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REVIEW ARTICLE

Pharmacological Activities of 1,3,4-Thiadiazole Derivatives-Review

Dhruv Kumar Chaudhary[1*] and Ramesh Pratap Chaudhary[2]

[1]Department of Pharmaceutical Chemistry, [2]Department of Pharmacognosy , Translam Institute of Pharmaceutical Education & Research, Mawana Road, Meerut, U.P., India

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ABSTRACT

Heterocyclic compounds occupy a central position among those molecules makes life possible. The chemistry of heterocyclic compounds has been an interesting field of study for a long time. Thiadiazole and its derivatives are important organic reaction intermediates and this review covers updated information on the most active thiadiazole derivatives that have been reported to show considerable pharmacological actions such as antimicrobial, anticancer, anticonvulsant, anti-inflammatory and analgesic, Leishmanicidal. So far, modifications of the thiadiazole ring have proven highly effective with improved potency and lesser toxicity.

Keywords: Thiadiazoles, Antibacterial, Anticancer, Anticonvulsant etc.

INTRODUCTION

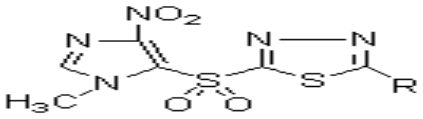
Heterocyclic moieties can be found in a large number of compounds which display biological activity. The biological activity of the compounds is mainly dependent on their molecular structures.1,3,4-thiadiazoles are very interesting compounds due to their important applications in many pharmaceutical, biological and analytical field. Schiff bases-bimolecular condensation products of primary amines with aldehydes-represent valuable intermediates in organic synthesis and, at the same time, compounds with various applications. Schiff bases resulted from aromatic aldehydes *ortho*-substituted with a hydroxyl group have initially arouse the researches interest because of their ability to act as bidentate ligands for transition metal ions. Schiff bases are important class of compounds due to their flexibility, structural similarities with natural biological substances and also due to presence of amine (N=CH-) which imports in elucidating the mechanism of transformation and racemization reaction in biological system. These novel compounds could also act as valuable ligands whose biological activity has been shown to increase on complexation. Derivatives of 1, 3, 4-thiadiazoles have been recognized as molecules with potential antimicrobial utility. Heterocyclic compounds are cyclic compound with the ring containing carbon and other element, the component being oxygen, nitrogen and sulphur. The simplest of the five membered heterocyclic compound are pyrrole, furan and thiophene, each of which contains a single heteroatoms. The five membered ring containing more than one or two hetero atoms also such as azole, pyrrole, thiazole, thiadiazole, oxadiazole, triazene etc.

Thiadiazole derivatives possess interesting biological activity probably conferred to them by the strong aromaticity of this ring system, which leads to great *in vivo* stability and generally, a lack of toxicity for higher vertebrates, including humans. When diverse functional groups that interact with biological receptors are attached to this ring, compounds possessing outstanding properties are obtained.

Antimicrobial activity

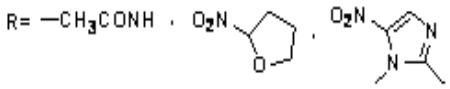
Synthesis of 2-(1-methyl-4-nitro-1*H*-imidazol-5-ylsulfonyl)-1,3,4-thiadiazoles derivatives **(1)** were reported by Bahram *et al.*,[1].The synthesize compounds **1a,1b,1c** were tested *in vitro* by the conventional agar dilution method against a panel of microorganisms including gram-negative and gram-positive bacteria. Compound **1b** shown promising antibacterial activities against gram-positive bacteria including *Staphylococcus aureus, Staphylococcus epidermidis* and *Bacillus subtilis*.

***Corresponding Author:** Dhruv Kumar Chaudhary**, Email:** dhruvchaudhary72@gmail.com

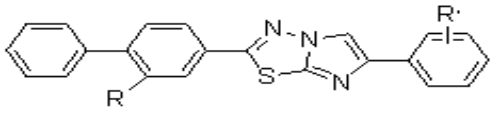


(1)

a. b. c.



