Triazolothiadiazoles and Triazolothiadiazines — Biologically Attractive Scaffolds

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Mini-review

Triazolothiadiazoles and triazolothiadiazines – Biologically attractive scaffolds

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ABSTRACT

Contemporary medicinal chemistry faces diverse challenges from several directions, including the need for both potency and specificity of any therapeutic agent. Therefore, in the present perspective, the triazolothiadiazoles and triazolothiadiazines with broad spectrum biological profile have matured into indispensable heterocyclic scaffolds. This review article is an effort to summarize medicinal chemistry investigations over the last decade, in search for new *N*-bridged heterocycles which can be a rich source of promising biological activities.

1. Introduction

The design, synthesis and production of molecules having value as human therapeutic agents remain one of the main objectives of organic and medicinal chemistry. During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged structures [1], with heterocyclic motifs receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry [2].

Synthesis of nitrogen containing heterocyclic systems has been attracting increasing interest over the past decade because of their utility in various applications. 1,2,4-Triazoles coupled to another heterocyclic ring exhibited wide spread applications as antibacterial, antiviral, antihypertensive, antidepressant, anti-inflammatory, anticonvulsant and antitumorial agents, pesticides, herbicides, lubricants, dyes and analytical reagents [3,4]. Among these, the most common systems are triazoles combined to thiadiazoles or thiadiazines, incorporated into a wide variety of therapeutically important compounds possessing a broad spectrum of biological activities such as antiviral, antifungal, antihelmintic, antitumor, antibacterial, anti-inflammatory, antitubercular, analgesic, antiviral, diuretics, CNS-stimulant, PDE4 inhibitors and hypoglycemic agents [5–14]. New analogs of triazolothiadiazoles and triazolothiadiazines have been synthesized by the modifications of the parent skeletons by the introduction of new substituents on 3 and 6 positions. This review summarizes the developments in this area to date with a focus on how the biological utility scope of these conjugated heterocycles has been expanded with the appropriate inclusion of various substituents on the basic frameworks.

2. Chemistry

2.1. Synthetic strategies toward triazolothiadiazoles and triazolothiadiazines

Several protocols for the synthesis of triazolothiadiazoles and triazolothiadiazines are available in the literature but 4-amino-1,2,4-triazol-3-thiones are considered as useful tools in combining to triazolothiadiazoles and triazolothiadiazines. This can be attributed to the amino and mercapto groups which are ready-made nucleophilic centers for the synthesis of condensed heterocyclic rings [15,16] as demonstrated by Demirbas and co-workers [17] (Scheme 1).

The most widely used approach for the synthesis of triazolothiadiazines is illustrated in Scheme 2. 1,2,4-Triazole is refluxed with α-haloacetophenone to afford the title compound as described by Turan-Zitouni et al. [18].

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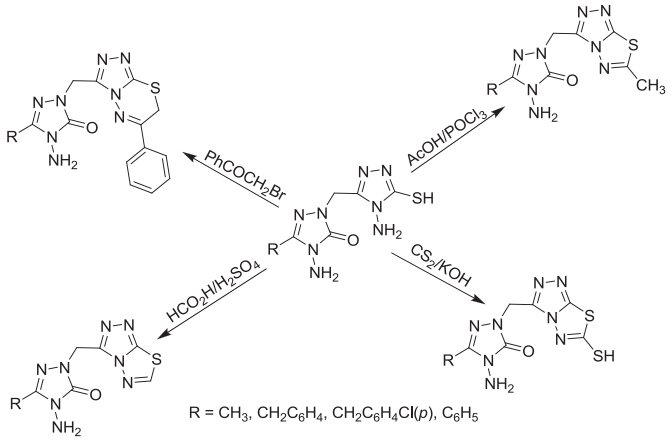


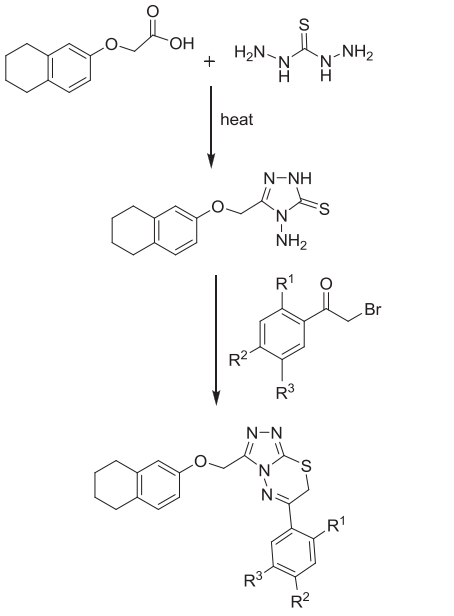
Scheme 1. Synthetic pathway of triazolothiadiazoles and triazolothiadiazines.

Farghaly et al. [19] reported the synthesis of triazolothiadiazoles and triazolothiadiazines by using oxadiazole thione as the key starting material and by the interaction of the triazolethione with chloro acetonitrile and sodium acetate fused in refluxing ethanol, respectively (Scheme 3).

An efficient conventional heating and microwave assisted protocol for the synthesis of fused heterocycles has been developed by El-Ashry and co-workers [20] as sketched in Scheme 4. 3-Chloro-2-chlorocarbonylbenzo[*b*]thiophene yielded 4-amino-1,2,4-triazole which was used as a versatile intermediate for condensed heterocycles. Better yields and shorter reaction times were achieved using MW.

Taha [21] accomplished the synthesis of triazolothiadiazoles by using 4-amino-4*H*-3-methylthio{7*H*-1,2,4-triazolo[1,5-*d*]tetrazol-6-yl}-1,2,4-triazole-5-thiol as a key intermediate. On the other hand, one-pot four component synthesis of triazolothiadiazines was done with two-carbon cyclizing reagents, namely chloroacetone, pyruvic acid, benzoylformic acid and benzoin (Scheme 5).

Microwave irradiation assisted synthesis of few novel triazolothiadiazole and triazolothiadiazine derivatives has been developed by Al-Soud et al. [22] as presented in Scheme 6.



Scheme 2. Synthesis of triazolothiadiazines.

Raval and co-workers [23] achieved the synthesis of coupled nucleus by the condensation of 4-amino triazole with aromatic aldehydes in the presence of catalytic amount of *p*-TsOH in DMF in borosil beaker under microwave irradiation as well as by conventional method (Scheme 7).

Recently, Badr and Barwa [24] accomplished the synthesis of triazolothiadiazoles by using 4-amino-1,2,4-triazole as a key intermediate, obtained by the coupling of aromatic acid with thiocarbohydrazide as sketched in Scheme 8.

Fascinated by the ongoing pioneering work in heterocyclic chemistry, Devi et al. [25] synthesized various triazolothiadiazoles and triazolothiadiazines encompassing 3-nitronaphtho[2,1-*b*]furan (Scheme 9).

Almajan et al. [26] disclosed the synthesis of triazolothiadiazine analogs by intermolecular condensation of 2-chloro-*N*-phenylacetamide, 2-chloroacetic acid, oxalylchloride and bromodiethylmalonate with 4-amino-1,2,4-triazole-3-thiol as presented in Scheme 10.

Recently, intramolecular base catalyzed C–C bond formation leading to exclusive stereoselective syntheses of *trans* 6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines has been carried out by Al-Etaibi et al. [27] as sketched in Scheme 11. The formation of the thiadiazine ring involves condensation through the amino group of the starting compound and the carbonyl group of acetophenone, abstraction of the methylene proton, and a nucleophilic attack of the resulting carbanion on the azomethine C atom with closure of the C–C bond of the thiadiazine ring. The cyclization is diastereospecific, probably because of steric hindrances: during the attack of the carbanion on the plane of the C=N bond with the formation of the C–C bond, the bulky aryl fragments are *trans* with respect to the thiadiazine ring. During stereoselective reactions, one of the two possible stereoisomers is formed in high yield as compared to other, so in this case *trans*-stereoisomer is formed in high yield that is converted into its *cis*-stereoisomer in polar solvents.

Another improved synthesis of dihydroindeno- and indenotriazolothiadiazines have been introduced by the cyclocondensation of α-bromoindanones and α,α-dibromoindanones with 4-amino-5-mercapto-1,2,4-triazoles by Prakash and coworkers [28] as shown in Scheme 12.

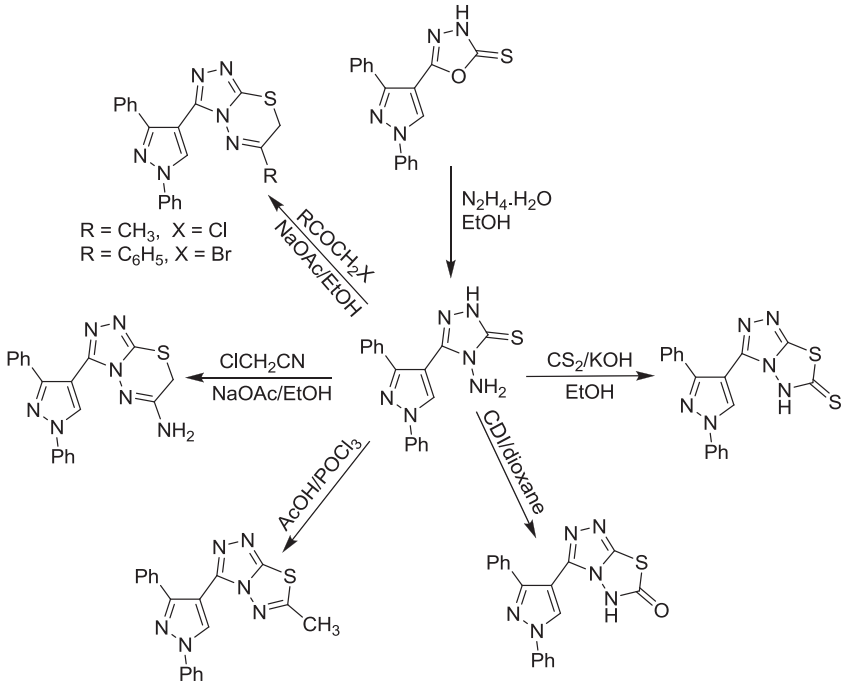
The introduction of different substituents on the parent skeleton of triazolothiadiazoles and triazolothiadiazines by the aforementioned synthetic methodologies alter biological activities. This review article focuses on the biological potential of recently synthesized (during the last decade) compounds differing in chemical structures.

