A mini review on thiadiazole compounds and their pharmacological interest

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Abstract
Various 1,3,4-thiazole derivatives have been reported to exhibit various biological activities. The 1,3,4-thiadiazole derivatives found to have diverse pharmacological activities such as, insecticidal, herbicidal, antiviral, anti-tumor, CNS stimulant, anti-bacterial, antifungal, antiangiogenic, antiglaucoma, antiischemic, and anti-inflammatory, antidepressant, anxiolytic, antiparasitic, antitumor, hypoglycemic, antihypertensive and CNS depressant activities The 1,3,4-Thiadiazoles have also been used in many fields and majority of applications as dyes, lubricants, analytical reagents and agents. The 1,3,4-Thiadiazole analogs are associated with diverse biological activities probably by virtue of toxophoric -N=C-S- group. Due to the wide range of applications we have studied thiadiazole derivatives for their biological significances.

Keywords: Thiadiazoles, Pharmacological, Triazolo.

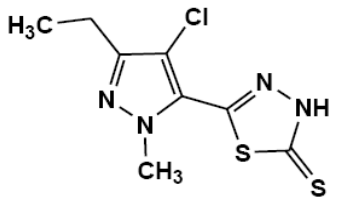
Introduction
Thiadiazole derivatives are well known for their significant biological activities. A large number of thiadiazoles have been reported to exhibit various biological activities. Some 1,3,4-thiadiazole derivatives found to have diverse pharmacological activities such as, insecticidal, herbicidal, anti-tumor, antifungal, antiangiogenic, antiglaucoma, antiischemic, and anti-inflammatory, antidepressant [HI], anxiolytic, anti-bacterial, antiparasitic, antitumor, hypoglycemic antihypertensive, antiviral, anti HIV, anti-HSVl, antiproteolytic, antiphage, antithyroidal, antiamoebic, anticonvulsant, neurotoxicity, insecticidal, herbicidal and also plant growth regulators, CNS depressant and CNS stimulant properties.[1-7] Many of them have potential biological usage and some have been tried for antituberculosis. They also find applications as dyes, lubricants, analytical reagents and antiviral agents. The 1,3,4-Thiadiazole analogs are associated with diverse biological activities probably by virtue of toxophoric -N=C-S- group. The 1,3,4-Thiadiazoles have applications in many fields and majority of applications are patented. Some of the thiadiazole analogue act as nematicides and cefazolin (5-methyl-l,3,4-thiadiazole-2-thiol derivative, is used as an antibacterial agent.[7-10]

The 1,3,4-Thiadiazole analogues have displayed activity against hepatitis B virus. 2-Amino-l,3,4-thiadiazole-5-thiol is an effective radioprotective agent. The most pronounced effect of amino thiadiazole on ribonucleotide pools of leukemia L 1210 cells is the lowering of guanine ribonucleotide pools. They act as potent orally active non-peptide antagonist for the bradykinin p2 receptor and induce mortality in frog embryos. A series of thiosemi-carbazides and investigated them as central cholecystokinin and neurokinin receptors. Thiosemicarbazides are also considered as psychotropic agents. The most important industrial uses of thiosemicarbazides are they act as corrosion inhibitors of copper, and carbon-steel, in aqueous chloride solutions. Also they act as thermal stabilizers for rigid poly vinyl chloride.[11-15] The thiadiazole drugs were the first effective chemotherapeutic agents to be employed systematically for the prevention and cure of bacterial infection in human beings (eg: Sulphamethizole).They are also choice for the drug as diuretic (eg: Acetazolamide). Thiadiazole derivatives are well known to have number of biological and antimicrobial, anti-inflammatory and anti-convulsant activities.

Chemistry: Thiadiazole is a heterocyclic compound featuring both two nitrogen atom and one sulphur atom as part of the aromatic five-membered ring. Thiadiazole and related compounds are called 1,3,4-thiadiazole (two nitrogen and one other heteroatom in a five membered ring). They occur in nature in four isomeric forms as. 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole.

Biological importance 1,3,4-Thaidiazoles: The Heterocyclic nucleus 1,3,4-thiadiazole constitutes an important class of compounds for new drug development. The synthesis of thiadiazole derivatives for their chemical and biological behaviors and have gained more importance in recent decades. In recent years there has been intense investigation of different classes of thiadiazole compounds, many of which possess extensive pharmacological activities.

