Research Article

Biological Activities of 1,3,4-Thiadiazine

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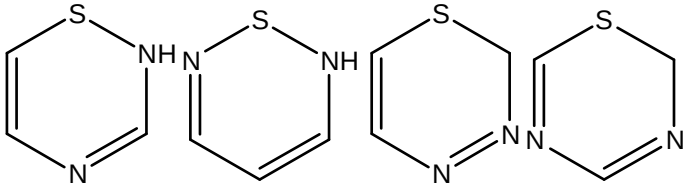
ABSTRACT
This article outlines the medicinal and biological significance of one of the most important heterocycles, the 1,3,4-Thiadiazine. 1,3,4-Thiadiazine is a highly active scaffold exhibiting wide variety of medicinal and biological activities when it is condensed with 1,2,4-Triazole. An attempt is made in this article to cover the medicinally active compounds, along with the recent discoveries, which were reported to posses various biological activities. This is might be helpful in the development of these novel lead molecules to potential drug candidates.

Keywords: Heterocycles, 1,3,4-Thiadiazine, 1,2,4-Triazole, Medicinal significance.

INTRODUCTION

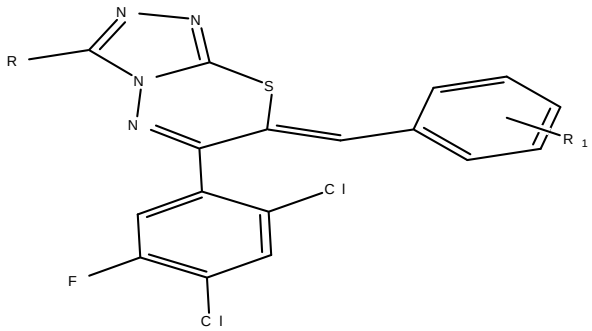
Thiadiazine is a six membered heterocyclic ring system having two nitrogen atoms and one sulphur atom. These may be of four types 2*H*-1,2,4-Thiadiazine (1), 2*H*-1,2,6-Thiadiazine (2), 2*H*-1,3,4-Thiadiazine (3) and 2*H*-1,3,5-Thiadiazine (4)[1-4].



(a) **(b)** **(c)** **(d)**

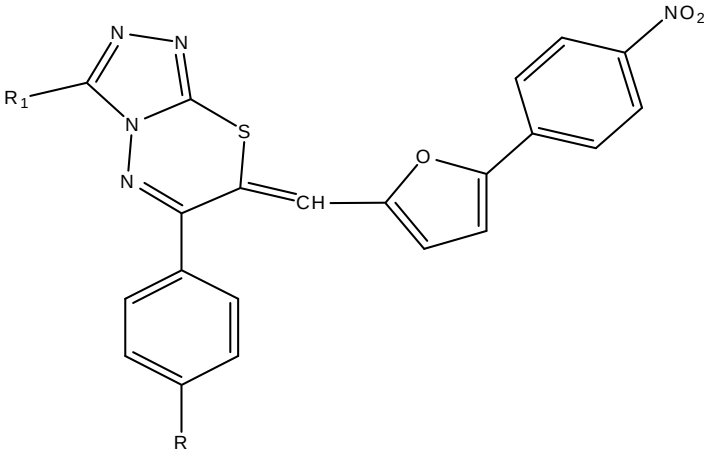
The literature survey reveals that there are not many examples of triazoles fused with thiadiazines. Those incorporating the N-C-S linkage as in the skeleton of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine exhibit a broad spectrum of antimicrobial activity.Many 1,3,4-thiadiazine derivatives involve in many biological processes and serves as a medicinally interesting compounds[8,9].The wide range of therapeutic activities of 1,3,4-thiadiazine are as under:
Antifungal[10],
Antibacterial[11],
Antimicrobial[12],
Antiinflammatory[13]
Cardiovascular[1],
AntiHIV[15],
Antidiabetic[16],
Antidepressant[17]
1,3,4-thiadiazine derivatives showed anti-HIV-1 activity at concentration slightly below cytotoxic levels. Consequently, in view of the above facts and as a part of an ongoing investigation into biologically more active and less toxic substances, our current interest is focused on the synthesis of a series of new condensed 1,2,4-triazolothiadiazine derivatives.Those incorporating the N-C-S linkage as in the skeleton of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazine exhibit a broad spectrum of biological activity.Various methods are available for the construction of 1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazine[24].