3. Biological applications of triazolothiadiazoles and triazolothiadiazines

Nitrogen containing heterocycles particularly triazolothiadiazoles and triazolothiadiazines are the central structural motifs of various compounds with activities of relevance to different areas such as pharmaceutical and agrochemicals. The most common applications are highlighted here.

3.1. Anticancer activity

Holla and co-workers [3] designed the synthesis of a series of novel 1,4-bis-[4-amino-5-mercapto-1,2,4-triazol-3-yl-methoxy] phenylenes and their triazolothiadiazole derivatives and studied their anticancer activity against the three cell lines like NCI-H 460 (lung), MCF 7 (breast) and SF 268 (CNS). Interestingly, 3,3′-(2,5-dichloro-1,4-phenylene)bis(oxy)bis(methylene)di-[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazole-6-thiol (**1**) was found to be the most active which was further tested against a panel of 60 cell lines derived



Scheme 3. Synthesis of the title compounds.

from seven cancer types namely, lung, colon, melanoma, renal, ovarian, CNS and leukemia.

In another study, Holla et al. [29] reported several structurally modified triazolothiadiazines and evaluated for their anticancer activity against full panel of 60 cell lines derived from seven cancer types. The screening results showed that compound (**2**) incorporating 2-chloroaryloxy methyl at C-3 and 4-chloro benzylidene at C-7 positions exhibited highest activity with GI_{50} value < 10 μM against all the tested cell lines. A sharp decrease in activity was observed when the substituent at C-3 was changed to 4-chloro-3-methyl-aryloxy methyl.

Subsequently, Poojary and co-workers [30] also reported several triazolothiadiazines and screened for their anticancer activity. Three of the newly synthesized compounds were screened for their anticancer activities under NCI screening programme [31,32] using 3-cell line one dose assay. The 3-cell lines used for investigation are NCI-H 460 (Lung), MCF 7 (Breast) and SF 268 (CNS). The structure–activity relationship studies indicated that the compounds containing chlorine atoms at various positions are more active as compared to compounds with other substituents and among them, 6-(4-chlorophenyl)-3-(2,4-dichloro-5-fluorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3**) was found to be the most potent.

Fascinated by the previous studies, Isloor and co-workers [33] carried out the synthesis of 6-[3-(4-fluorophenyl)-1*H*-pyrazol-4-yl]-3[(2-naphthyloxy)methyl][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole. The synthesized compound was evaluated for anticancer activity by using MTT assay which revealed the FPNT (**4**) as a potent compound. This activity may be due to the presence of fluorine on the aryl group.

Moreover, recently, in pioneering studies, Husain et al. [34] reported a library of triazolothiadiazole and triazolothiadiazine derivatives incorporating benzimidazole scaffold. These derivatives have been screened for their *in vitro* anticancer activity at the National Cancer Institute (NCI) against full NCI 60 human cell lines panel. The compounds possessed good results and among them, compound (**5**) turned out to be a lead candidate and may serve as a novel template for development of potential and selective agents in the field of cancer chemotherapy. The screened results indicated that benzimidazoles clubbed with triazolothiadiazole were found to exhibit better anticancer activities than those of benzimidazoles clubbed with triazolothiadiazine (**6**).

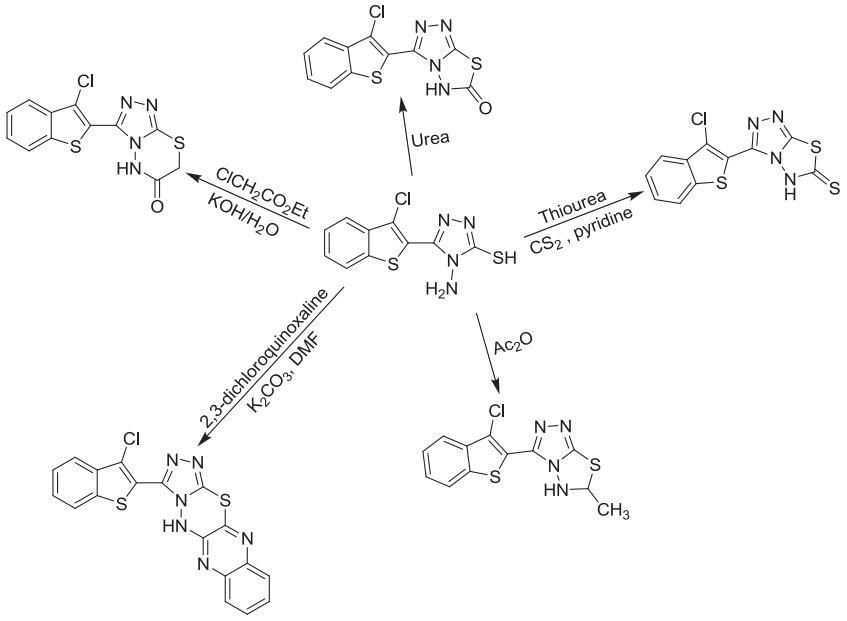
3.2. Antitumor activity

A notable advance was achieved by Poojary and co-workers [30] by screening a series of triazolothiadiazole derivatives for their antitumor activity. They were first evaluated in a 3-cell line, one-dose preliminary anticancer assay followed by a full panel of 60 human cell lines which showed variable antitumor activities. Compounds (**7**) and (**8**) were found to be highly active against leukemia MOLT-4, ovarian cancer OVCAR-3 and prostate cancer PC-3. This increase in activity may be attributed to the chloro groups present on the phenyl ring at position 6 of the title compounds.

New 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole and triazolothiadiazine analogs have been explored by Al-Soud et al. [22] for *in vitro* antitumor activity against a panel of tumor cell lines, using microculture tetrazolium assay. The synthesized compounds (**9**) and (**10**) exhibited activity against $CD4^+$ human acute T-lymphoblastic leukemia. The SAR analysis indicated that the synthesis of new analogs of the triazolothiadiazine series may lead to the discovery of more potent and selective inhibitors.

Following the developments in this area, Ibrahim [35] turned his attention toward the synthesis of 4-(3-substituted[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazol-6-yl) aniline, 2-amino-5-substituted-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl methyl-1,3-thiazol-4-ol and triazolo[3,4-*b*]thiadiazole derivatives to optimize the biological response of the new lead triazolothiadiazole derivatives. The synthesized compounds demonstrated inhibitory effects on the growth of a wide range of cancer cell lines generally at 10^{-5}–10^{-7} M concentrations. Their antitumor activity appears to be related to some structural requirements and to the presence of particular substituents, as a matter of fact, 4-chlorophenoxymethylene moiety plays an important role for the activity. Compounds (**11**) and (**12**) maintained the highest growth inhibition [36].

Recently, Hu and co-workers [37] explored a series of C-3/C-3 bis-fluoroquinolone coupled heterocycles cross-linked with a [1,2,4]-triazolo[3,4-*b*][1,3,4]-thiadiazole core against murine



Scheme 4. Conventional and microwave-assisted synthesis of the title compounds.

leukemia cell line (L1210), human leukocytoma cell line (HL60) and Chinese hamster ovary cell line (CHO) using the MTT assay. Compounds (**13**) and (**14**) exhibited the most potent activity against HL60 cells. This preliminary indication of antitumor activity suggests that di-(1-cyclopropyl)-substituted fluoroquinolones and bis-fluoroquinolone hybrid molecules are promising lead compounds for further developments.

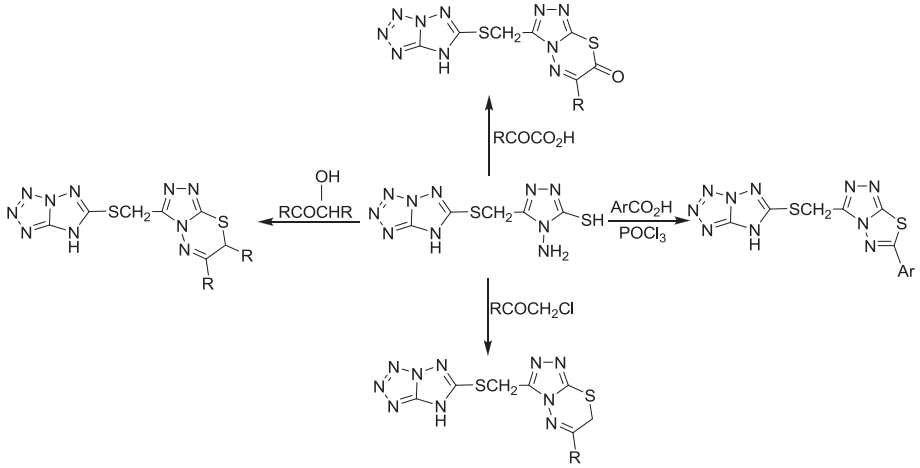
3.3. Anti-inflammatory activity

Mathew et al. [38] accomplished a series of fused heterocycles for the evaluation of their biological profile. All the synthesized compounds were tested for their anti-inflammatory activity using carrageenan induced rat hind paw edema method of Winter et al. [39]. Tested compounds exhibited weak to moderate activity as depicted by 3-[2-(*N*-methyl amino)phenyl]-6-[2-(2,4-dichlorophenoxy)ethyl]-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (**15**).

