atom as part of the aromatic five-membered ring. Thiadiazole is an important scaffold known to be associated with several biological activities. Thiadiazoles occur in nature in four isomeric forms as 1,2,3-thiadiazoles (**a**); 1,2,4-thiadiazole (**b**); 1,3,4-thiadiazole (**c**) and 1,3,5-thiadiazole (**d**) (Fig.1.). 1,3,4-thiadiazole are important because of their versatile biological actions and compounds bearing thiadiazole nucleus have almost all types biological activities. Differently substituted thiadiazole moieties have also been found to have improved interesting activities such as analgesic, antimicrobial, antitubercular, anticonvulsant and anti-hepatitis B viral activities (Mishra et al., 2011).

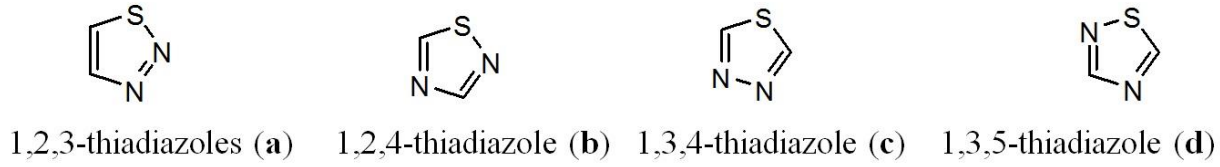
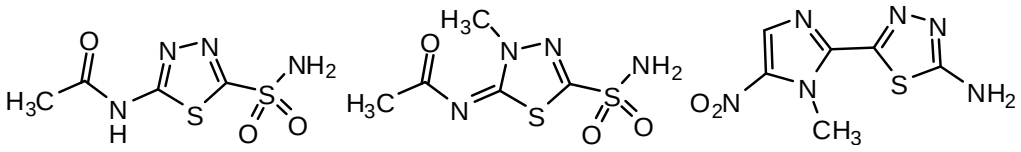



Figure1 Structure of isomeric thiadiazoles.

# Biological Activities of thiadiazoles

Thiadiazoles are important class of heterocycles and have great interest because of their broad spectrum of biological activities. Different thiadiazole compounds having heterocyclic nucleus have been shown to possess different activities. Thiadiazoles associated with large number of biological activities such as many drugs containing thiadiazole nucleus such as acetazolamide, methazolamide, megazol and antibiotic cefozopram (Supuran and Scozzafava. 2001; Iizawa et al., 1993).

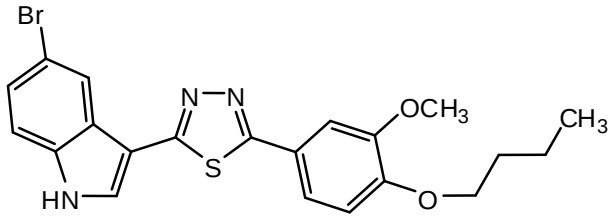


**Acetazolamide** **Methazolamide** **Megazol**

This review emphasizes on the biological activities of substituted thiadiazoles. There are several reports describing the thiadiazole derivatives for their various biological activities and recent studies have revealed that thiadiazole derivatives have a broad spectrum of pharmacological activities that can be classified into the following categories.

## Anticancer activity

The 5-(3-indolyl)-1,3,4-thiadiazoles exhibited anticancer activity (Kumar et al., 2010). Some compounds were identified as potent agents for inducing cytoselective toxicity. It was found that substitution on C-2 position of the 1,3,4-thiadiazole ring plays an important role in imparting the cytotoxic activity to the compound. Replacement of phenyl ring at C-2 position with benzyl, 4-(dimethylamino)phenyl, 3,4-dimethoxyphenyl and 4-benzyloxy group enhanced the antiproliferative activity, while replacement of the phenyl group with p-chlorophenyl and introduction of third methoxy group reduced the biological activity. Compound 2-(4-(Benzyloxy)-5-(5-bromo-3-indolyl)-3-methoxyphenyl)-1,3,4-thiadiazole (**1**) with 4-benzyl-oxy- 3-methoxyphenyl at C-2 position and 5-bromoindole at C-5 position was found to be the most potent compound of the series. Compound (4-hydroxyphenyl)(5-(2,6-dichloro)-2-thioxo-1,3,4-thiadiazol-3-yl)methanone (**2**) showed broad spectrum of growth inhibition activity against human tumor cells and remarkable cytotoxic activity on nonsmall lung cancer (HOP 92), colon cancer (HCC-2998) and significant cytotoxic activity on prostate cancer (PC-3) study revealed that electron withdrawing group at position C-5 of thiadiazol was favorable for activity (Bhole and Bhusari. 2010). Derivatives of 2-arylamino-5-aryl-1,3,4-thiadiazoles evaluated in vitro cytotoxic activity and 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 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 compounds were showed moderate activity and compound (**3)** displayed a greater potency toward pancreatic (PaCa2) cancer cell lines (Kumar et al., 2011). Quinolines derivatized with 1,3,4-thiadiazole via cyclization of quinoline thiosemicarbazones and investigated for their cytotoxic activity against cervical cancer cell lines (Hela). Compounds (**4**) 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). Several N1-acetylamino-(5-alkyl/aryl-1,3,4-thiadiazole-2-yl)-5-fluorouracil derivatives were evaluated for their anticancer activity on A-549 (human lung cancer cell), Bcap-37 (human breast cancer cell) by MTT assay. Compound (**5**) 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 (Zheng et al., 2008). Compound (E,E)-2,5-bis(4-(3-dimethyl–aminopropoxy) styryl)-1,3,4-thiadiazole (**6**) was found to be the most potent one by the MTT assay against A549, PC-3, and HA22T (Chou et al., 2003).



