Biological Profile of Thiadiazole

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Summary

Several five membered aromatic systems having three hetero atoms 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.

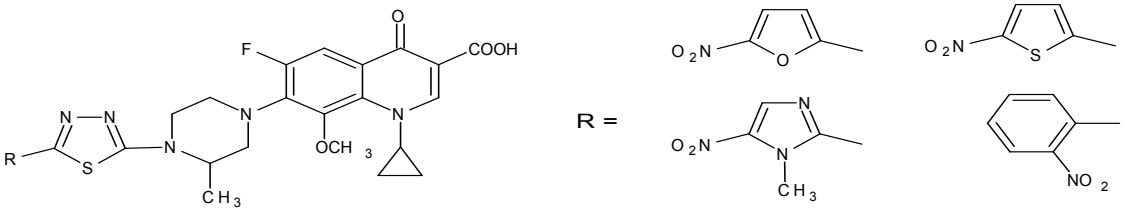
Keywords: Thiadiazoles, Biological activities, Structure activity relationship.

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

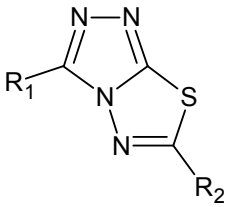
Antimicrobial Activity

Alireza *et al*[1] synthesized a series of gatifloxacin analogues containing a nitroaryl-1,3,4-thiadiazole moiety attached to the piperazine ring at C-7 position **(1)** and tested for in vitro antimicrobial activity against Gram positive and Gram negative bacteria. Among synthesized compounds, nitrofuran analog exhibited more potent inhibitory activity against Gram-positive bacteria including *Staphylococcus epidermidis*, *Bacillus subtilis*, *Enterococcus faecalis* and *Micrococcus luteus* with respect to other synthesized compounds and reference drug gatifloxacin.



(1)

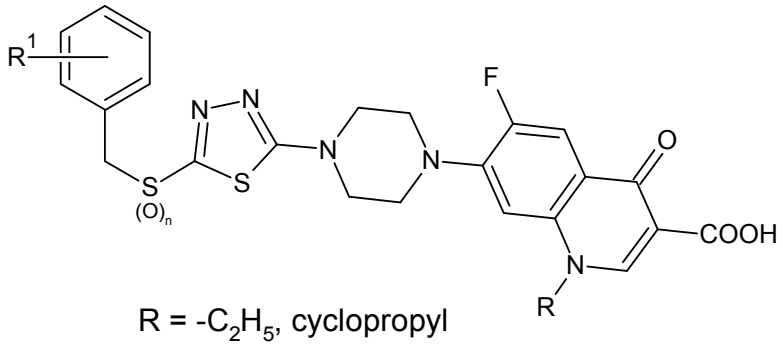
Some of the novel condensed heterocyclic 4,6-disubstituted-1,2,4-triazolo-1,3,4-thiadiazole derivatives **(2)** synthesized by Rangappa *et al*[2] and checked for their efficacy as antibacterials in vitro. Compounds 2b, 2c and 2d showed significant inhibition against all the strains tested, when compared to standard drugs.



(2)

	R_1	R_2
2a	$-CH_3$	$-2\text{-}ClC_6H_4$
2b	$-C_2H_5$	
2c	$-C_6H_5$	
2d	$-4\text{-}Cl\text{-}C_6H_4$	
2e	$-4\text{-}CH_3\text{-}C_6H_4$	
2f	$-CH_3$	$-CH(C_3H_7)_2$
2g	$-C_2H_5$	
2h	$-C_6H_5$	
2i	$-4\text{-}Cl\text{-}C_6H_4$	
2j	$-4\text{-}CH_3\text{-}C_6H_4$	

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.