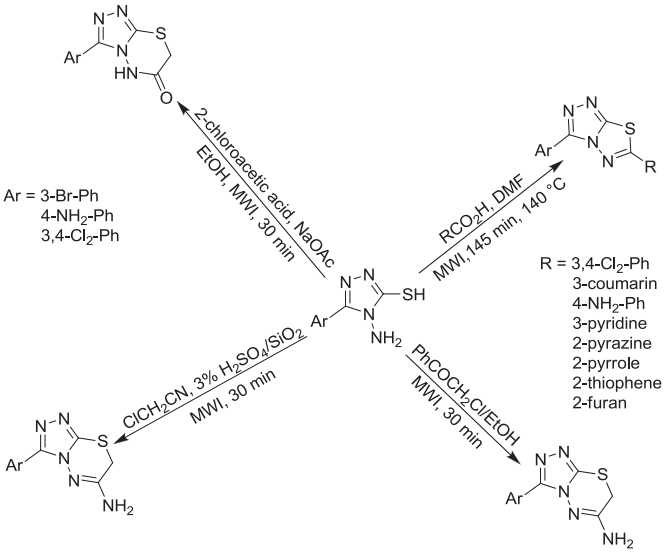
In another study, Mathew and co-workers [40] investigated that triazolothiadiazoles possessing indole ring exhibited good anti-inflammatory activity as shown by compound (**16**). From SAR analysis, it is revealed that the introduction of electron releasing groups like methyl or methoxy at the 5th position of indole ring produced a decrease in the anti-inflammatory activity.

Furthermore, triazolothiadiazole and triazolothiadiazine nuclei bearing trichlorophenyl moiety have been reported by Karegoudar and co-workers [41]. The prepared compounds were evaluated for anti-inflammatory activity which was conducted in acute inflammatory model. The compound (**17**) showed good activity among the tested compounds as it structurally resembles a known anti-inflammatory agent Dichlofenac sodium [42]. 6-(4-Chlorophenyl)-3-(2,3,5-trichlorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**18**) has been found to exhibit less activity. So, in preliminary examination, triazolothiadiazoles have found to be more potent anti-inflammatory agents as compared to thiadiazines.

Aytaç et al. [43] reported several triazolothiadiazine derivatives and screened for their anti-inflammation profile. Among the condensed derivatives, compound (**19**) bearing 3,4,5-trimethoxyphenylethyl at the 3rd position and 4-fluorophenyl at



Scheme 5. Synthesis of triazolothiadiazoles and thiadiazines.



Scheme 6. MWI assisted synthesis of triazolothiadiazoles and triazolothiadiazines.

the 6th position of the fused ring possessed the most prominent and consistent activity.

Husain and Naseer [44] synthesized a variety of 3,6-disubstituted-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazoles and *in vivo* anti-inflammatory activity was evaluated. The compounds exhibited good anti-inflammation profile, specifically, 3-(phenoxymethyl)-6-(3-oxo-3-phenylpropyl)-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazole (**20**) presented the highest anti-inflammatory activity better than the standard drug indomethacin. It was observed that the replacement of 3-oxo-3-phenylpropyl group at C-6 position by other groups resulted a decrease in anti-inflammatory activity. From the view point of structure–activity relationship, it is clear that the triazolothiadiazole derivatives of phenoxy acetic acid were found to be more active than phenyl acetic acid and salicylic acid derivatives.

Moreover, El-Shehry et al. [45] prepared a series of triazolothiadiazoles and triazolothiadiazines and assessed their anti-inflammatory activity. These condensed derivatives having 2,4-dichlorophenoxy group at C-6 position like (**21**) possess highest activity compared with indomethacin by protecting rats by 36–56% from inflammation. On the other hand, 3-((2,4-dichlorophenoxy) methyl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**22**) exhibited less activity as compared to triazolothiadiazole series.

Hussein et al. [46] reported a series of triazolothiadiazoles bearing pyridine moiety and screened for their *in vitro* anti-inflammatory effect by the carrageenan induced paw edema bioassay in rats using indomethacin as a reference drug. The compound (**23**) possessing pyridine moiety both at 3rd and 6th

i(a) Conventional method: *p*-TsOH/DMF, reflux, 10-12 h
i(b) Microwave method: *p*-TsOH/DMF/acidic alumina, μw
t_1 = 4.0-6.0 mins at p_1 = 350w, t_2 = 2.0-3.5 mins at p_2 = 500w

Ar = C_6H_5, 2-OCH_3-C_6H_4, 4-NO_2-C_6H_4, 2-OH-C_6H_4, 2-Cl-C_6H_4, 4-OCH_3-C_6H_4, 3-Br-C_6H_4, 3-OH-C_6H_4, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 2,4-diOCH_3-C_6H_3, 2,4-diCl-C_6H_3, 2,6-diCl-C_6H_3, 4-NO_2-C_6H_4

Scheme 7. Synthesis of triazolothiadiazoles by conventional and microwave methods.

position of triazolothiadiazole skeleton showed maximum anti-inflammatory activity [47].

More recently, Malladi and co-workers [48] synthesized a series of 3,6-disubstituted-1,2,4-triazolothiadiazoles bearing pyrazole moiety and evaluated their anti-inflammation efficacy. The results disclosed that 3-propyl-6-(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl) [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**24**) possess significant inhibition as compared to the standard drug Dichlofenac sodium.

3.4. Analgesic activity

Turan-Zitouni et al. [18] reported several triazolothiadiazine derivatives which have been tolerated for their analgesic activity by acetic acid test (Modified Koster Test) [49] in male albino mice (25–30 g). The results clearly demonstrated that the synthesized compounds exhibited an interesting profile of analgesic activity particularly compound (**25**) as compared to aspirin used as a standard. The presence of hydroxy and methoxy groups on the phenyl ring at position 6 may be responsible for the promising activity.

Mathew et al. [38] reported a series of 3,6-disubstituted-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles. The synthesized compounds have been screened for their analgesic activity by using Eddy's hot plate technique. 3-[4-(*N*,*N*-Dimethyl amino)phenyl]-6-[2-(2,4-dichlorophenoxy)ethyl]-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (**26**) was found to be the most active among the tested series.

A noteworthy contribution was made by the Karthikeyan and co-workers [50] who reported numerous triazolothiadiazole derivatives. The synthesized compounds were evaluated for analgesic activity by hot plate test by Eddy and Leimbach. The analgesic screening results revealed that the compounds (**27**) and (**28**) were found to be the most potent. The structure–activity relationship investigations indicated that the presence of halo groups like chloro and fluoro on both aryl rings at position 3 and 6 may be responsible for good results.

Moreover, Mathew and co-workers [40,51] found that the triazolothiadiazoles possessing indole ring at the 6th position exhibited good analgesic activity as shown by compound (**29**).

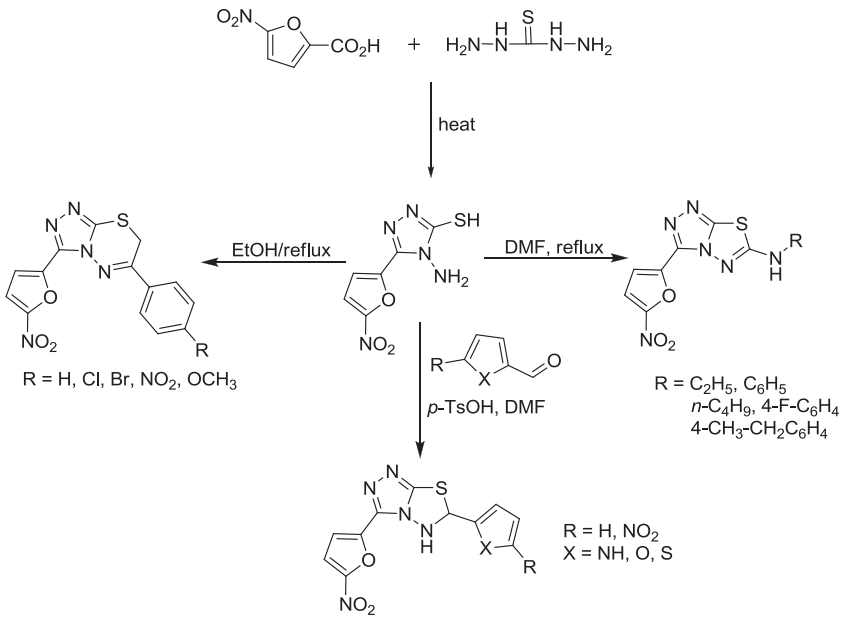
Aytaç et al. [43] reported a series of triazolothiadiazine derivatives and screened for their analgesic activity. Among the synthesized compounds, 3-[2-(3,4,5-trimethoxyphenyl)ethyl]-6-(4-chlorophenyl)-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (**30**) showed prominent activity. The methoxy groups are contributing significantly toward pronounced biological activity.

Husain and Naseer [44] prepared a series of triazolothiadiazole derivatives which were screened for the analgesic effects using acetic acid-induced writhing method. The results of analgesic activity indicated that compounds (**20**) incorporating 3-oxo-3-phenylpropyl group at C-3 of triazolothiadiazole ring showed better activity than that of standard drug acetylsalicylic acid (aspirin).

Recently, experiments conducted by Devi et al. [25] for the synthesis of triazolothiadiazoles and triazolothiadiazines encompassing 3-nitronaphtho[2,1-*b*]furan made notable contribution to the library of heterocyclic compounds showing analgesic effects. The activity of the synthesized compounds was compared with that of standard drug tremadol. The results revealed that compound (**31**) was found to be less active than that of (**32**).

3.5. Antitubercular activity

Interesting observations on the antitubercular activity of triazolothiadiazole derivatives were made by Karthikeyan and co-workers [50]. Tuberculosis Activity Antimicrobial Acquisition and Coordinating Facility (TAACF) of Southern Research evaluated some



Scheme 8. Synthetic pathway of the title compounds.

of the selected compounds for *in vitro* antitubercular activity against Mycobacterium tuberculosis HRv (ATCC 27294) in BACTEC 12B medium using a broth microdilution assay, the Microplate Alamar Blue Assay (MABA) [51]. The antitubercular screening results revealed that 3,6-bis(2,4-dichloro-5-fluorophenyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (**33**) showed an excellent inhibition of 97%. The presence of chloro and fluoro substituents on aryl ring may be responsible for inhibitory activity.