Various thiadiazole have been shown to possess different activities. The fungicidally active Pyrazolyl-Substituted-1,3,4-thiadiazole compounds, the preliminary bioassay tests indicated that compounds (1) and (2) have fungicidal activity.[16] A series of 2-sulfonamido/trifluoromethyl-6- substituted imidazo [2,1-*b*]-1,3,4-thiadiazole derivatives (3). The selected compounds were evaluated for their preliminary in vitro anti-tuberculosis activity against *Mycobacterium tuberculosis*. Some of the compounds exhibited moderate to good anti-tubercular activity.[17]



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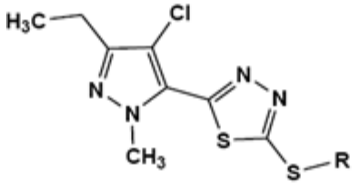
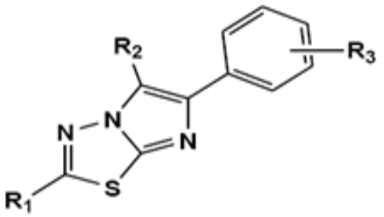
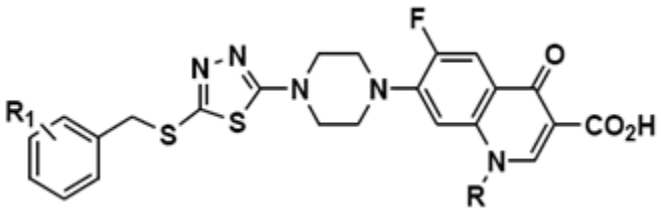


2 **R**=Methyl, propyl, Allyl, Amyl

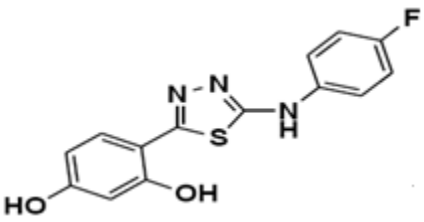


3 $\mathbf{R_1}$= $-SO_2NH_2$, $-(CH_3)_2N-C=N-SO_2-CH_3$, CF_3 $\mathbf{R_2}$= CH_3, Cl, OMe, Trimethoxy, NO_2 $\mathbf{R_3}$= H, -SCN, $-C=N-NH-C=N\ H-NH_2$

Antibacterial activity of *N*-(5-benzylthio-1,3,4-thiadiazol-2-yl) and *N*-(5-benzylsulfonyl-1,3,4-thiadiazol-2-yl)piperazinyl quinolone derivatives (4) against Gram-positive and Gram-negative microorganisms). Some of these derivatives exhibit high activity against Gram positive bacteria *Staphylococcus aureus* and *S. epidermidis*, comparable or more potent than their parent *N*-piperazinyl quinolones norfloxacin and Ciprofloxacin as reference drugs.[18] A set of N-substituted 2-amino5-(2,4-dihydroxyphenyl)-1,3,4-thaidaizole derivatives. Among these compound (5) showed a very good anticancer and neuroprotective activity.[19]



4 **R**= ethyl, cyclopropyl $\mathbf{R_1}$= H, NO_2



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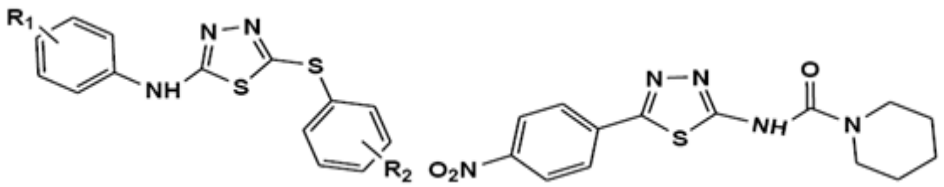
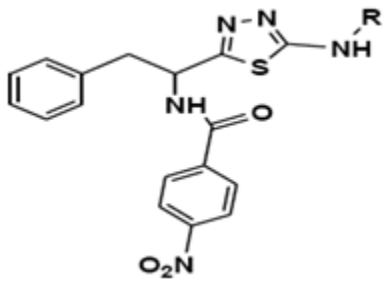
A series of selective cox-2 inhibitors with 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives (6) were selective inhibitiors of COX-2 and potentiated the activity of COX-1 enzyme. The presence of sulphonamide group is a required pharmacophore for selective inhibition of COX-2 enzyme.[20] The syntheses of various compounds were evaluated for antidiabetic activity. Among of these compounds (7) have shown significant antidiabetic activity.[21]



