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Review Article

TRIAZOLOTHIADIAZOLES AS ANTIMICROBIAL AGENT: A SHORT RIVIEW

Asif Husain*[1], Mohammad Asif[2], Rubina Bhutani[1], Manni Dutta[1]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard University, New Delhi-110062
[2]Department of Pharmacy, GRD (PG) Institute of Management and Technology, Dehradun, 248009, India

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ABSTRACT

Triazolothiadiazole is a fused heterocyclic contained triazole and thiadizole nucleus and exhibited immense pharmacological activities. The triazolothiadiazole nucleus is present in compounds are evaluating for new products that possess some remarkable pharmacological activities. triazolothiadiazole constitute an important class of biologically active drug molecules which has attracted attention of medicinal chemists due to their wide range of pharmacological properties. These compounds are being synthesized as drugs by many researchers in order to combat diseases with minimal toxicity and maximal effects. These predictions has provided therapeutic pathway to develop new effective biologically active triazolothiadiazole.

Keywords: Antimicrobial activities, fused heterocycles, Triazolothiadiazole

INTRODUCTION

It is interesting to use 1,2,4-triazole derivatives is an important biologically active heterocycle agent, which constitute an important class of organic compounds with diverse biological activities including antiparasitic, analgesic, anti-inflammatory, sedatives, antianxiety, and antimicrobial. Some drugs are reported as antifungal agents like fluconazole, intraconazole and voriconazole. Also, there are some other known drugs containing the 1,2,4-triazole group such as Triazolam, Alprazolam, Etizolam, and Furacylin. In addition, 1,3,4-thiadiazoles exhibited various biological activities such as anti-parkinsonism, hypoglycaemic, anti-histaminic, anticancer, anti-inflammatory, antiasthmatic and antihypertensive [1,2]. The activity of 1,3,4-thiadiazoles is possibly due to the presence of the =N–C–S moiety. The triazole system fused to another heterocyclic ring has shown a wide spectrum of biological activities such as antibacterial, antidepressant, antiviral, antitumorial and anti-inflammatory, pesticides, herbicides, dyes, lubricants and analytical reagents. The chemistry of condensed heterocycles such as the 1,2,4-triazolo-thiadiazole, occupies an extremely important niche within the family of 5 and 6 membered heterocyclic compounds. They play a central role in numerous molecules of established bioactivities, which includes fungicidal, insecticidal, bactericidal, herbicidal, anti-tumor, anti-inflammatory, antitubercular, central nervous system stimulant properties. They also find applications as dyes, lubricants and analytical reagents. A triazolo-thiadiazole system may be viewed as a cyclic analog of two very important components, thiosemicarbazide and biguanide, which often display diverse biological activities [3-5].

ANTIMICROBIAL ACTIVITIES OF TRIAZOLO THIADIAZOLE COMPOUNDS

ANTIBACTERIAL:

A series of new 3-(4-methylcoumarinyl-7-oxymethyl)-6-substitutedphenyl-5,6-dihydro-s-triazolo (3,4-b)(1,3,4)-thiadiazoles have been synthesized and some compounds were showed significant *in vitro* antimicrobial against *S. aureus* and *Escherichia coli* and antifungal against *C. albicans* activity. 3-nitrophenyl derivative showed highest degree of antibacterial activity against *S. aureus* and *E. coli*. Compounds 3-nitrophenyl derivative, 3,4-dimethoxyphenyl derivative and 4-hydroxy-3-ethoxyphenyl derivative showed better

***Corresponding Author Address:** Asif Husain, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard University, New Delhi-110062, India; E-mail: mohd.mpharm@gmail.com*

antifungal activity than rest of the compounds. Compounds 4-dimethylaminophenyl derivative and 4-chlorophenyl derivative showed moderate activity against *S. aureus* and *E. coli* [3]. A series of 1,2,4triazolo[3,4-b]-1,3,4 thiadiazoles bearing substituted (phenyl sulphonyl) phenyl moiety. Cyclocondensation of the SH and NH_2 functions of **(1)** with various substituted aromatic acids in the presence of phosphorus oxychloride, gave a series of 3-[4-(4-chloro-phenylsulfonyl)phenyl]-6-(substituted-phenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles**(2)** and was evaluated the series for antibacterial activity [4].

The best antimicrobial effect was found in compound **2(e)** i.e. 6-[(3-bromo-4-chloro)phenyl)]-3-[4-(4-chloro-phenylsulfonyl)phenyl]-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (against *S. aureus*, *E. coli*, and *C. albicans*) probably due to the cumulative electron-withdrawing effect of the chlorine and bromine atoms which are directly attached to the phenyl ring of the thiadiazole, in addition to the chlorine atom attached to the diphenylsulfone moiety. Result showed that substituents affect the activity of compounds in different series. Also, the presence of more halogen atom in the structure has considerable increased the biological activity. A series of novel bis[4-methoxy-3-(6-aryl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol)phenyl] methanes **(3a–l)** has been synthesized. All the newly synthesized compounds were screened for their antibacterial activity against *Bacillus subtilis*, *B. sphaericu*, *S. aureus*, *Pseudomonas aeruginosa*, *Klobsinella aerogenes* and *Chromobacterium violaceum* by disc diffusion method. The inhibition zones were measured and compared with the standard drug streptomycin. Compounds **3(e), 3(f), 3(h), 3(i), 3(k)** and **3(l)** exhibited potent activity against the test bacteria. [3]. The 6-(substituted aryl\aryloxy methyl)-3-(4-methylthio benzyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and evaluated them for antibacterial activity against *Escherichia coli*, *S. aureus*, *P. aeruginosa* and *Klebsiella pneumonia* bacterial strains by disc diffusion method. Ciprofloxacin was used as standard drug. Among the series, the compounds **4(a), 4(b), 5(a), 5(b)** have shown maximum activity against tested strains. [5]