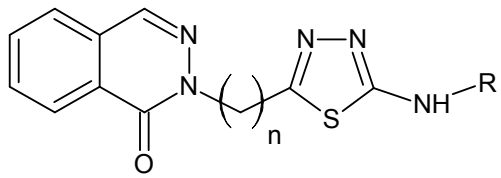


R = -C_2H_5, cyclopropyl

R^1 = -H, -NO_2; n = 0,2

(3)

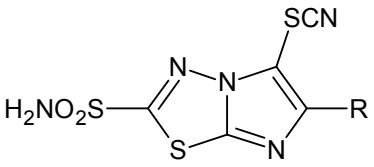
Some new 2-[[1(2*H*)-phthalazinone-2-yl] methyl/ethyl]-5-aryl amino-1,3,4-thiadiazole derivatives (**4**) were synthesized by Tijenonkol et al [4]. Antimicrobial properties of the titled compounds were investigated against two Gram-positive bacteria (*S. aureus* and *B. subtilis*), two Gram-negative 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.



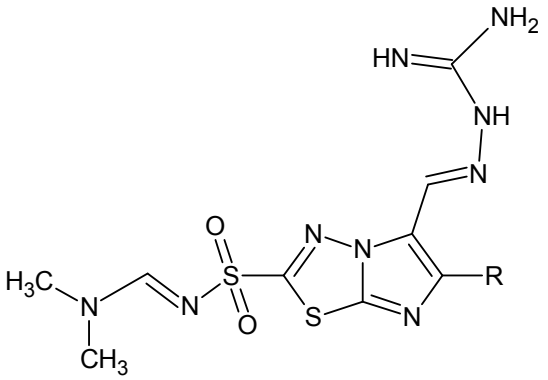
n= 1,2; R= -phenyl, benzyl, phenethyl, 4-chlorophenyl, 4-methylphenyl, 4-methoxyphenyl

(4)

A number of new 5-guanylhydrazone/thiocyanato-6-arylimidazo[2,1-b]-1,3,4-hiadiazole-2-sulfonamide derivatives **(5)** were synthesized and evaluated for their antibacterial activity by Andanappa *et al*[5].



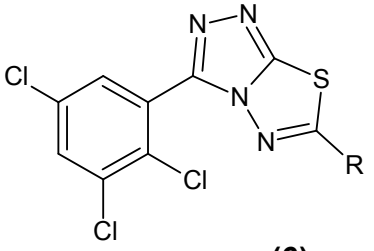
(5a)



(5b)

Compounds showed a high degree of antibacterial activity against both *Escherichia coli* and *Staphylococcus aureus* comparable to that of sulfamethoxazole and Norfloxacin. However, they were found to show moderate activity against *Salmonella typhi*, *Pseudomonas aeruginosa* and Pneumococci.

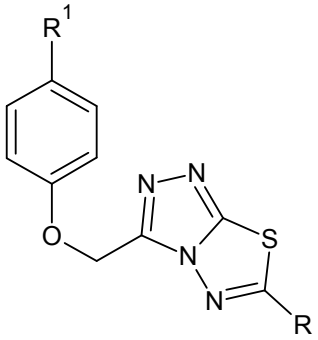
The research study by Karegoudar *et al*[6] reported the successful synthesis and antimicrobial activity of new 1,2,4-triazolo thiadiazoles bearing 2,3,5-trichlorophenyl moiety. The antimicrobial activity study revealed that all the compounds (**6a**-**f**) showed moderate to good antibacterial and antifungal 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.



R= 4-methoxyphenyl, 3,5-dichlorophenyl, phenoxymethyl, 5-quinolyl, pyridyl, 2-bromopyridyl

(6)

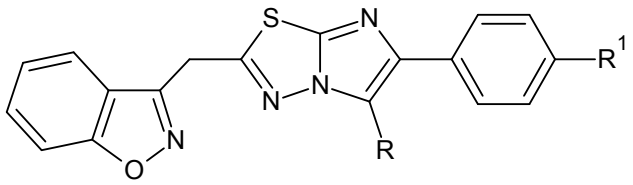
The successful synthesis and antimicrobial activity of new 1,2,4-triazolo thiadiazoles carrying 4-methyl/ethyl thio and methyl sulfonylurea phenoxy moieties at position 3 were reported by Karabasanagouda *et al*[7]. The antimicrobial activity study revealed that all the compounds (**7**) tested showed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



R= phenyl, 4-methoxyphenyl, 4-methylphenyl, 4-aminophenyl, 2,3-dichlorophenyl, benzyl
R^1= -SCH_3, -SC_2H_5, -SO_2CH_3

(7)

