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REVIEW ARTICLE

1, 3, 4-Thiadiazole Derivatives and their Biological Activities: A Review

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ABSTRACT

The Thiadiazole & their derivatives exhibit a wide variety of biological activities like anti microbial , anti inflammatory activity, anti tubercular activity, ant diabetic activity, diuretics, anti depressant & cytotoxic activity. These thiadiazole are the heterocyclic compound which contain the five member ring & nitrogen & sulphur. In this paper we mention the derivatives of 1,3,4-thiadiazole & their different activities.

Key words: 1, 3, 4-Thiadiazole Derivatives, Biological activities.

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INTRODUCTION

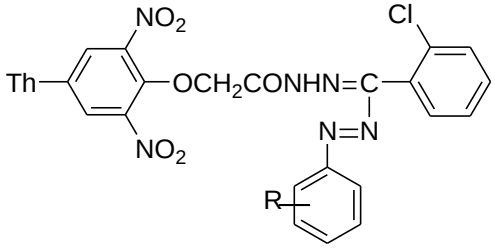
Heterocyclic compounds are cyclic compound with the ring containing carbon and other element, the component being oxygen, nitrogen and sulphur. The simplest of the five membered heterocyclic compound are pyrrole, furan and thiophene, each of which contains a single heteroatoms. The five membered ring containing more than one or two heteroatoms also such as azole, pyrrole, thiazole, thiadiazole, oxadiazole, triazene etc.

Thiadiazole contains five-membered disubstituted ring structure composed of two nitrogen atoms and one sulfur atom. There are four isomeric types: 1,2,3-thiadiazole; 1,3,4-thiadiazole; 1,2,4-thiadiazole; and 1,2,5-thiadiazole. 1,3,4-Thiadiazole represent an important heterocyclic system due to their pharmacological activities. 1,3,4-Thiadiazole and its derivatives possesses wide range of therapeutic activities like antimicrobial, antifungal, diuretics, antiepileptic, anti-leshmanial, antiulcer, anti-mycobacterial, anti-inflammatory, free radical scavenging, anticonvulsant, and antileukemia agents. In view of 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 antibacterial and antifungal, anti-inflammatory, anticancer, antitubercular, antidepressant, anticonvulsant, anti-leishmanial activities.

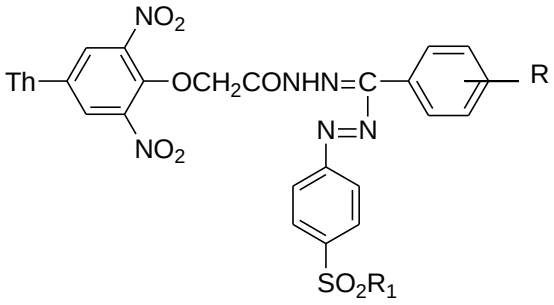
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY

Sah *et al*.,[1] synthesized a series of 5-(4-chlorophenyl amino)-2-mercapto-1,3,4-thiadiazole. The compounds **(1 a-g)** were tested for their *in vitro* antimicrobial activity against the two pathogenic bacterial strains. *Escherichia coli* and *Salmonella typhi*, three fungal strains *Aspergillus niger*, *Penicillium species* and *Candida albicans*. The compounds have shown moderate activity.



R=4-nitro, 2-methyl-4-nitro

(1 a-b)



R = 2-chloro, R_1 = hydroxyl, amino, guanidino

(1 c-e)

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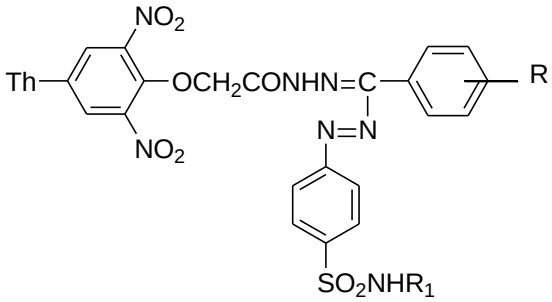
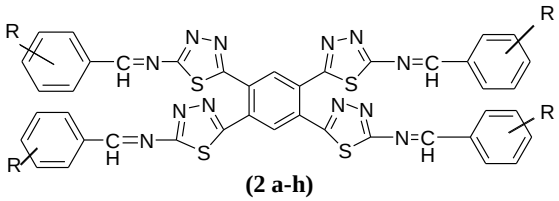


R = 3-methoxy, 4-hydroxy, R1 = pyrimidinyl, 4,6 dimethyl pyrimidinyl

(1 f-g)

Yousif *et al*., [2] novel tetra Schiff bases were synthesized by condensation of 1,2,4,5-tetra (5-amino-1,3,4-thiadiazole-2-yl)benzene with different aromatic aldehydes. All compounds **(2 a-h).** Were screened for antibacterial (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *icrococcus luteus*, *Bacillus cereus*, *Escherichia coli*, and *Pseudomonas aeruginosa*) and antifungal (*Aspergillus niger* and *Aspergillus fumigatus*) activities.