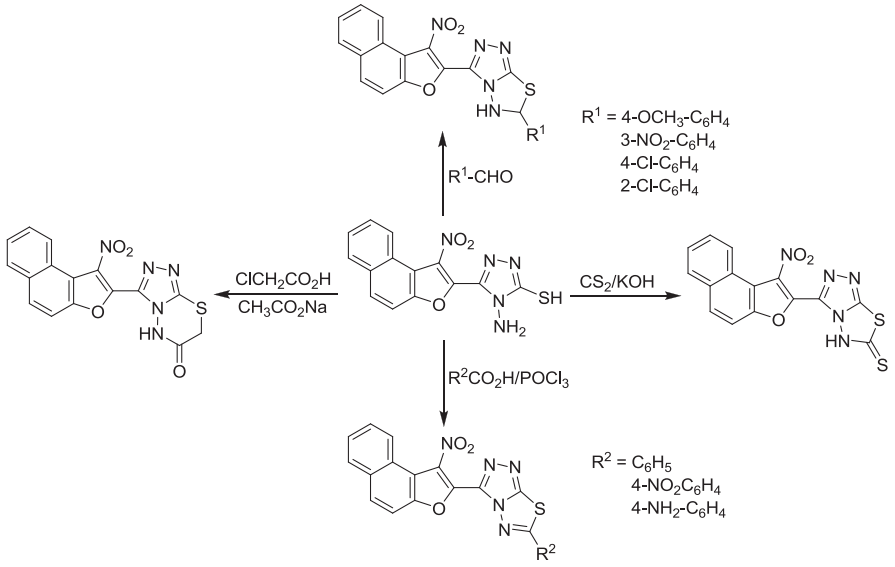
Kumar et al. [52] reported a novel series of 3-(4-isopropylthiazol-2-yl)-6-methyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles and triazolothiadiazines and screened for antitubercular activity against H37Rv strain. The *in vitro* antituberculosis screening results showed that all compounds were active, in particular, compound (**34**) exhibited excellent antitubercular activity when compared with first line drug such as Isoniazid. 6-(2,4-Difluorophenyl)-3-(4-isopropylthiazol-2-yl)-5,6-dihydro-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**35**) possess low activity as compared to the thiadiazine (**34**).

3.6. Anti-HIV activity

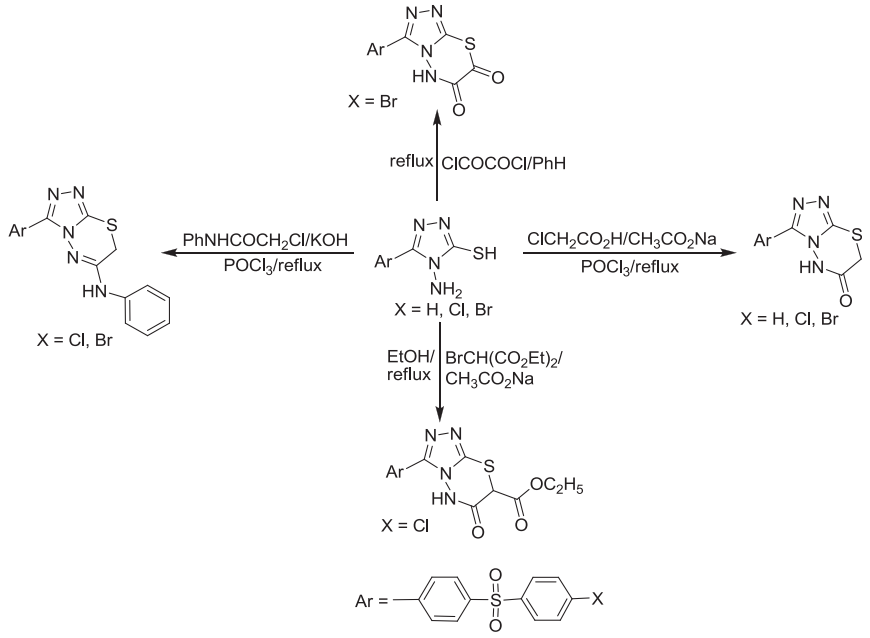
A series of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole analogs has been synthesized under microwave irradiation (MWI) by Al-Soud et al. [22]. These compounds were tested for their *in vitro* anti-HIV-1 (strain IIIB) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells using the MT-4/MTT assay [53]. Efavirenz [54] and capravirine [55] were used as standard drugs. Compound (**36**) possessing pyrazine moiety was found to be equipotent against HIV-1 and HIV-2 replication *in vitro* as compared to (**37**) which incorporate an unsubstituted phenyl ring.

3.7. Growth promoters

Zhang et al. [56] reported a series of fused heterocycles containing furan ring to investigate the effect of these compounds on sprouting of mung bean seeds. The results obtained revealed that compounds (**38**) and (**39**) increase mung bean sprout growth by



Scheme 9. Protocol for synthesis of the title compounds.



Scheme 10. Synthesis of triazolothiadiazine derivatives.

40%. This increase in growth may be attributed to the chloro and methoxy substituents present on the aryl ring at position 3 of triazolothiadiazole nucleus.

3.8. Anticonvulsant activity

Husain et al. [57] disclosed the synthesis of 3,6-disubstituted-1,2,4-triazolo-[3,4-*b*]1,3,4-thiadiazoles and screened for their anticonvulsant potential. The results indicated that halo-substituted aryl (bromophenyl) at position 6 of the triazolothiadiazole motif was essential for the activity. Few compounds like (**40**) and (**41**) showed more lipophilic character and were more active.

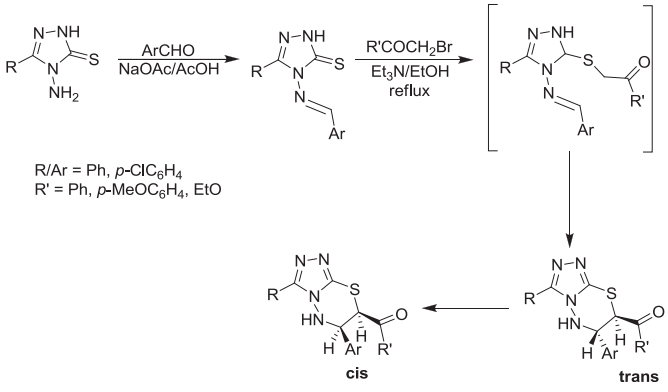
3.9. Molluscicidal agents

El-Shehry et al. [45] synthesized a series of 3-((2,4-dichlorophenoxy)methyl)-1,2,4-triazolothiadiazoles and thiadiazines and screened for their toxicity toward *Biomphalaria alexandrina* snails. An insight inspection of the results showed that 6-((2,4-dichlorophenoxy)methyl)-3-(4-methoxyphenyl)-[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazole (**42**) has high effect on the snails. The triazolothiadiazole derivatives have been found more active as compared to the thiadiazine series (**43**).

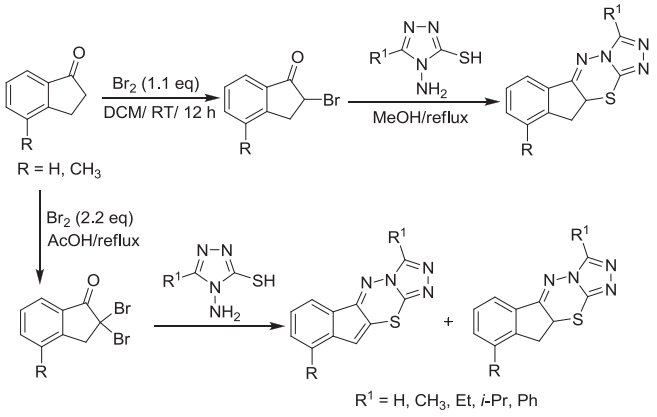
3.10. Cytotoxic activity

Sumangala et al. [58] reported a series of triazolothiadiazine derivatives containing methylsulfonyl group and evaluated for their cytotoxicity. The cytotoxicity study revealed that some of the 6-substituted-3-[2-(methylsulfonyl)benzyl]-7*H*-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazines, (**44**) and (**45**) containing phenyl and biphenyl groups, respectively at C-6 position of thiadiazine nucleus showed significant activity compared to the standard Doxorubicin. The cytotoxicity of thiadiazine containing biphenyl derivative is much better than the phenyl derivative.

A novel combinatorial library of 6-arylsubstituted-3-[2-(4-substitutedphenyl)propan-2-yl]-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazines were designed, synthesized and screened for their cytotoxic activities using trypan blue exclusion and MTT assay by Puthiyapurayil et al. [59]. The results of the short term *in vitro* cytotoxic activity against Ehrlich Ascites Carcinoma (EAC) cell lines by trypan blue exclusion method showed poor to moderate activity.



Scheme 11. Stereoselective synthesis of 6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*]1,3,4] thiadiazines.



Scheme 12. Synthesis of triazolothiadiazines.

In vitro cytotoxicity by MTT assay showed that, in EAC cells few compounds were found to be active. The enhanced activity of the compounds was mainly attributed to the presence of (2-phenylpropan-2-yl) and [2-(4-chlorophenyl)propan-2-yl] substituent at C-3 position of the triazolothiadiazine ring system. Compound (**46**) carrying 4-trifluoromethoxyphenyl group at C-6 position and [2-(4-chlorophenyl)propan-2-yl] substituent at C-3 position was the most lead molecule.

3.11. Anthelmintic activity

Puthiyapurayil et al. [59] synthesized numerous triazolothiadiazine derivatives and screened for their anthelmintic activity. The results revealed that compounds (**47**) and (**48**) showed good anthlemintic activity almost comparable with standard drug. The excellent activity of these compounds was attributed to the presence of 2,4-dichloro-5-fluorophenyl and 4-chloro-3-nitrophenyl groups on the C-6 phenyl ring and halogen groups (4-chloro and 4-bromo) on the C-3 position of the condensed triazolothiadiazine ring system.