Several methylene bridged benzisoxazolyl imidazo[2,1-b][1,3,4]thiadiazoles **(8)** were synthesized by Imtiyaz *et al*[8]. The antibacterial activity of the test compounds was evaluated against two Gram-positive bacteria, *Staphylococcus aureus*-ATCC 25923, *Bacillus subtilis*-ATCC 6633 and Gram-negative bacteria *Pseudomonas aeruginosa*-TCC 10145, *Escherichia coli*-ATCC 35218 and compared against standard drug Ampicillin. Antifungal activity was screened against two fungal strain, *Candida albicans* and Aspergilus fumigatus using Clotrimazole as standard drug. The investigation of antibacterial screening revealed that comounds with R= -Br, -SCN and R^1= -Cl showed very good activity against Bacillus subtilis-ATCC 6633 and Escherichia coli-ATCC 35218. Compound with R^1= -Br and R= -H showed very good antifungal activity.

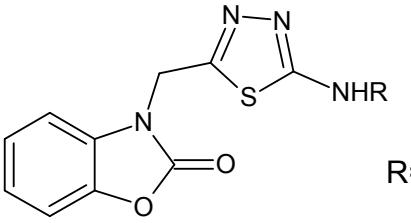


R= -H, -Br, -NO, -SCN
R^1= -H, -Br, -Cl, -NO_2, -OCH_3, -3-coumarinyl

(8)

Antiinflammatory Activity

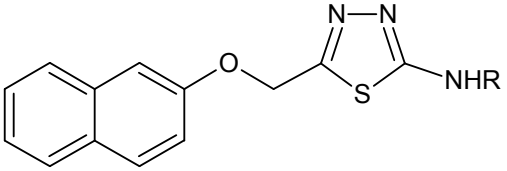
Various condensed 2-benzoxazolinone and substituted thiadiazoles **(9)** were synthesized by Salgin-Goksen *et al*[9] and screened for anti-inflammatory activity. Compound with phenyl substituent possessed the most prominent and consistent anti-inflammatory activity. An increase in the anti-inflammatory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



R= -CH_3, -C_2H_5, -C_6H_5

(9)

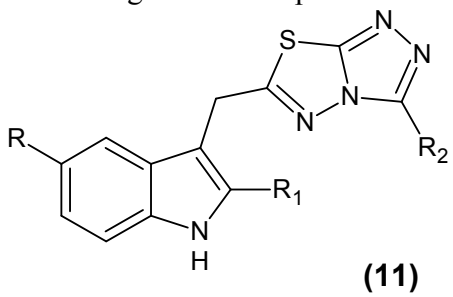
A series of 2-(2-naphthyloxymethyl)-5-substitutedamino-1,3,4-thiadiazole **(10)** was synthesized by Erhan *et al*[10] and evaluated for their anti-inflammatory activity by carrageenan hind-paw edema test. All the compounds were found to exhibit weak anti-inflammatory activity.



R= -CH_3, C_2H_5, -$CH_2CH{=}CH_2$, -C_6H_5

(10)

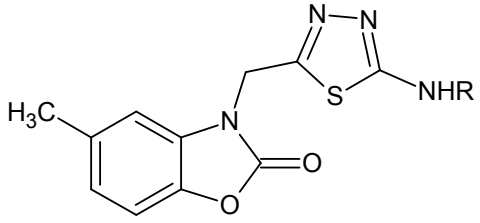
Anti-inflammatory activity screening of several 3,6-disubstituted-1,2,4-triazolo [3,4-b]-1,3,4- thiadiazole and their dihydro analogues done by Mathew *et al*[11]. Results revealed that maximum anti-inflammatory activity was shown in the tested compounds having indole ring at the sixth position of the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



R= -H, -OCH_3; R_1= -H, -CH_3
R_2= 5-methoxy-3-indolylmethyl,
5-methoxy-2-methyl-3-indolylmethyl,
3-indolylmethyl