(2 a-h)

Comp. No.	X
2a	*p*-H
2b	*p*-CH_3
2c	*p*-OH
2d	*o*-OH
2e	*p*-NO_2
2f	*p*-Br
2g	*p*-OCH_3
2h	*p*-Cl

Swamy *et al*., [3] The two series of 4,6-disubstituted 1,2,4-triazolo-1,3,4-thiadiazole derivatives **(3 a–e)** and **(4 a–e)** were synthesized. All compounds were screened for antibacterial (*Bacillus subtilis*, *Escherichia coli*, *Pseudomonas fluorescens*, *Xanthomonas campestris pvs*, *Xanthomonas oryzae*) and antifungal (*Aspergillus niger*, *Aspergillus flavus*, *Fusarium oxysporum*, *Trichoderma sp*, *Fusarium monaliforme*) activities.

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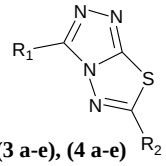
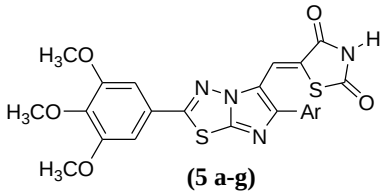


(3 a-e), (4 a-e)

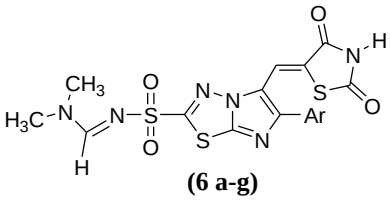
Comp. No.	R_1	R_2
3a	$-CH_3$	
3b	$-CH_2-CH_3$	
3c	$-C_6H_5$	
3d	$-4-CH_3-C_6H_5$	
3e	$-4-Cl-C_6H_5$	
4a	$-CH_3$	
4b	$-CH_2-CH_3$	
5c	$-C_6H_5$	
5d	$-4-CH_3-C_6H_5$	
5e	$-4-Cl-C_6H_5$	

Alagawadi *et al*., [4] synthesized a series of new 2,4-Thiazolidinones derivatives. The compounds **(5 a-g)** and **(6 a-g)** were tested for their *in vitro* antimicrobial activity against the Gram-positive *Staphylococcus aureus*, *Enterococcus faecalis*, Gram-negative *Escherichia coli*, *Pseudomonas aeruginosa bacteria* and *Candida albicans*, *Aspergillus flavus*, *Aspergillus niger*. The presence of 6-*p*-chlorophenyl and 6-*p*-bromophenyl derivatives showed increased activity.



(5 a-g)

Comp. No.	Ar
5a	C_6H_5
5b	$4-CH_3.C_6H_4$
5c	$4-OCH_3.C_6H_4$
5d	$4-NO_2.C_6H_4$
5e	$4-Br.C_6H_4$
5f	$4-Cl.C_6H_4$
5g	$2,5-(OCH_3)C_6H_3$



(6 a-g)

Comp. No.	Ar
6a	C_6H_5
6b	$4-CH_3.C_6H_4$
6c	$4-OCH_3.C_6H_4$
6d	$4-NO_2.C_6H_4$
6e	$4-Br.C_6H_4$
6f	$4-Cl.C_6H_4$
6g	$2,5-(OCH_3)C_6H_3$

Foroumadi *et al*., [5] A series of *N*-[5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole-2-yl] and *N*-[5-(nitrophenyl)-1,3,4-thiadiazole-2-yl] piperazinyl quinolone derivatives (**7 a-c** and **7 d-l**) were synthesized and evaluated for *in vitro* antibacterial activity against some Gram-positive and Gram-negative bacteria. The derivatives of **(7 a-c)** showed interesting activity against tested Gram-positive bacteria while they did not show good activity against Gram-negative organisms. The derivatives of **(7 d-l)** were inactive against both Gram-positive and Gram-negative bacteria. Among all of the tested compounds, **7a** (ciprofloxacin derivative in nitroimidazole series) exhibited excellent activity against *Staphylococcus aureus* and *Staphylococcus epidermidis*.

