Review Article

Chemical Review and Letters
journal homepage: www.chemrevlett.com
ISSN (online): 2645-4947 (print) 2676-7279

Recent Advances in Bioactive 1,5-Benzothiazepine-based Compounds: Highlights from 2012 to 2022

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ARTICLE INFO

Article history:
Received 28 November 2023
Received in revised form 15 December 2023
Accepted 16 December 2023
Available online 20 December 2023

Keywords:
1,5-benzothiazepine
biological activities
enzyme inhibitors
antitumor
antimicrobial
central nervous system

ABSTRACT

1,5-benzothiazepine has proven to be one of the most attractive and useful synthetic building blocks for clinical drugs such as diltiazem, quetiapine, thiazesim, and clentiazem. Benothiazepin generally is produced from the reaction of 2-aminothiophenols on α, and β-unsaturated carbonyl compounds. Nowadays, the replacement of toxic catalysts with green reactions especially solvent-free approaches, and microwave irradiation in place of conventional heating have been developed. The new green reaction in the synthesis of 1,5- benzothiazepine The heterocycles containing this moiety widely exist in various drugs with broad spectra of biological activities, mainly central nervous system, antimicrobial, antitumor, and enzyme inhibitors. The current minireview envisioned highlighting some recent and remarkable examples of This minireview mainly focuses on the green synthesis of 1,5-benzothiazepine diverse pharmacological properties associated with 1,5-benzothiazepine structure and covers the most relevant and recent references from 2012 to 2022.

1. Introduction

1,5-benzothiazepine is a bicyclic heteroaromatic compound with a benzene structure attached to the seven-membered ring containing nitrogen and sulfur (Fig. 1). 1,5-Benzothiazepine is a versatile pharmacophore extremely found in drug molecules. diltiazem and clentiazem, two well-known drugs, are prescribed as angina-relieving calcium channel blockers and coronary vasodilators to treat arrhythmias, angina pectoris, and other cardiac disorders [1]. Thiazesim and quetiapine fumarate are another class of 1,5-benzothiazepine derivatives as psychotropic agents in treating C.N.S. disorders [2]. Various interesting biological properties have also been explored, including anticonvulsants [3], anti-HIV [4], enzyme inhibitors [5], and antibacterial activities [6].

Their potential as drug molecules led scientists to develop novel, mild, green, and highly efficient synthetic routes for their synthesis of this molecule. A general method to construct 1,5-benzothiazepines is *via* nucleophilic attack of substituted 2-aminothiophenols on α,β-unsaturated carbonyl compounds that mostly result in poor yields or mixtures (Fig. 2) [7].

Due to the importance of this molecule, several reviews were published earlier with a focus on chemistry and synthetic routes [8] or a particular activity of the benzothiazepine derivatives [9-10]. This minireview mainly focuses on the green synthesis of 1,5-benzothiazepine diverse pharmacological properties associated with 1,5-benzothiazepine structure and covers the most relevant and recent references from 2012 onward.

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https://doi.org/ 10.22034/CRL.2023.427609.1262

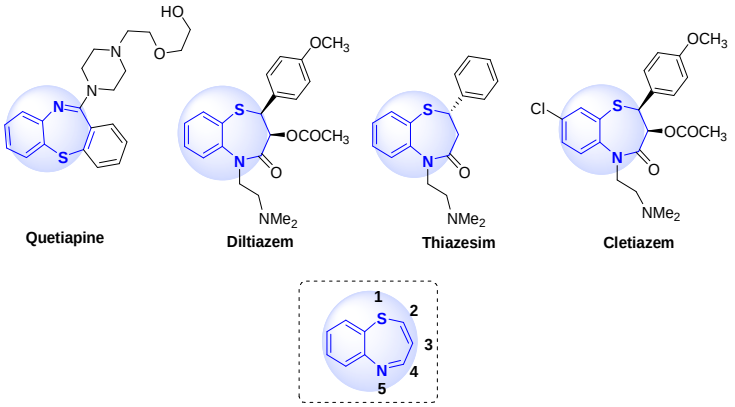


Fig. 1. Drugs with 1,5-benzothiazepine core

This collected data may be valuable for medicinal chemists to design novel derivatives with good and new biological activities.

2. Recent green-approaches to 1,5- benzothiazepine derivatives

The development of green approaches for example solvent-free, echo-friendly, applying microwave irradiation or ultrasound assisting, and catalyst-free reactions not only reduces the waste but also increases yield and shortened the time.

Kotalwar *et al.* reported an eco-friendly approach for the synthesis of biologically relevant 2,3-dihydro-1,5-benzothiazepines in glycerol under microwave irradiation at 120°C for 3-4 minutes to afford the final compounds in good to excellent yields [11]. Yadav *et al.* in 2019 used a similar route without any catalysts [12]. In 2012, Raval *et. al* applied an environmentally benign procedure under microwave irradiation to synthesize a variety of 4-methyl-N-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)-2-substituted phenyl- 2,3-dihydrobenzo [b][1,4]thiazepine-3-carboxamide compounds from 2-arylidene-3-oxo-N-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)butanamide which the structure and biological effects will be discussed in next section [13].