Water soluble fused heterocycles of triazolothiadiazole piperazine derivatives were evaluated as antibacterial agents. The compounds **6(a-e)** and **7(a** and **b)** have strong inhibitory activity against *S. aureus*, *E. coli* and *P. vulgaris* in vitro comparable to that of ciprofloxacin at the concentration of 0.1 mg/L, but compounds not having piperazine ring at the same concentration only displayed weak or poor activity and concluded that piperazine substituent exert an important role in the inhibitory activity of the tested compounds. [6] A series of 3,6-disubstituted 1,2,4–triazolo[3,4-b]-1,3,4-thiadiazoles from methyl {3-[(6-chloropyridin-3-yl)methyl]-4-oxo-3,4-dihydrophthalazin-1-yl}acetate in multiple steps and were screened for their antimicrobial activity against variety of human pathogenic bacteria's. Investigation on antimicrobial data of synthesised compounds revealed that, compounds substituted with 5-nitro-thiazole to triazolothiadiazole **8(f)** showed better activity compared to other analogues. The antibacterial activity of newly synthesized compounds **8(a-f)** was determined by well plate method in nutrient agar (antibacterial activity) The antimicrobial activity was carried out on strains of , *E. coli* , *S. typhi*, *B. subtilis* , *S. aureus* . [7]

A series of 5-{6-(substituted phenyl)-5,6-dihydro-(1,2,4) triazolo(3,4-b)(1,3,4)thiadiazol-3-yl}benzene-1,2,3-triol, **9(a-j)**. The in vitro antibacterial (*S. aureus, K. pneamoniae, P. aeruginosa, E. coli*) activity of compounds were evaluated by cup plate method, the minimum inhibitory concentration (MIC) of the compounds were also determined by agar streak dilution method. Among all the compounds **9(i)** and **9(j)** showed potent antimicrobial activity. [8]

A series of dichlorofluorophenyl containing triazolothiadiazoles by cyclocondensation of triazole with substituted benzoic, aryloxyacetic, and aniline acetic acids using $POCl_3$ as cyclizing agent and were screened for their antibacterial activity against *E. coli* (ATCC-25922), *S. aureus* (ATCC-25923), *P. aeruginosa* (ATCC-27853), *S. pyogenes*, and *K. pneumonia* (recultured) bacterial strains by the disc diffusion method. It was revealed that the compounds **10(a), 10(c), 10 (d), 11(a)** exhibited good antibacterial activity against all tested bacterial strains almost equivalent to that of the standard drug Ciprofloxacin.[9] Holla et al synthesized triazolothiadiazoles containing 6-chloropyridin-3-yl methyl moiety **12(a-e)** and some of the compounds were screened for their antibacterial activity. It was indicated that all the tested compounds was found to possess lesser degree of activity against all the tested organisms compared to standard [10].

K C Ravindra et al synthesized some triazolothiadiazole containing naptho [2,b]furan **(13,14,15)** and the few selected compounds was evaluated for antibacterial activity. It was revealed that all the newly synthesized compounds exhibited promising antibacterial activity against all the tested organism [11]. A series of 6-substituted-

1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazole derivatives of isoniazid were synthesized and pharmacologically evaluated for their in vitro antimicrobial activity by Sadaf Jamal Gilani et al. It was revealed that the compounds **16(a), 16(b), 16(c)** showed comparatively good activity against all the bacterial strains. It was found that the good activity is because of the presence of pharmacologically active 2,4-dichloro 16(a), methyl 16(b), 4-nitro 16(c) groups attached to phenyl group at position 6 of the triazolo-thiadiazole ring [12]. Xu et al synthesized new 6-aryl-3-cinchopheny-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and some of the compounds were screened for antibacterial activity in diluted agar media. Among the three compounds screened, **17(c)**, (3-cinchopheny-6-(3-chlorophenyl)-s-triazolo[3,4-b]-1,3,4-thiadizole) exhibited antibacterial activities against sclerotium blight of colza, gray mold of cucumber and cercospora brown spot of peanut, the antibacterial rates respectively were 50.0%,41.1% and 36.3%. If o, m-on 6-phenyl of compounds 17(b) and 17(a) were substituted by fluorine, their antibacterial rates changed to 0%, 29.4%, 27.2% and 0%, 41%, 27.2%. [13]

A series of new [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazoles were evaluated for antibacterial activity. All newly synthesized compounds exhibited promising activities against *Enterococcus faecalis* (Ef), *Staphylococcus aureus* (Sa) and *Bacillus subtilis* (Bs). It was observed that compound 8a exhibited highest activity with the MIC value of 2 µg/mL. Marginal activities were observed against *Escherichia coli* (Ec), *Klebsiella pneumoniae* (Kp), *Yersinia pseudotuberculosis* (Yp) and *Pseudomonas aeruginosa* (Pa).