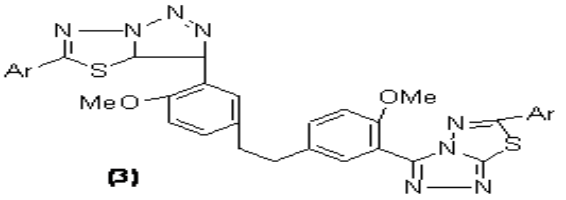
Synthesis of some novel heterocyclic derivatives **(2)** were reported by Yadav *et al.,*[2]. The structures of the newly synthesised compounds were characterized by various spectral techniques and screened for antibacterial activity against strains of *Escherichia coli, Pseudomonas aeruginosa* and *Bacillus subtilis*, and antifungal activity against *Candida albicans, Saccharomyces cerevisiae and Aspergillus niger*.



(2)

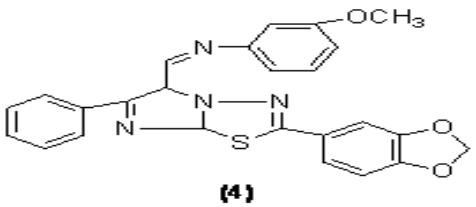
R=H,F.
R·=H ,4Cl,4F ,4NH_2 ,4Br.

Synthesis and evaluation of novel Bis [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazoles derivatives **(3)** were reported by Reddy *et al.,*[3]. As potent antimicrobial agents and evaluated the antibacterial activity against various gram negative and positive bacteria.



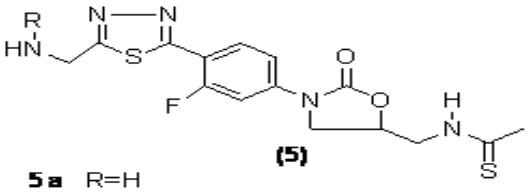
(3)

Synthesis and different biological activities of some Schiff bases of imidazo-[2, 1b]-1, 3, 4-thiadiazole derivatives **(4)** were reported by Jalhan *et al.,*[4]. The substituted derivative show moderate biological activity. The derivative has shown moderate to good activity when compared with standard antibiotic ampicillin. Schiff bases have different biological activities such as antimicrobial.



(4)

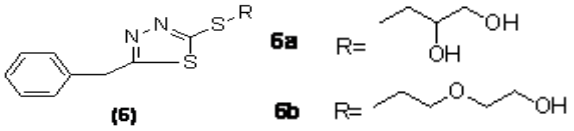
Synthesis and Antibacterial Activity of 1,3,4-Thiadiazole Phenyl Oxazolidinone Analogues **(5)** were reported by Thomasco *et al.,*[5]. Replacement of the morpholine C-ring of linezolid with a 1,3,4-thiadiazolyl ring leads to oxazolidinone analogues **5a** and **5b** having potent antibacterial activity against both gram-positive and gram-negative organisms. Conversion of the C_5 acetamide group to a thioacetamide further increases the potency of these compounds.



(5)

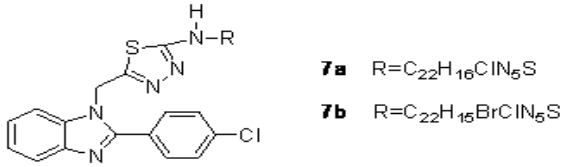
5a R=H
5b R=CH_3

Synthesis a number of new substituted tetrazole and their hydrazide derivatives **(6)** were reported by Sofan *et al.,*[6]. The synthesized compounds **6a,** and **6b** displayed the highest inhibition activity against *Sreptomyces Species* also with MIC value of 75 µg/ml. Some of the other compounds revealed moderate activity while others revealed little.



(6) **6a** **6b**

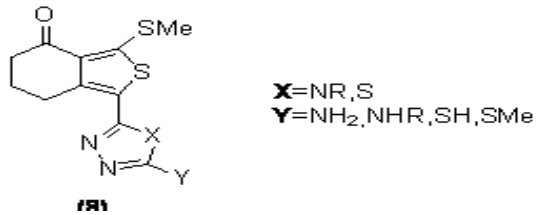
Synthesis of Some 2-(2-(p-chlorophenyl)benzimidazol-1-ylmethyl)-5-substituted amino-[1,3,4]-thiadiazoles derivatives **(7)** were reported by Kilcigll *et al.,*[7].The synthesized and their *in vitro* antimicrobial activities were tested against *Staphylococcus aureus, Bacillussubtilis, Escherichia coli, Candida albicans* and *Candida krusei*. Compounds **7a** and **7b** which possess remarkable activity against *C. albicans* and marginal activity against *C. krusei* were found to be the most active compounds in this series.