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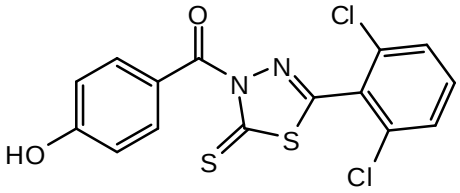

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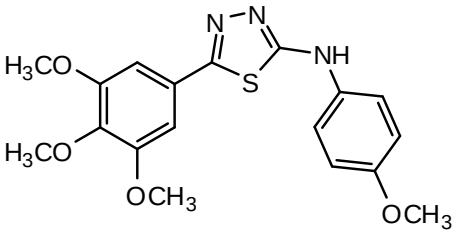

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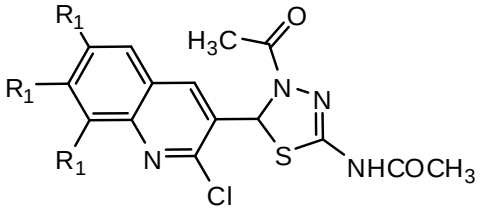
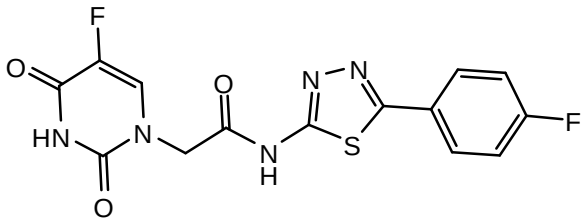
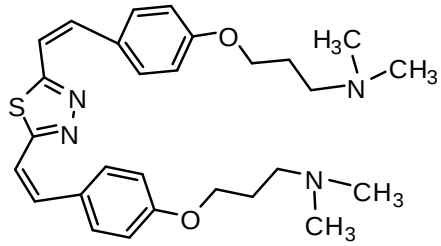


**Compound 4**



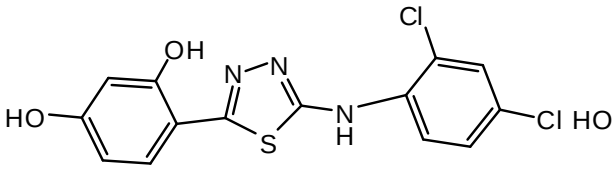
**Compound 5**



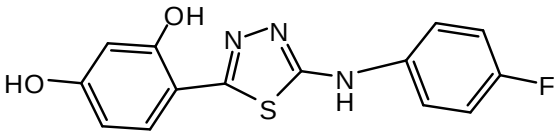
**Compound 6**

A number of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole derivatives were investigated as anti-proliferative agent against the four human cell lines: SW707 (rectal), HCV29T (bladder), A549 (lung), and T47D (breast) as anticancer agents. Compound 2-(2,4-dichlorophenyl amino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (**7**). 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 and Opolski. 2006). Compound 2-(4-fluorophenylamino)-5-(2,4-dihydroxy phenyl)-1,3,4-thiadiazole (**8**) 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). 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-methoxy-benzyloxy)-1,3,4-thiadiazole (**9**) showed activity against HCV29T bladder cancer cell line (Matysiak et al., 2006). The 2,5-disubstituted 1,3,4-thiadiazoles possessing c-butenolide moiety, compound (**10**) was screened against Hela cell lines exhibited $IC_{50}$ of 0.9 μM (Wei et al., 2009). Focal adhesion kinase (FAK) is a 125 kDa protein that was involved in multiple cellular functions like cell proliferation, survival, motility, invasion, metastasis, and angiogenesis. The inhibition of

FAK plays an important role in cancer therapy through decreased cellular viability, growth inhibition, or apoptosis. The FAK was proposed to be a potential therapeutic target in cancer. A series of 1,3,4-thiadiazole derivatives containing 1,4-benzodioxan and evaluated their activity as FAK inhibitors. The results of the inhibitory activity of the designed compounds showed that compound (**11**) possessed high potency against FAK ($EC_{50}$=0.79 μM). Compound (12) showed $EC_{50}$ values of 14.21–32.45 μg/mL against HEPG2, HELA, SW1116 and BGC823 cell lines. The study suggested that substitution with different acids led to different antitumor activity, and the potency order was phenylpropinic acid > phenylacetic acid > benzoic acid (Sun et al., 2011).



**Compound 7**



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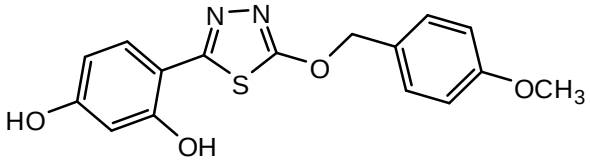

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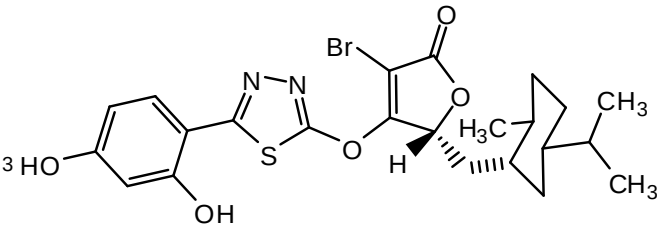

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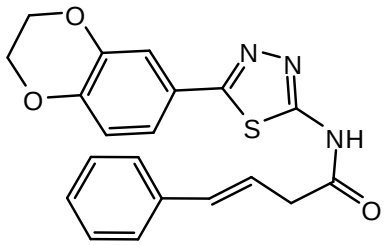
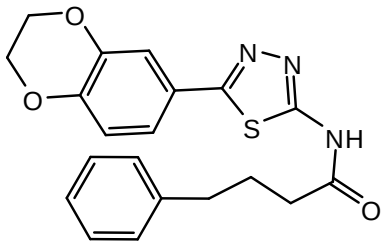