It was seen that all the tested compounds exhibited relatively better activities against Gram positive bacteria than those of Gram negative bacteria. [14] Zi-Yi-Zhang et al carried out the studies on the condensation of heterocyclic compounds and 6-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-3-(4-pyridyl)-s-triazolo[3,4-b]-1,3,4-thiadiazoles also reported the antibacterial activity of several representative compounds screened against *B. subtili* and *E. coli*. [15] A series of 3-substituted [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazole-6-yl-2-(2,4-dichloro-5-fluorophenyl) quinolines were synthesized by Holla et al. The quinoline-4-carboxylic acids and their triazolothiadiazole derivatives were screened for their in-vitro antibacterial activity against *S. aureus*, *E. coli* and *B. subtilis*. The standard drug used was nitrofurazone. It was noted that compounds **20a, 20b, 20c, 20d, 20e** showed very good antibacterial activity. [16]

ANTIFUNGAL:

A series of dichlorofluorophenyl containing triazolothiadiazoles and the newly prepared compounds were screened for their antifungal activity against *Aspergillus niger, Candida albicans, Aspergillus fumigatus, Penicillium marneffei* and *Trichophyton mentagrophytes* (recultured) in DMSO by agar diffusion method. The antifungal screening data showed that compounds 10(a), 10(c), 10(d), 11(a), 11(b) showed good activity against *C. albicans* and *A. fumigatus*. Compounds **10 (a), 10 (c), 10 (d)** exhibited good antifungal activity against all tested fungal strains almost equivalent to that of the standard drug Griseofulvin.[10] A series of substituted triazolothiadiazoles bearing 4-methylthiobenzyl moiety have been synthesized by D.J. Prasad et al and were evaluated for their antifungal activity against *Candida albicans* (NICMNo.300), *Aspergillus fumigatus* (NICMNo.902), *Aspergillus flavus* (NICMNo.524) and *Trichophyton mentagrophytes* (recultured) in DMSO by serial plate dilution method. Activity of each compound was compared with Fluconazole as standard. Compounds **21(a), 21(b), 21(c), 21(d), 22(a), 22(b), 22(c), 22(d)** showed comparatively good activity against all the tested fungal strains. The groups 4-methylthio, 2,4-dichloro-5-fluoro and 2-chloro-4-nitro which are directly attached to the phenyl ring of the triazole system were responsible for the good antifungal activity. The groups 4-chloro-2-nitro, 2-trifluoromethy l,4-bromo and 4-methoxy which are attached to the aryl furyl ring were responsible for the good antifungal activity. [17] Some new [1,2,4] triazolo[3,4-b][1,3,4]thiadiazoles bearing 2,3,5-trichlorophenyl moiety were reported their antimicrobial activity. Newly prepared compounds were screened for their antifungal activity against *Aspergillus flavus* [NCIMNo.524], *Aspergillus fumigatus* [NCIMNo.902], *Penicillium marneffei* and *Trichophyton mentagrophytes* in DMSO by serial plate dilution method. Activity of each compound was compared with Ciclopiroxolamine as standard. The compounds **23(a-e)** showed good activity against all the fungal strains. The good activity is attributed to the presence of - CH_3, OCH_3, 2,3-dichloro, 4-hydroxy-3-amide, 4-chloro, SCH_3, phenyl groups attached to phenyl ring, pyridyl and bromopyridyl groups of the thiadiazole [18]. A series of 6-substituted-3-(4-methyl-1,2,3-thiadiazolyl)[1,2,4]triazolo[3,4-b][1,3,4]thiadizoles and were evaluated for their fungicidal activity. 3-(4-Methyl-1,2,3-thiadiazolyl)-6-n-propyl[1,2,4]triazolo[3,4-b][1,3,4]thiadizole, **24(a)** and 3-(4-methyl-1,2,3-thiadiazolyl)-6-trichloromethyl [1,2,4]triazolo[3,4-

b][1,3,4]thiadizole, **24(b)** were found to have potential wide spectrum. [19]

A series of novel bis[4-methoxy-3-(6-aryl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol)phenyl] methanes **25(a–l)** has been synthesized and were screened for their antifungal activity against *Candida albicans, Aspergillus fumigatus, Trichophyton rubrum and Trichophyton mentagrophytes.* Results of antifungal activity showed that compounds **25(k)** and **25(l)** bearing heterocyclic ring on the carbon of N–C–S fragment of the thiadiazole ring had highest activity against all the fungi tested. The activity of these compounds is almost equal to the standard. Compounds **25(h)** and **25 (i)** bearing 4-nitrophenyl and benzyl moieties also showed good inhibition towards *A. fumigatus* and *T. mentagrophytes* [5]. A series of 3, 6-disubstituted-1, 2, 4-triazolo-[3, 4-b]-1,3,4-thiadiazoles **26(a-j)** and was evaluated for antifungal activity against *Candida albicans* and *Aspergillus niger*. The compounds **26(c)** and **26(i)** showed moderate activity against both the strains. The compounds **26(d)**, **26(f)** and **26(h)** in which triazolo thiadiazole moiety bearing hydroxy phenyl ring exhibited good inhibitory activity against both the microorganisms. It was concluded that compounds bearing electron donating aromatic ring in 6 position of triazolo-thiadiazole system showed significantly good antifungal activities. [20] A number of new 4,6-disubstituted 1,2,4-triazolo-1,3,4-thiadiazole derivatives were synthesized and screened for their antifungal activity against the various pathogenic strains. Nystatin was used as standard drug against fungi. Compounds **27(b), 27(c), 27(d), 28(b), 28(c) and 28(d)** showed potent inhibition against the all antifungal strains when compared to standard drugs. [21]

Mathew et al synthesized several 3,6-disubstituted-1,2,4-triazole [3,4-b]-1,3,4-thiadiazoles and their dihydro analogues were screened for their antifungal activities. It was reported that maximum activity was shown in the tested compounds of compound **(29)** having 2-flouro pyridine group at sixth position of the triazolothiadiazole system. It was concluded that antifungal activities of some of the compounds are comparable to those of positive controls [22].