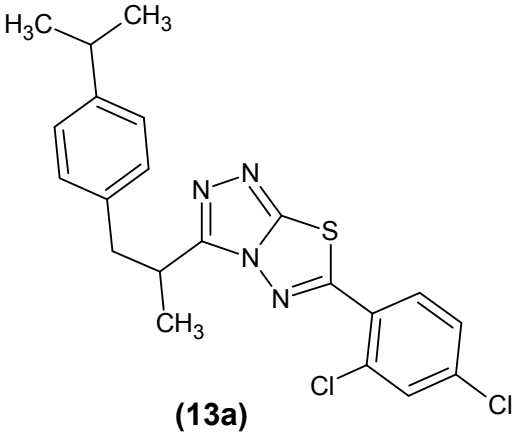
(11)

Synthesis and evaluation of analgesic-anti-inflammatory activity of 1,3,4-thiadiazoles bearing 5-methyl-2-benzoxazolinone moiety **(12a-c)** was done by Nesrin *et al*[12]. The analgesic activity of **(12a)** was higher than those of both morphine and aspirin. All the compounds showed very good anti-inflammatory activity.

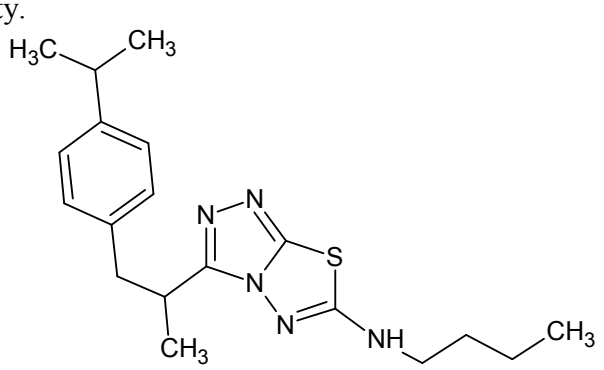


12a: R= -CH_3
12b; R= -C_2H_5
12c: R= -C_6H_5

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 (**13** and **13b**) having 2,4-dichlorophenyl and nbutyl 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.

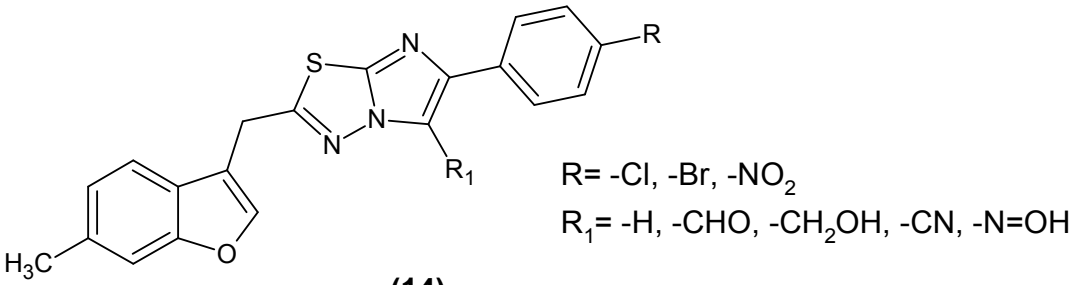


(13a)



(13b)

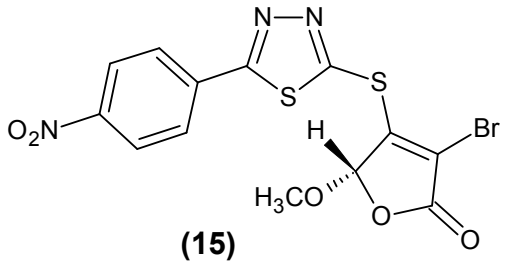
A series of 6-substituted and 5,6-disubstituted 2-(6-methyl-benzofuran-3-ylmethyl)-imidazo[2,1-b][1,3,4]thiadiazoles **(14)** was synthesized by Kulkarni *et al*[14] and evaluated as anti-inflammatory agents. Amongst the stubstituents at R_1, formyl and hydroxymethyl substituted compounds showed best effects.



(14)

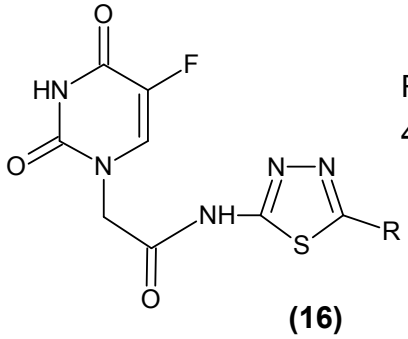
Anticancer Activity

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 (**15**) exhibited the best inhibitory activity with an IC50 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 **(15)** for 24 h, the growth inhibition rate of Hella cell lines was 59.2%.