**Compound 11**

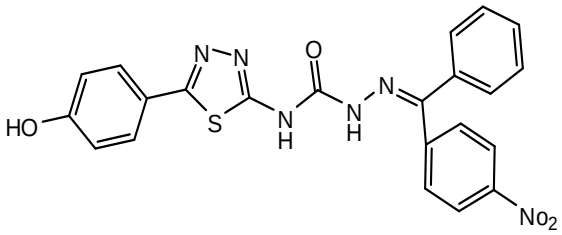


**Compound 12**

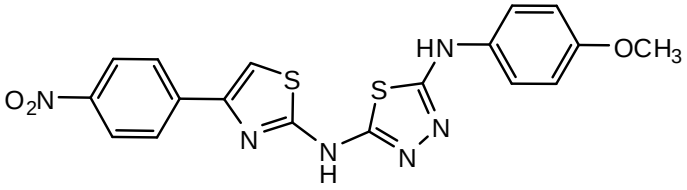
## Anticonvulsent activity

Although for the last twenty years new antiepileptic drugs have been introduced into clinical practice, the maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test are the most widely used animal models of epilepsy to characterize the anticonvulsant activity (Locher and Schmidt. 2002). Some 2,5-Disubstituted 1,3,4-thiadiazoles were evaluated their potential anticonvulsant activity. Compound with 4-nitrophenyl-substituted semicarbazone (**13**) were the most active compound comparable with carbamzepine. The 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 activity. The effect of electron withdrawing and electron

releasing groups on phenyl ring attached to thiazole and thiadiazole moiety on their anticonvulsant activity. Compound (**14**) 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 (Rajak et al., 2009; Siddiqui and Ahsan. 2011).

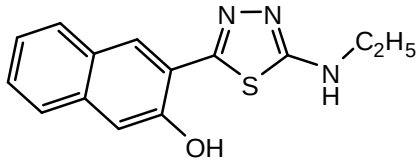


**Compound 13**

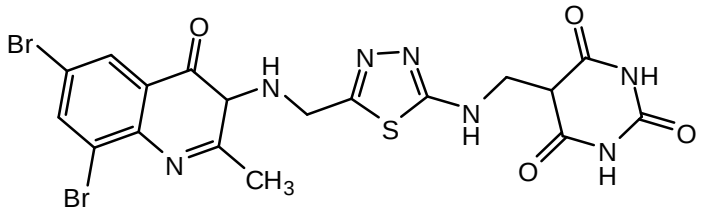


**C ompound 14**

In an attempt to improve the potency and selectivity of 2,5-Disubstituted-1,3,4-thiadiazoles, a series of 2-(N-alkyl/aryl-Nacetylamino)-5-(3-acetyloxy-2-naphthyl)-1,3,4-thiadiazoles. Compound 2-ethylamino-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole (**15**) showed 90% protection against PTZ-induced generalized convulsions. Further, substitution of ethyl and acetylation of thiadiazoles resulted in loss of activity. Compound 5-{2′-amino-5′-(3″-aminomethylene-2″- methyl-6″,8″-dibromoquinazolin-4″ (3″H)-onyl)-1′,3′,4′-thiadiazol-2′-yl}-2-thiobarbituric acid (**16**) showed high percentage protection 90% (50 mg/kg ip) in both MES and PTZ models (Dogan et al., 2002; Srivastava and Kumar. 2004).

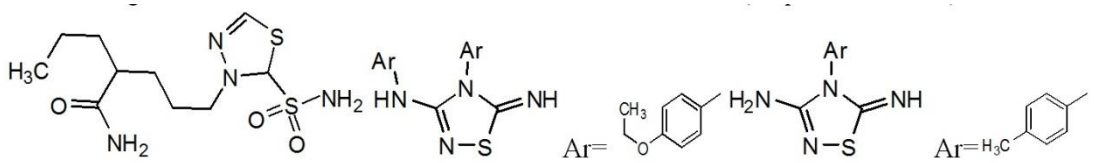


**Compound 15**



**Compound 16**

A series of sulfonamides incorporating valproyl and other lipophilic moieties has been study. The effect of different alkyl/arylcarboxamido/ sulfonamido/ureido moieties on the 5th position of 1,3,4-thiadiazolesulfonamide on its anticonvulsant activity. Their findings revealed that the valproyl derivative of acetazolamide (5-valproylamido-1,3,4-thiadiazole-2-sulfonamide) (**17**) was the best in the series as it exhibited very strong anticonvulsant activity in an MES test in mice (Masereel et al., 2002). A series of 3-aryl amino/amino-4-aryl-5-imino-D2-1,2,4-thiadiazolines 18**(a-b)** were evaluated against MES and scPTZ induced seizure models in mice (Gupta et al., 2008).



**Compound 17** **18a** **18b**

The 2-Phenylamino-5-(4-pyridyl)-1,3,4-thiadiazole derivatives were evaluated for their anticonvulsant activity by MES method. Among of these compounds, compounds **19a-e** showed good activity (Yar and Akhter. 2009). A series of aromatic aldehyde imine derivative of 2-thiobenzyl-1,3,4-Thiadiazole **20a-c** were showed good anticonvulsant activity. The chlorobenzyl substituted compound showed the potent anticonvulsant activity against MES method (Ahamad and Yusuf. 2010). A series of new 3-(5-substituted phenyl-1,3,4-thiadiazol-2-yl)-2-styryl quinazoline -4(3*H*)-ones were evaluated for anticonvulsant activity in the MES induced seizures and scPTZ-induced seizure models. Compound **21a-c** showed good anticonvulsant activity (Jatav et al., 2008).