Antibacterial Agent



(a)
7-arylidene-6-(2,4-dichloro-5-fluorophenyl)-3-substituted -1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines

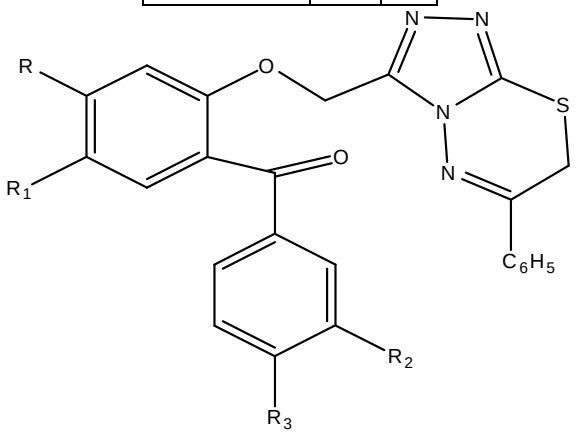
Compound	R	R1
A	H	3,4-methylene-dioxy
B	CH_3	3,4-methylene-dioxy
C	C_2H_5	3,4-methylene-dioxy
D	C_3H_7	3,4-methylene-dioxy
E	C_6H_5	3,4-methylene-dioxy
F	CH_3O-C_6H_4	3,4-methylene-dioxy
G	CH_3	4-chloro
H	C_2H_5	4-chloro
I	C_3H_7	4-chloro
J	C_6H_5	4-chloro
K	CH_3O-C_6H_4	4-chloro
L	H	3,4-dimethoxy
M	CH_3	3,4-dimethoxy
N	C_2H_5	3,4-dimethoxy
O	C_3H_7	3,4-dimethoxy
P	C_6H_5	3,4-dimethoxy
Q	CH_3O-C_6H_4	3,4-dimethoxy



(b)
3 -substituted-6 -aryl-7 -[5 -(p-nitrophenyl) -2 -furfurylidene] -1,2,4 –triazolo [3,4 -b] -1,3,4–thiadiazines

COMPOUND	R1	R
A	Me	H

B	Et	H
C	Pr	H
D	Ph	H



©

3-(2-aroylaryloxy)methyl-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4] thiadiazine

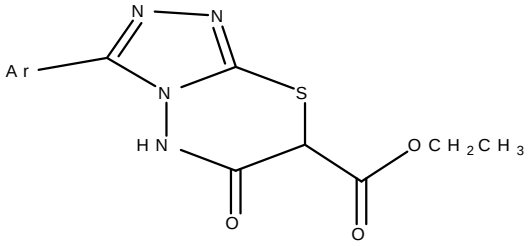
a) $R=R_3=H, R_1=CH_3, R_2=Cl$

b) $R=R_2=R_3=H, R_1=Cl$

c) $R_1=R_2=R_3=H, R=Br$

d) $R=R_2=H, R_1=CH_3, R_3=OCH_3$

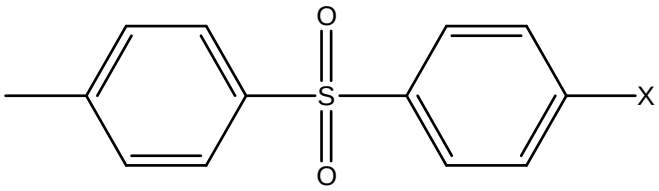
e) $R=R_2=H, R_1=R_3=CH_3$

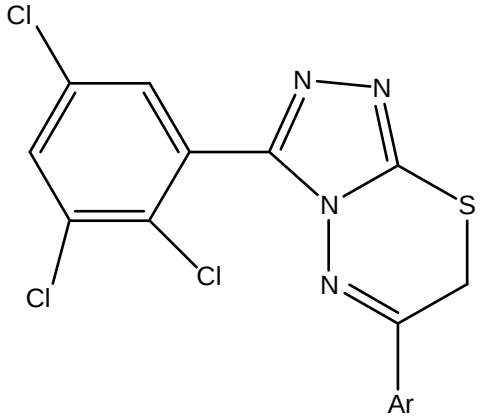


(d)