(7)

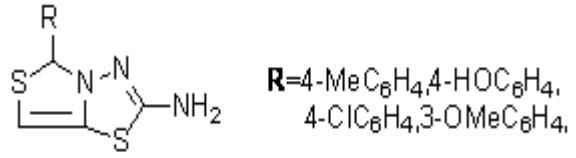
7a R=$C_{22}H_{16}ClN_5S$
7b R=$C_{22}H_{15}BrClN_5S$

Synthesis of 1-[1,2,4-triazol-3-yl] and 1-[1,3,4-thiadiazol-2-yl] -3-methylthio-6,7 dihydrobenzo [*c*] thiophen-4 (5*H*) ones **(8)** were reported by Tehranchian *et al.,*[8]. The synthesized and tested to demonstrate *in vitro* antimicrobial activity. Some of these compounds exhibited a good activity against *Staphylococcus aureus, S. epidermidis* and *Bacillus subtilis*.



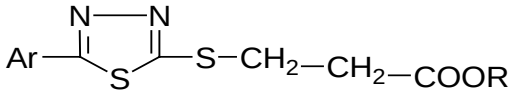
(8)

Synthesis of 2-amino-5-aryl-5*H*- thiazolo [4,3,-b]-1,3,4- thiadiazole **(9)** were reported by Kargar *et al.*,[15]. The synthesized by using aromatic aldehydes, thioglycolic acid and thiosemicarbazid Fungicidal activity against two fungi *A. niger* and *C. albicans* and bactericidal activity against two gram +ve bacteria *S. aureus, E. fecalis and two* gram –ve bacteria *E. coli, Klebsiella Pneumonia* and found to be activity against these microorganism.



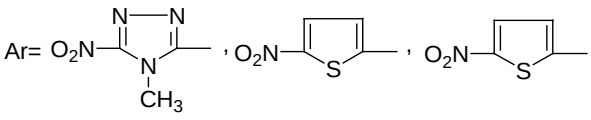
(9)

Synthesis of 2- and 3-[5-(nitroaryl)-1,3,4-thiadiazol-2-ylthio, sulfinyl and sulfonyl] propionic acid alkyl esters **(10)** were reported by Foroumadi *et al.*,[10].The synthesized and screened for antituberculosis activity against *Mycobacterium tuberculosis*. The MIC values for the compounds showing more than 90% inhibition were determined. The compound propyl 3-[5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-ylthio]propionate was the most active one.



(10)

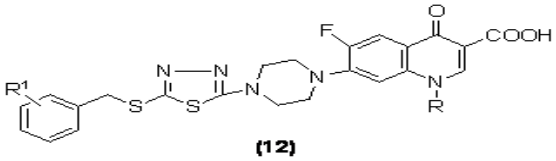
R=methyl,ethyl,n-propyl,n-butyl,H



Synthesis of fused 1,2,4-triazoles with diphenylsulfone moiety are prepared utilizing 4-amino-5-[4-(4-Brmo-phenylsulfonyl)phenyl]-4*H*-1,2,4-triazole-3-thiol **(11)** were reported by Almajan *et al.*,[11]. New synthesized compounds were screened for their antimicrobial activities. The preliminary results revealed that some of the compounds exhibited promising antimicrobial activities.

(11)

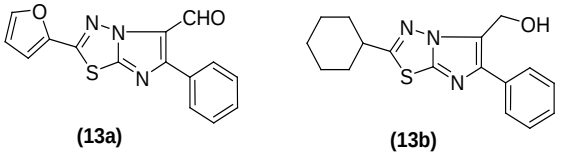
Synthesis of *N*-(5-benzylthio-1,3,4-thiadiazol-2-yl) and *N*-(5-benzylsulfonyl-1,3,4- thiadiazol -2-yl) derivatives **(12)** were reported by Emami *et al.*,[12].The synthesized and evaluated for antibacterial activity against Gram-positive and Gram-negative microorganisms. Some of these derivatives exhibit high activity against Gram-positive bacteria *Staphylococcus aureus* and *Staphylococcus epidermidis*.