<table>
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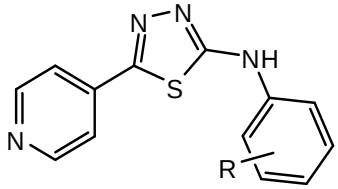
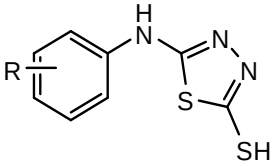
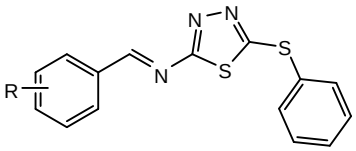
<td>  <br>Compound (19a-e)</td>
<td>19a= O-$CH_3$;<br>19b= P-$CH_3$;<br>19c= O-$OC_2H_5$;<br>19d= P-$OC_2H_5$;<br>19e= Cl</td>
<td>  <br>Compound 20a</td>
<td>  <br>Compound 20b</td>
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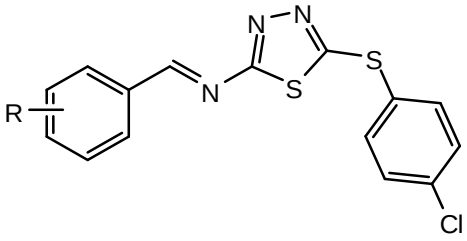
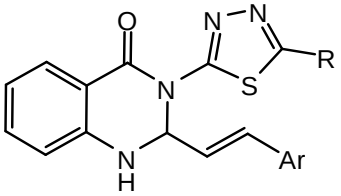
<td colspan="2">  <br>Compound 20c</td>
<td>  <br>Compound (21a-c)</td>
<td>21a=$C_6H_5$ p-$ClC_6H_4$;<br>21b=m-$ClC_6H_4$b-$ClC_6H_4$;<br>21c=p-$ClC_6H_4$,  </td>
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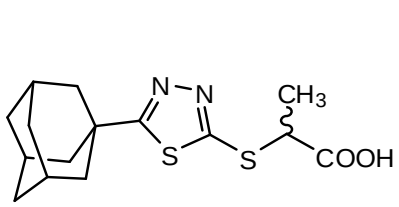
</table>

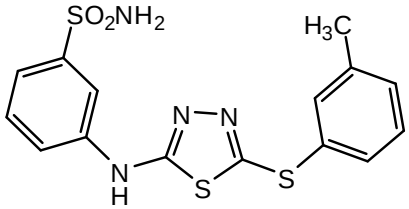
# Anti-inflammatory activity (COX-inhibitors)

Thiadiazole incorporated in different heterocyclic templates has been reported to possess potent anti-inflammatory activity. Most of the thiadiazole derivatives exert anti-inflammatory activity by inhibition of the enzyme involved in the first step of the conversion of arachidonic acid to prostaglandins (PGs). Anti-inflammatory activity of series of 5-(1-adamantyl)-1,3,4-thiadiazole derivatives, compound (**22**), substituted with propionic acid at 2nd position of

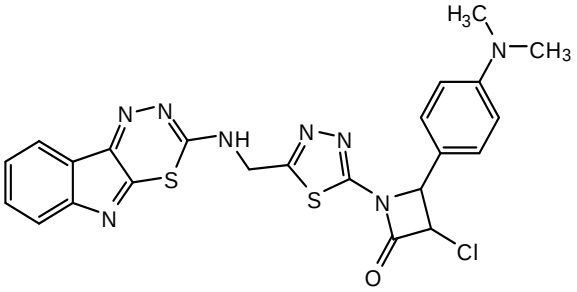
1,3,4-thiadiazoline-2-thiones, showed almost equal anti-inflammatory activity at 20 mg/kg to that of Indomethacin (5 mg/kg). Replacement of 2-propionic acid with acetic and 3-propionic acid was slightly detrimental to the anti-inflammatory activity. Several 2- amino-5-sulfanyl-1,3,4-thiadiazoles and concluded that the compounds were associated with lesser degree of anti-inflammatory activity when compared to indomethacin. Only compound 4-(5-(4-Fluorophenyl sulfanyl)-(1,3,4)thiadiazol-2-ylamino) benzene sulfona-mide (**23**) showed 65.90% inhibition after 3 h at 56 mg/kg (body weight) dose and 66.40% protection in acetic acid induced inflammation in mice (Kadi et al., 2010; Sainy et al., 2009). The anti-inflammatory activity showed by 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 (**24**). 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 and Kumar. 2008). Several 1,3,4- thiadiazole derivatives of biphenyl-4-yloxy acetic acid (**25**). 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).



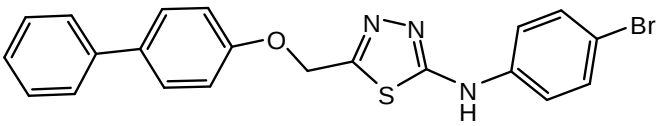

**Compound 22**




**Compound 23**

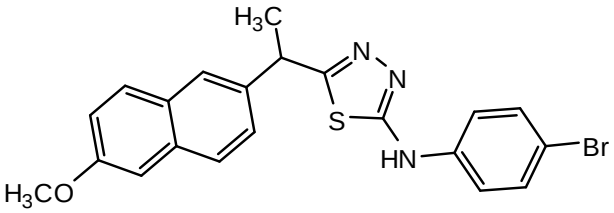



**Compound 24**

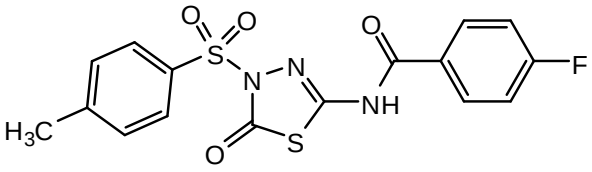



**Compound 25**

1,3,4-thiadiazole analogs of naproxen carriying a 4-bromophenyl amino group (26) at second position of the thiadiazole ring showed 78.02% inhibition in rat paw edema (Amir et al., 2007). The presence of the tolyl substituent on the sulfonamide moiety on 4th position of 1,3,4-thiadiazole ring was found to be suitable for increasing the analgesic and anti-inflammatory activity. Substituent on the amide chain affected the activity which became more evident for example halogenated substituents on the para-position of the aromatic ring of the amide moiety improved the activity profile. Compound (28) with a p-fluoro phenyl substituent was the most active compound among the benzoyl sulfonamido derivatives (Schenone et al., 2006).