6-oxotriazolothiadiazin-7-carboxylate

Ar =





(e)

7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines
***Ar*=4-Methylphenyl**
4-Methoxyphenyl
3,5-dichlorophenyl
3,5-Dimethylphenyl
Phenoxymethyl
5-Quinolyl
Phenyl

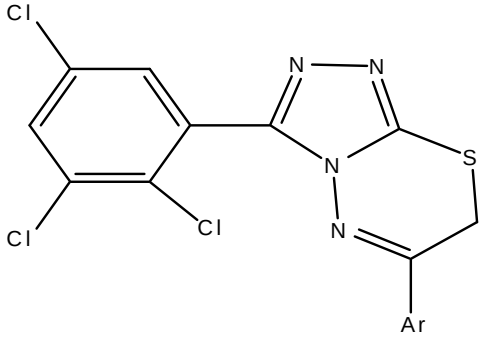
Determination of Antimicrobial activity

The antimicrobial activities of compounds were evaluated in vitro by serial tube dilution technique at different concentrations (0.5, 1.0, 1.5,.....12 mM). Some fungi such as *C. albicans, C. krusei*and *C. parapsilosis,A. flavus, A. ochraceous, F. moniliforme*and *C. gloeosporioides* and bacteria such as *E. coli, P. solanacearum, P. fluorescens* and*B. subtilis*were used. Fluconazole and chloramphenicol were used as reference standard in antifungal and antibacterial activity studies, respectively. The stock solutions of the compounds were prepared in chloroform. To the culture tubes containing 1.9 ml of media, 0.1 ml of test solution was added at sterile conditions. To all the tubes including standard and controls, the fresh inoculums was added using Himediaflexiloop 4 calibrated to 0.001 ml. After incubating all the tubes at 37 °C for 24 h, their absorbance was recorded at 640 nm along with reference. Percentage of inhibition was calculated using the following equation.

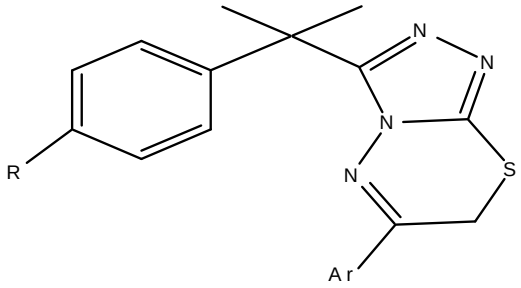
% Inhibition = 100 ($m - n$)/m

Where m = absorbance without the test sample and n = absorbance with test sample[20-23].

Antifungal Agent



(f)

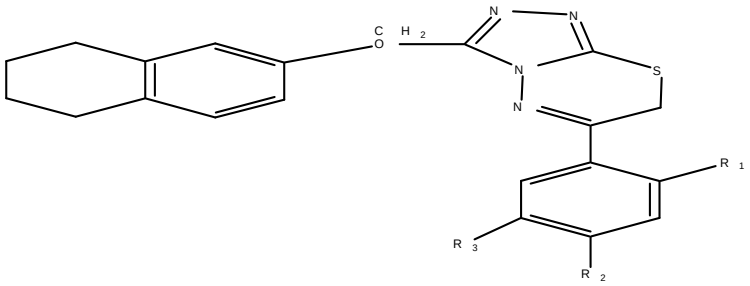


(g)
R = H, Cl, Br
6-arylsubstituted-3-[2-(4-substitutedphenyl)propan-2-yl]-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines

