Thiadiazoles: Progress Report on Biological Activities

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Abstract

Several five membered aromatic systems having three heteroatoms at symmetrical positions such as thiadiazoles have been studied extensively owing to their interesting pharmacological activities. This review article covers the most active thiadiazole derivatives that have shown considerable biological actions such as antimicrobial, anti-inflammatory, anticancer, anticonvulsant, antidepressant, antioxidant, radioprotective and anti-leishmanial. This review also discusses the structure-activity relationship of the most potent compounds. It can act as an important tool for medicinal chemists to develop newer compounds possessing thiadiazole moiety that could be better agents in terms of efficacy and safety.

Keywords: Thiadiazoles, Biological activities, Structure activity relationship.

Introduction

The resistance towards available drugs is rapidly becoming a major worldwide problem. The need to design new compounds to deal with this resistance has become one of the most important areas of research today. Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities. Thiadiazole moiety acts as “hydrogen binding domain” and “two-electron donor system”. It also acts as a constrained pharmacophore. Many drugs containing thiadiazole nucleus are available in the market such as acetazolamide, methazolamide, sulfamethazole, etc. Thiadiazole can act as the bio-isosteric replacement of the thiazole moiety. So it acts like third and fourth generation cephalosporins, hence can be used in antibiotic preparations. Thiadiazole is a 5-membered ring system containing two nitrogen and one sulphur atom. They occur in nature in four isomeric forms viz. 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole. The 1,3,4-thiadiazole isomer of thiadiazole series and its dihydro-derivatives provide a bulk of literature on thiadiazole. A glance at the standard reference work shows that more work has been carried out on the 1,3,4-thiadiazole than all other isomers combined. Members of this ring system have found their way into such diverse application as pharmaceuticals, oxidation inhibitors, cyanine dyes, & metal complexing agents. The literature review showed that the thiadiazole nuclei have antimicrobial, anti-inflammatory, anticancer, anticonvulsant, antidepressant,

antioxidant, radio protective, and anti-leishmanial activities.

Antimicrobial Activity

Padmavathi et al [1]. synthesized a few 2-(aryl-methanesulfonylmethyl)-5-aryl-1,3,4-thiadiazoles and tested for *in vitro* antimicrobial activity against Gram positive bacteria *S. aureus*, *B. subtilis*; Gram negative bacteria *Klebsiella pneumoniae*, *Proteus vulgaris* and Fungi *Fusarium solania*, *Aspergillus niger*, etc. and found them to be active with compound(**1**) having maximum activity. The presence of benzylsulfonyl group and chloro substituent enhances the activity of the compound.

Some of the novel methylene bridged benzisoxazolyl imidaozo [2,1-b] [1,3,4] thiadiazoles and their bromo, nitroso and thiocyanato derivatives synthesized by Lamani et al [2] were screened for antibacterial activity against *S. aureus*, *B. subtilis* and *E. coli* and also antifungal activity against *C. albicans* and *Aspergillus fumigatus*. Some of the compounds displayed very good antibacterial (**2a**-**e**) and antifungal activity (**2f**-**k**).

A series of *N*-(5-benzylthio-1,3,4-thiadiazol-2-yl) and N-(5-benzylsulfonyl-1,3,4-thiadiazol-2-yl) derivatives of piperazinyl quinolones were synthesized by Foroumadi et al [3] and evaluated for antibacterial activity against Gram positive and Gram negative microorganisms. Some of these derivatives (**3**) exhibit high activity against Gram-positive bacteria *S. aureus* and *S. epidermis*, (MIC = 0.03-4 μg/mL) comparable or more potent than their parent *N*-piperazinyl quinolones norfloxacin and ciprofloxacin as reference drugs. The SAR indicates that both the structure of the benzyl unit and the S or SO_2 linker dramatically impact antibacterial activity.

Some new 2-[[1(2*H*)-phthalazinone-2-yl] methyl/ethyl]-5-aryl amino-1,3,4-thiadiazole derivatives (**4**) were synthesized by Tijenonkol et al [4]. Antimicrobial properties of the titled compounds were investigated against two Gram-positive bacteria (*S. aureus* and *B. subtilis*), two Gram-negative bacteria (*P. aeruginosa*, *E. coli*) and two yeast-like fungi (*C. albicans* and *C. parapsilosis*). Generally the compounds were found to be active against *B. subtilis* and the fungi.