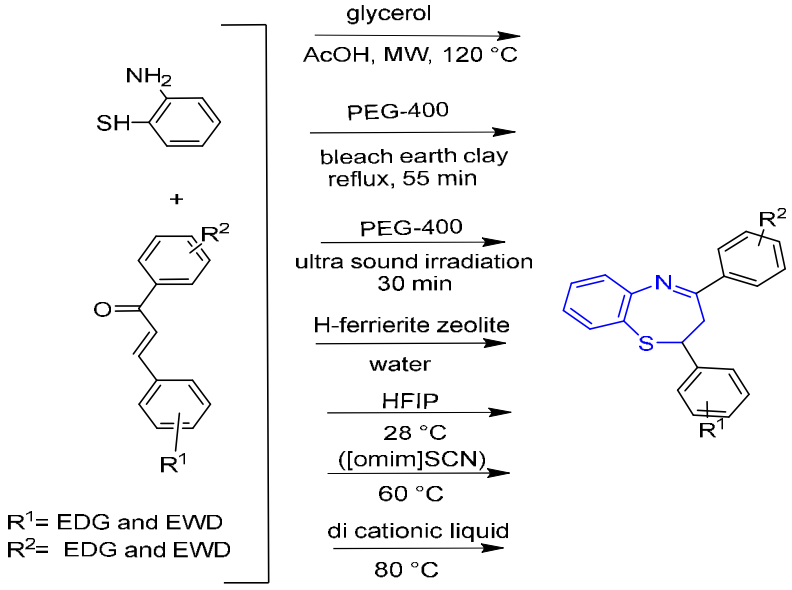


Fig. 2. Green synthetic routes to 1,5-benzothiazepines

In 2022, Haroun *et al.* synthesized 1,5-benzothiazepine derivatives using a green PEG-400 solvent in the presence of bleaching clay in a short time and good yield [14].

Applying polyethylene glycol PEG-400 as a medium and promoter followed by ultrasound irradiation was reported by Devkate as a green method in the synthesis of 1,5-benzothiazepine [15]. H-ferrierite zeolite is another effective and reusable heterogeneous catalyst which applied in the synthesis of 1,5-benzothiazepine under solvent-free conditions [16]. 2,3-Dihydro-1,5-benzothiazepines have been obtained through a domino Michael addition/ in situ cyclization at room temperature

using hexafluoro 2-propanol (HFIP) as an efficient neutral medium [17]. Sharifi *et al.* developed thia-Michael addition of thiophenols to α,β-unsaturated carbonyl compounds in 1-octyl-3-methyl imidazolium thiocyanate ([omim]SCN) as an environmentally ionic liquid medium without any catalysts [18]. Using an environmentally friendly di-cationic liquid as a solvent resulted in the synthesis of 1,5-benzothiazapines in excellent yields (Fig. 2) [19].

3. The biological significance of 1,5-benzothiazepine-containing analogs

1,5-benzothiazepine and its derivatives are vital pharmacophores in medicinal chemistry and have featured in several clinically used drugs. Studies in the last decade articles revealed that 1,5-benzothiazepine analogs tolerate a broad spectrum of pharmacological activities, which can be classified into the following categories:

3.1 Anticancer activity

In 2021, Wang *et al.* designed new series of diaryl benzo[*b*][1,4]thiazepine derivatives. Among the 36 compounds, 2-(2-chlorophenyl)-4-(3,4,5-trimethoxyphenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepine1inhibited the growth of several cancer cell lines (IC_{50} values= 1.48 μM for HeLa, 1.47 μM for MCF-7, 1.52 μM for HT29, and 1.94 μM for A549). The results of the flow cytometry assay revealed this compound could induce mitotic catastrophe and the death of living cancer cells [20]. Recently this group developed their research on this scaffold to evaluate the inhibitory effect for breast cancer. They assessed the M.T.T. for some of the selective compounds to investigate the accuracy of the in silico studies. The M.T.T. assay confirmed the modeling outcomes. As expected, compound (*E*)-2,3-dihydro-4-(4-methoxyphenyl)-2-(naphthalene-3-yl)benzo[*b*][1,4]thiazepine 2, the best calculated anticancer properties, exposes the best inhibition against breast cancer cell line *in vitro* [21]. In 2012, Ameta *et al.* reported the synthesis of benzothiazepine 3 under microwave irradiation. These compounds inhibited the growth of the breast cancer cell line (MDA-MB-435) as compared to adriamycin as the reference drug (Fig. 3) [22]. Fluorinated-1,5-benzothiazepines were synthesized and evaluated against four human cancer cell lines, namely lung (A549), breast (MCF-7), liver (HEPG2), and prostate (PC-3). Compound 4 exhibited good activity with GI_{50}<10 μg/mL against all four human cancer cell lines compared to the standard drug adriamycin (Fig. 3) [23]. M.T.T. assay-based cell line of compound 5 showed potential anticancer activities against prostate cancer (DU145), breast cancer (MCF7), and colon cancer cell lines (HT29)(IC_{50} values of 16 μg/mL, 27 μg/mL, and 28 μg/mL respectively) [24]