(15)

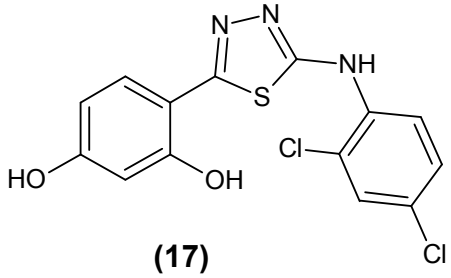
Synthesis and biological evaluation of N1-acetylamino-(5-alkyl/aryl-1,3,4-thiadiazole-2-yl)-5-fluorouracil derivatives **(16)** as novel class of potential anti-tumor agents A-549 (human lung cancer cell), Bcap-37 (human breast cancer cell) done by Jun *et al*[16]. While comparing activity with standard drug 5-fluorouracil; phenyl, 4-fluorophenyl, 4-methylphenyl, 3,5-dinitrophenyl substituted compounds showed higher activity against A-549 and 4-fluorophenyl, 4-methylphenyl, 3,5-dinitrophenyl substituted compounds showed higher activity against Bcap-37.



R= -CH_3, -C_2H_5, -C_3H_7, -$CH(CH_3)_2$, -C_6H_5, 4-ClC_6H_4, 4-FC_6H_4, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 3,5-$(NO_2)_2C_6H_3$

(16)

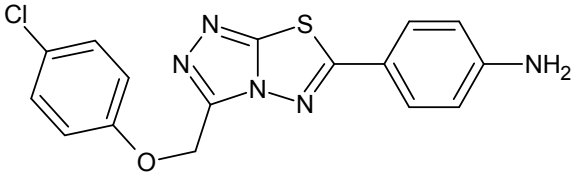
A number of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles were synthesized and evaluated for their antiproliferative activity by Matysiak *et al*[17]. The panel substitution included alkyl, aryl and morphinoalkyl derivatives. The cytotoxicity in-vitro against the four human cell lines: 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 (**17**), with ID50 two times lower (SW707, T47D) than for cisplatin studied comparatively as the control compound.



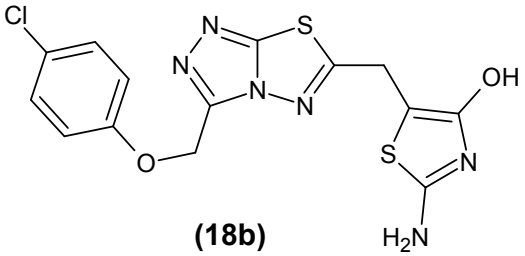
(17)

In the search of new class of potential anticancer agents, Ibrahim synthesized a series of 3,6-disubstituted triazolo[3,4-b]thiadiazole derivatives and were evaluated for their cytotoxic activity against a panel of 60 human cancer cell lines. They showed inhibitory

effect at 10-5M and 10-7M concentration level. compounds **18a** and **18b** maintained the highest growth inhibition activity at micromolar concentrations in different human tumor cell lines.

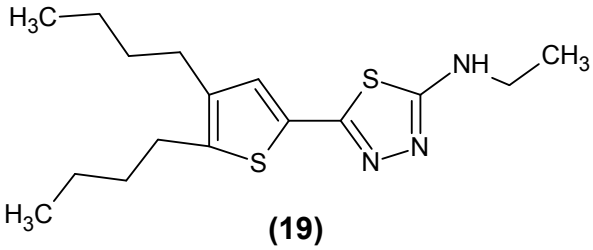


(18a)



(18b)