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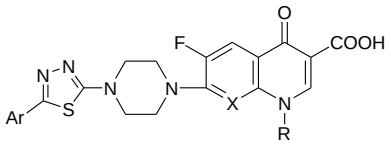
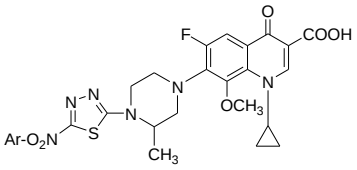


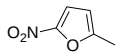
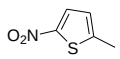
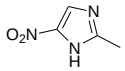
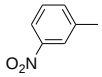
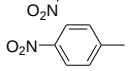
(7 a-l)

Comp. No.	Ar	X	R
7a	1-methyl-5-nitro-2-imidazolyl	CH	Cpr
7b	1-methyl-5-nitro-2-imidazolyl	CH	Et
7c	1-methyl-5-nitro-2-imidazolyl	N	Et
7d	2-nitrophenyl	CH	Cpr
7e	2-nitrophenyl	CH	Et
7f	2-nitrophenyl	N	Et
7g	3-nitrophenyl	CH	Cpr
7h	3-nitrophenyl	CH	Et
7i	3-nitrophenyl	N	Et
7j	4-nitrophenyl	CH	Cpr
7k	4-nitrophenyl	CH	Et
7l	4-nitrophenyl	N	Et

Jazayeri *et al*., [6] synthesized a series of nitroaryl-1,3,4-thiadiazole derivatives. The synthesized compounds **(8 a-f)** were tested against Gram-positive bacteria including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumonia*, *Bacillus subtilis*, *Enterococcus faecalis*, *Micrococcus luteus* and Gram-negative including *Escherichia coli*, *Salmonella typhi*, *Shigella flexneri*, *Klebsiella pneumonia*, *Serratia marcescens* and *Pseudomonas aeruginosa*.



(8 a-f)

Comp.No.	NO_2Ar
8a	
8b	
8c	
8d	
8e	
8f	

Gadad *et al*., **[7]** synthesized series of 5-guanylhydrazone/thiocyanato-6-arylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide derivatives. Compounds **(9 a-d)** and **(10 a-e)** 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*.

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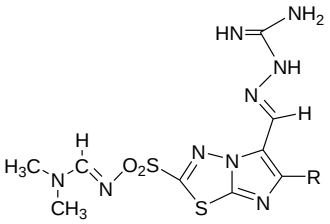
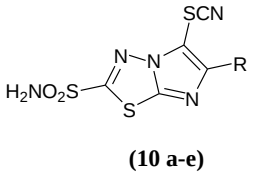


(9 a-e)

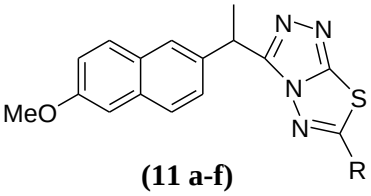


(10 a-e)

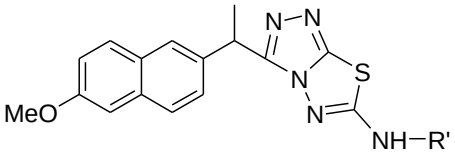
a, R = C_6H_5
b, R = *p*-Cl.C_6H_4
c, R = *p*-Br.C_6H_4
d, R = *p*-CH_3.C_6H_4
e, R = *p*-NO_2.C_6H_4

ANTI-INFLAMMATORY ACTIVITY

Amir *et al*., [8] Some 6-substituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives by cyclisation of 4-amino-5-[1-(6-methoxy-2-naphthyl)ethyl]-3-mercapto-(4*H*)-1,2,4-triazole with various substituted aromatic acids and aryl/alkyl isothiocyanates, through a single step reaction. All compounds **(11 a-f** and **12 a-d)** were screend for anti-inflammatory activity.



(11 a-f)

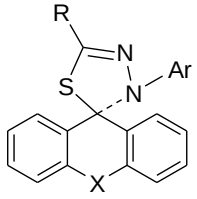


(12 a-d)

R = a: C_6H_5; b: 4-Cl-C_6H_4; c: 2,4-$(Cl)_2$-C_6H_3; d: 2,4-$(Cl)_2$-$C_6H_3OCH_2$; e:2-NH_2-C_6H_4; f: 4-NH_2-C_6H4

R' = a: n-C_6H_9; b: C_6H_5; c: 4-F-C_6H_4; d: 2,4-(CH_3)-C_6H_3

Hafez *et al*., [9] Synthesized a series of novel spiro-thioxanthene **(13 a-g)** and spiro-xanthene-9'2-[1,3,4]thiadiazole **(14 a-g)** derivatives. Some of newly synthesized compounds were tested for antiinflammatory and analgesic activities comparable to ibuprofen. Compounds **(13 a,d,e)** and **(14 a,d,e)** showed significant activity compared to standard drug.



(13 a-g), X = S
(14 a-g), X = O

a; R = Ar = C_6H_5
b; R = $COCH_3$, Ar = C_6H_5
c; R = $COCH_3$, Ar = p-C_6H_4-Br
d; R = $COCH_3$, Ar = p-C_6H_4-Cl
e; R = $COCH_3$, Ar = p-C_6H_4-NO_2
f; R = $COOC_2H_5$, Ar = p-C_6H_5
g; R = $COOC_2H_5$, Ar = p-C_6H_4-CH_3

Jadhav *et al*., [10] synthesized a series of 6-substituted and 5,6-disubstituted 2-(6-methyl-benzofuran-3-ylmethyl)-imidazo[2,1-b][1,3,4]thiadiazoles. The new compounds **(15-20)** have been tested for their *in vivo* analgesic, anti-inflammatory activities. Some of the compound showed good anti-inflammatory activity.