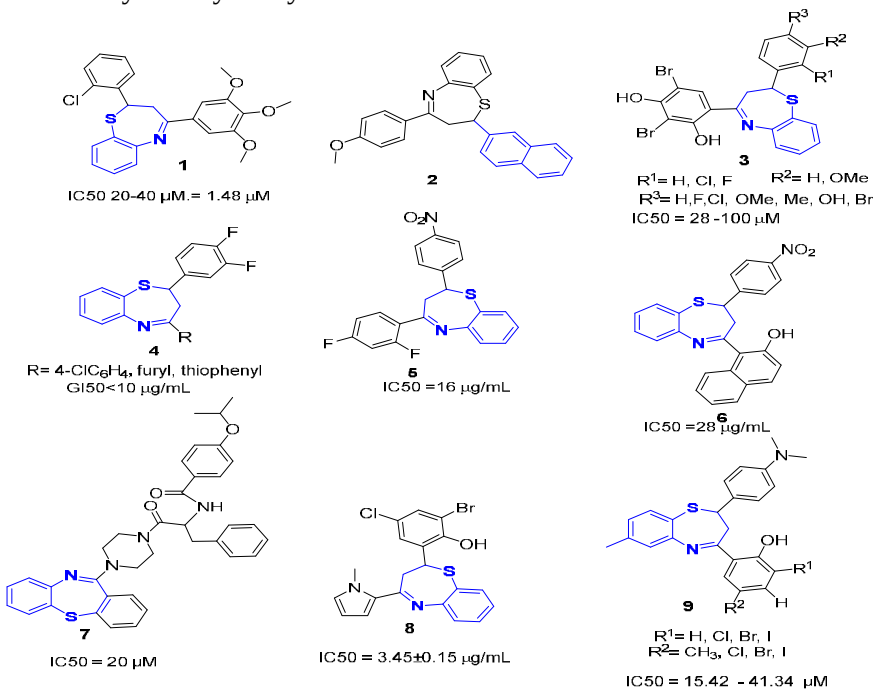
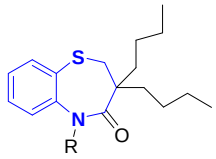


Fig. 3. Structures of benzo[*b*][1,4]thiazepine analogs with potential anticancer activity

In 2022, Borra and his team synthesized 2,3-dihydro-2-substituted-4(naphthalene-2-ol)-yl-1,5-benzothiazepines and screened their cytotoxicity. They discovered that compound 6 with a nitrophenyl moiety in its structure was the most active against the same cell lines, MCF-7, DU-145, and HT29 cell lines (IC_{50} values of μ28 g/mL, 27

μg/mL, and 16 μg/mL respectively) [25].In 2017, Gudisela and colleagues focused on the synthesis and anticancer evaluation of novel compounds using 1,5-benzothiazepine structures like quetiapine and amino acids as starting materials [26]. The anticancer study of product 7 was performed *in vitro* against three different cancer cells; human chronic myeloid leukemia cells (K562), human colon carcinoma cells (Colo-205), and human breast cancer cell line (MDA-MB 231). The IC_{50} values proved that synthesized compound 7 had shown desirable anticancer activity. Pyrrole appended-1,5-benzothiazepines 8 exhibited significant cytotoxicity at ED_{50} values 3.45±0.15 μg/mL using Brine shrimp lethality assay (Fig.3) [27]. Haroun *et al.* utilized a novel catalyst based on bleaching clay and PEG-400 in the cyclization of α, β-unsaturated carbonyl compounds with benzothiazepine to obtain hybrid 9. The cytotoxic activity of synthetic compounds against liver cancer cell lines was examined. The halogenated phenyl substitution on the second position of benzothiazepine explored more activity [14] (Fig. 3).

The ability of angiogenesis is a suitable method for tumor treatment, then researchers have tried to design novel compounds with antiangiogenic activity. Deepu *et al.* developed an efficient synthetic pathway to access 1, 5-benzodiazepine-4 (5H)-ones 10 with antiangiogenic and antioxidant properties [28] (Fig.4).



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R= C_2H_5, n-Butyl, isobutyl, isopropyl urea, 1-propylpiperidine

Fig. 4. 1, 5-benzothiazepin-4(5H)-ones as antiangiogenic agent

3.2 Anticonvulsant/CNS depressant activity

In all neurodegenerative diseases, deregulation of the intracellular [Ca^{2+}] occurs [29]. Calcium signaling that is likely caused by changes in the concentration of calcium ion [Ca^{2+}] in various subcellular compartments of neurons led to oxidative damage [30-31].