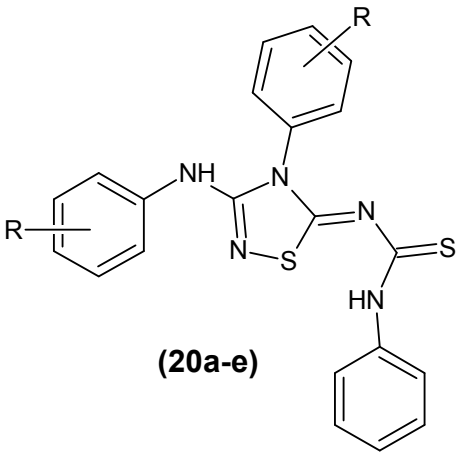
Novel derivatives of 2,5-substituted-1,3,4-thiadiazoles were synthesized and evaluated for their cytotoxicity by Mavrova *et al*[19]. The biological study indicated that n-ethyl-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-1,3,4-thiadiazole-2-amine **(19)** possessed high cytotoxicity in-vitro against thymocytes. The corresponding IC50 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)

Anticonvulsant Activity

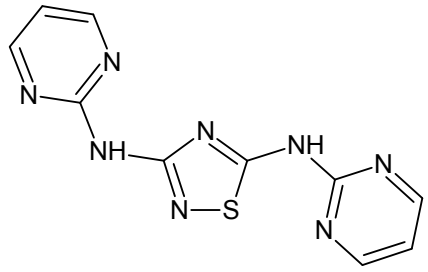
A series of 1,2,4-thiadiazoles (**20a-e**) were prepared and evaluated for anticonvulsant activity by Siddiqui *et al*[20]. The compound with para-chloro substitution showed maximal activity in MES test and blocked strychnine seizures to some extent whereas other compounds of the series were less active.



(20a-e)

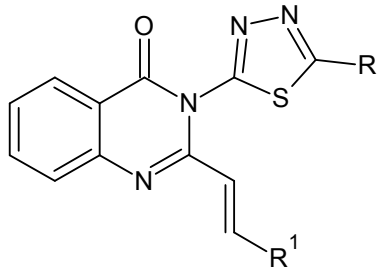
R= 2-Cl, 4-Cl, 4-NO_2, 2-CH_3

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 (**21**) showed protection against MES (maximal electroshock-induced seizures) screen after 0.5 h. It may be concluded that the synthesized compounds were potent against MES-induced seizures than ScPTZ induced and showed low potency as sedative-hypnotic agent which is advantageous.



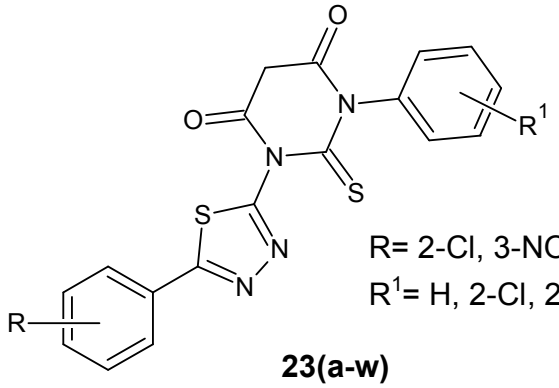
(21)

A series of new 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones was synthesized by Sushil *et al*[22] and were examined in the maximal electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice. Out of 18 compounds only **22a**, **22b** and **22c** showed anticonvulsant activity in one or more test models.



22a: R= $-C_6H_5$; R^1= p-ClC_6H_4
22b: R= m-ClC_6H_4; R^1= p-ClC_6H_4
22c: R= p-ClC_6H_4; R^1= 4-pyridinyl

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 **23**(**a-w**) were designed, synthesized in good yields and characterized by Siddiqui *et al*[23]. The compounds were evaluated for anticonvulsant activity. The compounds (**23d**, **23f**, **23l**, **23m**, **23n**, **23o**, **23t** and **23v**) were potent in MES test and were less neurotoxic as compared to standard drug phenytoin.