A series of 3,6-disubstituted 1,2,4–triazolo[3,4-b]-1,3,4-thiadiazoles were screened for antifungal activity. *Aspergillums niger* and *Candida albicans* were used to investigate the antifungal activities. It was reported that compounds substituted with 5-nitro-thiazole to triazolothiadiazole **(30)** showed better activity compared to other analogues [8]. The triazolothiadiazoles containing naptho [2,b]furan and were evaluated for antifungal activity. The fungi used were *A. flavus, A. niger and Curvuliaria lanata*. It was noted that compound **(31)** showed equipotent activity against all the three fungal strains [12]. N-and S-a-L-arabinopyranosyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles was synthesized by N.S.A.M. Khalil and were evaluated for antifungal activity against *A. fumigatus, P. italicum, S. racemosum*. It was found that among the synthesized compounds, compound **(32)** showed higher inhibitory effect as compared to compound **(33).** [23]

Several 3,6-disubstituted-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles were evaluated for antifungal activity against *Candida albicans*. The synthesized compounds showed weak antifungal activity against *C. albicans*, except for compound **(34)** that showed half of the activity of the antifungal drug (ketoconazole) [24]. Cerrtain 3-substituted-6-aryamino-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles (**35, 36)** [25] and certain 3-alkyl-8-aryl-5,6-dihydro-2-triazolo[3,4-b][1,3,4] thiadiazoles were exhibited antifungal activity [26]. The bioactivity of s-triazolo[3,4-b][1,3,4]thiadiazoles, s-triazolo[3,4-b][1,3,4] thiadiazines and s-triazolo [3,4b][1,3,4]-thiadiazino [5,6-b]-guinoxaline, some of the compounds were evaluated for antifungal activity [27]. A series of 6/8-substituted-3-(3-substituted anilinomethyl-1,2,4-triazole[3,4-b]-1,3,4-thiadiazol-6-yl)-2-chloroquinolines were showed antifungal activity [28].

ANTITUBERCULAR ACTIVITY

Tuberculosis (TB) still remains a major public health threat and TB is responsible for more than three million deaths annually worldwide was reported by world health organization (WHO) [29]. The raise is attributed to increase in emergence of drug-resistant strains of *Mycobacterium tuberculosis*, multi-drug-resistant (MDR) TB and extensively drug-resistant (XDR) TB. For this reason it is considered critical to discover new drugs acting with different mechanism from those drugs used in current therapy [30]. There is an urgent need for developing new anti-tubercular drugs which will effectively kill MDR strains, less toxic, shortened duration of therapy, rapid mycobactericidal mechanism of action in the intracellular environment. Triazolo-thiadiazoles have been reported to possess assorted biological properties including anti-tubercular. A series of dichlorofluorophenyl containing triazolothiadiazoles were synthesized by cyclocondensation of triazole with substituted

benzoic, aryloxyacetic, and aniline acetic acids using POCl3 as cyclizing agent. Selected compounds were screened for their antitubercular activity against *M. tuberculosis*. It was revealed that compound **39a** showed excellent activity and compound **39b** displayed a moderate antitubercular activity. [9]

A series of clubbed isopropyl thiazole derived dihydro triazolothiadiazoles were evaluated for antitubercular activity against *M. tuberculosis* H37Rv strain. It was found that 6-(2,4-difluorophenyl)-3-(4-isopropylthiazol-2-yl)-5,6-dihydro-[1,2,4]triazolo[3,4-b] [1,3,4] thiadi- azoles (**40**) comprising difluoro substitution exhibited excellent inhibition against *M. tuberculosis H37Rv* compared to its antifungal inhibition. They found that this increased activity is attributed to presence of fluorine atoms (highly electron negative) in the molecule which increases the lipophilicity and affects the partitioning of a molecule into membranes and facilitates hydrophobic interactions of the molecule with specific binding sites on either receptor or enzymes [31].

ANTIVIRAL ACTIVITY

A series of [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazoles were and some other compounds were evaluated for their antiviral potential. They found that none of the compounds inhibited the cytopathicity induced by vesicular stomatitis virus, Coxsackie virus B4, respiratory syncytial virus, parainfluenza-3 virus, reovirus-1, Sindbis virus and Punta Toro virus, herpes simplex virus-1 (KOS) or herpes simplex virus-2 (G), and vaccinia virus at subtoxic concentrations in HeLa, Vero or E6SM cell cultures, respectively [33]. A series of acyclic C-nucleosides 1',2'-O-isopropylidene-D-ribo-tetritol-1-yl) [1,2,4]triazolo [3,4-b] [1,3,4] thiadiazoles bearing aryl sulfonamide(5–8)and aryl carboxamide residues, were evaluated for their in vitro anti-HIV activity by using the IIIB strain for HIV-1 and the ROD strain for HIV-2in human T-lymphocyte(MT-4) cells and found that all the compounds were inactive [34].