Benzothiazepine is a compound that interferes with the mitochondrial Na^{+}/Ca^{2+} exchange system. This compound, CGP37157, is a good neuroprotector [32]. It also exhibited 20-fold higher blocking activity of the mitochondrial sodium/calcium exchanger than the previously studied ligands [33–36] (Fig. 5).

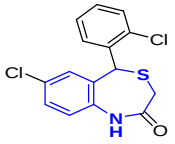

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Fig. 5. Structure of CGP37157

Chaudhri synthesized 1-[4-methyl-2-substitutedphenyl-2,5-dihydro-1,5-benzothiazepin-3-yl]-ethylidene-hydrazine derivatives 12 and screened anticonvulsant activity of leads. Among the products, the chloro derivative was the most potent [37]. In 2020, Parjane *et al.* synthesized 2-(2-phenyldiazenyl)-5-4-phenylbenzo[*b*][1,4]thiazepin-2-yl)phenol derivatives 13 and evaluated the *in-vivo* anticonvulsant activity by the M.E.S. model in mice. They explored that compounds with an electron-withdrawing group on benzothiazole had increased activity compared to compounds with an electron-releasing group (Fig. 6) [38]. In 2017, Malik applied green chemistry and microwave irradiation to the synthesis of 2-aryl/heteroaryl substituted-4-(naphthalene-2-ol)-yl-2, 3-dihydro-1, 5-benzothiazepines 14 with anticonvulsant and C.N.S. depressant activities [39]. A simple microwave approach was applied in the synthesis of indole-based benzothiazepines. The C.N.S. depressant activity of compound 15 was analyzed compared to diazepam as a reference, and different dosages of synthesized compounds were used and revealed good activity. The anticonvulsant assay and also P.T.Z. the test was satisfactory. Molecular docking data clarified that the product anticonvulsant activity could stem from being a GABA-A receptor agonist [40] (Fig.6).

3.3.Antimicrobial activity

1,5-benzothiazepine derivatives 16 obtained from the reaction of isobutyl chalcones with 2-amino thiophenol and explored antimicrobial activities. The products with halogen atoms, especially fluorine, and chlorine, exhibited superior antimicrobial activity compared to the standard drugs amoxicillin and fluconazole (MIC= 0.4-

3.2 μg/ml) [41]. Gaikwad synthesized benzothiazepine hybrids 17 through a three-step reaction. They applied a catalytic amount of zinc chloride for the acetylation of substituted α-naphthol. Then, the acetylated compound was refluxed with an aromatic aldehyde in ethanol and potassium hydroxide to obtain 2,4-substituted-1,5-substituted-benzothiazepine 17. All the targets showed good antimicrobial and antifungal activities [42]. The heterocycle with aryl sulfonate moiety is known to exhibit marked antimicrobial activity. 2-(-3-benzoylbenzo[*b*] [1,4] thiazepin-2-yl)phenyl 4- methylbenzene sulfonate 18 was one of the targets with a good antimicrobial outcome that was designed by Kendre and coworkers (Fig. 7) [43]. 2-(2,4-dichlorophenyl)-4-(4-chlorophenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepine 19 can be used as a potent antifungal agent against candida albicans, Aspergillus niger and Aspergillus flavus [44]. Kendre *et al*. synthesized 2, 4-(substituted-hydroxy phenyl)-2, 3-dihydro- 1, 5-benzothiazepines 20 in the presence of lanthanum nitrate as a catalyst and evaluated their antibacterial activities. Most of the compounds showed significant activity [45]. Antibacterial activity data revealed that the bis-1, 5-benzothiazepines compound 21 prepared from bis-chalcone precursors in the presence of piperidine in good yield. The compounds, including 4-chlorophenyl, 4-methoxyphenyl, and furan substituents have exhibited significant activities against both gram-positive and gram-negative bacteria [46]. In 2014, Kumar *et al.* synthesized the series of 1, 4-benzothiazepine 22 and 23 with moderate to good antibacterial activity (Fig. 7) [47].