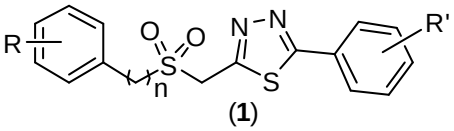
A number of new 5-(1*H*-indol-3-yl methyl)-*N*-(substituted phenyl)-1,2,4-thiadiazol-2-amine derivatives were synthesized and evaluated for their antibacterial and antifungal activity by Siddiqui et al [5]. Compounds (**5a**) and (**5d**) showed 80% and 72% inhibition respectively against S. aureus while compounds (**5b**), (**5c**) and (**5d**) showed 76% inhibition against *E. coli*. Compounds (**5a**), (**5d**) and (**5h**) showed 70%, 85% and 65% inhibition respectively against *C. albicans*.

The research study by Karegoudar et al [6]. reports the successful synthesis and antimicrobial activity of new 1,2,4-triazolo thiadiazoles bearing 2,3,5-trichlorophenyl moiety. The antimicrobial activity study revealed that all the compounds (**6a**-**f**) showed moderate to good antibacterial and antifungal activities against pathogenic strains. SAR of title compounds showed that presence of 2,3,5-trichloro, -OCH_3, 2,3-dichloro, 4-hydroxy-3-amido, 4-chloro, SCH_3 groups attached to phenyl ring as well as pyridyl, and bromopyridyl groups attached to the thiadiazole ring of the title compounds are responsible for good antimicrobial activity.

The successful synthesis and antimicrobial activity of new 1,2,4-triazolo thiadiazoles carrying 4-methyl/ethyl thio and methyl sulfonylurea phenoxy moieties at position 3 were reported by Karabasanagouda et al [7]. The antimicrobial activity study revealed that all the compounds

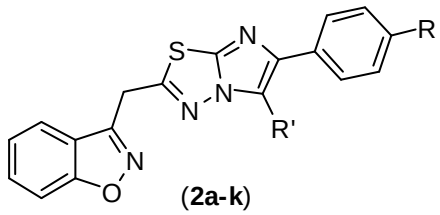
(**7**) tested showed moderate to good antibacterial and antifungal activities against pathogenic strains. SAR of title compounds showed that the presence of 4-thioalkyl phenoxy groups at position 3 and biologically active groups like -CH_3, OCH_3, NH_2 and 2,3-dichloro groups at aryl moiety attached to position 6 of title compounds are responsible for increased antimicrobial activity.

Several 3,6-disubstituted-1, 2,4-diazole [3,4-b]-1,3,4-thiadiazoles and their dihydro analogues were synthesized by Mathew et al [8]. The synthesized compounds were studied for their antibacterial and antifungal activities. Some of the tested compounds showed significant pharmacological activity of compound (**8**). It was observed that maximum antimicrobial activity was shown in the tested compounds having 2-flouro pyridine group at sixth position of the triazolothiadiazole system.



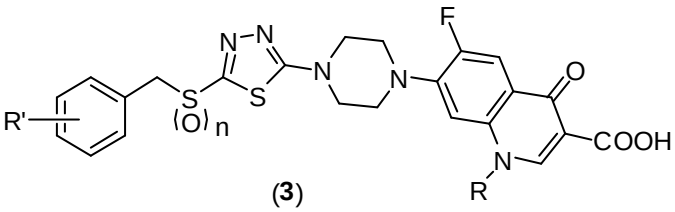
(**1**)

n = 1; R = 4-Cl; R' = 2-Cl



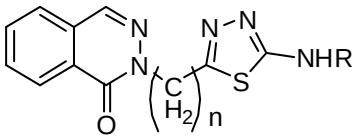
(**2a-k**)

	R	R'		R	R'
2a	Cl	H	**2g**	Br	H
2b	Br	H	**2h**	OMe	H
2c	Cl	Br	**2i**	3-coumarinyl	H
2d	OMe	Br	**2j**	OMe	SCN
2e	Cl	SCN	**2k**	3-coumarinyl	SCN
2f	H	H			