(12)

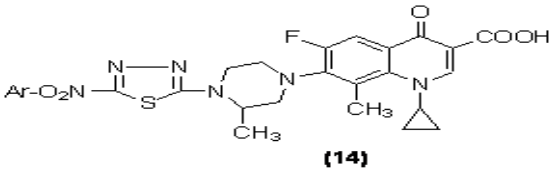
R=ethyl,cyclopropyl
R1=H,NO2

Synthesis of 2,6-disubstituted and 2,5,6-trisubstituted imidazo[2,1-*b*][1,3,4] thiadiazoles **(13)** were reported by Kolavi *et al.*,[13]. The synthesized structures of the compounds **13a** and **13b** were elucidated and screened for antitubercular activity against *Mycobacterium tuberculosis* and antibacterial activity against *Escherichia coli* and *Bacillus cirrhosis*, and antifungal activity against *Aspergillus niger* and *Penicillium wortmanni.*



(13a) (13b)

Synthesis of a number of gatifloxacin analogues containing a nitroaryl-1,3,4-thiadiazole derivatives **(14)** were reported by Jazayeri *et al.*,[14].The synthesized compounds, nitrofuran analog exhibited more potent inhibitory activity against Gram-positive bacteria including *Staphylococcus epidermidis*, *Bacillus subtilis*, *Enterococcus faecalis* and *Micrococcus luteus.*

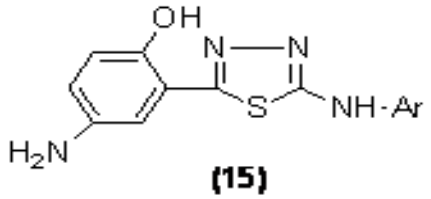


(14)

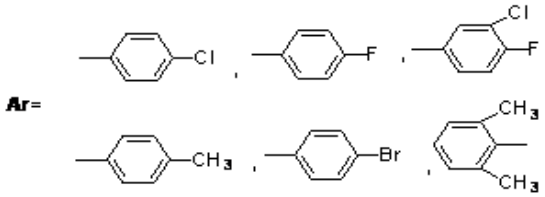
NO2.Ar =5-nitrofuran-2-yl,5-nitrothiophen-2-yl,
1-methyl-5-nitromidazol-2-yl,nitrophenyl.

Synthesis of 4-amino-2-{5-[(4-substituted phenyl)amino]-1,3,4- thiadiazole-2-yl} phenol **(15)** were reported by Hussain *et al.*,[15]. The

synthesized and evaluated for their antibacterial and antifungal activity. The compounds showed significant antibacterial activity against *S. aureus* (gram-positive) and *E.coli* (gram-negative) bacteria and antifungal activity against *A. niger*.

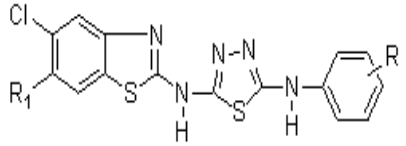


(15)



Anticonvulsant activity

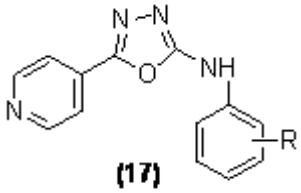
Synthesis of various *N*-(5-chloro-6-substituted-benzothiazol-2-yl)-*N*'-(substituted phenyl) [1,3,4] thiadiazole-2,5-diamines derivatives **(16)** were reported by Siddiqui *et al.,*[16]. The newly synthesized compounds were screened for their anticonvulsant activity and Interestingly, all the compounds showed protections against seizures in the range 50–100 % indicative of the promising nature of the compounds against seizure spread. Compounds **16a** and **16b** showed complete protection against MES induced seizures.



(16)

	R	R_1
16a	4-Br	Cl
16b	3-Cl	Cl

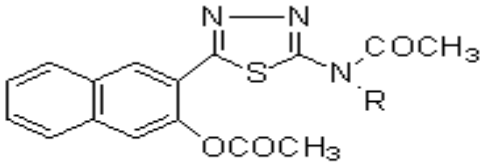
Synthesis of five membered heterocyclics **(17)** were reported by Yar *et al.,*[17].The newly synthesized compounds showed activity in the range of 33-100 % in comparison to phenytoin which completely inhibited the convulsions produced by electroconvulsometer in albino mice. Compounds **17a** showed maximal activity whereas compounds **17b** showed good anticonvulsant activity.