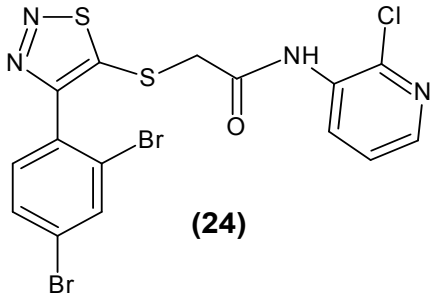


R= 2-Cl, 3-NO_2, 4-F
R^1= H, 2-Cl, 2-CH_3, 3-Cl, 3-CH_3, 4-Cl, 4-CH_3

23(a-w)

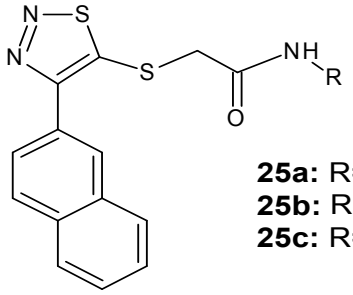
Anti-HIV Activity

A novel synthetic route and anti-HIV activity evaluation of a new series of 2-(4-(2,4-dibromophenyl)-1,2,3-thiadiazol-5-ylthio)acetamide derivatives were described by Xinyong *et al*[24]. Bioactivity assay indicated that most of the title compounds showed good activities against HIV-1. In particular, compound **24** displayed the most potent anti-HIV-1 activity (EC_{50} = 36.4 nM), inhibiting HIV-1 replication in MT-4 cells more effectively than nevirapine (by sevenfold) and delavirdine (by eightfold).



(24)

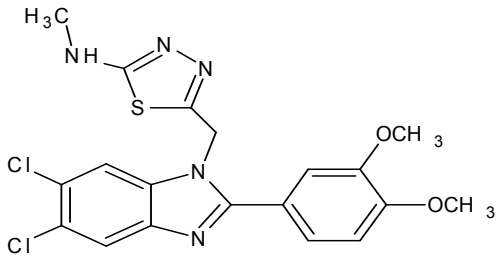
A series of 2-(4-(naphthalen-2-yl)-1,2,3-thiadiazol-5-ylthio)acetamide (TTA) derivatives were synthesized and evaluated as potent inhibitors of HIV-1 by Peng *et al*[25]. Amongst the tested compounds, **25a**, **25b** and **25c** were the most potent inhibitors of HIV-1 replication of the series (EC_{50}=0.17±0.02, 0.36±0.19 and 0.39±0.05 mM, respectively).



25a: R= 2-chloropyrin-3-yl
25b: R= 4-acetyl-2-bromophenyl
25c: R= 2-nitrophenyl

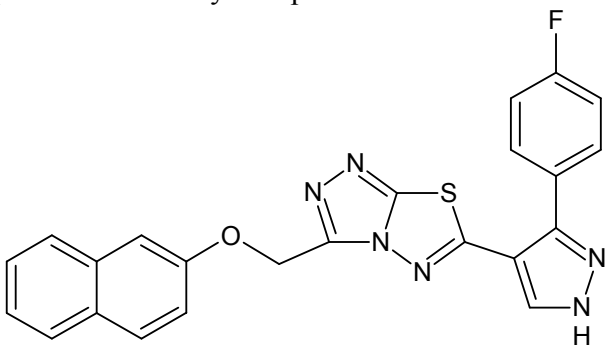
Antioxidant/ Radio-protective Activity

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* [26] using various in vitro systems. Compound (**26**), which is the most active derivative inhibited lipid peroxidation slightly at 10^{-3} M concentration.

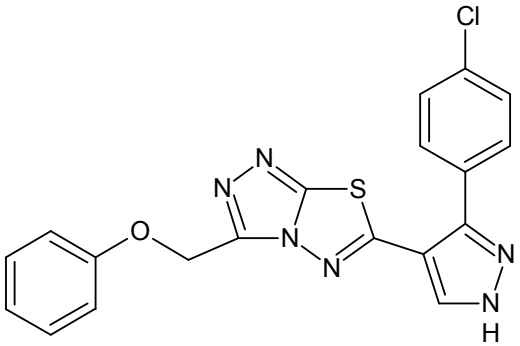


(26)

Dhanya Sunil and his group[27] had investigated the in vitro antioxidant property of two triazolothiadiazoles, 6-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-3-[(2-naphthyloxy)methyl][1,2,4] triazolo [3,4-b]-[1,3,4] thiadiazole (FPNT) **(27a)** and 6-[3-(4-chlororophenyl)-1H-pyrazol-4-yl]-3-[(phenyloxy)methyl]-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazole (CPPT) **(27b)** by spectrophotometric DPPH and ABTS radical scavenging methods as well as by lipid peroxide assay. The significant antioxidant activity of FPNT with low IC_{50} values when compared to standard is clearly evident from DPPH, ABTS free radical scavenging and in vitro lipid peroxidation assays. The in vitro lipid peroxidation assay also proved FPNT to be an excellent antioxidant.