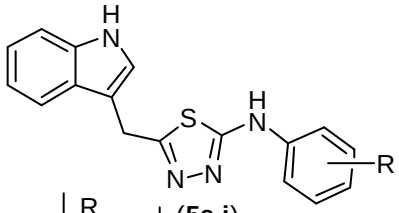
(**3**)

R = -C_2H_5, cyclopropyl; R' = H, NO_2; n = 0, 2



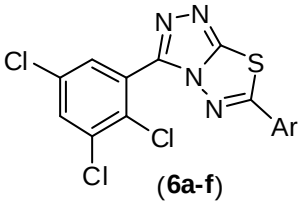
(**4**)

n = 1, 2; R = Phenyl, Benzyl, Phenthyl, 4-ClC_6H_4, 4-$OCH_3C_6H_4$, 4-$CH_3C_6H_4$



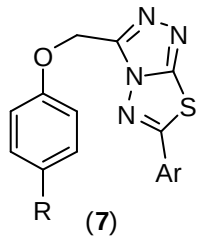
	R
5a	H
5b	2-Cl
5c	3-Cl
5d	4-Cl
5e	2-CH_3
5f	3-CH3
5g	4-CH_3
5h	2-OCH_3
5i	3-OCH_3
5j	4-OCH3

(**5a-j**)



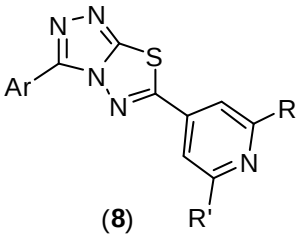
(**6a-f**)

6a = Ar = 4-$OCH_3C_6H_4$, **6b** = Ar =3,5-$Cl_2C_6H_3$,
6c = Ar = phenoxymethyl, **6d** = Ar = 5-quinolyl,
6e = Ar = pyridyl, **6f** = Ar = 2-bromopyridyl



(**7**)

R = SCH_3, SC_2H_5, SO_2CH_3
Ar = C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$,
4-$NH_2C_6H_4$, 2,3-$Cl_2C_6H_3$, $CH_2C_6H_5$



(**8**)

R = OH, Cl, F; R' = OH, H
Ar = 2,6-$(OH)_2$-4-pyridinyl, 2-Cl-4-pyridinyl
2-F-4-pyridinyl

Antiinflammatory Activity

Various condensed 2-benzoxazolinone and substituted thiadiazoles were synthesized by Salgin-Goksen et al [9] and screened for anti-inflammatory activity. Compound (**9c**) possessed the most prominent and consistent anti-inflammatory activity. An increase in the anti-inflammatory activity was observed with replacement of alkyl chain to phenyl ring.

A series of *N*-[5-oxo-4-(arylsulfonyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl]-amides were synthesized by Schenone et al [10] and evaluated for their anti-inflammatory activity. The activity is prevalent in the benzoyl-sulfonamido series, with (**10a**) and (**10b**) being the most active compounds. Also compound (**10c**) and (**10d**) showed interesting inhibition values

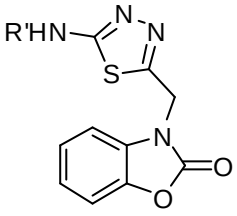
Anti-inflammatory activity screening of several 3,6-disubstituted-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazole and their dihydro analogues done by Mathew et al [11] indicated that some of the tested compounds **11-13** (**a** and **c**) and (**13b**) showed good anti-inflammatory activity. Results revealed that maximum protection was shown in the tested compounds having indole ring at the sixth position of the triazolothiadiazole system.

Synthesis and evaluation of anti-inflammatory activity of 1,2,4-triazolo [3,4-b][1,3,4]thiadiazoles bearing trichlorophenyl moiety was done by Karegoudar et al [12]. Compound (**14a**), (**14b**) and (**14c**) carrying 4-methyl phenyl, 4-methoxyphenyl and iso-quinolyl substituents exhibited good anti-inflammatory activity against indomethacin.

Synthesis and evaluation of anti-inflammatory activity of 1,2,4-triazolo [3,4-b][1,3,4]thiadiazole derivatives of ibuprofen and biphenyl-4-yloxy acetic acid was performed.