(17)

	R
17a	p-Cl
17b	H

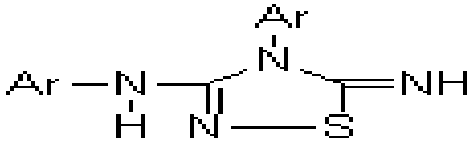
Synthesis of 2,5-disubstituted-1,3,4-thiadiazoles derivatives **(18)** were reported by Dogan *et al.,*-[18].The synthesized for their possible anticonvulsant activities. The degree of protection afforded by these compounds at a dose of 100 mg/kg ip against pentylenetetrazole- induced convulsions in mice ranged from 0 to 90%. Among these compounds showed maximum protection.



(18)

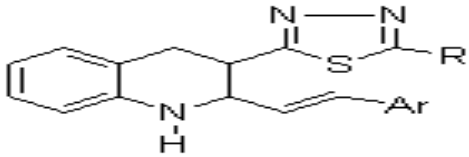
R= ethyl,phenyl,p-bromophenyl,p-chlorophenyl, p-fluorophenyl, m-fluorophenyl,p-methoxyphenyl, m-trifluoromethylphenyl.

Synthesis of new substituted 1,2,4-thiadiazoles **(19)** were reported by Gupta *et al.,*[19].The synthesized by appropriate route and screened for anticonvulsant, neurotoxic and sedative-hypnotic activity. the synthesized compounds were potent against MES-induced seizures than ScPTZ induced and showed low potency as sedative-hypnotic agent which is advantageous.



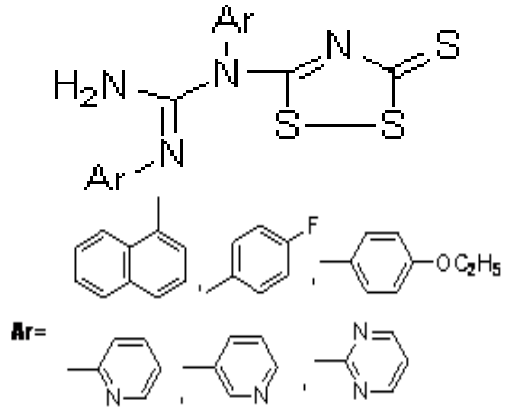
(19)

Synthesis of new 3-[5-substituted phenyl-1,3,4-thiadiazol-2-yl]-2-styryl quinazoline- 4(3*H*)-ones **(20)** were reported by Jatav *et al.,*[20].The evaluated for anticonvulsant activity .Compounds were examined in the maximal electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (scPTZ)-induced seizure models. Compound showed good anticonvulsant activity in the test models.

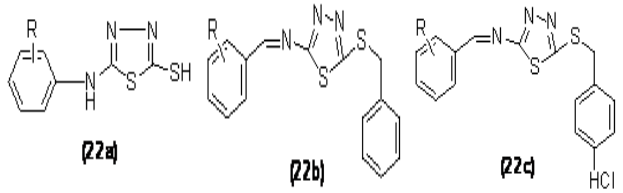


(20)

Synthesis of 1,2,4-dithiazole **(21)** were reported by Gupta *et al.,*[21].The synthesized from 1,2,4-thiadiazoles in the presence of CS_2 and evaluated for their anticonvulsant, and neurotoxicity potential. The compounds provided significant protection against maximal electroshock-induced seizures and seizures induced by 300 mg/kg of subcutaneous pentylenetetrazole administration.

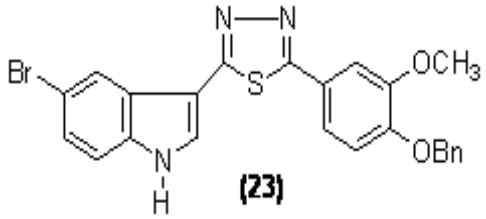


Synthesis of aromatic aldehyde amine derivative of 2-thiobezyl-1,3,4-Thiadiazole derivatives **(22)** were reported by Ahmed *et al.*,[22].The synthesized compounds **22a, 22b, 22c.** show good anticonvulsant activity. Among of these compounds chlorobenzyl substituted compound show the potent anticonvulsant activity against MES method.