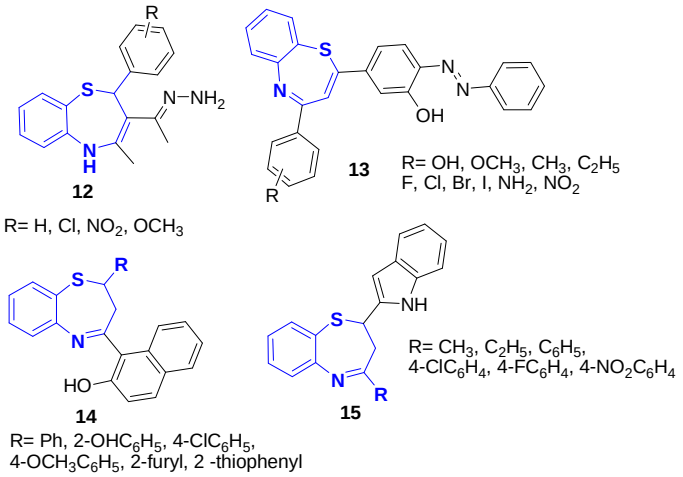

Fig. 6. 1,5- benzodiazepine derivatives with anticonvulsant activity

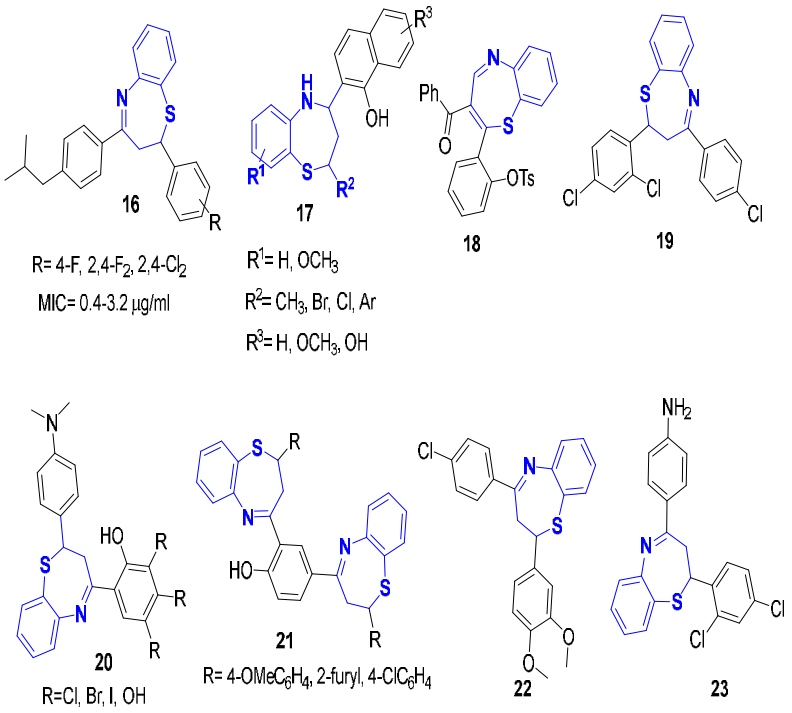

Fig. 7. Structures of benzo[*b*][1,4]thiazepine analogs with potential antimicrobial activity

Tetralone-based benzothiazepine derivatives 24 showed antibacterial activity (M.I.C. values 0.078-0.337mg/mL) [48]. 11-*p*-substituted-phenyl-12-phenyl-11*a*,12-dihydro-11*H*-indeno[2,1-*c*][1,5]benzothiazepines 25indicated antibacterial activities (MIC = 0.026-0.11 µg/mL) (Fig. 8) [49].

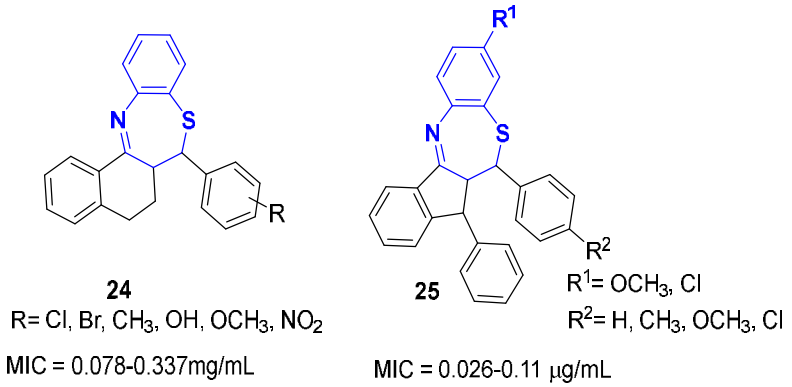

Fig. 8. Structures tetralone-based benzothiazepine analogs with potential antibacterial activity.

In 2017 Patel Navin and colleagues intended to synthesize antimicrobial and antifungal compounds containing benzothiazepine and 1, 3, 4-oxadiazole core 26. Antibacterial, antifungal, and antiprotozoal activities were analyzed *in vitro* against several gram-positive and negative bacteria, fungal, and protozoal species. ampicillin, chloramphenicol, and griseofulvin were picked as standards for antimicrobial activity. The biological activity of the compounds relies on electron-withdrawing or electron-donating substitutes on aryl rings at 1,3,4-oxadiazole moiety. Also, the presence of thiophene, pyridine, and furan at the benzothiazepine ring is determinative, and all targets showed good antimicrobial activity (MIC= 62.5–100 µg/mL) [50]. Raval *et al.*mentioned a practical microwave-assisted method to synthesize 4-methyl-*N*-(4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl)-2-substituted-phenyl-2,3-dihydrobenzo [*b*][1,4]thiazepine-3-carboxamide compounds 27 in 2012. As this reaction has a polar transition state, the ease of molecular polarization happens by microwave irradiation and results in a faster and high-yield reaction. The antibacterial study was carried out *in vitro*. The minimum

inhibition concentration (M.I.C.) was evaluated for different derivatives and compared with reference compounds like ampicillin, amoxicillin, penicillin, and fluconazole. The antimicrobial property was examined against gram-positive and gram-negative. The reported M.I.C. values for the synthesized benzothiazepines were impressive but lower than standard drug values [13].2-Naphtofuran moiety on the 2-position of benzothiazepine led to an increase in antimicrobial activities. The best results have been shown in compound 28 with the electron-donating group on phenyl substituent [51].