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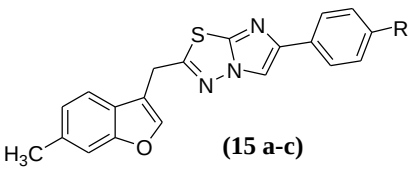
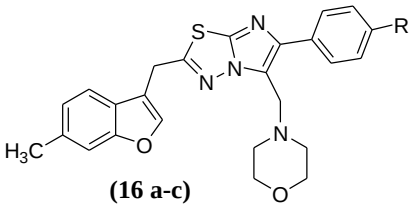
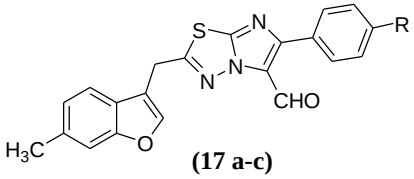


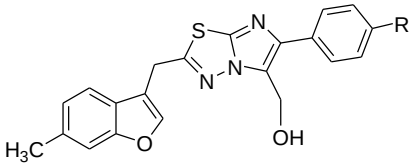
(15 a-c)



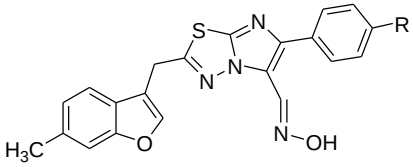
(16 a-c)



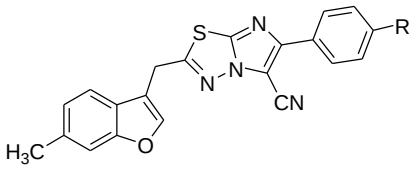
(17 a-c)



(18 a-c)



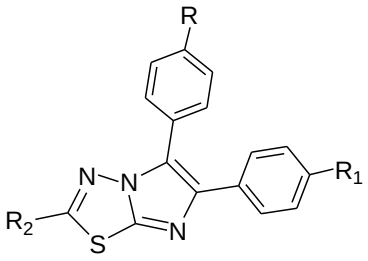
(19 a-c)



(20 a-c)

R = Br, Cl, NO_2: a = Cl, b = Br, c = NO_2

Gadad *et al*., [11] synthesized a series of 2-trifluoromethyl/sulfonamide-5,6-diarylsubstituted imidazo[2,1-b]-1,3,4-thiadiazole derivatives. The compounds tested showed selective inhibitory activity toward COX-2 over COX-1, amongst them compounds **(21 a-j)** showed appreciable COX-2 selective inhibitory activity. These compounds also exhibited anti-inflammatory activity.



(21 a-j)

Comp. No.	R	R_1	R_2
21a	H	SCH_3	CF_3
21b	OCH_3	SCH_3	CF_3
21c	OCH_3	SCH_3	CF_3
21d	OCH_3	H	CF_3
21e	H	CH_3	CF_3
21f	H	SO_2CH_3	CF_3
21g	OCH_3	OCH_3	SO_2NH_2
21h	OCH_3	H	SO_2NH_2
21i	OCH_3	F	SO_2NH_2
21j	OCH_3	SO_2CH_3	SO_2NH_2

Amir *et al*., [12] A series 3,6-disubstituted-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles were prepared by condensation of 4-amino-5-substituted-3-mercapto-(4*H*)-1,2,4-triazoles with various substituted aromatic acids and aryl/alkyl isothiocyanates through a one-pot reaction. The new compounds **(22-25)** have been tested for their *in vivo* anti-inflammatory activities.

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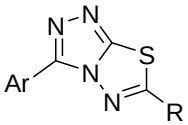
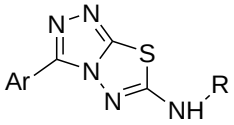
These compounds showed potent anti-inflammatory activity, compared to those of ibuprofen and flurbiprofen.



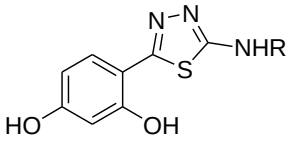
(22, 24)



(23, 25)

ANTICANCER ACTIVITY

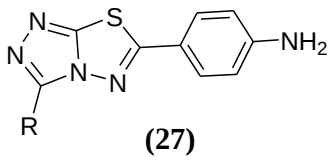
Matysiak *et al*., [13] A series of *N*-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles were synthesized and evaluated for their antiproliferative activity. The panel substitution included alkyl, aryl and morphinoalkyl derivatives. The cytotoxicity in vitro against the four human cell lines: SW707 (rectal), HCV29T (bladder), A549 (lung) and T47D (breast) wes 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 **(26)**, with ID_{50} two times lower (SW707, T47D) than cisplatin studied comparatively as the control compound.