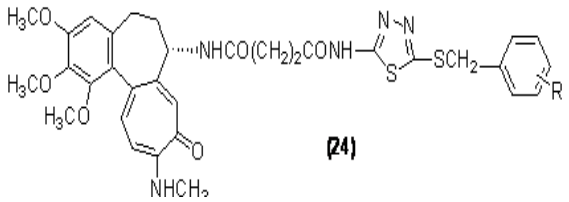


Anticancer activity

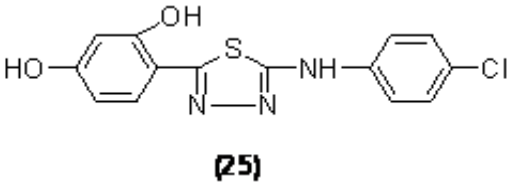
Synthesis a series of 5-(3-indolyl)-2-substituted-1,3,4-thiadiazoles **(23)** were reported by Kumar *et al.*,[23]. The synthesized and their cytotoxicity analyzed against six human cancer cell lines. The compounds shown significant cytotoxicity against multiple cancer cell lines. Introduction of 4-dimethylamino and 3,4,5-trimethoxy groups in the C-2 phenyl ring induced selectivity against MCF7 and MDA-MB-231 cancer cell lines.



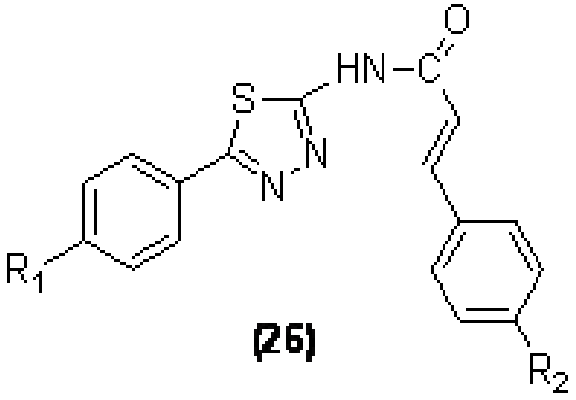
Synthesis of *N*-methyl colchicein amide derivatives containing 1,3,4-thiadiazole moieties **(24)** were reported by Shen *et al.*,[24]. The synthesized and Cytotoxicity of these compounds was evaluated by MTT assay *in vitro* against four human tumor cell lines, *i.e.* A2780, A549, BEL7402, and MCF-7. The compounds showed more potent cytotoxic activities of all screened cancer cells than colchicine.



Synthesis of aminothiadiazole derivative 2-(3-chlorophenyloamino)-5-(2,4dihydroxy phenyl)-1,3,4-thiadiazole **(25)** were reported by Juszczak *et al.*,[25]. The anti-cancer effect was attributed to decreased DNA synthesis, prominent changes in tumor cell morphology as well as reduced cell motility. In antiproliferative concentrations, 4ClABT was not toxic to normal cells. Our study showed prominent anti-cancer effects of the tested aminothiadiazole derivative in the absence of toxicity in normal cells.



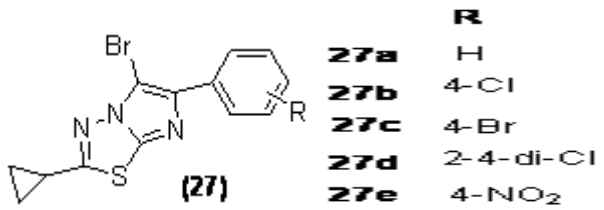
Synthesis of cinnamic acyl 1,3,4-thiadiazole amide derivatives **(26)** were reported by Yang *et al.*,[26]. The synthesized and their biological activities were also evaluated as potential antiproliferation and tubulin polymerization inhibitors. Among all the compounds, **26a** showed the most potent activity *in vitro*, which inhibited the growth of MCF-7 and A549 cell lines. The compound **26a** with potent inhibitory activity in tumor growth may be a potential anticancer agent.



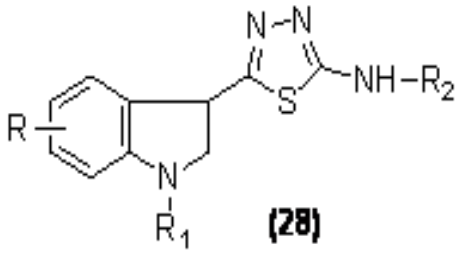
	R_1	R_2
26a	OCH_3	OCH_3
26b	OCH_3	H
26c	OCH_3	F
26d	CH_3	OCH_3

Synthesis of 2,5,6-trisubstituted imidazo[2,1-b][1,3,4]-thiadiazole derivatives **(27)** were

reported by Noolvi *et al.*,[27] .The synthesized of these substituents on antitumor activity. The compounds tested **27b** (NSC D-96022/1) was found to be the most active candidate of the series at five dose level screening with degree of selectivity toward Leukemic cancer cell line.