6 R_1= F, CH_3, CF_3, SO_2NH_2 R_2= SO_2NH_2, **7**

The 1,3,4-thiadiazole, that containing a phenylalanine moiety were synthesized by intra-molecular cyclization of 1,4-thiosmicrbazides (8), in acid and alkaline media and the synthesized compounds was evaluated by anti-inflammatory activity.[22] The 2-(arylmethanesulfonylmethyl)-5-aryl-1,3,4-thiadiazoles (9) exhibited high activity on both Gram (+ve) and Gram (-ve) bacteria.[23]



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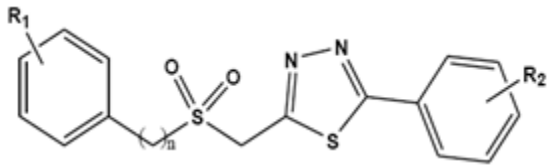
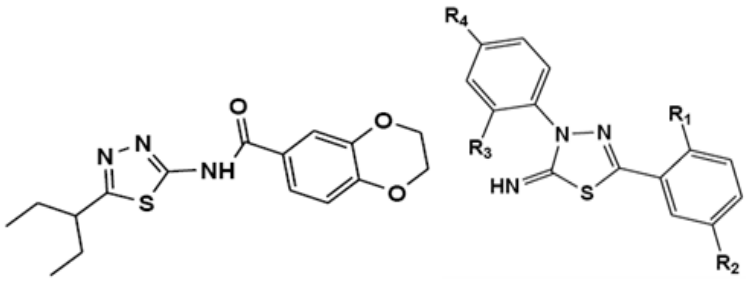


9

The investigation to identify selective antagonists, and they found that aminothiadiazole that is compound (10) was identified from a high throughput screen as having good antagonist activity for human EP3.[24] Derivatives of 2,4-

Substituted diphenyl-5-imino-Δ^2-1,3,4-thiadiazole (11) were evaluated their antimicrobial properties. These compounds exhibited promising antimicrobial activity.[25]

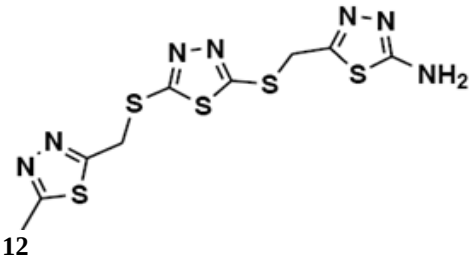


10

R1	R2	R3	R4
H	H	H	H
H	H	NO2	NO2
Cl	H	H	H
Cl	H	NO2	NO2
H	Cl	H	H
H	Cl	NO2	NO2
H	NH2	H	H
H	NH2	NO2	NO2

11

A series of 1,3,4-thaidaizoles, the synthesized compounds were screened for their in vitro antibacterial activity. All the newly synthesized compounds (12) were initially screened for their in vitro antibacterial activities against the Gram-positive (*S. aureus, S. cerevisiae* and *C. diphtheriae*) and the Gram negative (*E.coli* and *P. aeruginosa*) bacteria by agar cup-plate method not disc diffusion method.[26] A series of 2-amino-5-aryl-thiazolo [1,3,4]-Thiadiazole derivatives (13) were prepared. Some of the synthesized compounds showed very good antitubercular activity.[27]



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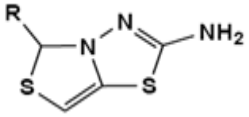
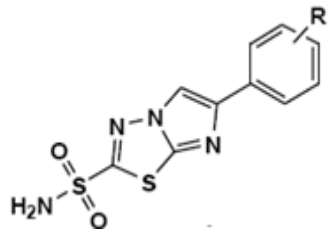


13 R=Ph, 4-MeC_6H_4,4-OHC_6H_4, -$NO_2C_6H_4$, 4$Me_2NC_6H_4$, 2ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2$OMeC_6H_4$, 3-$OMeC_6H_4$

The 2,4-Thiazolidinediones bearing Imidazo[2,1-b][1,3,4] Thiadiazole derivatives (14-16) show very good antimicrobial activity.[28]



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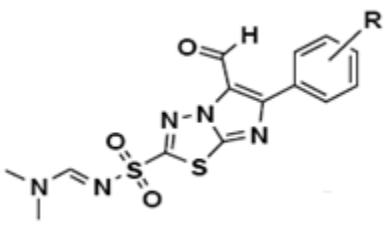