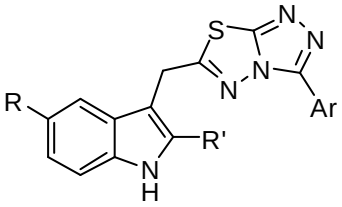
Amir et al [13] observed that compounds (**15**) and (**16**) having 2,4-dichlorophenyl and n-butyl amino groups, respectively, was found to be the highest, being slightly less than ibuprofen, but equivalent to flurbiprofen. In general the presence of 2,4-dichlorophenyl, 4-chloroprene, n-butyl amino and 4-aminophenyl groups at C-6 of triazolo-thiadiazole ring resulted in high anti-inflammatory activity.

A facile regioselective synthesis of novel spiro-thioxanthene and spiro-xanthene-9′,2-[1,3,4]thiadiazole derivatives as potential anti-inflammatory agents was done by Hafez et al [14]. The derivatives (**17**) and **(18**) having a 4-nitro phenyl group at position 3 and acetyl group at position 5 showed the maximum activity. Also the spiro compounds having two phenyl groups at position 3 and 5, showed high activity respectively. Whereas when the 4-nitro group was replaced by the hydrogen, chlorine and bromine showed good activity.



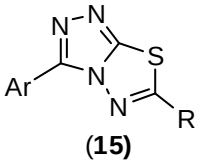
(**9a-c**)

9a = R' = CH_3
9b = R' = C_2H_5
9c = R' = C_6H_5



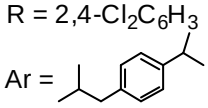
(**11-13a-c**)

R = OCH_3, H; R' = CH_3, H
Ar = 5-OCH_3-3-indolyl methyl (**11a-c**)
5-OCH_3-2-methyl-3-indolylmethyl (**12a-c**)
3-indolylmethyl (**13a-c**)

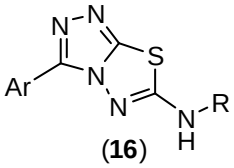


(**15**)

R = 2,4-$Cl_2C_6H_3$

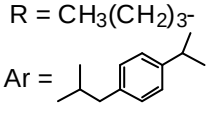


Ar =

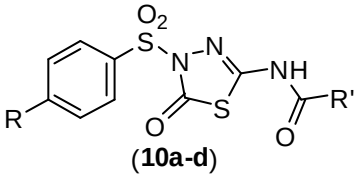


(**16**)

R = $CH_3(CH_2)_3$-

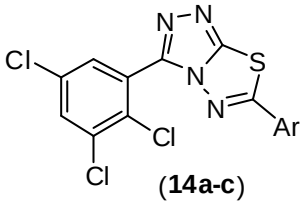


Ar =



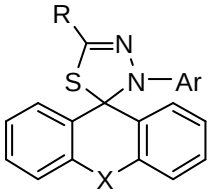
(**10a-d**)

10a = R = H; R' = 4-$CF_3CH_2C_6H_4$,
10b = R = H; R' = 4-FC_6H_4,
10c = R = H; R' = 4-$OCH_3C_6H_4$,
10d = R = H; R' = 4-furoyl



(**14a-c**)

14a = Ar = 4-$CH_3C_6H_4$,
14b = Ar = 4-$OCH_3C_6H_4$,
14c = Ar = 5-isoquinolyl



(**17, 18**)

R = $COCH_3$, Ar = 4-$NO_2C_6H_4$
X = S (**17**), O (**18**)

Anticancer Activity

A new series of chiral 1,3,4-thiadiazole derivatives possessing γ-substituted butenolide moiety were synthesized and evaluated for *in-vitro* anticancer properties by Wei et al [15]. All the compounds showed good anticancer activities against Hella cell lines. Of all the studied compounds, compound (**19**) exhibited the best inhibitory activity with an IC_{50} of 0.9

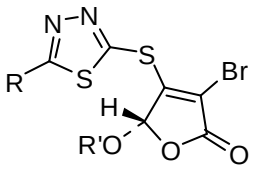
μM. This might have relationship with the hydrophile ability of nitro group on the benzene ring. After being treated with 0.1 μg/mL compound **(19)** for 24 h, the growth inhibition rate of Hella cell lines was 59.2%.