(26)

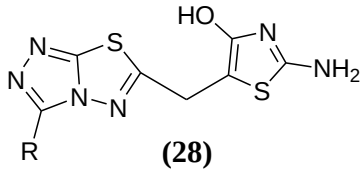
R = 2,4-dichlorophentl

Ibrahim, [14] Synthesized a new series evaluation of 3,6-disubstituted triazolo[3,4-b]thiadiazole derivative. The newly synthesized compounds were evaluated for their cytotoxic activity against a panel of 60 human cancer cell lines by the National Cancer Institute (NCI) and some of them demonstrated inhibitory effects on the growth of a wide range of cancer cell lines generally at 10^{-5} M level and in some cases at 10^{-7} M concentrations. Compounds **(27)** and **(28)** maintained the highest growth inhibition.



(27)

R = -CH_2O-Ph(*p*-Cl)



(28)

R = -CH_2O-Ph(p-Cl)

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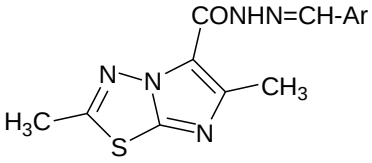
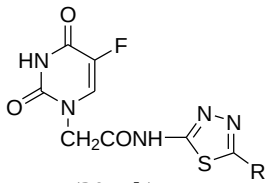
Terzioglu *et al*., **[15]** synthesized some novel 2,6-dimethyl-N'-substituted phenylmethylene-imidazo [2,1-b][1,3,4]thiadiazole-5-carbohydrazides. The newly synthesized compounds **(29a-h)** were evaluated in the National Cancer Institute's 3-cell line, one dose in vitro primary cytotoxicity assay Compounds **(29 c)** and **(29 h)** which passed the criteria for activity in this assay (20-29% growth percentages) were scheduled automatically for evaluation against the full panel of 60 human tumor cell lines at a minimum of five concentrations at 10-fold dilutions. 2,6-Dimethyl-N'-(2-hydroxyphenylmethylidene)imidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazide **(29 c)** showed the most favorable cytotoxicity.



(29 a-h)

Comp. No.	Ar
29a	C_6H_5
29b	4-$CH_3C_6H_4$
29c	2-HOC_6H_4
29d	4-$CH_3OC_6H_4$
29e	4-BrC_6H_4
29f	4-ClC_6H_4
29g	4-FC_6H_4
29h	4-NO_2C_6H4

Zheng *et al*., [16] A new series of N^1-acetylamino-(5-alkyl/aryl-1,3,4-thiadiazole-2-yl)-5-fluorouracil derivatives were designed and synthesized. The *in vitro* antitumor activities of the synthesized 5-fluorouracil derivatives **(30 a-k)** against A-549 (human lung cancer cell), Bcap-37 (human breast cancer cell) were evaluated by the standard MTT assay. As compared to 5-Fu, compounds **(30 a-d)** show weak anticancer activity, but **(30-e, g, I, j, k)** all show higher activity against A-549; **(30-e, I, j)** show higher activity against Bcap-37.

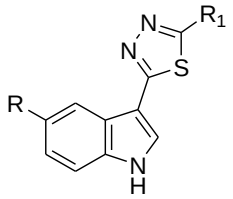


(30 a-k)

R = a: CH_3; b: CH_3CH_2; c: $CH_3CH_2CH_2$; d: $(CH_3)_2CH$; e: C_6H_5; f: 4-ClC_6H_4; g: 4-FC_6H_4; h: 4-$CH_3C_6H_4$; i: 4-$CH_3OC_6H_4$; j: 3,5-$(NO_2)_2C_6H_3$; k: 3-Py;

Kumar *et al*., [17] A series of 5-(3-indolyl)-2-substituted-1,3,4-thiadiazoles **(31 a-m)** were synthesized and their cytotoxicity analyzed against six human cancer cell lines. These derivatives were screened against prostate (PC3, DU145 and LnCaP), breast (MCF7 and MDA-MB-231) and pancreatic (PaCa2) cancer cell lines. The compounds **(31-b, e, h)** bearing C-2 substituent as benzyl, 3,4-dimethoxyphenyl and 4-benzyloxy-3-methoxyphenyl, respectively, have shown significant cytotoxicity against multiple cancer cell lines. Introduction of 4-

dimethylamino **(31-d, k)** and 3,4,5-trimethoxy **(31 l)** groups in the C-2 phenyl ring induced selectivity against MCF7 and MDA-MB-231 cancer cell lines (compounds **(31-d, k, l)**.