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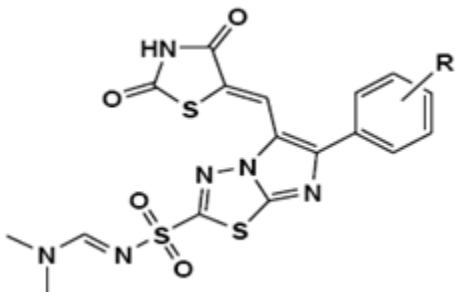
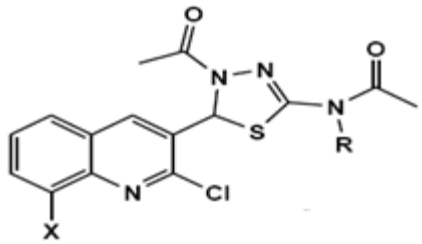


16

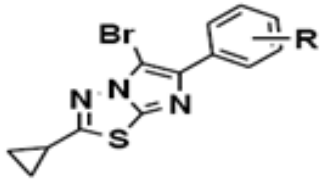
R= H, 4-Br, 4-Cl, 2, 5-(OMe) 2, 4-CH_3, 4-OMe, 4-NO_2

A series of 3-(1,3,4-Thiadiazole-2-yl) quinoline derivatives (17) from chloroquinone with an aim to explore their effect on in vitro growth of microorganisms causing microbial infection.[29] The 6-aryl-2-(2-aryl-2*H*-1,2,3-triazol-4-yl) imidazo[2,1-*b*]-1,3,4- thiadiazoles (18). Some of these compounds were found to possess slight to moderate activity against the microorganisms *Staphylococcus aureus, Candida albicans, Pseudomonas aeruginosa,* and *Escherichia coli.*[30]



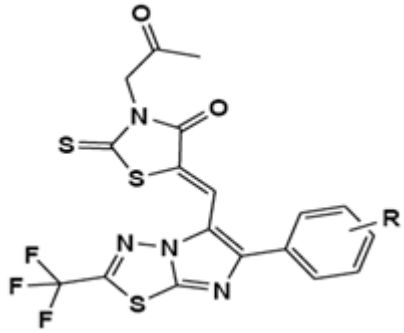
17 **X**= H, Cl, CH_3 **R**=H, Cyclohexyl, O-tolyl, 4-nitrophenyl, cyclopentyl, 2,5-difluoro phenyl,

A series of 2-cyclopropyl Imidazo [2,1-*b*] [1,3,4]-Thiadiazole derivatives, among the compounds tested, compound (19,20) found to be the most active candidate of



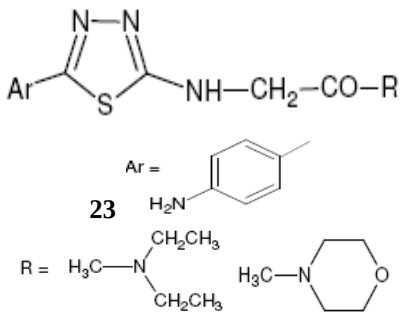
19 **R**=H, 4-Cl, 4-Br, 4-F, 2,4-Di-Cl, 2,4-di-OH, 3-NH_2, 4-NH_2, 3-NO_2, 4-NO_2,

A series of novel Imidazo [2,1-*b*][1,3,4]-thiadiazole carrying rhodanine-3-acetic acid as potential antitubercular agents (21). Among synthesized compounds, some of the compounds showed very good vitro antitubercular activity



21 **R** = H, Cl, Br, F, CH_3, OCH_3, NO_2

Some 1,3,4-thiadiazoles (23) act as possible antimicrobial; anti-inflammatory and antidiabetic agents.[34] Fluoro benzothiazole incorporated with 1,3,4-Thiadiazoles



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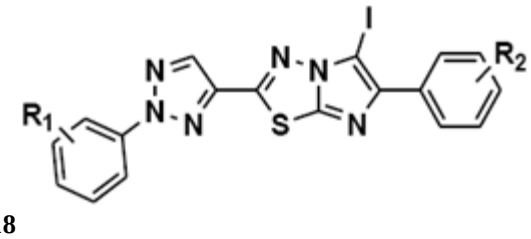