3.12. Antimicrobial agents

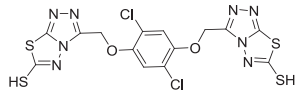
Holla et al. [4] reported several nitrophenylfurfurylidene-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines and tested for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Bacillus subtilis*. Among the tested compounds, (**49**) carrying *p*-nitrophenyl and a methyl group showed excellent antibacterial activities against all the bacterial strains.

Demirbas and co-workers [17] described a series of new [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles and triazolothiadiazines. The possible antimicrobial activities of the synthesized compounds were investigated to ten standard organisms including bacterial and fungal strains. All newly synthesized compounds exhibited promising activities against *Enterococcus faecalis* (Ef), *S. aureus* (Sa) and *B. subtilis* (Bs). The highest activity was observed for 4-amino-3-methyl-1-((6-methyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl) methyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**50**).

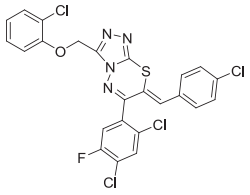
Holla et al. [29] reported a series of fluorine containing 7-arylidene-6-(2,4-dichlorophenyl)-3-aryloxymethyl/anilinomethyl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines and screened for their antibacterial activity against *E. coli*, *S. aureus*, *P. aeruginosa* and *B. subtilis* bacterial strains by serial plate dilution method. Almost all the screened compounds exhibited comparable activity with standard nitrofurazone. *Z*-3-((4-Chloroaryloxy)methyl)-6-(2,4-dichloro-5-fluorophenyl)-7-(3,4-dimethoxybenzylidene)-7*H*-[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazine (**51**) showed highest activity against all the tested bacteria.

In another study, Holla and co-workers [60] reported a series of triazolothiadiazoles and triazolothiadiazines containing 6-chloropyridin-3-yl moiety and initially screened for their *in vitro* antibacterial activities against different bacterial strains by serial plate dilution method. Furacin was used as a standard drug. The synthesized derivatives exhibited mild activities as represented by compounds (**52**) and (**53**).

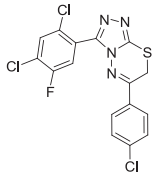
1,2,4-Triazolo[3,4-*b*]-1,3,4-thiadiazoles and 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines carrying thioalkyl and sulfonyl phenoxy moieties were reported by Karabasanagouda et al. [61]. The newly synthesized compounds were screened for their antibacterial activity against *E. coli* (ATTC-25922), *S. aureus* (ATTC-25923), *P. aeruginosa* (ATCC-27853) and *Klebsiella pneumoniae* (recultured) bacterial strains by serial plate dilution method. The investigation of antibacterial and antifungal screening data revealed that all the tested compounds showed moderate to good inhibition and they deserve more consideration as potential antimicrobials. The good activity is attributed to the presence of pharmacologically active $-CH_3$, $-OCH_3$, $-NH$ and 2,3-dichloro groups attached to phenyl ring at position 6 of the thiadiazole nucleus as depicted by compounds (**54**) and (**55**).



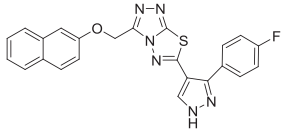
3,3'-(2,5-Dichloro-1,4-phenylene)bis(oxy)bis(methylene)di-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiol (**1**)



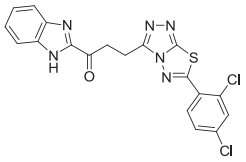
(*Z*)-7-(4-Chlorobenzylidene)-3-((2-chlorophenoxy)methyl)-6-(2,4-dichloro-5-fluorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**2**)



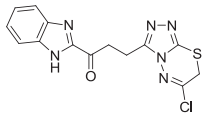
6-(4-Chlorophenyl)-3-(2,4-dichloro-5-fluorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**3**)



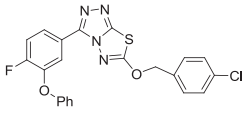
6-[3-(4-Fluorophenyl)-1*H*-pyrazol-4-yl]-3[(2-naphthyloxy)methyl][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**4**)



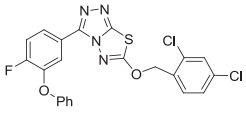
1-(1*H*-Benzo[*d*]imidazol-2-yl)-3-(6-(2,4-dichlorophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)propan-1-one (**5**)



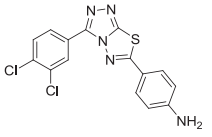
1-(1*H*-Benzo[*d*]imidazol-2-yl)-3-(6-chloro-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)propan-1-one (**6**)



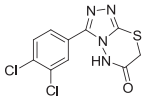
6-(4-Chlorobenzyloxy)-3-(4-fluoro-3-phenoxyphenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**7**)



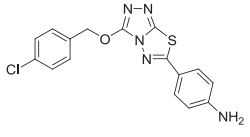
6-(2,4-Dichlorobenzyloxy)-3-(4-fluoro-3-phenoxyphenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**8**)



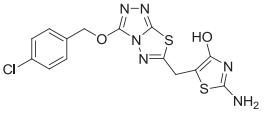
4-(3-(3,4-Dichlorophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)aniline (**9**)



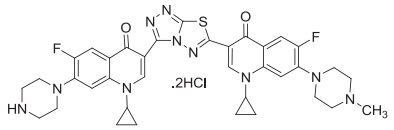
3-(3,4-Dichlorophenyl)-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6(7*H*)-one (**10**)



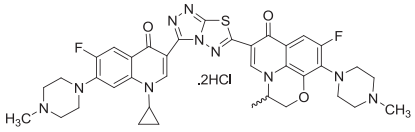
4-(3-(4-Chlorobenzyloxy)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)aniline (**11**)



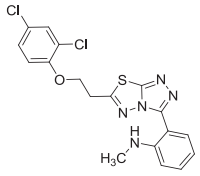
2-Amino-5-((3-(4-chlorobenzyloxy)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)methyl)-thiazol-4-ol (**12**)



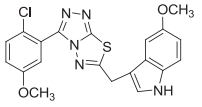
1-Cyclopropyl-3-(3-(1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinolin-3-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)-6-fluoro-7-(4-methylpiperazin-1-yl)quinolin-4(1*H*)-one (**13**)



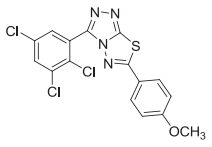
6-(3-(1-Cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinolin-3-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-2*H*-[1,4]oxazino[2,3,4-*ij*]quinolin-7(3*H*)-one (**14**)



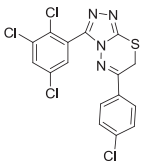
3-[2-(*N*-Methyl amino)phenyl]-6-[2-(2,4-dichlorophenoxy)ethyl]-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (**15**)



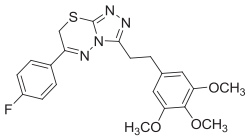
3-(2-Chloro-5-methoxyphenyl)-6-((5-methoxy-1*H*-indol-3-yl)methyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**16**)



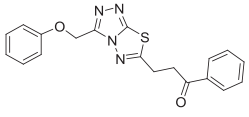
6-(4-Methoxyphenyl)-3-(2,3,5-trichlorophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**17**)



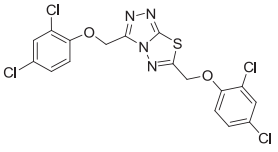
6-(4-Chlorophenyl)-3-(2,3,5-trichlorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**18**)



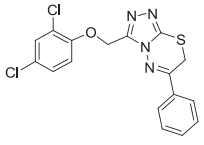
3-[2-(3,4,5-Trimethoxyphenyl)ethyl]-6-(4-fluorophenyl)-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (**19**)



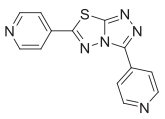
3-(Phenoxymethyl)-6-(3-oxo-3-phenylpropyl)-[1,2,4]-triazolo[3,4-*b*][1,3,4]-thiadiazole (**20**)



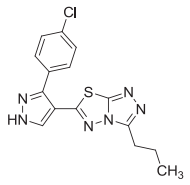
3,6-Bis((2,4-dichlorophenoxy)methyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**21**)



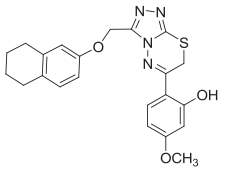
3-((2,4-Dichlorophenoxy)methyl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**22**)



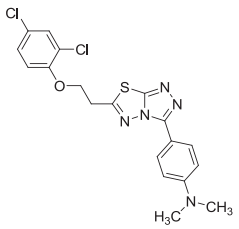
3,6-Di(pyridin-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**23**)



3-Propyl-6-(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**24**)



5-Methoxy-2-(3-((5,6,7,8-tetrahydronaphthalen-2-yloxy)methyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)phenol (**25**)



3-[4-(*N*,*N*-Dimethyl amino)phenyl]-6-[2-(2,4-dichlorophenoxy)ethyl]-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (**26**)

A series of dichlorofluorophenyl containing triazolothiadiazoles were reported by Karthikeyan and co-workers [50] and tested their antimicrobial efficacy using disc diffusion method. The antibacterial screening data revealed that few compounds were active against *S. aureus* and *E. coli* especially 3-(2,4-dichloro-5-fluorophenyl)-6-(4-chlorophenyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (**56**) exhibited good antibacterial activity against all tested bacterial strains almost equivalent to that of the standard drug Ciprofloxacin. The newly prepared compounds were also evaluated for their antifungal activity against *Aspergillus niger*, *Candida albicans*, *Aspergillus fumigatus*, *Penicillium marneffei* and *Trichophyton mentagrophytes* in DMSO by agar diffusion method. The antifungal screening data showed that several compounds exhibited good activity against *C. albicans* and *A. fumigatus* especially compounds (**56**) exhibited good antifungal activity against all tested fungal strains almost equivalent to that of the standard drug Griseofulvin. This enhanced activity may be attributed to the presence of chloro and fluoro groups on both the aryl rings at 3rd and 6th position of condensed nucleus.