Pyrazine is an important heterocyclic compound with various biological properties [52-53]. Shaik *et al.* designed new scaffolds based on the conjugation of pyrazine and benzothiazepine from the reaction of chalcone precursor and 2-amino thiophenol. Biological evaluation of targets showed that among twenty synthetic benzothiazepines, compounds containing chloride group on phenyl group (compound 29) had significant antimicrobial activity (MIC=19.01 μM) [54]. Kumara Prasad reported the synthesis and antibacterial evaluation of substituted 2,3-dihydro-2-phenyl-4-(pyrazin-2-yl)-1,5-benzothiazepine 30. The synthetic compounds revealed good activity against gram-positive and negative bacteria compared to ofloxacin and fluconazole as standard (Fig. 9) [55]. The biological results of synthetic 2,3-dihydro-1,5-benzothiazepine derivatives 31 exhibited that derivatives with substituents on the para position of phenyl had notable antibacterial activity as well as penicillin (Fig. 9) [56].

The antimicrobial activity of pyrrole appended-1,5-benzothiazepine 32 was evaluated using the agar well diffusion assay method (MIC= 4.17 μg/mL) [27].2,3-dihydro-benzo[*b*][1,5] thiazepine bearing 2-chloro-6-substituted quinoline-3-yl 33 possessed moderate antimicrobial activities (Fig. 9) [57]. 1-(3-methyldibenzo[*b,f*][1,2,4]triazolo[4,3-*d*][1,4]thiazepin-6-yl)ethanone 34 was synthesized from benzothiazepinone derivatives and exhibited promising antifungal and antibacterial activities against *E. coli*, *Enterobacter cloacae*, *S. aureus* and antifungal screening against *Candida albicans* and *Fusarium* (Fig. 9) [58].

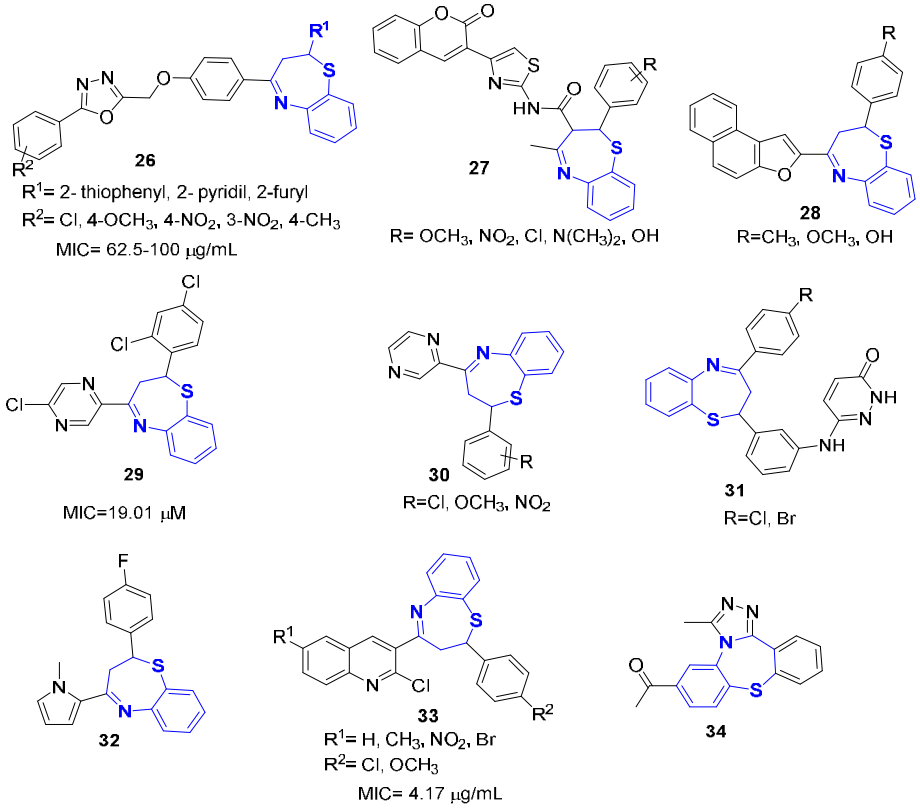

Fig. 9. Structure of heterocycle-1,5-benzothiazepine hybrids with antimicrobial activity

3.4.Antiviral activity

Frimayanti *et al.* performed *in silico* study of mean molecular docking and molecular dynamic simulation for twelve chalcone-based-1,5-benzothiazepines as a potential agent against the Zika virus [59]. Of the twelve compounds, 35 and 36 were the best inhibitors, with binding free energy values of -4.6490 and -4.9291 kcal/mol, respectively (Fig. 10).