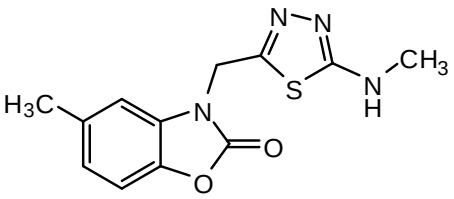


**Compound 27**

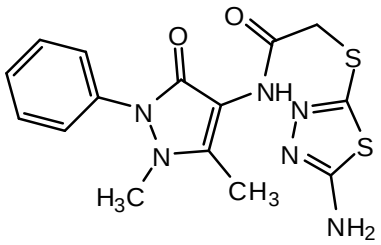


**Compound 28**

1,3,4-thiadiazoles containing 5-methyl-2-benzoxazolinone derivatives and evaluated their anti-inflammatory activity. All the compounds exhibited anti-inflammatory activity (at 50 mg/kg p.o.) of varying degree from 53.2% to 85.3% in inhibition of edema (Salgin-Goksen et al., 2007). Compound (29) with methyl group showed analgesic activity similar to that of morphine and aspirin. Conversion of the amino group to the carbamate or phenylthioureido functionalities at 5th position of the 2-(5-amino-1,3,4-thiadiazol-2-ylthio)-N-(2,5-dihydro-2,3-dimethyl-5-oxo -1-phenyl-1H-pyrazol-4-yl)acetamide (30) decreased anti-inflammatory as well as analgesic activity (Rostom et al., 2009).

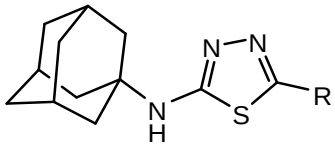


**Compound 29**



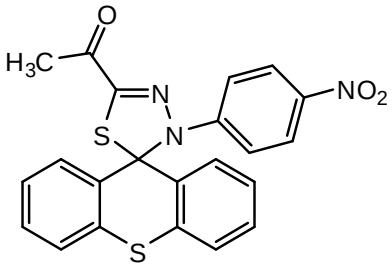
**Compound 30**

2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazole derivatives (31) were found to be associated with lesser degree of anti-inflammatory activity compared with indomethacin, while 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles appeared to exhibit good dose-dependent anti-inflammatory activity (Kadi et al., 2007). The spirothiadiazole derivative having 4-nitrophenyl group (32) exhibited promising maximum activity in induced paw inflammation model using mice and leukocyte accumulation in a carrageenan pleurisy model in the rat. Significant decrease in activity was found for the compounds with the replacement of 4-nitrophenyl group with the 4-bromophenyl and phenyl group (Hafez et al., 2008).



R = -$C_6H_5$, *p*-$C_6H_4$, *p*-Cl-$C_6H_4$, *p*-Br-$C_6H_4$, *p*-$NO_2$-$C_6H_4$, 2-thienyl, 1-adamantyl

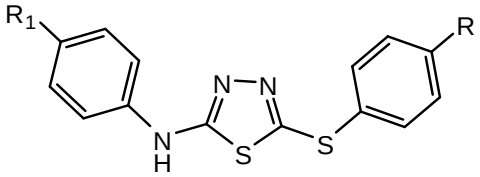
**Compound 31**



**Compound 32**

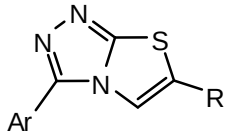
A new series of selective cox-2 inhibitors with 2-amino-5-sulfanyl-1,3,4-thiadiazole Derivatives 33a-d were selective inhibitiors of COX-2 and potentiated the activity of COX-1 enzyme. The

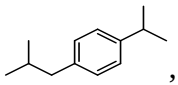
presence of sulphonamide group is a required pharmacophore for selective inhibition of COX-2 enzyme (Sharma et al., 2008). Compounds 34 (a-b) were evaluated for its anti-inflammatory activity. Due to the presence of 2,4-dichlorophenyl, 4-chloroprene, n-butyl amino and 4-aminophenyl groups of triazolo-thiadiazole ring have high anti-inflammatory activity (Amir et al., 2008).



**Compound (33a-c)**

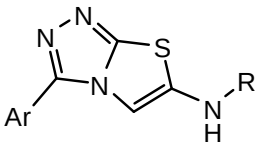
$R_1$=-$SO_2NH_2$; R=**33a**= -F; **33b**=-$CH_3$; c=-$CF_3$; **33d**=-$SO_2NH_2$

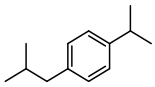


Ar =  ,

R=2,4-$Cl_2C_6H_3$

Compound **34 a**



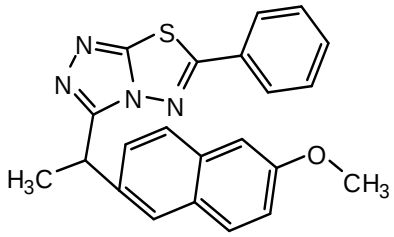
Ar =  ,

R=$CH_3(CH_2)_3$

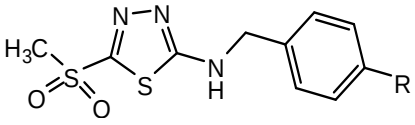
**Compund 34 b**

A series of aromatic acids and aryl/ alkyl isothiocyanates substituted-1,2,4-triazolo(3,4-b)-1,3,4-thiadiazole derivatives **35a** were (Amir et al., 2007) evaluated for anti-inflammatory activity. Among of these compounds **35a** have showed higher antiinflammatory activity.

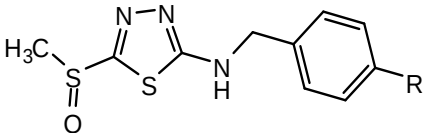
Compound **36a** by the compelte S-oxidation of correspounding methylsulfide derivatives performed by hydrogen per oxide and titanium trichloride and on the other hand oxidation of sulfide derivatives with m-choloro benzoic acid furnished the sulphoxide derivatives **36b** and evaluates the activity of anti-inflammatory, analgesic, and antiplatelet properties(Varandas et al., 2005).