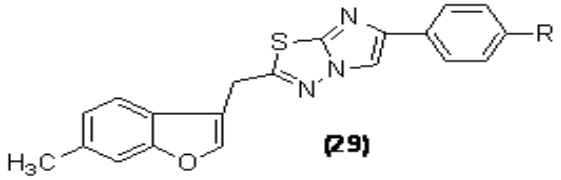
Synthesis of 2-arylamino-5-(indolyl)-1,3,4-thiadiazoles **(28)** were reported by Kumar *et al.*,[28]. They prepared and studied for their anticancer activity against selected human cancer cell lines. Most of the synthesized compounds showed selective cytotoxicity towards human breast cancer cell line (MDA-MB-231). the synthesized 2-arylamino-5-(indolyl)-1,3,4-thiadiazoles, compound **28d** is the most potent towards tested cancer cell lines.



Comp.	R	R_1	R_2
28a	H	H	C_6H_5
28b	H	H	4-$CH_3C_6H_4$
28c	H	CH_3	4-ClC_6H_4
28d	H	H	3,4,5-$(OCH_3)_3C_6H_2$
28e	5-OCH_3	H	4-$OCH_3C_6H_4$
28f	6-OCH_3	H	4-$OCH_3C_6H_4$

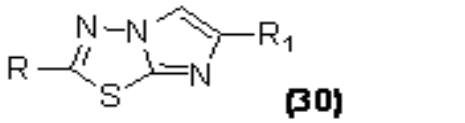
Analgesic and anti-inflammatory activities

Synthesis of 6-substituted and 5,6-disubstituted 2-(6-methyl-benzofuran-3-ylmethyl)-imidazo[2,1-*b*][1,3,4] thiadiazoles **(29)** were reported by Jadhav *et al.*,[29].The synthesized of new compounds have been tested for their *in vivo* analgesic, anti-inflammatory activities. Introduction of formyl group at C-5 position of the imidazole ring increased the anti-inflammatory and analgesic activity.



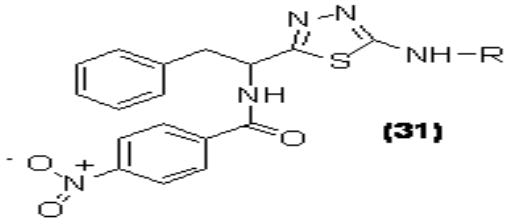
R=Br,Cl,NO_2

Synthesis of 6-carbamic acid-2,6-dimethylimidazo[2,1-b][1,3,4]thiadiazoles **(30)** were reported by Abignente *et al.*,[30]. Their for antiinflammatory, analgesic, antipyretic and ulcerogenic activities using indomethacin as standard drug. The compounds exhibited analgesic activity in the acetic acid writhing test and were completely devoid of analgesic activity in the hot plate test and yeast-induced pyrexia.

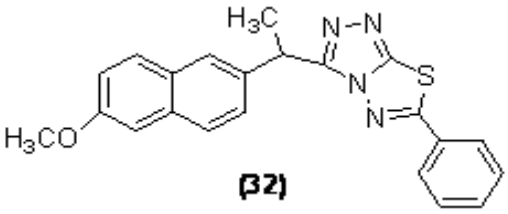


R=H,CH_3,C_2H_5
R_1=$COOC_2H_5$,$CH_2COOC_2H_5$

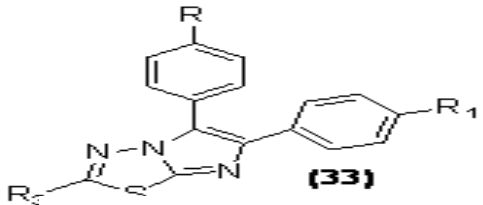
Synthesis of 1,3,4-thiadiazole derivatives, **(31)** were reported by Moise *et al.*,[31]. That containing a phenylalnine moiety were synthesized by intermolecular cyclization of 1,4-thiosmicrbazides in acid and alkaline media and the synthesized compounds was evaluated by anti-inflammatory activity.



Synthesis of aromatic acids and aryl/ alkyl isothiocyanates substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives **(32)** were reported by Mohammad *et al.*,[32].These have been synthesized and evaluated for anti-inflammatory activity .Among of these compounds have showed higher antiinflammatory activity.