A number of 3,6-disubstituted 1,2,4-triazolo [3,4-b] [1,3,4] thiadiazole derivatives, containing the adamantly moiety and examined in various viral test systems. All compounds were in active against the replication of HIV-1 (IIIB) and HIV-2 (ROD) at subtoxic concentrations in acutely infected MT-4 cells whereas most of the compounds were cytotoxic for the host cells. It was found that none of the compounds inhibited vesicular Stomatitis virus, Coxsackie virus, respiratory syncytial virus, para influenza-3 virus, reovirus, Sindbis virus PuntaToro virus, herpes simplex virus type 1 and 2, and vaccinia virus-induced cytopathicity at subtoxic concentrations in HeLa,Vero or E6SM cell culture. [35]

Various triazolo and thiadiazole derivatives are associated with diverse pharmacological activities such as antibacterial, antifungal, antituberculosis, antiinflammatory, analgesic, anticonvulsant, antiviral and antitumor activities. Encouraged by these observations and established pharmacological activities of triazolo and thiadiazoles with a hope of obtaining improved pharmacological active compounds [36-38]. Triazolothiadiazoles possess varied biological activities as well as organic intermediate for preparation of various important chemical agents. A number of triazolothiadiazole derivatives having different substituent at different positions. These different substituent causes diversify biological activities as well as different extents of activities [39-40]. To enable further evaluation of the potential usefulness of triazolo-thiadiazoles and in continuation of our search for as pharmacologically active heterocycles with antimicrobial activities against various pathogenic microbes like bacteria, fungi and viruses. [41-42].

CONCLUSION

Triazolothiadiazole compounds have also been reported to possess varied biological activities. A number of Triazolothiadiazole derivatives have been reported to exert notably antimicrobial, analgesic, anti-inflammatory, antituberculosis, and antiproliferative activities. This review highlights antimicrobial activities shown by triazolothiadiazole and focuses on potential activities that are new in development. Triazolothiadiazole compounds have been synthesized with diverse biological interest for antimicrobial and various other anticipated biological activities.

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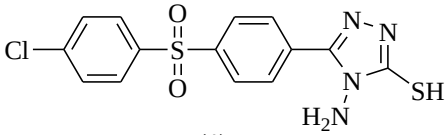
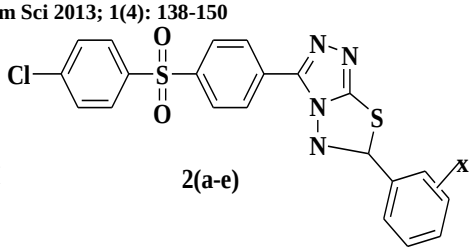
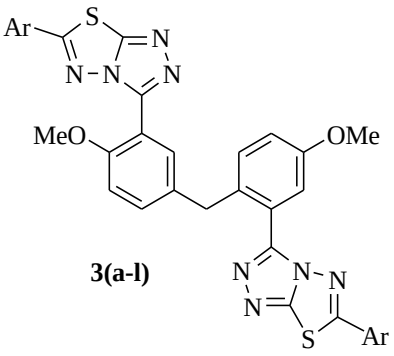


(1)



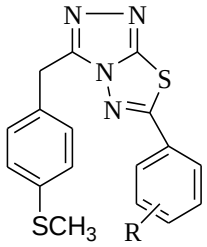
2(a-e)

2a:X=4-Br
2b:X=4-Cl
2c:X=4-OCH_3
2d:X=4-NH_2
2e:X=3-Br-4Cl



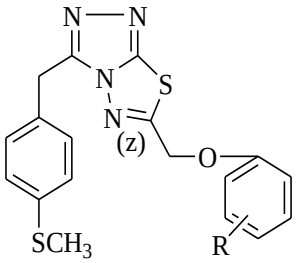
3(a-l)

3a: Ar= phenyl;
3b: Ar= 2-chlorophenyl;
3c: Ar= 4-chlorophenyl;
3d: Ar= 4-methylphenyl;
3e: Ar= 4-hydroxyphenyl;
3f: Ar= 4-methoxyphenyl
3g: Ar = 3-nitrophenyl;
3h: Ar= 4-ni-trophenyl;
3i: Ar= benzyl;
3j: Ar= 4-chlorobenzyl;
3k: Ar= 3-pyridyl;
3l: Ar= 2- pyrazinyl.