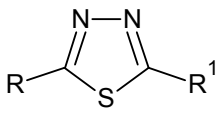


(27a)



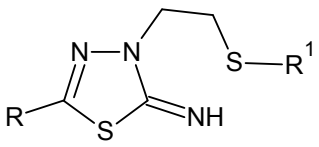
(27b)

The antioxidant activity evaluated by Cressier *et al*[28]. demonstrated that the thiol, thiosulfonic acid and phosphorothioate derivatives of thiadiazoles (**28a-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.



R= -SCH_2CH_3, -CH_2CH_3
R^1= -SH, -$NHCH_2CH_2SH$

(28a)

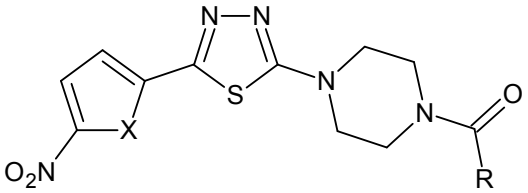


R= -SCH_2CH_3, -CH_2CH_3
R^1= -SO_3H, -$PO(OH)_2$

(28b)

Anti-leishmanial activity

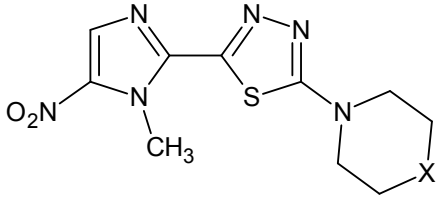
A series of 1-[5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-yl]- and 1-[5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-yl]-4-aroylpiperazines **(29)** were synthesized and evaluated for *in-vitro* leishmanicidal activity against promastigote and amastigote forms of Leishmania major by Foroumadi *et al*[29]. From biological results, it was concluded that 5-nitrofuran derivatives were more active than the corresponding 5-nitrothiophene analogues.



X= O, S
R= 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4,
2-thienyl, 2-chloro-5-thienyl

(29)

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 **30**(**a-g**) had strong and much better leishmanicidal activity than the reference drug pentostam. Compound (**30c**) (piperazine analog) was the most active one (IC_{50} = 0.19 μM).

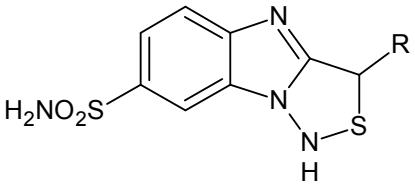


34a = X = CH_2, **34b** = X = O, **34c** = X = NH **34d** = X = NMe, **34e** = X = NPh, **34f** = NCOMe **34g** = NCOPh

(30)

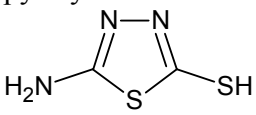
Carbonic anhydrase inhibitors

A series of Benzimidazo[1,2-c][1,2,3]thiadiazole-7-sulfonamides (**31**) were synthesized by Daumantas *et al*[31] as inhibitors of two isozymes of Carbonic anhydrase, human carbonic anhydrase I (hCAI) and bovine carbonic anhydrase II (bCAII). The strongest binder to both isozymes of carbonic anhydrase was compound **31a** with the observed Kd of about 0.04 lM. The most specific binder of hCAI was compound **31b**that bound about fourfold stronger to hCAI than to bCAII. The **31c** compound bound threefold tighter to bCAII than to hCAI.



31c: R= -Cl
31b: R= $-SO_2CH_3$
31c: R= $N(CH_2CH_3)_2$

Almajan *et al*[32] assayed a series of heterocyclic mercaptans incorporating 1,3,4-thiadiazole 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 (**32**) and its acetylated derivative. 5- (2-pyridylcarboxamido)-1,3,4-thiadiazole-2-thiol is the first hCA I selective inhibitor.



(32)

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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