The research group of Karegoudar [41] reported a series of new triazolothiadiazole and triazolothiadiazine derivatives and screened for their antibacterial activity against *E. coli*, *S. aureus*, *P. aeruginosa* and *K. pneumoniae* bacterial strains by serial plate dilution method. The newly prepared compounds were also screened for their antifungal activity against *Aspergillus flavus*, *A. fumigatus*, *P. marneffei* and *T. mentagrophytes* in DMSO by serial plate dilution method. The investigation of antimicrobial screening data revealed that all the tested compounds showed moderate to good inhibition. The good activity is attributed to the presence of pharmacologically active $-OCH_3$, 2,3-dichloro, 4-hydoxy-3-amide, 4-chloro, $-SCH_3$ groups attached to phenyl ring, pyridyl, bromopyridyl and aryloxy groups of the thiadiazole as shown by compounds (**57**) and (**58**).

Furthermore, in a continuation of their previous studies, Prasad and co-workers [62] reported some new triazolothiadiazoles bearing 4-methylthiobenzyl moiety and evaluated for antimicrobial activities. The investigation of the antibacterial and antifungal screening studies revealed that all the tested compounds showed moderate to good inhibition in DMSO. The good activity can be attributed to the presence of pharmacologically active groups like 2,3,4-trichloro, 4-methylthio, 2,4-dichloro-5-fluoro, which are directly attached to the phenyl ring of the triazole system, and the groups like 4-nitro, 4-fluoro, 2-nitro-4-

chloro, 2-trifluoromethyl, 4-chloro, 4-methyl which are directly attached to the arylfuryl ring as shown by 3-(4-(methylthio)benzyl)-6-(2,3,4-trichlorophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**59**).

Mathew et al. [51] reported a new series of conjugated heterocycles and a filter-paper disc-method was employed for the *in vitro* study of antibacterial and antifungal effects against *E. coli*, *P. aeruginosa*, *B. subtilis*, *S. aureus*, *A. niger* and *C. albicans*, respectively. The screening results evidenced that the electron-withdrawing group substituted on hetero-aromatic ring at the 6th position of triazolothiadiazole system enhanced the antimicrobial action of the tested compounds. Pyridine derivatives with 2-fluoro substitution (**60**) showed maximum inhibitory action against all the tested bacterial strains.

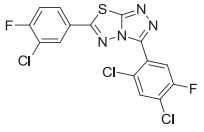
(4-*X*-Phenylsulfonyl)phenyl containing 6-amino-[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazines and [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-ones were synthesized by Almajan et al. [26]. The synthesized compounds were tested for their *in vitro* antibacterial activity against the Gram-positive (*E. faecalis* ATCC 29212; *S. aureus* ATCC 25923; *Staphylococcus epidermidis* ATCC 14990; *Bacillus cereus* ATCC 13061) and Gram-negative (*Acinetobacter baumanii* ATCC 19606; *Citrobacter freundii* ATCC 27853; *Enterobacter clocae* ATCC 49141; *E. coli* ATCC 25922; *P. aeruginosa* ATCC 9027) bacteria by using the broth dilution method for determination of MIC. Tetracycline and ampicillin were used as control drugs. The data generated from this study showed that compounds displayed low to moderate activity. The obtained results can be attributed to quite bulky structure of the tested compounds but they may be associated with the nature of tested bacterial species. The most active compound with triazolothiadiazine nucleus of this series is 3-[4-(phenylsulfonyl)phenyl]-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6(7*H*)-one (**61**) against *S. epidermidis*.

In a similar study, Kumar et al. [52] synthesized a novel series of clubbed isopropylthiazole derived triazolothiadiazoles and triazolothiadiazines and tested for antimicrobial activities. The antibacterial activity of the synthesized compounds was performed by broth dilution method [20,21] against the following standard bacterial strains; *S. aureus* (ATCC 11632), *Streptococcus faecalis* (ATCC 14506), *B. subtilis* (ATCC 60511), *K. pneumoniae* (ATCC 10031), *E. coli* and *P. aeruginosa* (ATCC 10145) and antifungal activity against Yeasts: *Saccharomyces cerevisiae* (ATCC 9763, Sc) and *Candida tropicalis* (ATCC 1369, CT), mould: *A. niger* (ATCC 6275). The prepared compounds exhibited interesting trends in structure–activity relationship (SAR) studies. The linkage between $-NH_2$ and $-SH$ groups depicted moderate antimicrobial activity whereas the aforementioned moieties linked through methylene spacer exhibited significant activity against both Gram-positive and Gram-negative strains. Interestingly, 3-(4-isopropylthiazol-2-yl)-6-(4-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**62**) demonstrated significant activity against tested bacterial and fungal species.

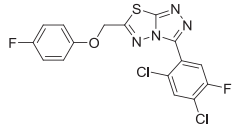
Aggarwal et al. [63] reported a series of novel nalidixic acid based triazolothiadiazole and triazolothiadiazine derivatives and screened for their antibacterial efficacy using broth dilution technique. Streptomycin drug was used as a standard. Compound (**63**) bearing chloro substituent at 2-position on aromatic ring showed maximum antimicrobial potency against all tested microorganisms which was comparable to the standard drug. This could be due to the inductive and mesomeric effect. The triazolothiadiazine derivatives were found to be less active as compared to the triazolothiadiazole series.

Prakash et al. [28] reported a series of dihydroindeno- and indeno[1,2-*e*][1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazines and explored their effect on *in vitro* growth of microorganism causing microbial infection. Antimicrobial results revealed that all the tested compounds possessed moderate to excellent antibacterial activity against both Gram-positive (*S. aureus*, *B. subtilis*) and Gram-negative bacteria (*E. coli*, *P. aeruginosa*). On the basis of zone of inhibition against test bacteria, most of the synthesized compounds showed excellent activity against *S. aureus* showing the maximum zone of inhibition >25.0 mm as compared with standard drug ciprofloxacin which showed the zone of inhibition of 26.6 mm against *S. aureus*. It should be noted that out of these compounds, 3-propyl-10,10*a*-dihydroindeno[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine (**64**) was found to be most potent member showing zone of inhibition even greater than the standard drug.

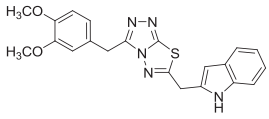
All the compounds were also tested for their *in vitro* antifungal activity against three fungal strains, namely, *A. niger*, *A. flavus* and *Penicillium* species through poisoned food method. Standard drug fluconazole was used for comparison with antifungal activity. From the careful comparison of the results, it has been revealed that mainly the 9-methylindeno[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**65**) showed excellent antifungal activity with >65% inhibition of mycelial growth against all the fungal strains.



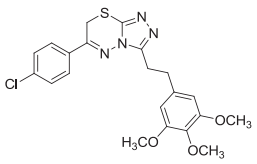
6-(3-Chloro-4-fluorophenyl)-3-(2,4-dichloro-5-fluorophenyl)1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (**27**)



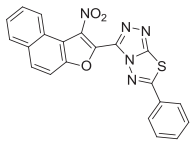
3-(2,4-Dichloro-5-fluorophenyl)-6-[(4-fluorophenoxy)methyl]1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (**28**)



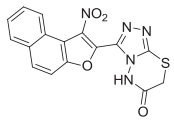
6-((1*H*-Indol-2-yl)methyl)-3-(3,4-dimethoxybenzyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**29**)



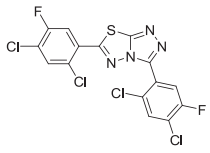
3-[2-(3,4,5-Trimethoxyphenyl)ethyl]-6-(4-chlorophenyl)-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (**30**)



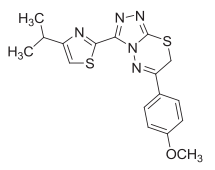
3-(1-Nitronaphtho[2,1-*b*]furan-2-yl)-6-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**31**)



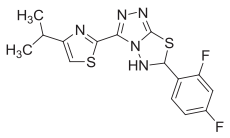
3-(1-Nitronaphtho[2,1-*b*]furan-2-yl)-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6(7*H*)-one (**32**)



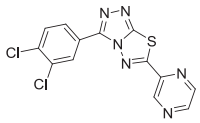
3,6-Bis(2,4-dichloro-5-fluorophenyl)-1,2,4-triazolo[3,4-*b*]1,3,4-thiadiazole (**33**)



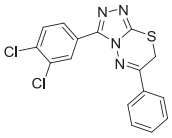
3-(4-Isopropylthiazol-2-yl)-6-(4-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**34**)



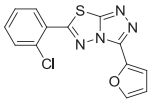
6-(2,4-Difluorophenyl)-3-(4-isopropylthiazol-2-yl)-5,6-dihydro-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazole (**35**)



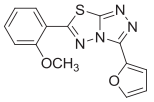
3-(3,4-Dichlorophenyl)-6-(pyrazin-2-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**36**)



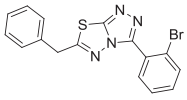
3-(3,4-Dichlorophenyl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(37)**



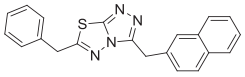
3-(2-Furanyl)-6-(2-chlorophenyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole **(38)**



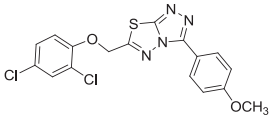
3-(2-Furanyl)-6-(2-methoxyphenyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole **(39)**



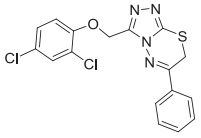
6-Benzyl-3-(2-bromophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **(40)**



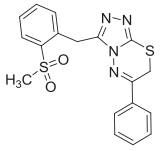
6-Benzyl-3-(naphthalen-2-ylmethyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **(41)**



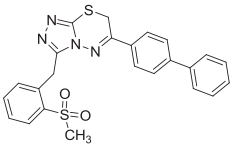
6-((2,4-Dichlorophenoxy)methyl)-3-(4-methoxyphenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **(42)**



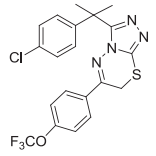
3-((2,4-Dichlorophenoxy)methyl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(43)**