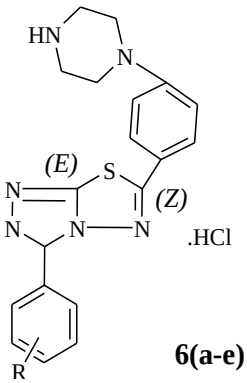
(4)

4a:R=4-Cl
4b:R=2,4-Dichloro



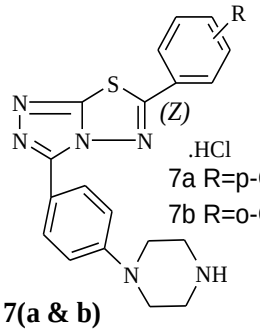
(5)

5 a:R=4-Cl
5 b:R=2,4-Dichloro



6(a-e)

6a:R=H
6b:R=p-CH_3
6c:R=m-CH_3O

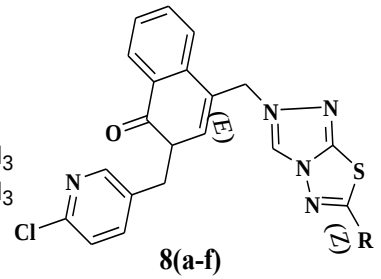


.HCl

7a R=p-OCH_3

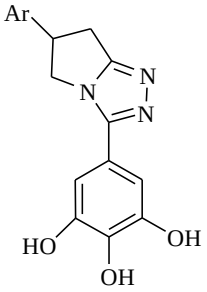
7b R=o-OCH_3

7(a & b)



8(a-f)

R=f=3-chloro-4-methoxy phenyl



9a-j

Ar

a=2-OH-C_6H_4

b=3-OH-C_6H_4

c=4-OH-C_6H_4

d=2-NO_2-C_6H_4

e=3-NO_2-C_6H_4

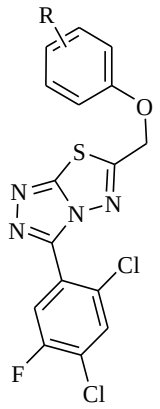
f=4-NO_2-C_6H_4

g=2-Cl-C_6H_4

h=3-Cl-C_6H_4

i=4-$N(CH_3)_2$-C_6H_4

j=3,4,5-$(OCH_3)_3$-C_6H_2



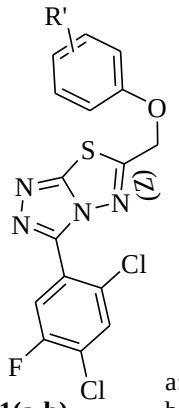
10

a=R=4-Cl

b=R=4-F

c=R=4-F,5-OC_6H_5

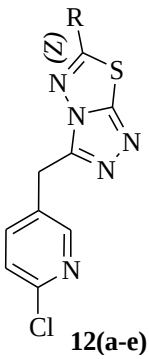
d=R=2,4-Cl_2,5-F



11(a-b)

a:R'=4-F

b:R'=4-Me



12(a-e)

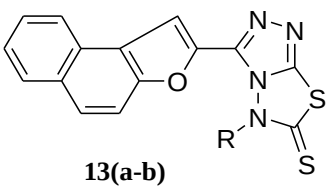
a:R=C_6H_5

b:R=4-Cl-C_6H_4

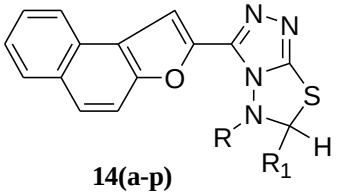
c:R=4-F-C_6H_4

d:R=4-CH_3O-C_6H_4

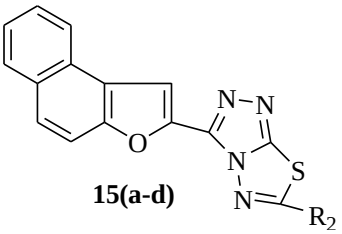
e:R=4-CH_3-C_6H_4



13(a-b)



14(a-p)

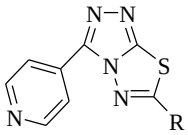


15(a-d)

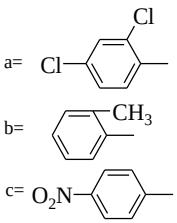
13	R
a	H
b	Ph

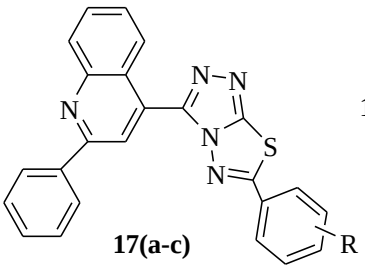
14	R_1
a, i	C_6H_5
b, j	3-Cl-C_6H_4
c, k	4-Cl-C_6H_4
d, l	3-OH-C_6H_4
e, m	4-OH-C_6H_4
f, n	4-OCH_3-C_6H_4
g, o	3-NO_2-C_6H_4
n, p	4-NO_2-C_6H_4

15	R_2
a	C_6H_5
b	4-NO_2-C_6H_4
c	4-Cl-C_6H_4
d	4-NH_2-C_6H_4



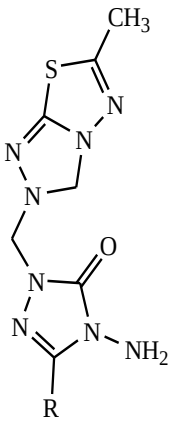
16(a-c)



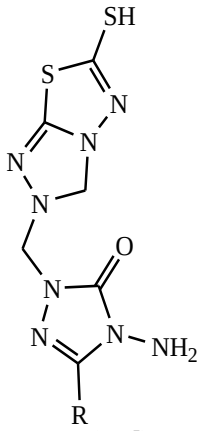


17(a-c)

17	R
a	p-F
b	m-F
c	m-Cl

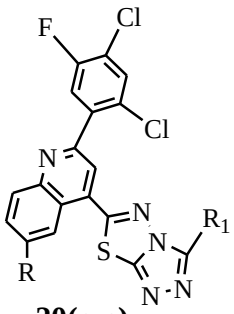


18(a-d)