**Compound 35a**

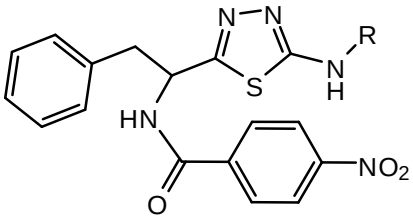


**Compound 36a**

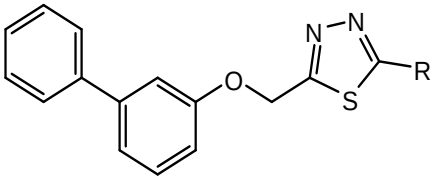


**Compound 36b**

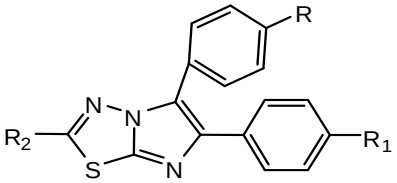
The 1,3,4-thiadiazole, that containing a phenylalnine moiety were synthesized by intramolecular cyclization of 1,4-thiosmicrbazides (**37**), and the compounds was evaluated by anti-inflammatory activity (Moise et al., 2009). The 1,3,4-thiadiazole derivatives of biphenyl-4-yloxy acetic acid (**38**) that are evaluated by anti-infalmmatory activity , analgesic activity (Kumar et al., 2008). A series of 2-trifluoromethyl/sulphonamido-5,6-diarylsubtituted imidazo(2,1-b-)-1,3,4-thiadiazole derivatives (**39**) have been evaluated by the vitro cyclooxgenage inhibitory activity against COX-2 & COX-1enzyme (Gadad et al., 2008).



**Compound 37**



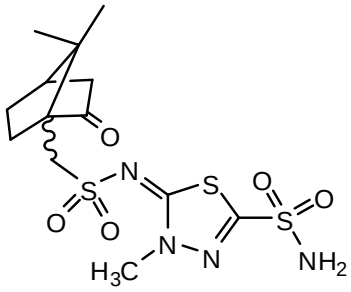
**Compound 38**



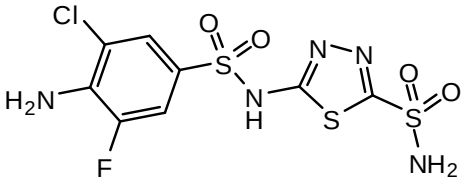
**Compound 39**

## Carbonic anhydrase inhibitory activity

1,3,4-Thiadiazole-2-sulfonamides were earlier known as carbonic anhydrase inhibitors. Carbonic anhydrase enzymes (CAs) are ubiquitous zinc enzymes. These enzymes catalyze the interconversion between carbon dioxide and the bicarbonate ion and are involved in crucial physiological processes connected with respiration and transport of $CO_2$/$HCO_3$-between metabolizing tissues and the lungs, pH and $CO_2$ homeostasis, electrolyte secretion in a variety of tissues and organs, biosynthetic reactions such as gluconeogenesis, lipogenesis, and ureagenesis, bone resorption, calcification, tumorigenicity and several other physiological and pathological processes. Inhibition of CAs would be clinically useful in the treatment of various diseases such as glaucoma, epilepsy, congestive heart failure, mountain sickness, gastric and duodenal ulcers, and other neurological disorders (Supuran. 2008; Krishnamurthy et al., 2008). Several (R)-/(S)-10-camphorsulfonyl-substituted aromatic/ heterocyclic sulfonamides and evaluated the inhibition of several mammalian isoforms of the zinc enzyme carbonic anhydrase. Compounds having R- and S-10-camphorsulfonyl moiety represented more susceptibility toward to inhibition against mitochondrial isoform hCA VA. Generally the R-enantiomer (**40**) was more active than the corresponding S-isomer (Maresca and Supuran. 2011). The inhibition of various sulfonamides and sulfamates on two b-carbonic anhydrases isolated from the bacterial pathogen *Salmonella enterica* serovar Typhimurium. Compound 3-Fluoro-5-chloro-4-aminobenzolamide (**41**) showed an inhibition constant of 51 nM against stCA 1 and of 38 nM against stCA 2, while acetazolamide inhibited stCA 1 and stCA2 with KI of 59 and 84 nM, respectively (Nishimori et al., 2011).



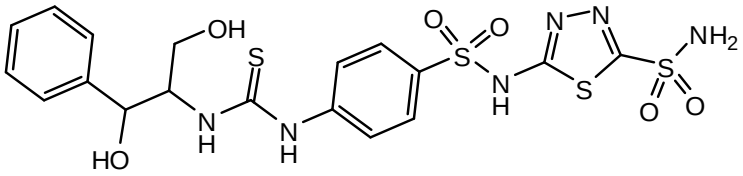
**Compound 40**

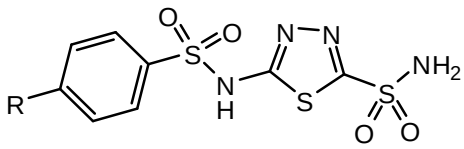


**Compound 41**

The thiadiazole derivatives were investigated as inhibitors of the cytosolic isozymes hCA I and II, as well as the tumor-associated isozyme hCA IX. Some compounds showed excellent inhibitory activities (Cecchi et al., 2004). Compound (**42**) showed maximum activity against the tested isoenzymes. The

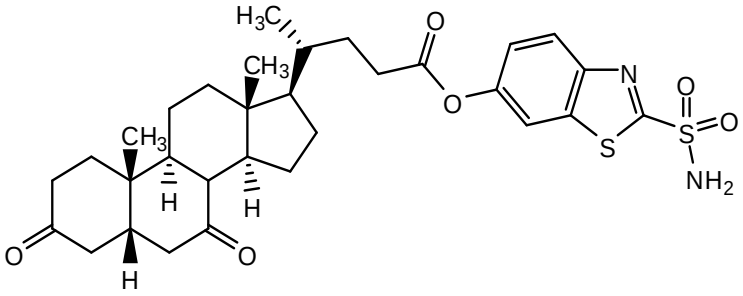
sulfanilamides acylated at the 4-amino group with short aliphatic/aromatic moieties incorporating 2–6 carbon atoms showed modest hCA XIV inhibitory activity which was found to be more potent than sulfanilamide. Compound (**42**) and (**43**) substituted with bromo and nitro group at 4th position of phenyl ring showed 3.15–4.10 times more effective than the lead compound acetazolamide (Ozensoy et al., 2005). Sulfanilamide derivatives incorporating heterocyclic amines like morpholine, piperidines, and piperazines, compound was exhibited much better inhibition of carbonic anhydrase isoenzymes than the parent compounds. Among sulfanilamide derivatives, the derivatives containing morpholine ring revealed best inhibitory activity (Turkmen et al., 2005).