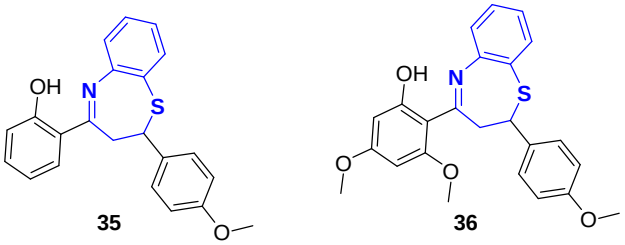

Fig. 10. Diaryl-1,5-benzotiazepine with anti-Zika virus activity

The tobacco mosaic virus (TMV) is a widespread plant pathogen that infects several crops, including tobacco, tomato, cucumber, etc. [60]. The synthetic compound 37 exhibited antiviral activity against the tobacco mosaic virus (EC_{50}= 352.2 μM) (Fig. 11) [61].

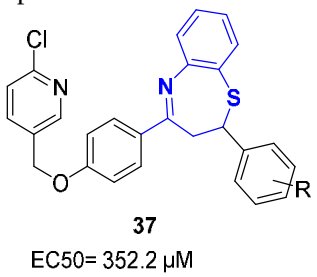

Fig. 11. Diaryl-1,5-benzotiazepine as anti-TMVagent

3.5.Enzyme inhibitor activity

The reaction of α,β-unsaturated ketones such as cholest-5-en-7-one with 2-amino thiophenol in the presence of acetic acid as catalyst in dimethylformamide (DMF) under ultrasonic irradiation afforded the corresponding steroidal [5,7-*bc*]-2′,3′-dihydro-1′,5′-benzothiazepines 38 with anticholinesterase activity (IC_{50}= 0.31 ± 0.1 μM) (Fig. 12) [62].

2,3-dihydro-2-(thiophen-2-yl)benzo[*b*][1,4]thiazepin-4-yl)phenol 39 had cholinesterase inhibitory potential (IC_{50}= 5.9 for AChE and IC_{50}= 6.8 for BChE) [63]. Mostofi *et al.* designed and synthesized benzofuran-1,5-benzothiazepine hybrids 40 with selective inhibitory effect for butyrylcholinesterase (BChE). Biological evaluation exhibited BChE inhibitory activity with IC_{50} value ranging between 1.0 ± 0.01 to 72 ± 2.8 μM. Among the targets, compounds with the methoxy group showed the highest BChE inhibition with IC_{50} values of 1.0, 1.0, and 1.8 μM, respectively (standard donepezil; IC_{50}= 2.63±0.28 μM) (Fig. 12) [64].

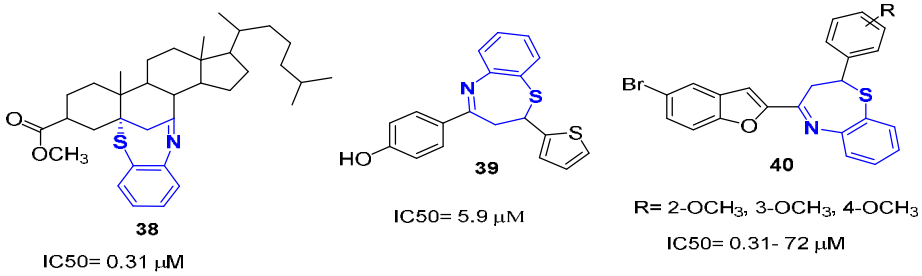

Fig. 12. Benzothiazepine derivatives as cholinesterase inhibitors

In silico analysis of compounds 41, 42, and 43 showed that three compounds bind the active site of β-secretase 1 (BACE1). Swiss ADME results exhibited no toxicity for these compounds (Fig. 13) [65].

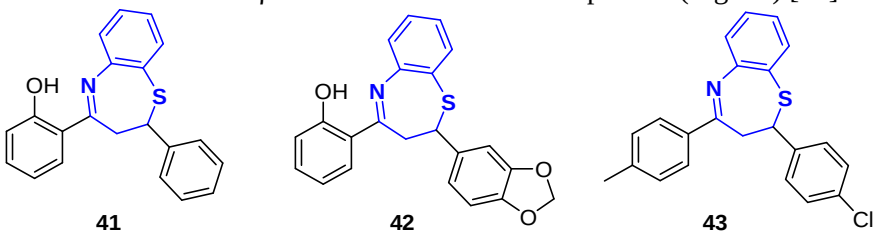

Fig. 13. Benzothiazepine derivatives as β-secretase 1 inhibitor

Recently, Rabia and coworkers disclosed that 2,3-dihydro-1,5-benzothiazepines 44 and 45 have α-glucosidase inhibitory potency with IC_{50} values ranging from 2.62±0.16 to 10.11 ± 0.32 μM as compared to standard acarbose (IC_{50}= 37.38±1.37 μM). Compounds containing methoxy groups on phenyl ring showed potency with IC_{50} values of 2.62± 0.30 and 3.01μM compared to standard acarbose (Fig. 14) [66].