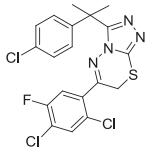
3-(2-(Methylsulfonyl)benzyl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(44)**



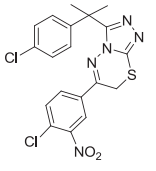
6-(Biphenyl-4-yl)-3-(2-(methylsulfonyl)benzyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(45)**



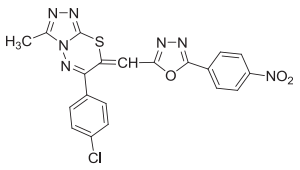
3-(2-(4-Chlorophenyl)propan-2-yl)-6-(4-(trifluoromethoxy)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(46)**



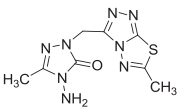
3-(2-(4-Chlorophenyl)propan-2-yl)-6-(2,4-dichloro-5-fluorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(47)**



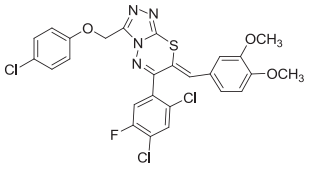
6-(4-Chloro-3-nitrophenyl)-3-(2-(4-chlorophenyl)propan-2-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(48)**



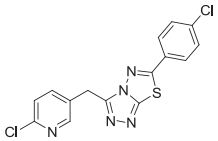
2-((6-(4-Chlorophenyl)-3-methyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-ylidene)methyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole **(49)**



4-Amino-3-methyl-1-((6-methyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)methyl)-1*H*-1,2,4-triazol-5(4*H*)-one **(50)**



(*Z*)-3-((4-Chlorophenoxy)methyl)-6-(2,4-dichloro-5-fluorophenyl)-7-(3,4-dimethoxybenzylidene)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(51)**



6-(4-Chlorophenyl)-3-((6-chloropyridin-3-yl)methyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **(52)**

Badr and Barwa [24] reported a series of triazolothiadiazoles and triazolothiadiazines derived from 5-nitro furoic acid and tested for their *in vitro* antibacterial activity against *S. aureus* (Gram-positive bacteria) and *E. coli* (Gram-negative bacteria). For comparison, ampicillin was used as a reference drug. All the synthesized compounds exhibited considerable activity against *S. aureus* and most of them are found to be as effective as reference drug. The obtained results revealed that antibacterial activity of the newly synthesized heterocyclic compounds, containing 1,2,4-triazole moiety fused with 1,3,4-thiadiazole ring depend on the basic skeleton of the molecule rather the substituents and all were found to be as effective as reference drug ampicillin. The representative example is 3-(5-nitrofuran-2-yl)-*N*-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-amine (**66**). Meanwhile, among triazolothiadiazine derivatives it was noticed that the activity relies upon the substituents rather the basic skeleton of the molecule. The compounds, bearing *p*-chlorophenyl moiety and *p*-bromophenyl moiety respectively at position 6 of the thiadiazine ring were found to be as effective as reference drug against *S. aureus*. The representative example is 6-(4-chlorophenyl)-3-(5-nitrofuran-2-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**67**). However, compounds bearing *p*-nitrophenyl moiety and *p*-methoxyphenyl moiety respectively, at position 6 of the thiadiazine ring exhibited moderate activity, while compound bearing unsubstituted phenyl moiety at position 6 of the thiadiazine ring showed weak activity.

Hussein et al. [46] reported 3,6-disubstituted-1,2,4-triazolothiadiazole derivatives and screened for their antibacterial activity. Results from the tested compounds showed that 6-(pyridin-3-yl)-3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**68**) exhibited higher antibacterial activity than ampicillin, used as a standard drug.

Sumangala et al. [58] reported a new series of 6-aryl-3-[4-(methylsulfonyl)benzyl]-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines and evaluated for their antimicrobial activity. Among the screened samples, compound (**69**) showed excellent antibacterial activity against *E. coli* which may be due to the presence of 2,4-dichlorophenyl group at C-6 position of thiadiazine. The antifungal activity of the derivatives has much better results for many of the compounds like (**70**). The significant activity of this compound may be due to the presence of 3-coumarinyl group at C-6 position of thiadiazine ring.

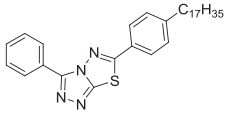
Puthiyapurayil et al. [59] reported a series of triazolothiadiazine derivatives and screened for their antimicrobial activity. The compound (**71**) showed comparatively very good activity against all bacterial strains. The good activity was may be due to the presence of pharmacologically active $-OCF_3$, fluorine, (highly electro negative) in the molecules, which increases the lipophilicity and affects the partitioning of molecules into membranes and facilitates hydrophobic interactions of the molecules with specific binding sites on either receptor or enzyme. Results showed that combination of triazolothiadiazine containing thioether linkage and presence of pharmacologically active fluorine, chlorine and $-OCF_3$ groups gave an enhanced biological activity against all microbial strains.

Moreover, new triazolothiadiazole derivatives showing considerable antibacterial efficacy have been reported by Hanif et al. [64]. Ciprofloxacin was used as a standard drug. Compound bearing

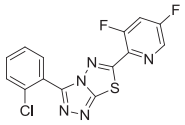
fluoro group on phenyl ring at position 6 exhibited significant activity as depicted by 6-(2,5-difluorophenyl)-3-(2,5-dimethoxybenzyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**72**). Overall, most of the tested compounds in both the series expressed excellent antibacterial activity as compared to standard drug ciprofloxacin.

Recently, the research group of Jubie [65] reported some novel stearic acid analogs such as 6-(heptadecyl)-3-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole and tested for their antibacterial potential. The results of preliminary antimicrobial testing of compounds revealed that (**73**) showed pronounced antibacterial and antifungal activities against *B. subtilis*, *P. aeruginosa* and *C. albicans*, respectively. This good inhibition may be attributed to the presence of an alkyl chain at position 6 of the condensed skeleton.

Very recently, in a continuation of their previous studies [64], the research groups of Rama and Lee [66] have reported several pyridyl- and thiophenyl-substituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives and screened for their antibacterial activity. Almost all the tested compounds were potent against four different strains of bacteria when compared with that of reference drug ciprofloxacin. In particular, compound (**74**) was found to possess the most potent activity (MIC: 0.156 μg/mL) against all the tested strains. The least activity was shown by compound containing methoxy group on phenyl ring at position 3 and thiophen-2-yl methyl group at position 6.



6-(4-Heptadecylphenyl)-3-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**73**)



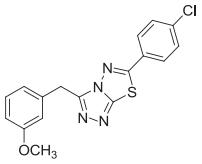
3-(2-Chlorophenyl)-6-(3,5-difluoropyridin-2-yl)-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazole (**74**)

3.13. Antioxidant activity

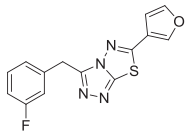
Sunil et al. [33] reported two triazolothiadiazoles 6-[3-(4-fluorophenyl)-1*H*-pyrazol-4-yl]-3-[(2-naphthyloxy)methyl][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (FPNT) and 6-[3-(4-chlororophenyl)-1*H*-pyrazol-4-yl]-3-[(phenyloxy)methyl][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (CPPT) and investigated the *in vitro* antioxidant property by spectrophotometric DPPH and ABTS radical scavenging methods as well as by lipid peroxide assay. The screening results proved that FPNT (**4**) possess remarkable antioxidant potential.

Recently, Hanif et al. [64] reported various triazolothiadiazole derivatives possessing methoxybenzyl and methoxyphenethyl groups and evaluated for their antioxidant potential. The triazolothiadiazole class of compounds was found to be significantly active against superoxide anion radical. The screening results indicated that 6-(4-chlorophenyl)-3-(3-methoxybenzyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**75**) possess significant antioxidant potential with an IC_{50} value of 9.04 μM at such a low concentration, even lower than standard. The activity of (**75**) is enhanced in this class due to the presence of methoxy and chloro groups on phenyl rings at 3rd and 6th positions of condensed skeleton, respectively.

More recently, Rafiq et al. [67] have reported a new series of triazolothiadiazole derivatives and screened for their antioxidant potential. In the DPPH free radical scavenging assay, *n*-propyl gallate with an IC_{50} value of 40.8 μM was used as a reference drug. Compound (**76**) with an IC_{50} value of 31.54 μM was the most active compound of the series. Compound (**76**) has 3-fluorobenzyl group as substituent attached with triazolothiadiazole ring, showing greater electron donating ability. Compound with 3-methoxyphenyl group as substituent was found to be the least active.



6-(4-Chlorophenyl)-3-(3-methoxybenzyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**75**)



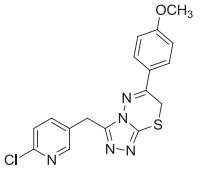
3-(3-Fluorobenzyl)-6-(furan-3-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**76**)

3.14. Antidepressant activity

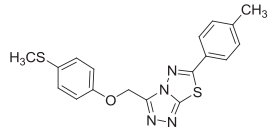
Recently, Jubie et al. [65] synthesized 6-(heptadecyl)-3-phenyl-[1,2,4]triazolo[3,4-*b*]-1,3,4-thiadiazole and screened for antidepressant activity in swiss albino mice by forced swim test (FST). The compound (**73**) showed significant antidepressant activity.

3.15. Urease inhibitors

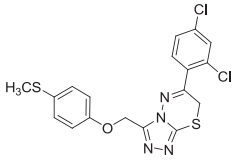
Hanif et al. [64] have reported a series of triazolothiadiazoles and evaluated for their urease inhibition potential. Almost all the compounds showed remarkable urease inhibition more than the standard inhibitor (thiourea) determined through the standard urease assay. 3-(2,5-Dimethoxybenzyl)-6-*p*-tolyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**77**) was found to be the promising candidate for urease inhibition.