Synthesis and biological evaluation of 3,6-disubstituted [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives as novel class of potential anti-tumor agents done by Ibrahim [16] demonstrated inhibitory effects on the growth of a wide range of cancer cell lines generally at 10^{-5}M - 10^{-7}M concentrations. Their anti-tumor activity appears to be related to some structural requirements and to the presence of particular substituents, as a matter of fact 4-chlorophenoxymethylene moiety plays an important role for the activity. Compounds (**20**) and (**21**) maintained the highest growth inhibition.

A number of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles were synthesized and evaluated for their antiproliferative activity by Matysiak et al [17]. The panel substitution included alkyl, aryl and morphinoalkyl derivatives. The cytotoxicity in-vitro against the four human cell lines: SW707 (rectal), HCV29T (bladder), A549 (lung) and T47D (breast) was determined. Alkyl and morphinoalkyl derivatives exhibited significantly lower effect than phenyl ones. The highest antiproliferative activity was found for 2-(2,4-dichlorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (**22**), with ID_{50} two times lower (SW707, T47D) than for cisplatin studied comparatively as the control compound.

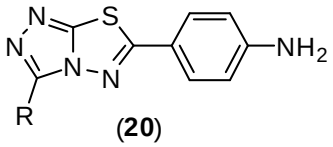
A series of new 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles has been synthesized and evaluated for their antiproliferative activity by Matysiak et al [18]. The panel substitution included alkyl, alkoxy, aryl and heteroaryl derivatives. The highest antiproliferative activity was found with ID_{50} values comparable (HCV29T and SW707) or significantly lower (T47D) than for cisplatin. Compounds (**23a**) and (**23b**) proved to be most active. The presence of another atom of high electro negativity in the vicinity of C-5 ring probably causes formation of a strong electron gap at this atom of carbon which may be essential in ligand-receptor interactions.

Novel derivatives of 2,5-substituted-1,3,4-thiadiazoles were synthesized and evaluated for their cytotoxicity by Mavrova et al [19]. The biological study indicated that n-ethyl-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-1,3,4-thiadiazole-2-amine (**24**) possessed high cytotoxicity in-vitro against thymocytes. The corresponding IC_{50} being 5.2 x 10^{-6} μM. The derivatives containing ethyl-amino group at the second position of 1,3,4-thiadiazole cycle resulted in good activity.



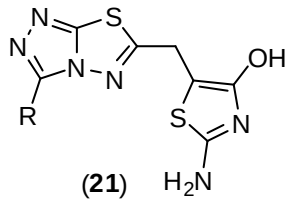
(**19**)

R = 4-$NO_2C_6H_4$
R' = 1-menthyl



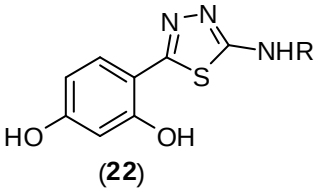
(**20**)

R = CH_2O-Ph (p-Cl)



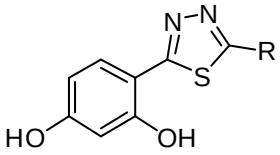
(**21**)

R = CH_2O-Ph (p-Cl)

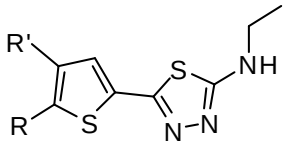


(**22**)

R = 2,4-dichlorophenyl



23a = R = 4-$(CH_3)_3C$-C_6H_4
23b = R = 4-OCH_3-C_6H_4-CH_2O



(**24**)

R = R' = -$(CH_2)_4$

Anticonvulsant Activity

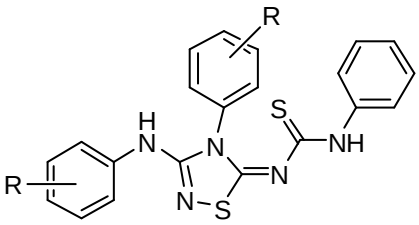
A series of 1,2,4-thiadiazoles (**25a-e**) were prepared and evaluated for anticonvulsant activity by Siddiqui et al [20]. The compound with para-chloro substitution (**25c**) showed maximal activity in MES test and blocked strychnine seizures to some extent whereas other compounds of the series were less active.