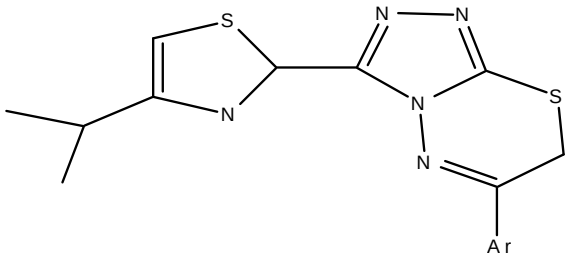
Determination of Antifungal activity

Newly prepared compounds were screened for their antifungalactivity against Aspergillusflavus[NCIM No.524], Aspergillusfumigatus [NCIM No. 902], Penicilliummarneffei[recultured] and Trichophytonmentagrophytes[recultured] in DMSO by serial plate dilution method [30,31]. Agar media were prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Agar media of 20 mL were poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 C for 1 h. Using an agar punch each labelled well were made on these seeded agar plates and minimum inhibitory concentrations of the test compounds in dimethylsulfoxide (DMSO) were added into each labelled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dish were prepared in triplicate and maintained at 37 C for 3-4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. Activity of each compound was compared with Ciclopiroxolamine as standard. Zones of inhibition were determined for the above compounds[18-22].

Anti-inflammatory Agent

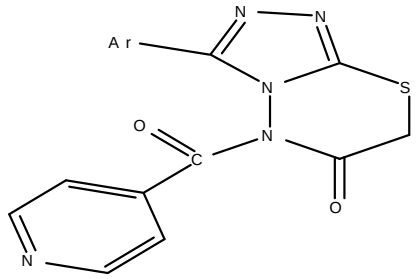


(h)
R_1:H,OH
R_2:H,Cl,NO_2,$N(CH_3)_2$,OCH_3, R_3:H,Cl
3 -[(5,6,7,8 -*Tetrahydronaphthalen*-2 -*yl*)*oxymethyl*] -6 -*aryl*-7*H*-1,2,4 -*triazolo*[3,4 -*b*] - 1,3,4 – *thiadiazines*



(i)

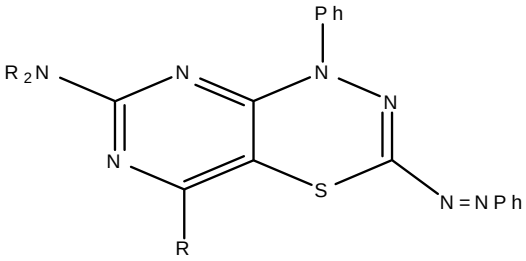
3-(4-isopropylthiazol-2-yl)-6-substituted-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines



(j)

Ar

a)4-Methylphenyl b)4-Nitrophenyl
c)4-Cholorophenyl d) 4-Methoxyphenyl

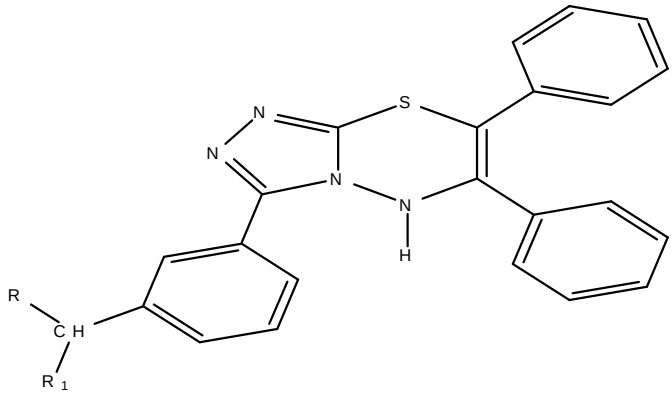


(k)

PYRIMIDO[4,5-*E*][1,3,4]THIADIAZINE
a) R= methyl, R2NH= piperidine
b)R= methyl, R2NH= morpholine
c) R= methyl, R2NH= 4-methylpiperazine
d)R= propyl, R2NH= piperidine
e) R= propyl, R2NH= morpholine
f)R= propyl, R2NH= 4-methylpiperazine