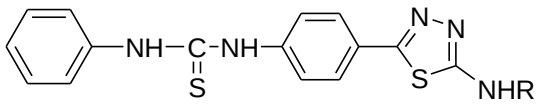


(31 a-m)

Comp. No.	R_1	R
31a	C_6H_5	H
31b	$CH_2C_6H_5$	H
31c	4-ClC_6H_4	H
31d	4-*N*,*N*'$(CH_3)_2C_6H_4$	H
31e	3,4-$(OCH_3)_2C_6H_3$	H
31f	3,4,5-$(CH_3O)_3C_6H_2$	H
31g	3,4-$(OCH_2O)C_6H_3$	H
31h	4-BnO-3-$OCH_3C_6H_3$	H
31i	3-pyridyl	H
31j	4-pyridyl	H
31k	4-*N*,*N*'$(CH_3)_2C_6H_4$	Br
31l	3,4,5-$(CH_3O)_3C_6H_2$	Br
31m	4-BnO-3-$OCH_3C_6H_3$	Br

ANTI-TUBERCULAR ACTIVITY

Karakus *et al*., [18] Synthesized a series of *N*-phenyl-*N*'-[4-(5-alkyl/arylamino-1,3,4-thiadiazole-2-yl)phenyl]thiourea derivatives. Antituberculosis activities of the synthesized compounds **(32 a-h)** were screened in vitro using BACTEC 460 Radiometric System against *Mycobacterium tuberculosis* H37Rv at 6.25 µg/ml.



(32 a-h)

R = propyl, cyclohexyl, phenyl, 4-chlorophenyl, benzyl, 4-fluorophenyl, 2-methylphenyl, 4-methoxyphenyl

Kolavi *et al*., [19] synthesis aseries of 2,6-disubstituted and 2,5,6-trisubstituted imidazo[2,1-b][1,3,4]thiadiazoles and screened for antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ using the BACTEC 460 radiometric system. Among the tested compounds **(33-34)** have shown the highest (100%) inhibitory activity.

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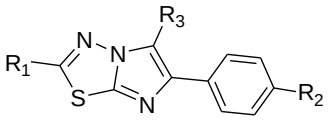
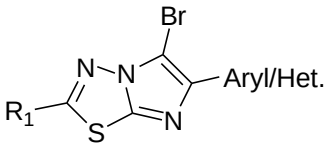


(33 a-f), (34 a-f)

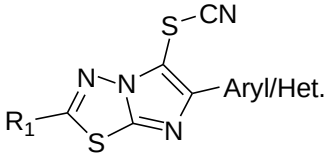
Comp. No.	R_1	R_2	R_3
33a	Cyclohexyl	H	CHO
33b	Cyclohexyl	Br	CHO
33c	2-Furyl	H	CHO
33d	2-Furyl	Br	CHO
33e	2-Thienyl	H	CHO
33f	2-Thienyl	Br	CHO
34a	Cyclohexyl	H	CH_2OH
34b	Cyclohexyl	Br	CH_2OH
34c	2-Furyl	H	CH_2OH
34d	2-Furyl	Br	CH_2OH
34e	2-Thienyl	H	CH_2OH
34f	2-Thienyl	Br	CH_2OH

Gadad *et al*., [20] Synthesized a series of 2-sulfonamido/trifluoromethyl-6-(40-substituted aryl/heteroaryl)imidazo[2,1-b]-1,3,4-thiadiazole derivatives. The selected compounds **(35-37)** were evaluated for their preliminary in vitro anti-tuberculosis activity against *Mycobacterium tuberculosis* $H_{37}Rv$ strain using radiometric BACTEC. The results show that compounds exhibited moderate to good anti-tubercular activity at a MIC of >6.25 µg/mL.



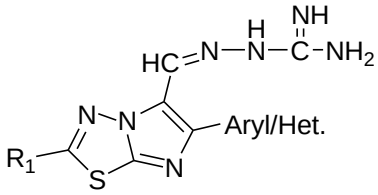
(35)

$R_1 = SO_2NH_2$
Aryl = 3',4',5'-OCH_3 Ph



(36)

$R_1 = SO_2NH_2$
Aryl = 4'-Me Ph; 4'-Cl Ph



(37)

$R_1 = SO_2N{=}CH\text{-}N(CH_3)_2$
Aryl = 4'-MePh; 4'-Cl Ph

ANTIDEPRESSANT ACTIVITY

Yusuf *et al*., [21] A number of new imine derivatives of 5-amino-1, 3, 4-thiadiazole-2-thiol have been synthesized, and their anti-depressant activity was tested using imipramine as reference drug. Two compounds namely 5-{[1-(4-chlorophenyl)-3-(4-methoxy-phenyl)prop-2-en-1-ylidene]-amino}- 5-benzylthio-1, 3,4 –thiadiazole **(38 a)** and 5-{[1-(4-chlorophenyl)-3-(4-dimethyl-aminophenyl)-prop-2-en-1-ylidene]amino}-5-benzylthio-1,3,4-thiadiazole **(38 b)** have shown significant anti-depressant activity.