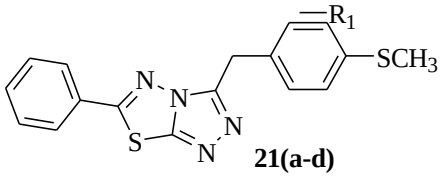
19(a-d)

	R
a	-CH_3
b	-$CH_2C_6H_5$
c	-$CH_2C_6H_7Cl$(p)
d	-C_6H_5



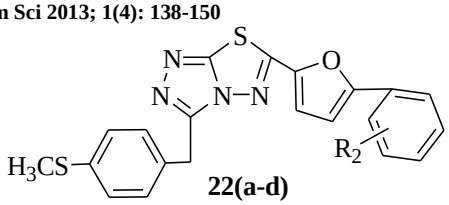
20(a-e)

	R	R_1
a	H	2-$ClC_6H_4OCH_2$
b	H	2,4-$Cl_2C_6H_3OCH_2$
c	Br	2-$ClC_6H_4OCH_2$
d	Br	2,4-$Cl_2C_6H_3OCH_2$
e	Br	4-Cl-3-$CH_3C_6H_3OCH_2$



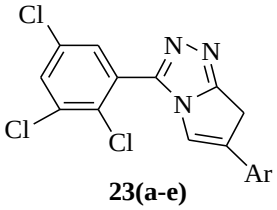
21(a-d)

a=R_1=4-S-CH_3-C_6H_4-CH_2
b=R_1=2,4-Cl_2-5-F-C_6H_2
c=R_1=4-OH-C_6H_4
d=R_1=2-Cl-4-NO_2-C_6H_3-



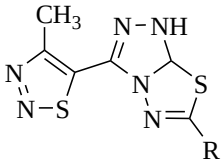
22(a-d)

a=R_2=4-Cl_2-NO_2-C_6H_5-
b=R_2=2-CF_3-$C_{10}H_6$-
c=R_2=2-CF_3-$C_{10}H_6$-
d=R_2=4-OCH_3-$C_{10}H_6$-



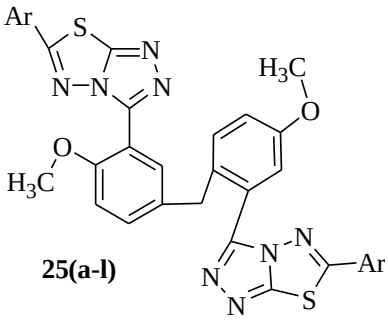
23(a-e)

Ar
a= 4-Methoxyphenyl
b= 3,5-dichlorophenyl
c= 5-Quinolyl
d= Pyridyl
e= 2-Bromopyridyl



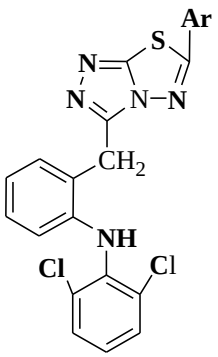
24(a-b)

a:R=CCl_3
b:R=$CH_2CH_2CH_3$



25(a-l)

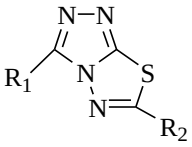
Ar
a= phenyl
b= chlorophenyl
c= chlorophenyl
d= methylphenyl
e= 4-hydroxyphenyl
f= 4-methoxyphenyl
g=3-nitrophenyl
h= 4-nitrophenyl
i= benzyl
j= 4-chlorobenzyl
k= 4-pyridyl
l= pyrazinyl

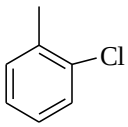


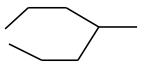
26(a-j)

Ar

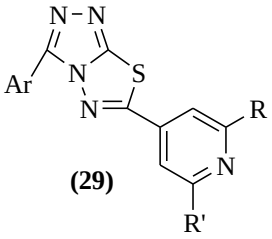
a	2-chloro phenyl
b	2-nitro phenyl
c	3-methoxy phenyl
d	5-sulpho salicyl
e	3-bromo phenyl
f	4-hydroxy phenyl
g	2,4-dichloro phenyl
h	3,4dihydroxyphenyl
i	3,4-dimethoxy phenyl
j	3-pyridyl



27	R_1	R_2
a	$-CH_3$	
b	$-CH_2$ $-CH_3$	
c	$-C_6H_5$	
d	$-4\text{-}CH_3$ $-C_6H_5$	

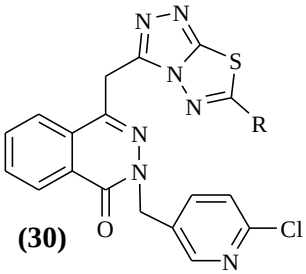
28	R_1	R_2
a	$-CH_3$	
b	$-CH_2$ $-CH_3$	
c	$-C_6H_5$	
d	$-4\text{-}CH_3\text{-}C_6H_5$	

27, 28 (a-d)



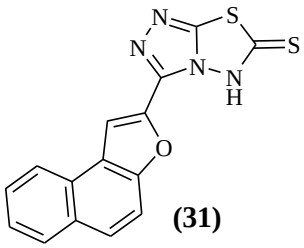
(29)