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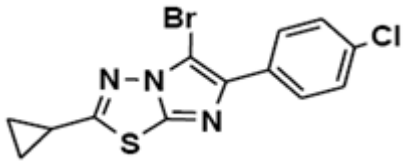
the series at five dose level screening with degree of selectivity towards Leukemic cancer cell line.[31]



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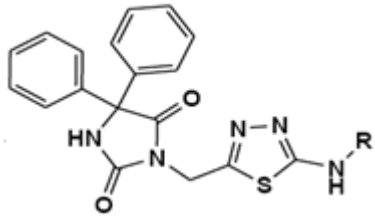
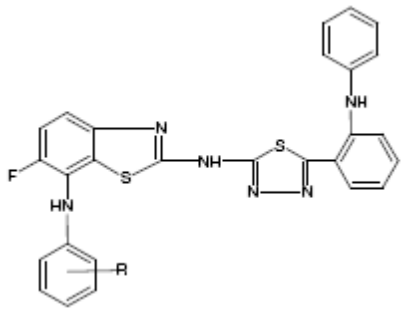
against *M. tuberculosis.*[32] The phenytoin derivatives and studied its anticonvulsant activity. Among the synthesized compounds, only phenyl substituted (22) showed promising anticonvulsant activity.[33]

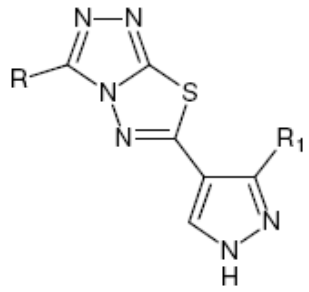


22 R= C_2H_5, C_6H_5, 4-$CH_3C_6H_4$, 4-OMe-C_6H_4, 4-Cl-C_6H_4

(24) were exhibited Anti-microbial activity of.[35] Synthesis, characterization and anticancer activity of 1,2,4-Triazolo [3,4-b]-1,3,4-thiadiazoles (25) on Hep G2 cell lines.[36]

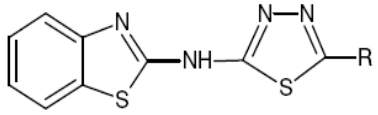


24 R = o, m, p – methoxy

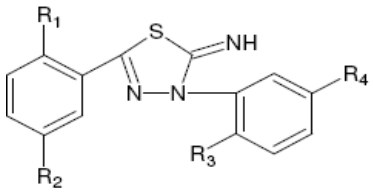


25 R = Phenoxy methyl, R1 = p-chloro phenyl

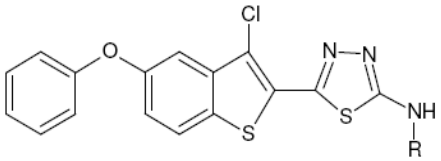
Synthesis of pharmaceutically important 1,3,4-thiadiazole and imidazolinone derivatives (26) as antimicrobials.[37] The 2,4-Di substituted-5-Imino-1,3,4-Thiadiazole Derivatives (27) were exhibited antiinflammatory activities.[38] Some Thiosemicarbazide and 1,3,4- Thiadiazole Heterocycles Bearing Benzo[b] Thiophene Nucleus (28) as a Potent Antitubercular and Antimicrobial Agents.[39]



26 R = Phenyl, 4-chloro phenyl, 4-nitro phenyl

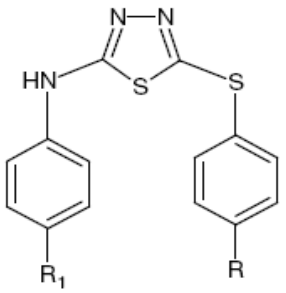


27 R_1, R_2, R_3, R_4 = H

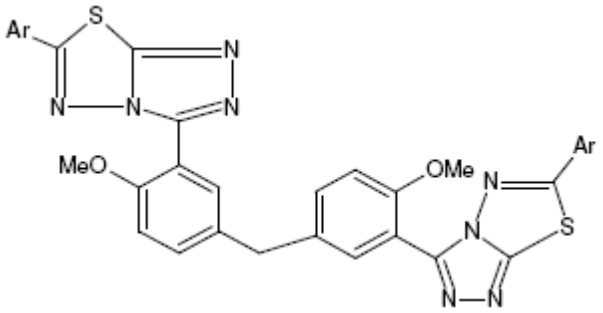


28 R = Aryl

Synthesis of 2-Amino-5-sulfanyl-1,3,4-thiadiazoles (29), a series of selective cyclooxygenase-2 inhibitors.[40] Evaluation of Bis[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (30) as Potent Antimicrobial Agents.[41]