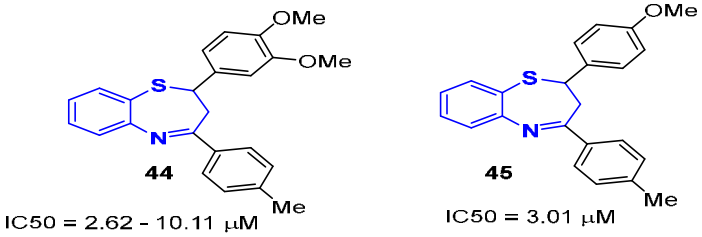

Fig. 14. Benzothiazepines as α-glucosidase inhibitor

In this study, the novel synthesized 1,4-benzothiazepines were investigated *in vitro* as thrombin inhibitors and 3,3-dibutyl-7-(2-chlorophenyl)-8- methoxy-2,3-dihydrobenzo[*b*] [1,4]thiazepin-4(5H)-one 46 with IC_{50} of 3.85 μM showed the best result. It was indicated that compounds with electron-withdrawing substituent groups on the aromatic ring are stronger inhibitors. Some tests like plasma recalcification that represents the clotting time of human plasma, the effect of D.C.T. on activated partial thromboplastin time (A.P.T.T.), and prothrombin time which assay two possible paths of blood coagulation, thrombin clotting time (T.C.T.) and the effect of 46 on agonist-induced platelet aggregation were done and 46 was potent to inhibit A.D.P., collagen, and thrombin and considered as an antiplatelet agent. Disorders of D.C.T. should be examined in future studies (Fig. 15) [67].

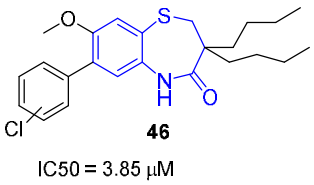

Fig. 15. Synthetic benzothiazepine derivatives as thrombin inhibitors

3.6.Anti-inflammatory activity

In 2014, Mhaske *et al.* reported the synthesis and evaluation of pyrazolyl benzothiazepine 47 and 48 with significant anti-inflammatory activity [68]. The presence of hydroxy, methoxy, and chloride groups at the para position of benzene in 2,3-dihydro-2,4-diphenylbenzo[*b*][1,4]thiazepine derivatives 49 led to an increase in the anti-inflammatory activity of compounds which is consistent with *in silico* study (Fig. 16) [69].

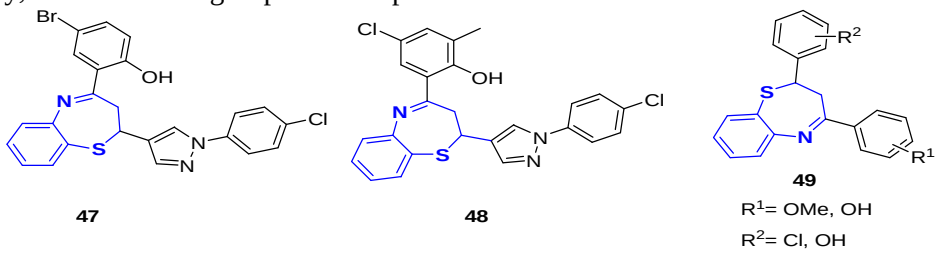

Fig. 16. Pyrazolyl benzothiazepine with anti-inflammatory activity

4. Conclusion

This minireview provides an overview of the scaffolds with 1,5-benzothizepine structures and their biological activities. Connecting various heterocycles to benzothiazepine will make a novel library with unique medical properties. The novel green processes including solvent-free reactions, microwave irradiation or ultrasonic wave will be interested the medicinal chemist. By presenting this minireview, we hope the scientific community will be beneficial from developing a new synthetic resourceful heterocyclic system with better biological outcomes.

List of abbreviations

The following abbreviations are used in this manuscript:
Activated Partial Thromboplastin Time (A.P.T.T.)
Butyryl Cholinesterase (BChE)
β-secretase 1 (BACE1)
Central Nervous System (C.N.S.)

Dimethyl Formamide (D.M.F.)
3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT)
Maximal Electroshock Seizure (M.E.S.)
Minimum Inhibitory Concentration (M.I.C.)
Pentylene Tetrazole (PTZ)
Thrombin Clotting Time (T.C.T.)

Conflicts of interest

There are no conflicts to declare.

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