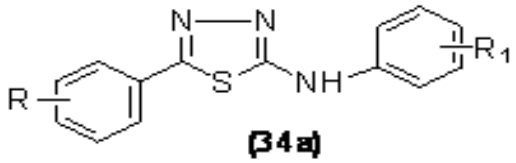
Synthesis of 2-trifluoromethyl sulfonamido-5,6-diarylsubstituted imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives **(33)** were reported by Gadad *et al.*,[33]. These have been synthesized by the reaction of 2-amino-5- trifluoromethyl/sulphonamido-1,3,4-thiadiazoles and substituted by a-bromo-1,2-(p-subsitued)diaryl-1-ethanones and the compound were evaluated by the vitro cyclooxgenage inhibitory activity against COX-2 & COX-1 enzyme.



(33)

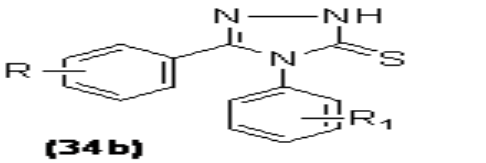
R=H,OCH_3.
R_1=H,F,CH_3,OCH_3,SCH_3,SO_2CH_3.
R_2=CF_3,SO_2NH_2

Synthesis of 4,5-disubstituted-2,4-dihydro-3H-1,2,4-triazole-3-thiones and 2,5-disubstituted-1,3,4-thiadiazoles **(34)** were reported by Khan *et al.*,[34]. The synthesized compounds were screened for their antioxidant and urease inhibition activities. The compounds **34a** showed excellent antioxidant activity more than the standard drug where as **34b** exhibited potent urease inhibitory activities.



(34a)

R=4-NO_2
R_1=2,4-di-CH_3

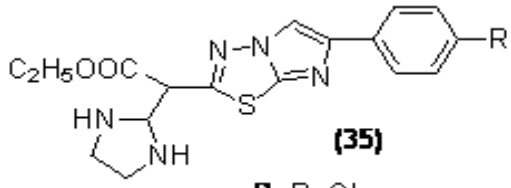


(34b)

R=3-NO_2
R_1=2,4-di-CH_3

Leishmanicidal activity

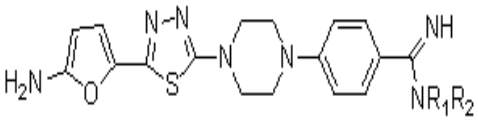
Synthesis of 2-benzylsulfanyl-6-(4-chloro-phenyl)- imidazo[2,1-b][1,3,4]thiadiazoles **(35)** were reported by Ram *et al.*,[35]. These compound less than 30% inhibition against L. Donovani. These reported as compared to standard drug sodium stibogluconate.



(35)

R=Br,Cl.

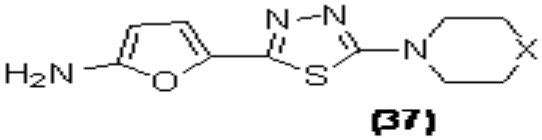
Synthesis of 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazoles **(36)** were reported by Tahghighi *et al.*,[36]. All compounds were tested for *in vitro* activity against the promastigote and amastigote forms of Leishmania major. The compound **36a,36b,36c** showed very good activity in both forms of promastigote and amastigote. The most active compound was **36a** with IC50 value of 0.08 mM in promastigote model.



(36)

Comp.	R_1	R_2
36a	H	n-C_3H_7
36b	H	n-C_4H_4
36c	H	$PhCH_2$

Synthesis of 2-(1-methyl-5-nitroimidazol-2-yl)-5-(1-piperazinyl, 1-piperidinyl and 1-morpholinyl)-1,3,4–thiadiazoles **(37)** were reported by Foroumadi *et al.*,[37]. The leishmanicidal data revealed that compounds (**37a**–**g)** had strong and much better leishmanicidal activity than the reference drug pentostam. Compound **37c** was the most active compound.



(37)

X=CH_2,O,NH,NMe,NPh,
NCOMe,NCOPh.

CONCLUSION

The above study reveals, the synthetic and biological research in the field of imidazo[2,1 b][1,3,4]thiadiazole heterocycles has resulted in some therapeutically potential analogs. Some compounds have shown encouraging activities and are needed to be investigated further to get better agents that can have strong future commitments.

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