R= OH,Cl,F
R'= OH,H
Ar= 2,6-(OH)2-4-pyridinyl,
2-Cl-4-pyridinyl,
2-F-4-pyridinyl

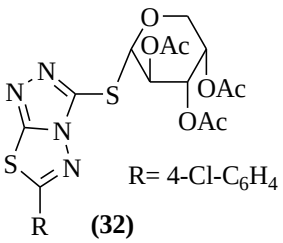


(30)

R= 3-chloro-4-methoxyphenyl

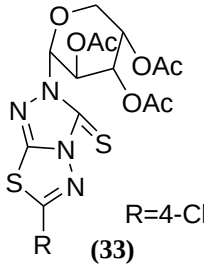


(31)



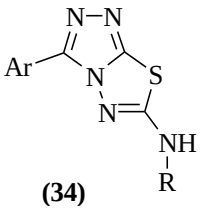
R= 4-Cl-C_6H_4

(32)

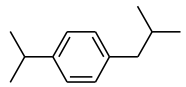


R=4-Cl C_6H_4

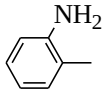
(33)



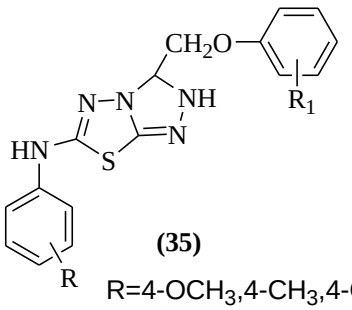
Ar=



R=

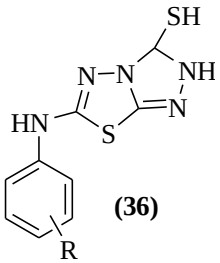


(34)

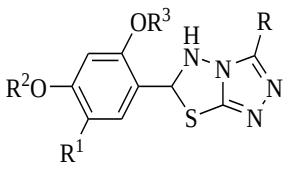


(35)

R=4-OCH_3,4-CH_3,4-Cl,H; R_1=$_4$-Cl,4-CH_3

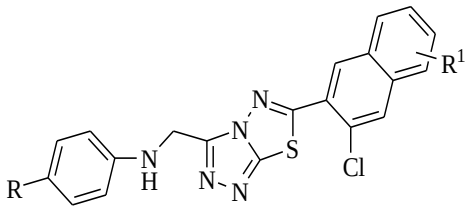


(36)



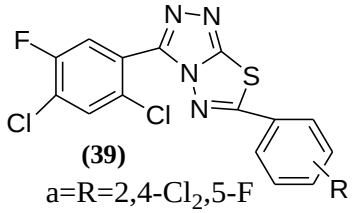
R=CH3
R^1=C_2H_5
R^2=CH_3
R^3=CH_3

(37)



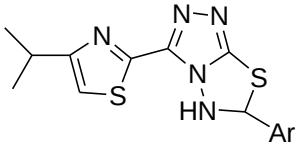
R=H,Cl,CH_3,OCH_3
R^1=H,6-CH_3,8-CH_3,6-OCH_3

(38)

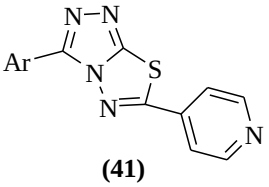


(39)

a=R=2,4-Cl_2,5-F
b=R=4-Cl

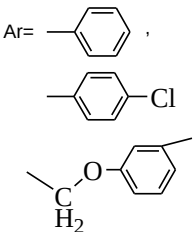


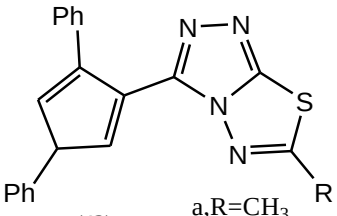
(40)



(41)

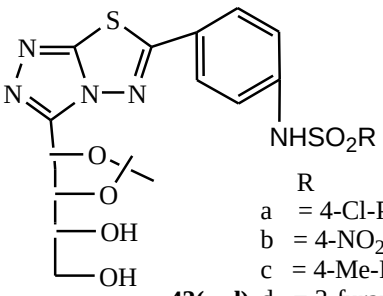
Ar=





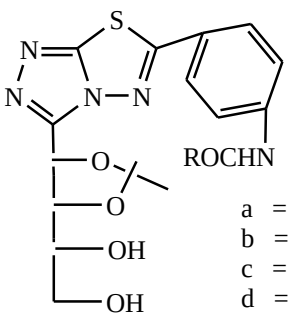
(42)

a,R=CH_3
b,R=C_6H_5



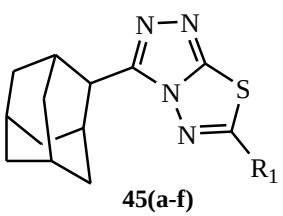
43(a-d)

R
a = 4-Cl-Ph
b = 4-NO_2-Ph
c = 4-Me-Ph
d = 3-furan



44(a-d)

R
a = furan
b = thiophene
c = 2-F-Ph
d = 4-quinoline



45(a-f)

R_1
a = CH_3
b = CH_2CH_3
c = 4-$NO_2C_6H_4$
d = 2,4diClC_6H_3
e = 4-FC_6H_4
f = $CH_2C_6H_5$

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