A series of new substituted 1,2,4-thiadiazoles were synthesized and screened for anticonvulsant activity by Gupta et al [21]. All the compounds except (**26g**) showed protection against MES screen after 0.5 h. It may be concluded that the synthesized compounds were potent against MES-induced seizures than scPTZ induced.

A series of 3-aryl amino/amino-4-aryl-5-imino-D2-1,2,4-thiadiazoline have been synthesized by Gupta et al [22]. The anticonvulsant activity of all the synthesized compounds was evaluated against maximal electroshock induced seizures (MES) and subcutaneous pentylenetetrazole (ScPTZ) induced seizure models in mice. Among the compounds tested, all except (**27i**) showed protection from MES seizures, whereas only (**27ii**) was found to be active in the ScPTZ test. The present results revealed that a number of 3-aryl amino/amino-4-aryl-5-imino-D2-1,2,4-thiadiazolines exhibit a range of activities in anticonvulsant screen.

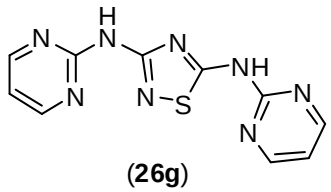
A series of 1-(substituted phenyl)-3-[(5-substituted phenyl)-1,3,4-thiadiazol-2-yl]-2-thioxodihydropyrimidine-4,6 (1*H*,5*H*)-diones **28**(**a-w**) were designed, synthesized in good yields and characterized by Siddiqui et al [23]. The compounds were evaluated for anticonvulsant activity. The compounds (**28d**, **28f**, **28l**, **28m**, **28n**, **28o**, **28t** and **28v**) were potent in MES test and were less neurotoxic as compared to standard drug phenytoin.

A variety of new 3-[5-substituted phenyl-1,3,4-thiadiazol-2-yl]-2-styryl quinazoline-4(3*H*)-ones were synthesized and evaluated for anticonvulsant activity by Jatav et al [24]. Compounds were examined in the maximal electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (scPTZ)-induced seizure models. Compound (**29a**), (**29b**) and (**29c**) showed good anticonvulsant activity in the test models.

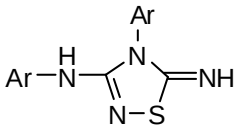


(**25a-e**)

R = H, 2-Cl, 4-Cl, 4-NO_2, 2-CH_3

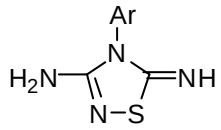


(**26g**)



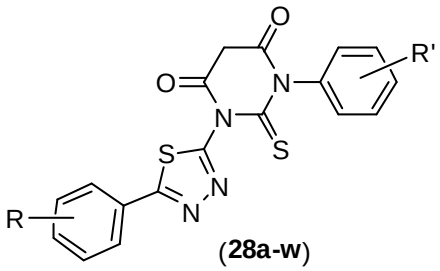
(**27ii**)

Ar = C_2H_5O



(**27i**)

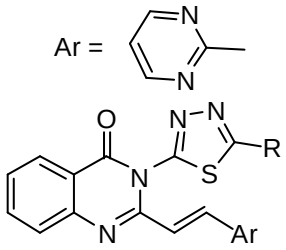
Ar =



(**28a-w**)