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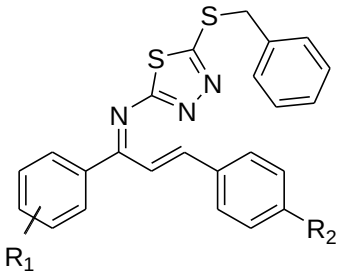
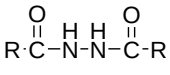


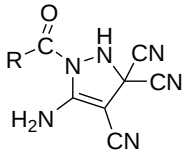
(38 a-b)

a = R_1 = OCH_3, R_2 = Cl
b = R_1 = $(CH_3)_2N$, R_2 = Cl

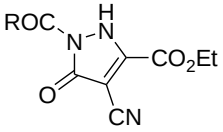
Abdel-Aziz *et al*., [22] Substituted carboxylic acid hydrazides reacted with ethenetetracarbonitril in dimethyl formamide with the formation of diacylhydrazines **(39 a–d)** and 5-amino-1-substiuted pyrazole-3,3,4-tricarbonitriles **(40 a–d)**. On the other hand, 1a–d reacted with diethyl (E)-2,3-dicyanobutenedioate 3 to give oxadiazole derivatives and pyrazolone derivatives **(41 a–d)**, respectively. The prepared compounds were evaluated each for antidepressant activity.



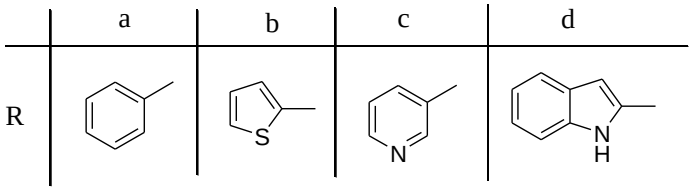
(39 a-d)



(40 a-d)

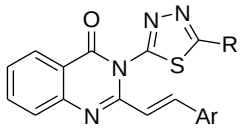


(41 a-d)



ANTICONVULSANT ACTIVITY

Jatav *et al*., [23] a series of new 3-[5-substituted phenyl-1,3,4-thiadiazol-2-yl]-2-styryl quinazoline-4(3*H*)-ones and evaluated for anticonvulsant activity .Compounds were examined in the maximal electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (scPTZ)-induced seizure models. Compound **(42 a-c)** showed good anticonvulsant activity in the test models.



(42 a-c)

a = R = C_6H_5; Ar = 4-ClC_6H_4
b = R = 3-ClC_6H_4; Ar = 4-ClC_6H_4
c = R = 4-ClC_6H_4; Ar = pyrIdyl

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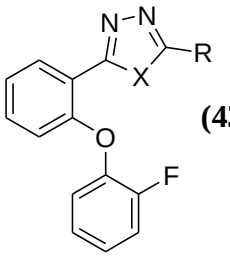
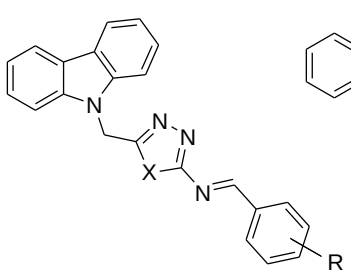
Almasirad *et al*., [24] A series of new 2-substituted-5-[2-(2-fluorophenoxy) phenyl]-1,3,4-oxadiazoles **(43 a-f)** has been synthesized and screened for their anticonvulsant activities. Compound **(43 a)** shows considerable anticonvulsant activity both in PTZ and MES models.



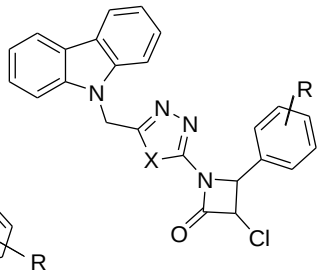
(43 a-f)

Comp. No.	X	R
43a	O	NH_2
43b	O	SH
43c	O	SCH_3
43d	O	OH
43e	N	SH
43f	N	OEt

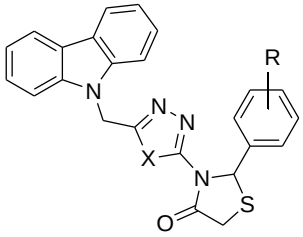
Kumar *et al*., [25] A novel substituted oxa/thiadiazolylazetidinonyl/ thiazolidinonyl carbazoles **(44a-c)**, **(45a-c)** and **(46a-c)** were synthesized and screened for their anticonvulsant activities. It is concluded from the results compound **(46 c)** showed promising anticonvulsant activity.