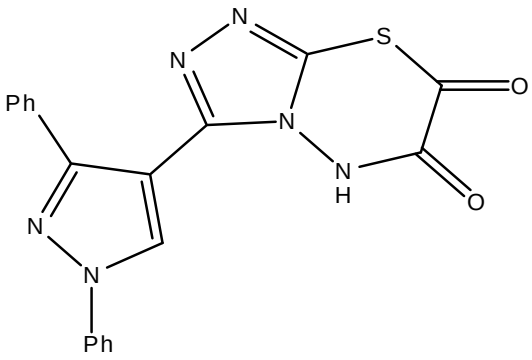
Antiviral Agent

Compounds belonging to the triazolo-thiadiazines series were subjected for their assay against two animal viruses viz. *Japanese encephalitis virus* (JEV) (strain P20778), an RNA virus of high pathogenicity, and *Herpes simplex virus-1* (HSV-1) (strain 753166), a DNA virus, originally obtained from National Institute of Virology, Pune[30].



(l)

5-[(3'-aralkyl amido/imido alkyl) phenyl]1,2,4-triazolo-[3,4-*b*]1,3,4-thiadiazines

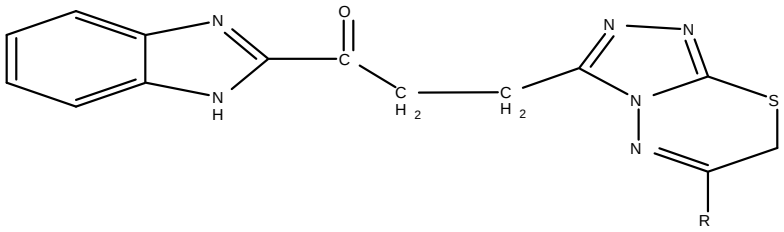


(m)

3-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-6,7-dione

ANTICANCER AGENTS

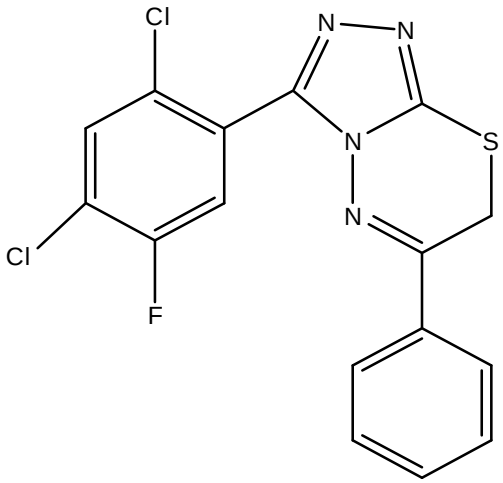
The Anticancer compounds Triazolo [1,3,4] –thiadiazinewere submitted to National Cancer Institute(NCI), USAfor evaluation of their *in vitro* anticancer activity at single dose (1x10-5M) against full NCI 60cell lines panels representing on full nine human systems as leukemia, melanoma and cancers oflung, colon, brain, breast, ovary, kidney and prostate. The compounds added at a concentration(1x10-5M) and the culture incubated for 48 h. End point determinations made with a proteinbinding dye, sulforhodamine B [31]. Results for each compound were reported asa meangraph of the percent growth of the treated cells. Results of each test agents are reported aspercentage growth of the treated cells when compared with untreated control cells[27,28].



(n)

1-(1*H*-benzo[*d*]imidazol-2-yl)-3-(6-substituted-7*H*-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazin-3-yl)propan-1-one

Antitumor Agent



(o)
3-(2,4-dichloro-5-fluorophenyl)-6-aryl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines

CONCLUSION

This has been noticed so far, that modifications on 1,3,4-Thiadiazine moiety displayed valuable biological activities. It will be interesting to observe that these modifications can be utilized as potent therapeutic agents in future. Thus the quest to explore many more modifications on 1,3,4-thiadiazine moiety needs to be continued for the use of mankind.

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