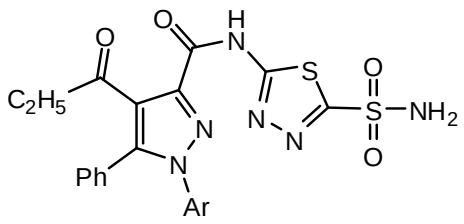




**Compound 41** **Compound 42**= R = Br; **Compound 43** = R = $NO_2$

Scozzafava and Supuran synthesized a series of sulfonamides incorporating bile acid moiety. A large number of such derivatives showed strong inhibitory activity against three isozymes of carbonic anhydrase, that is CA I, II and IV. SAR study revealed that heterocyclic sulfonamide attached to acylating moiety dehydrocholic acid (44) showed most active inhibitory activity against hCA II and bCA IV (Scozzafava and Supuran. 2002). Several pyrazole derivatives of 5-amino-1,3,4-thiadiazole- 2-sulfonamide (45) were synthesized and their inhibitory activity against hydratase and esterase property of carbonic anhydrase isoenzymes hCA I and hCA II were studied. Derivatives showed more inhibitory activity than parent compounds, 5-amino-1,3,4-thiadiazole-2-sulfonamide and acetazolamide (Kasımogullari et al., 2010).

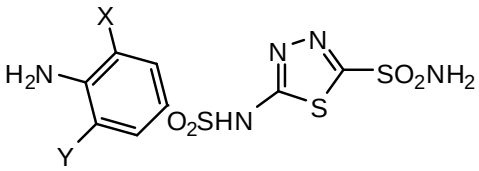


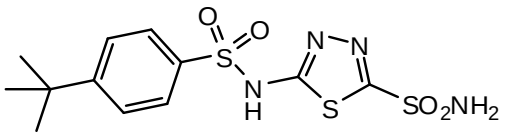


**Compound 44** **Compound 45**

Two series of halogenated sulfanilamide and aminobenzolamide containing one or two halogens (F, Cl, Br, I) were investigated for inhibitory activity against carbonic anhydrase isoenzymes hCA I, hCA II, hCA IV and hCA IX. Aminobenzyloamides were found to be more active than sulfonamides against hCA I, hCA II and hCA IV. Bromo derivatives were more active than fluoro derivatives which in turn were more active than iodo derivatives and least activity was observed in chloro derivatives. Different patterns were seen in activity against hCA IX. Both sulfanilamide and aminobenzolamide derivatives were found to be very potent inhibitors. 3-Flouro-5-chloro-4-aminobenzenesulfonamide derivative of sulphonylthiadiazole (46) showed the best hCA IX inhibition which was two times more active than acetazolamide (Ilies et al., 2003).

Independent strains of H. pylori were obtained from different kinds of gastric mucosal lesions and from these hpCA (bacterial carbonic anhydrase) DNAs were cloned and sequenced. Library of sulfonamides was evaluated for inhibitory activity against hpCA. Derivatives of 4-tert-butylphenylcarboxamido were found to be slightly less efficient in inhibiting hpCA than corresponding 4-tert-butylphenylsulfonamido derivatives. Compounds 5-(4-tert-butylphenyl-sulfonamido)-1,3,4-thiadiazole- 2-sulfonamide (47) and 5-(4-tert-butylphenylcarboxamido)-1,3,4-thiadiazole-2-sulfonamide (48) were found to be very strong inhibitors of hpCA with KI of 12–13 nM (Nishimori et al., 2006).

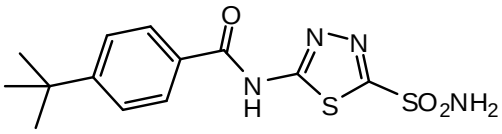


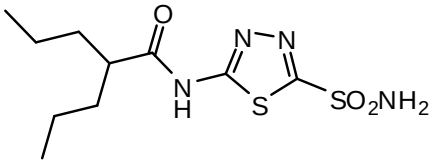




X= Cl, Br, I, F; Y=Cl, Br, I, F

**Compound 46** **Compound 47**

A series of compounds first by reacting valproic acid with aromatic and heterocyclic sulfonmaides in the presence of carbodiimides and secondly reacting valproyl chloride with sulfonamide in the presence of base. Derivatives were evaluated for inhibitory action against carbonic anhydrase enzymes, namely hCA I, hCA II, and bCA IV. 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 (49) was found to be more effective than acetazolamide and methazolamide against all three enzymes (Masereel et al., 2002).



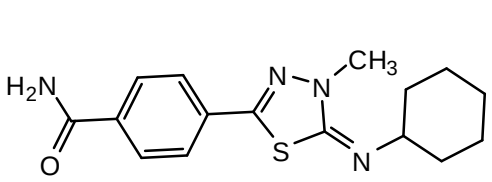




**Compound 48** **Compound 49**

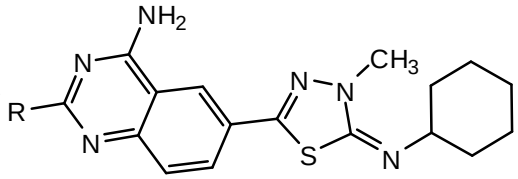
## Other activities

A series of novel small thiadiazoles as inhibitors of PDE7. Out of the synthesized compounds, derivatives with 4-CONH2 on benzene ring (50), 4-aminoquinazoline (51) and 2-methyl-4-aminoquinazoline (52) on C-5 of thiadiazole ring exhibited high PDE4 inhibitory activity with an IC50 value of 0.061, 0.027, and 0.0039 lM, respectively. They concluded that the 4-amino-quinazoline derivatives along with hydrophobic steric bulk attached with nitrogen of C-2 of thiadiazole showed an increase in activity because of its structural similarity with the adenine part of cAMP. Replacement of the cyclohexyl moiety with smaller ring was not as selective and found to be detrimental to the enzymatic activity (Vergne et al., 2004). Introduction of an OH group on 3rd position of cyclohexyl group of (53) represented IC50 of 0.088 nM toward PDE7.