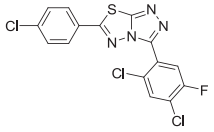
3-((6-Chloropyridin-3-yl)methyl)-6-(4-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**53**)



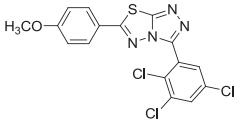
3-((4-(Methylthio)phenoxy)methyl)-6-*p*-tolyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**54**)



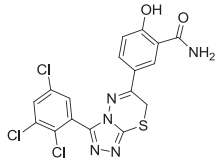
6-(2,4-Dichlorophenyl)-3-((4-(methylthio)phenoxy)methyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**55**)



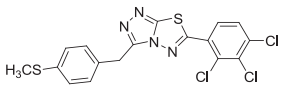
3-(2,4-Dichloro-5-fluorophenyl)-6-(4-chlorophenyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole (**56**)



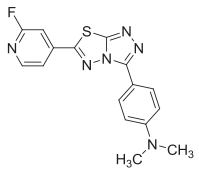
6-(4-Methoxyphenyl)-3-(2,3,5-trichlorophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**57**)



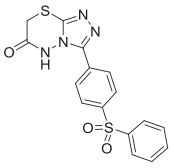
6-(3-Amido-4-hydroxyphenyl)-3-(2,3,5-trichlorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (**58**)



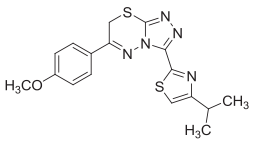
3-(4-(Methylthio)benzyl)-6-(2,3,4-trichlorophenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **(59)**



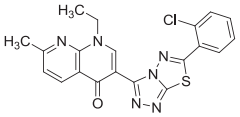
3-(4-(*N*,*N*-Dimethylamino)phenyl)-6-(2-fluoro-pyridin-4-yl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole **(60)**



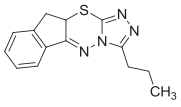
3-[4-(Phenylsulfonyl)phenyl]-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6(7*H*)-one **(61)**



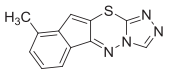
3-(4-Isopropylthiazol-2-yl)-6-(4-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(62)**



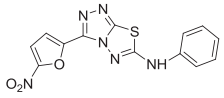
3-{6-(2-Chlorophenyl)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl}-1-ethyl-7-methyl-1,8-naphthyridin-4(1*H*)-one **(63)**



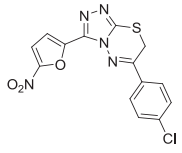
3-Propyl-10,10*a*-dihydroindeno[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(64)**



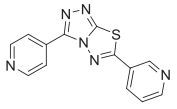
9-Methylindeno[1,2-*e*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(65)**



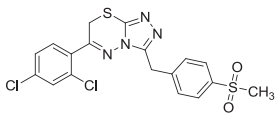
3-(5-Nitrofuran-2-yl)-*N*-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-amine **(66)**



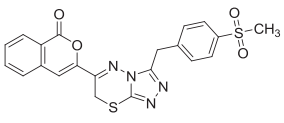
6-(4-Chlorophenyl)-3-(5-nitrofuran-2-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(67)**



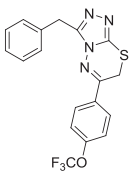
6-(Pyridin-3-yl)-3-(pyridin-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **(68)**



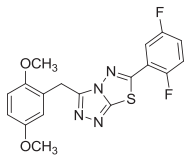
6-(2,4-Dichlorophenyl)-3-[4-(methylsulfonyl)benzyl]-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(69)**



3-{3-[4-(Methylsulfonyl)benzyl]-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl}-1*H*-isochromen-1-one **(70)**

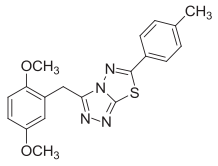


3-(2-Phenylpropan-2-yl)-6-[4-(trifluoromethoxy)phenyl]-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(71)**

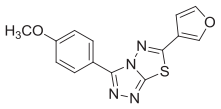


6-(2,5-Difluorophenyl)-3-(2,5-dimethoxybenzyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **(72)**

Recently, Rafiq et al. [67] have demonstrated the synthesis of a series of triazolothiadiazole derivatives and screened for their urease inhibitory activity. Almost all the compounds showed excellent urease inhibition more than the reference thiourea. Compound (**78**) with an IC_{50} value of 0.764 ± 0.03 and K_i value of 0.450 ± 0.06 μM was the most potent compound of the series. Most active compound (**78**) has 4-methoxyphenyl group attached with rigid triazolothiadiazole moiety. The replacement of methoxy group with chloro group leads to the decrease in inhibitory activity.



3-(2,5-Dimethoxybenzyl)-6-*p*-tolyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **(77)**



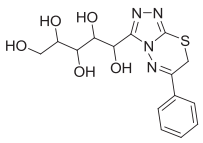
6-(Furan-3-yl)-3-(4-methoxyphenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **(78)**

3.16. Plant growth regulators

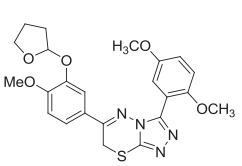
Jin et al. [68] synthesized a series of novel 6-aryl-3-(D-galactopentitol-1-yl)-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines and investigated the effects of these compounds on sprouting of wheat and radish seeds. From the results, it was interesting to note that 1-(6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)pentane-1,2,3,4,5-pentaol (**79**) showed inhibitory activities toward the growth of the dicotyledon (radish) at two concentration levels, but under the same conditions it expressed stimulative activities toward the growth of the monocotyledon (wheat). It has a good level of activity and is worthy of further study to establish a relationship between structure and activity.

3.17. PDE4 inhibitors

Thomas and co-workers [14] showcased a series of substituted 7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine and evaluated as PDE4 inhibitors. Several analogs were also explored with varying substitutions on the phenyl ring attached to the C-3 position of the 1,2,4-triazole ring system. Substitutions included methoxy, fluoro, chloro and trifluoromethyl groups on the *ortho*, *meta* and *para* positions of the phenyl ring. Analysis of these analogs confirmed that various substitutions at one of the *ortho* positions were necessary to maintain potent PDE4A inhibition. From the screening results, compound (**80**) was identified as highly potent PDE4 inhibitor.



1-(6-Phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)pentane-1,2,3,4,5-pentaol **(79)**



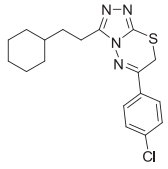
3-(2,5-Dimethoxyphenyl)-6-(4-methoxy-3-(tetrahydrofuran-2-yloxy)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **(80)**

3.18. Anticandidal activity

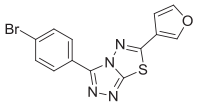
Altıntop et al. [69] synthesized several triazolothiadiazine derivatives and tested *in vitro* against *Candida* species and compared with ketoconazole. The compound bearing cyclohexyl moiety and *p*-chlorophenyl substituent on triazolothiadiazine ring (**81**) was found to be the most potent derivative against *C. albicans* (ATCC 90028), *Candida parapsilosis*, *C. albicans* (NRRL Y-12983) and *Candida glabrata*. It is apparent that there is a positive correlation between anticandidal activity and two functional moieties, namely cycloaliphatic group and *p*-chlorophenyl substituent on triazolothiadiazine ring. It can be attributed to $+\pi$ effect of chloro substituent and cyclohexyl group.

3.19. Alkaline phosphatase inhibition

Rafiq et al. [67] have reported a new series of triazolothiadiazole derivatives and screened for their alkaline phosphatase inhibitory activity. Potassium dihydrogen phosphate was used as a standard drug. Compound (**82**) with an IC_{50} value of 0.061 ± 0.001 μM was the most active compound of the series. It has 4-bromophenyl group as substituent attached with triaozolothiadiazole ring which may be responsible for the highest inhibition.



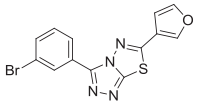
3-[2-Cyclohexylethyl]-6-(4-chlorophenyl)-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine (**81**)



3-(4-Bromophenyl)-6-(furan-3-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**82**)

3.20. Acetylcholinesterase inhibition

The research groups of Rama and Seo [67] have described the synthesis of a new series of triazolothiadiazoles and tested their acetylcholinesterase inhibitory activity. Neostigmine methyl sulfate with an IC_{50} value of 69.1 ± 8.2 μM and Donepezil with an IC_{50} value of 0.021 ± 0.004 μM were used as reference drugs. Almost all of the compounds showed more activity than Neostigmine methyl sulfate. Most active compound (**83**) with an IC_{50} value of 0.344 ± 0.012 μM showed comparable activity to that of Donepezil reference drug. All other compounds showed IC_{50} values ranging from 1.78 ± 0.16 to 78.21 ± 0.43 μM. It is clear from the results that acetylcholinesterase inhibition activity is highly dependent on substituents present on phenyl ring attached at position 3. Most active compound (**83**) has 3-bromo group as substituent on aryl ring.



3-(3-Bromophenyl)-6-(furan-3-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**83**)

4. Conclusions

In summary, this review article provided a compact overview of the synthetic methodologies leading to the triazolothiadiazole and triazolothiadiazine analogs as well as the tolerance of these derivatives against various biological activities. This study also revealed that these compounds are the central structural motifs of biologically interesting molecules which are of high interest to the pharmaceutical industry. The activity profile of these scaffolds relies upon the substitution on the parent skeleton of both heterocycles and the indicated pharmacophores can be synthesized based on the SAR analysis for further exploration of biological efficacy. The potential biological activities such as anticancer, antitumor, anti-inflammatory, analgesic, anti-HIV, antidepressant, anticandidal, anthelmintic, anticonvulsant, antimicrobial, antioxidant, antitubercular, molluscicidal and cytotoxicity have been exhibited by these analogs and comprehensively showcased in this review. These derivatives have also been used as plant growth regulators and various enzyme inhibitors such as PDE4, urease, alkaline phosphatase and acetylcholinesterase and have witnessed important progress in recent years. In view of the increasing significance of triazolothiadiazole and triazolothiadiazine scaffolds, we speculate that the design and exciting developments of novel synthetic methodologies combined with potential biological profile will provide a future insight in this rapidly evolving research area.

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