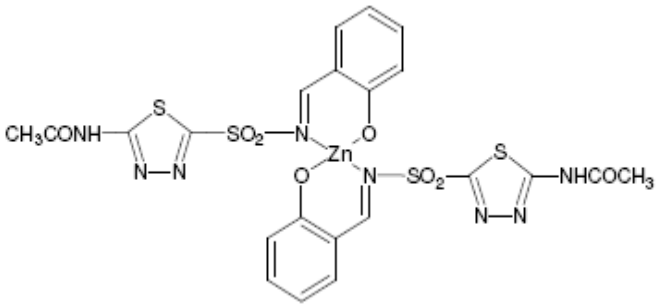


29 R = SO_2NH_2 R_1 = Cl



30 Ar = Phenyl, 2- chloro phenyl, 4-methyl phenyl

The Zn(II) Complex of Schiff Base Derived from 5-Acetazolamido-1,3,4 -Thiadiazole-2-Sulphonamide (31), act as Diuretic Drug.[42] Antimicrobial activity of 2-(2'-substituted-benzylidene-hydrazino-acetyl)–mercapto-5-methyl-1,3,4-thiadiazoles (32) and 2-[2'-{4-substituted-aryl-3-chloro-2-oxo–azetidine}–acetyl-amino-mercapto]-5-methyl-1,3,4-thiadiazoles.[43]



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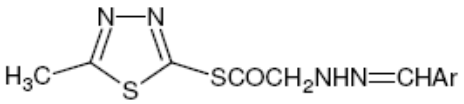
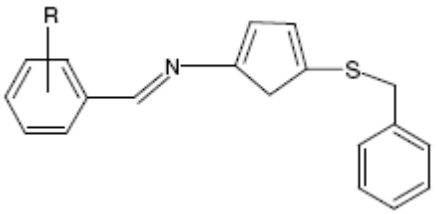
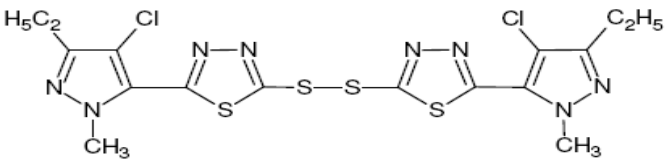


32 Ar = Substituted aryl groups

The aromatic aldehyde imine derivatives of 2-thiobenzyl-1,3,4-thiadiazole (33) was exhibited anticonvulsant activity.[44] Fungicidally Activity exhibited by Pyrazolyl-Substituted 1,3,4-Thiadiazole (34) Compounds.[45]

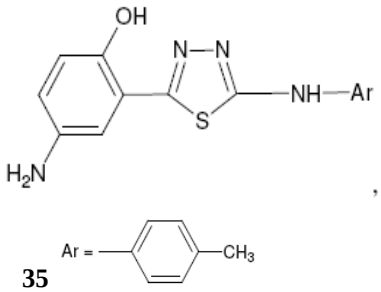


33 R = 2-Cl, 4-Cl, 2-NO_2, 4-NO_2



34

The 1,3,4-Thiadiazole Derivatives of 5-Amino-2-Hydroxybenzoic Acid (35) was exhibited Antimicrobial Activity.[46] Some 1,3,4-Thiadiazole Derivatives (36) were exhibited Antimicrobial Activity.[47]



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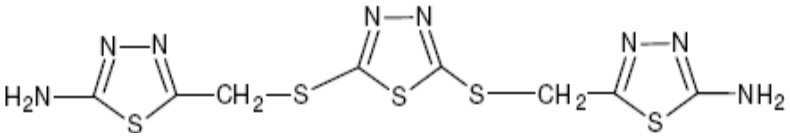
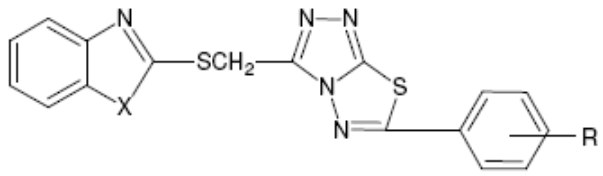
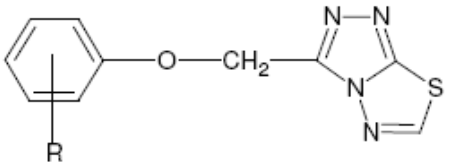