R = 3-NO_2, 4-F, 2-Cl

R' = H, 2-CH_3, 3-CH_3, 4-CH_3, 2-Cl, 3-Cl, 4-Cl



29 a = R = C_6H_5; Ar = 4-ClC_6H_4

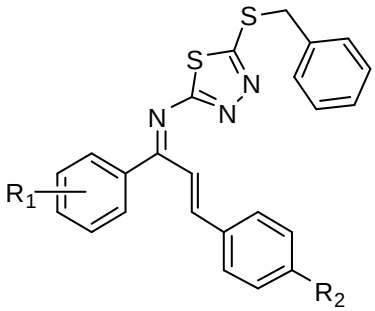
29 b = R = 3-ClC_6H_4; Ar = 4-ClC_6H_4

29 c = R = 4-ClC_6H_4; Ar = pyridyl

Antidepressant Activity

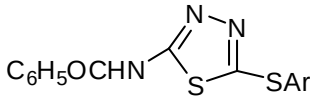
A number of new imine derivatives of 5-amino-1,3,4-thiadiazole-2-thiol have been synthesized and their antidepressant activity was tested using imipramine as reference drug by Yusuf et al [25]. Two compounds namely 5-{[1-(4-chloroprene)-3-(4-methoxy-phenyl)prop-2-en-1-ylidene]-amino}-5-benzylthio-1,3,4-thiadiazole (**30a**) and 5-{[1-(4-chloroprene)-3-(4-dimethyl-aminophenyl)prop-2-en-1-ylidene]-amino}-5-benzylthio-1,3,4-thiadiazole (**30b**) have shown significant antidepressant activity.

The newly synthesized 2-amino-5-sulfanyl-1,3,4-thiadiazole were evaluated by Pattanayak et al [26] for antidepressant activity. Three of the tested compound (**31a**), (**31b**) and (**31c**) exhibited excellent antidepressant activity in comparison to reference drugs.



29a = R_1 = OCH_3, R_2 = Cl

29b = R_1 = $(CH_3)_2N$, R_2 = Cl



(**30a-c**)

30a = Ar = 4-$C_6H_4SO_2Cl$

30b = Ar = 4-$C_6H_4SO_2NH_2$

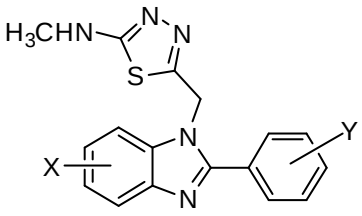
30c = Ar = 4-$C_6H_4CF_3$

Antioxidant/ Radio-protective Activity

Some novel 5-[(2-(substituted phenyl)-1*H*-benzimidazole-1-yl)methyl]-*N*-methyl-1,3,4-thiadiazole-2-amines were synthesized and tested for antioxidant properties by Kus et al [27] using various *invitro* systems. Compound (**32**), which is the most active derivative inhibited lipid peroxidation slightly at 10^{-3} M concentration.

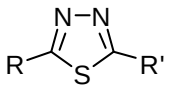
Thiol and aminothiol compounds are among the most efficient chemical radioprotectors. Prouillac et al [28] synthesized thiol and aminothiol compounds derived from thiadiazole structures (**33a**, **33b**, **33c**). They examined them for their ability to scavenge free radicals ($DPPH^{\bullet}$, $ABTS^{\bullet+}$, $^{\bullet}OH$). Thiol derivatives with a thiadiazole structure are the most active compounds scavenging $DPPH^{\bullet}$ and $ABTS^{\bullet+}$ free radicals, with an IC_{50} of 0.053 ± 0.006 and 0.023 ± 0.002 mM, respectively, for the derivative (**33a**). Moreover compound (**33a**) at 60 μM gave 83% protection against 2-deoxyribose degradation by $^{\bullet}OH$. In both the test thiol derivatives were most efficient. Compound (**33a**) totally inhibit DNA strand breaks at the concentration of 50 μM.

The antioxidant activity evaluated by Cressier et al [29]. demonstrated that the thiol, thiosulfonic acid and phosphorothioate derivatives of thiadiazoles (**34a-b**) exhibit evident antioxidant activity. This good activity of thiol derivatives shows the hypothesis of a direct link between thiol function and an aromatic ring to be a good one. The thiol catches the radical and after, the aromatic ring permit's the trapping of this radical. Moreover aminothiol derivative of thiadiazole shows a better activity.