(44 a-c)



(45 a-c)



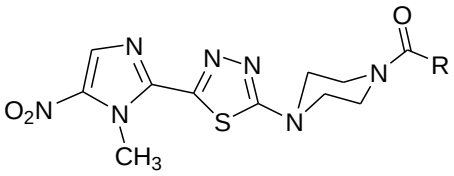
(46 a-c)

Comp. No.	R	X
44a	4-OH	O
44b	2,4-OH	O
44c	4-OH,3-OCH_3	S
45a	4-OH	O
45b	2,4-OH	O
45c	4-OH,3-OCH_3	S
46a	4-OH	O
46b	2,4-OH	O
46c	4-OH,3-OCH_3	S

ANTI-LEISHMANIAL ACTIVITY

Foroumadi *et al*., [26] A series of 2-(1-methyl-5-nitroimidazol-2-yl)-5-(1-piperazinyl, 1-piperidinyl and 1-morpholinyl)-1,3,4–thiadiazoles **(47 a–g)** were synthesized and evaluated for in vitro leishmanicidal activity against *Leishmania major* promastigotes. The leishmanicidal data revealed that compounds **(47 a–g)** had strong and much better leishmanicidal activity than the

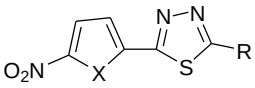
reference drug pentostam. Compound **(47 c)** (piperazine analog) was the most active compound (IC_{50} = 0.19 µM).



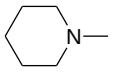
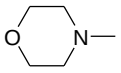
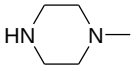
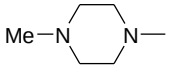
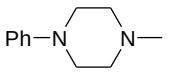
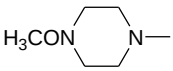
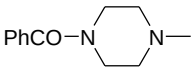
(47 a-g)

Comp. No.	R
47a	Phenyl
47b	2-Cl-phenyl
47c	3-Cl-phenyl
47d	4-Cl-phenyl
47e	Thiophen-2-yl
47f	5-Cl-thiophen-2-yl
47g	5-Br-thiophen-2-yl

Shafiee *et al*., [27] A series of 2-(5-nitro-2-furyl) and 2-(5-nitro-2-thienyl)-5-substituted-1,3,4-thiadiazoles **(48 a–b** and **49 a–e)** were synthesized and evaluated against *Leishmania major* promastigotes using ^{3}H-thymidine incorporation. Most of the compounds showed activity better than the reference drug sodium stibogluconate (Pentostam). The most active compound was (49c) (IC_{50} = 0.1 µM).



(48a-b), (49 a-e)

Comp. No.	X	R
48a	O	
48b	O	
49a	O	
49b	O	
49c	O	
49d	O	
49e	O	

Ardestani *et al*., [28] we studied 5-nitroimidazole, 5-nitrofuran and 5-nitrothiophene analogs of N-substituted-piperazinyl-1,3,4-thiadiazoles. We investigated 21 representative compounds **(50 a-g)** and **(51 a-g)** for the following properties: selectivity and efficiency against different *Leishmania* wild type species and intracellular parasite, toxicity against host cells and inhibition of topoisomerases I and II. Our results indicate that the nitroimidazole analogs **(50 a)** and **(50 f)**, and nitrofuran derivatives **51a**, **51b**, **51c**, **51f**, and **51g** exhibited low toxicity against the host cells (IC_{50}>80 µM), but high selectivity against intracellular amastigotes (selectivity

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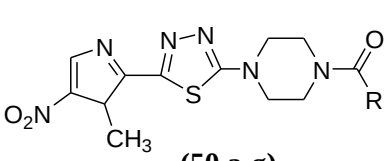
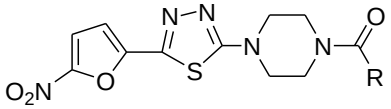
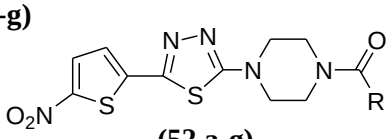
index > 12). *Leishmania* topoisomerases revealed impressive sensitivity to the agents (%inhibition >50 at IC_{50} doses of compounds against *Leishmania*).



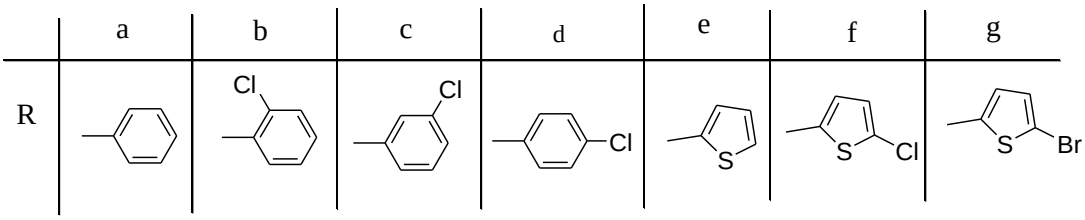
(50 a-g)



(51 a-g)



(52 a-g)



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