36

The 3-[2-benzothiazolyl/benzimidazolyl methyl-1,2,4-triazolo[3,4,b][1,3,4]thiadiazole-6-yl-subsituted (37) as possible anthelmintics.[48] The 1,3,4-thiadiazole derivative (38) was exhibited fungicidal activity.[49]

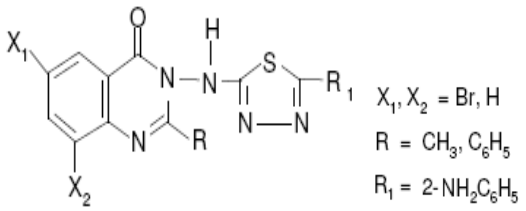


37 X = S, O,

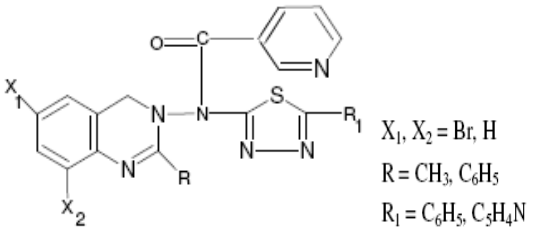


38

The 1,3,4-thiadiazole derivative (39) were exhibited antinflamatory activity.[50] The nicotinyl incorporated quinazolinonyl thiadiazoles (40) were exhibited possible NSAID activity.[51]

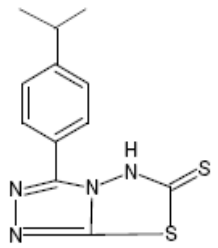


39

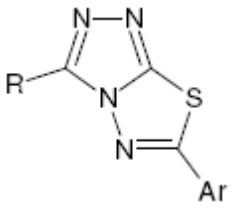


40

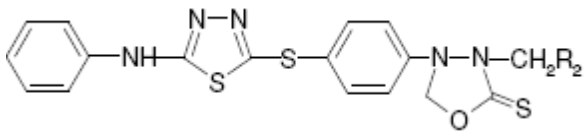
The triazolo[3,4-b][1,3,4]thiadiazole (41) was exhibited antimicrobial activity.[52] The 1,3,4-thiadiazole derivatives (42) were exhibited antimicrobial and anti-inflammatory activities.[53] The pyrazole, pyrazolones and oxadiazole bearing 2-arylamino-5-mercapto-1,3,4-thiadiazoles (43) were exhibited antimicrobial activities.[54]



41

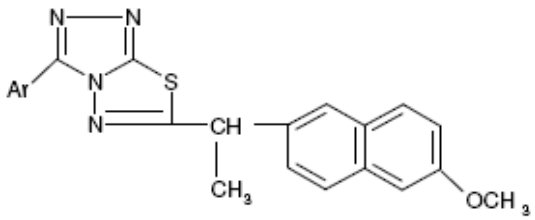


42Ar =$C_6H_5OCH_3$, $CH_2OC_6H_5Cl$

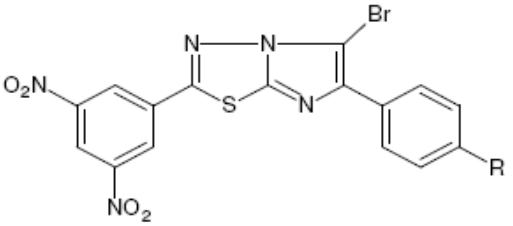


43 R_1=H, CH_3, Cl
R_2 = Five membered Hectrocyclic moiety

The 3,5 disubstituted-s-triazolo (3,4-b)-1,3,4-thiadiazole (44) were exhibited antimicrobial and antinflamatory activities.[55] The imidazolo[2,1-b]-1,3,4-thiadiazole (45) was exhibited antimicrobialactivity.[56]

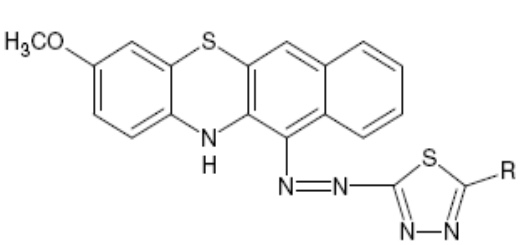


44

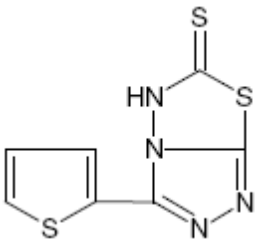


45

The 1-(2-diazo-5-arylalkyl-1,3,4-thiadiazolyl)-6-methoxy benzophenothiazines (46) were exhibited antiviral and antifungal activities.[57] The 3-(2-thienyl)-s-triazolo[3,4-b][1,3,4]thiadiazole (47) were exhibited antimicrobial and diuretic activities.[58]