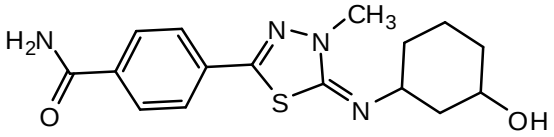
Modification of 4-$CONH_2$ group with sulfonamide (54) significantly improved the pharmacokinetic profile and binding affinity for PDE7 (Vergne et al., 2004).



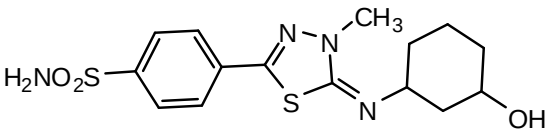
**Compound 50**



**Compound 51**= R = H; **Compound 52** = R = -$CH_3$

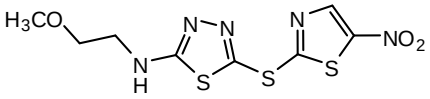


**Compound 53**

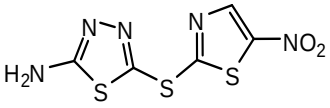


**Compound 54**

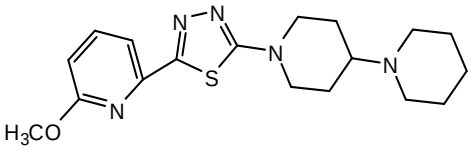
Small molecules thiadiazole derivatives as c-Jun N-terminal kinase inhibitors, on the basis of a lead structure from high throughput screening, they identified that substitution on 2nd-position with either 2-methoxyethyl group, sec-butyl group or n-propyl group improved the pepJIP1 displacement (DELFIA) and the kinase activity (LANTHA) assays (De et al., 2010). Compounds (**55**) showed an $IC_{50}$ of 4.8 lM in the kinase assay substrate and it displaced pepJIP1 with an $IC_{50}$ of 158 nM. Modification on 4-(2,3-dihydrobenzo(b)(1,4)dioxin-6-yl)-5-(5-nitrothiazol -2-ylthio) -4H-1,2,4-triazol-3-ol which showed competitive inhibition of the interactions between JNK and pepJIP1 with an $IC_{50}$ of 280 nM resulted the discovery of (**56**) which could bind at the JIP site with the nitrothiazol group crossing the ridge close to residues Arg127 and Cys163 of enzyme side with an $IC_{50}$ of 239 nM (De et al., 2009). The 2-piperidinopiperidine-5-arylthiadiazoles as H3 antagonists which lead to increase histamine levels by blocking the histaminergic neurons irreversibly and may be useful in treating obesity, diabetes as well as other CNS disorders such as cognitive disorders like Alzheimer's and Parkinson's disease. The o, m and p substituent such as polar groups OMe, CN, and COCH3 on phenyl ring increases the H3 receptor antagonistic activity. Further replacement of phenyl ring with 2-pyridyl was found to be favorable, while pyrimidine and pyrazole offered less activity. Compound (**57**) with 3-methoxy group at 2-pyridyl ring substituted on C-5 of thiadiazole was found to be the most active (Xiao et al., 2011).



**Compound 55**



**Compound 56**

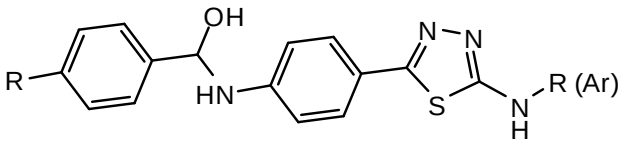


**Compound 57**

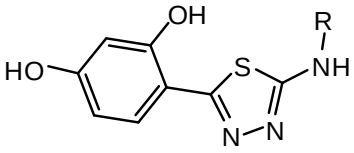
## Cytotoxic activity

Compound 5-(-4-(4fluorobezoylolamino)phenyl)-2-subsitutedamino-1,3,4-thiadiazole (58) and evaluate the cytotoxic activity (Karakus et al., 2010). A series of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles (59) were evaluated for their antiproliferative activities

against human cancer cell lines. The cytotoxicity in vitro against the four human cell lines: SW707 (rectal), HCV29T (bladder), A549 (lung), and T47D (breast) was determined. The highest antiproliferative activity was found for 2-(2,4-dichlorophenylamino) 5-(2,4-dihydroxy phenyl)-1,3,4-thiadiazole, with ID50 two times lower (SW707, T47D) than for cisplatin studied comparatively as the control compound (Matysiak and Opolski. 2006).




**Compound 58**

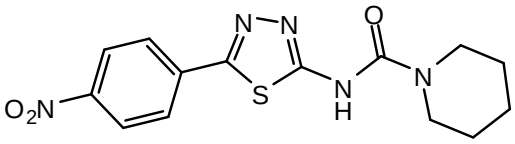



**Compound 59**

R= alkyl,aryl, morpholinoalkyl

## Antidiabetic activity

Some thiadoazole compounds were evaluated for antidiabetic activity. These compounds 60 has shown significant to moderate antidiabetic activity (Pattan et al., 2009).




**Compound 60**

## Conclusions

Thiadiazole is a unique template that is associated with several biological activities. The potency of 4-thiazolidinone nucleus is clearly evident from the clinically used drugs such as acetazolamide, methazolamide, and megazol. Though the antibacterial, antitubercular, carbonic anhydrase inhibitors and antiulcer are the major areas of clinical use, other potential targets are still to be explored. Most of the positions were explored for improving the activity profile of thiadiazole. The literature analyzed to provide a meaningful overview of the structural requirements for activity, wherever possible (Jain et al., 2013).

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