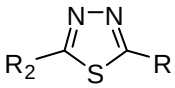


(**31**)

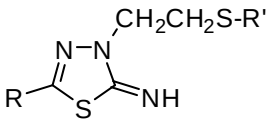
X = 5,6-dichloro
Y = 3,4-dimethoxy



33a = R = $-SCH_2CH_3$, $-CH_2CH_3$;
R' = $-SH$, $-NHCH_2CH_2SH$



32a = R = SH, $R_2 = SCH_2CH_3$
32b = R = SH, $R_2 = CH_2CH_3$
32c = R = $NHCH_2CH_2SH.HCl$, $R_2 = SCH_2CH_3$

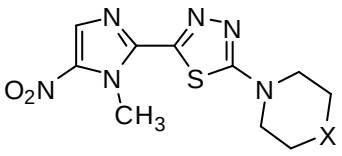


33b = R = $-SCH_2CH_3$, $-CH_2CH_3$;
R' = $-SO_3H$, $-PO(OH)_2$

Anti-leishmanial activity

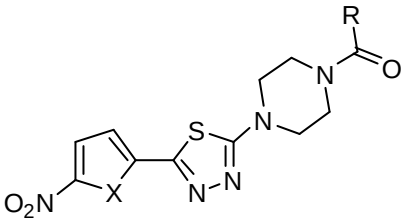
A series of 2-(1-methyl-5-nitroimidazol-2-yl)-5-(1-piperazinyl, 1-piperidinyl and 1-morpholinyl)-1,3,4-thiadiazoles were synthesized and evaluated for *in-vitro* leishmanicidal activity against Leishmania major promastigotes by Foroumadi et al [30]. The leishmanicidal data revealed that the compounds **35**(**a-g**) had strong and much better leishmanicidal activity than the reference drug pentostam. Compound (**35c**) (piperazine analog) was the most active one (IC_{50} = 0.19 μM). The antileishmanial activity of these new nitroimidazolyl-1,3,4-thiadiazole derivatives may be due to the reduction potential of the single-electron transfer $ArNO_2/ArNO_2^{\bullet-}$.

The synthesis and anti-leishmanial activity of nitroheteroaryl-1,3,4-thiadiazole based compound including 1-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]-4-aroylpiperazines and 1-[5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-yl]-4-aroylpiperazines were described by Fardmoghadam et al [31]. Most of the synthesized compound exhibited potent anti-leishmanial activity against both promastigote and amastigote forms of Leishmania major at non-cytotoxic concentrations. In general, 5-nitrofuran derivatives (**36a**) were more active than the corresponding 5-nitrophene analogues (**36b**). Under the aerobic conditions, the nitro radical anion reacts with oxygen to form superoxide anion and hydroxy radical. The resulting free radical would damage the enzyme, DNA or important structures in the surrounding cell, and result in a cytotoxic action. Under anaerobic conditions, the radical anion can be transformed into the corresponding nitroso-derivative. This nitroso form has been put forward as an efficient scavenger of essential thiols in the cell.



(**34a-g**)

34a = X = CH_2, **34b** = X = O, **34c** = X = NH
34d = X = NMe, **34e** = X = NPh, **34f** = NCOMe
34g = NCOPh

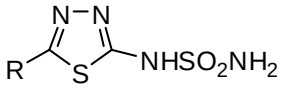


35a = X = O
35b = X = S

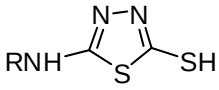
Carbonic anhydrase inhibitors

A series of 2-substituted-1,3,4-thiadiazole-5-sulfamide (**37**) were assayed by Smaine et al. [32] as inhibitors of several Carbonic anhydrase isoforms, the cytosolic CAI and II, the membrane-associated CAIV and the mitochondrial CA VA and VB. The new compounds were low low nanomolar inhibitors of hCA VA and hCA VB. These sulfamides were made the first selective CA VA/VB inhibitors.

Almajan et al assayed a series of heterocyclic mercaptans incorporating 1,3,4-thiadiazole. [33] for inhibition of three physiologically relevant CA isozymes, the cytosolic human isozymes I and II, and the transmembrane, tumor-associated hCA IX. The best inhibitors were simple derivative 5-amino-1,3,4-thiadiazole-2-thiol (**38**) and its acetylated derivative. 5-(2-pyridylcarboxamido)-1,3,4-thiadiazole-2-thiol is the first hCA I selective inhibitor.



(**37**)



(**38**)

Conclusion

The plethora of research subscribed in this review indicates a wide spectrum of pharmacological activities exhibited by 1,3,4-thiadiazoles; 1,2,4-thiadiazoles and 1,2,4-triazolo thiadiazole derivatives. The biological profiles of these new generations of thiadiazoles would represent a fruitful matrix for further development of better medicinal agents.

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