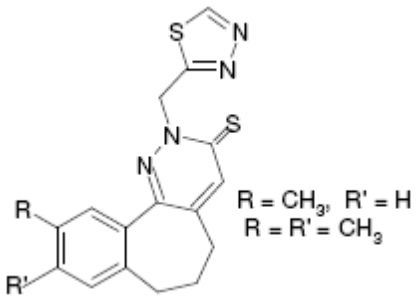


46

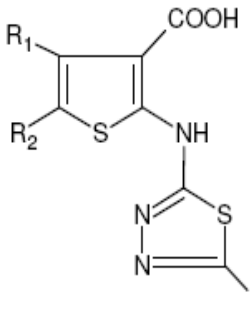


47

The 2,5-disubstituted 1,3,4-thiadiazole derivatives (48) were exhibited antibacterial activity.[59] The N-(1,3,4-thiadiazole-2-yl)5-substituted-2-amino-4,5-disubstituted-thiophen-3-carboxalic acid (49) exhibited analgesic and anti inflamatory agent.[60]

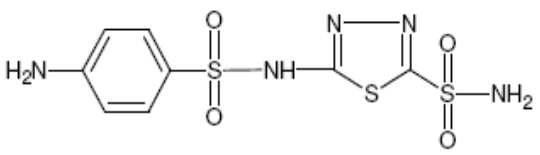


48

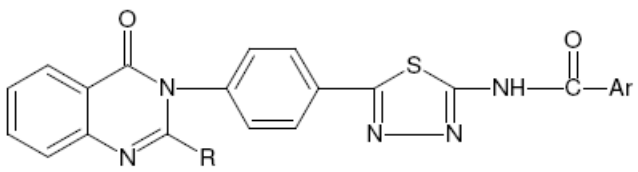


49 R = C_6H_5NH, CH_3NHCH_2 R_1=R_2 = CH_3, $(CH_2)_4$

Some 1,3,4-thiadiazole derivatives (50) were exhibited free radical scavenging activity.[61] The aryl-N-(5-{4-[2-chlorophenyl)-4-oxo(3-hydroquinazoline)]-phenyl}(1,3,4-thiadiazol-2-yl)amides (51) were exhibited antibacterial and antifungal activities.[62]

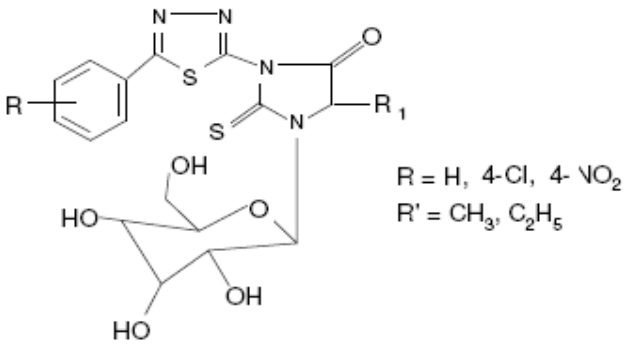


51



52R= 2-chlorophenyl Ar=Different aryl groups

Some 3-(5-aryl-1,3,4-thiadiazole-2-yl)-1-(β-D-glucopyra–nosyl)-5-alkyl-2-thio-4-imidazo-lidinones (53) were exhibited fungicidal activity.[63]



Conclusion

The thiadiazole posses various pharmacological activities including anticancer, anti-inflammatory, antitubercular, antioxidant, antimicrobial, anticonvulasant, and analgesic activities, above observations promoted us to synthesize the new thiadiazole compounds with potent biological activities.[64] The 1,3,4-thiadiazole are important because of their versatile biological actions. In particular, compounds bearing the 1,3,4-thiadiazole nucleus is known to have unique antibacterial and anti-inflammatory activities. Differently substituted thiadiazole moieties have also been found to have other interesting activities such as analgesic, antimicrobial, antitubercular, anticonvulsant and anti-hepatitis B viral and other useful activities.

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