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Review Paper

Diverse biological activities of [1,5]-benzothiazepines: An updated review

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Abstract: Heterocyclic compounds and their analogues/derivatives have attracted strong interest due to their biological and pharmacological properties. In recent years, [1,5]-benzothiazepines have emerged as an important class of compounds possessing diverse biological activities. Compounds containing [1,5]-benzothiazepine nucleus have been evaluated for various biological activities, such as antimicrobial, anticancer, antifungal, anthelmintic, anti-diabetic, amyloid imaging agents and anticancer agents. In this review, we have added some of the important and recent developments in the field of [1,5]-benzothiazepines and covered the literature of last five years.

Introduction

In the field of drug and pharmaceutical research, benzothiazepines belong to an important class of bicyclic heterocyclic compounds having benzene nucleus fused to a seven-membered ring containing one nitrogen and one sulfur atom. Benzothiazepine and its derivatives have received considerable attention due to their wide range of pharmacological activities such as anticonvulsant[1-2], antidepressant[3], vasodilator[4-5],

antihypertensive[6], calcium-channel blocker[7], antiulcer[8-9], antiarrhythmic[10], calcium antagonist [11-13], anticancer [14-15], antimicrobial [16-20] and antifungal activities [21]. In addition, it also behaves as free-radical scavengers and selective inhibitor of esterase, urease, and alpha-glucosidase [22].

Some of the [1,5]-benzothiazepines (Figure-1) include diltiazem **1** and cletiazem **2** prescribed for their cardiovascular action [5, 23-24], thiazesim **3**, and quetiapine fumarate **4**[3, 25] is employed clinically for CNS disorders. Two derivatives, namely, 7-bromo-3(S)-butyl-3-ethyl-8-hydroxy-5-phenyl-2,3,4,5-tetrahydro-[1,5]-

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benzothiazepine-1,1-dioxide (GW-577) **5**, is under preclinical study for the treatment of lipoprotein disorders and inhibition of the transporter of ileal bile acids[26] and 5-[*N*-[2-(3,4-dimethoxyphenyl)ethyl]- β -alanyl]-2,3,4,5-tetrahydro-[1,5]-benzothiazepine (KT-363) **6**, is under phase-II clinical trials for antihypertensive, antiarrhythmic, calcium (Ca^{2+}) channel antagonist activity [27-28]. There are some interesting reviews in the literature describing the synthesis, reactions, spectroscopy, and applications of [1,5]-benzothiazepine derivatives [29].

In our previous review [30], we have discussed the diverse pharmacological properties associated with various [1,5]-benzothiazepines and reviewed the literature upto the year 2008. In this present review, we have extended our previous report by inclusion of recent literature and related advancement in this area. Most of the synthetic methods used for their preparation are based on the reaction of α,β -unsaturated ketones with 2-aminothiophenol as given in the scheme-1. Cyclo-condensation of the Phenolic β -diketones **7a–d** with *o*-amino thiophenol proceeded under oxidation to give oxygen-bridged [1,5]-benzothiazepines **8a–d** in a reasonable yield[31].

Pharmacological Profile

In the literature from 2008 to till date, various [1,5]-benzothiazepines have been reported for different biological activities. For better understanding, we have divided this section under following heading.

2.1 [1,5]-benzothiazepines as Antimicrobial and antifungal Agents

Research and development for the search of potent antimicrobial agents in the past few decades represents significant advances in therapeutics, not only in the control of

serious infections, but also in the prevention and treatment of some infectious complications of other therapeutic modalities such as cancer chemotherapy and surgery. Fungal infections also cause a continuous and serious threat to human health and life [32]. Various causes of fungal infections in humans includes: (a) allergic reactions through fungal proteins, (b) toxic reactions by toxins present in certain fungi and (c) fungal infections (mycoses). Opportunistic pathogens may be endogenous (*Candida* infections) or acquired from the environment (*Cryptococcus*, *Aspergillus* infections) [32] that leads to fungal infections. Fungal organisms produces invasive fungal infections and dermatomycoses in individuals that are highly vulnerable such as neonates, cancer patients receiving chemotherapy, organ transplant patients, and burns patients, apart from those with acquired immune deficiency syndrome (AIDS). Other risk factors include use of drugs such as corticosteroid and antibiotic, disease condition such as diabetes, lesions of epidermis and dermis, malnutrition, neutropenia and surgery [33-36]. It has been found that the incidences and severity of fungal diseases has increased, particularly in patients with impaired immunity and pathogens such as *Candida albicans*, *Cryptococcus neoformans*, *Pneumocystis carinii* and *Aspergillus fumigatus*. These pathogens are the major cause of morbidity and mortality in immuno-compromised patients [37-38].

Therefore, there is always need for potent and effective antimicrobial and antifungal agents, considering the difficulties of dealing with the treatment of infections of hospitalized patients and protection of immunosuppressed and HIV-infected patients. However, in recent years, much attention has been focused to overcome the complications from multi-drug resistant

(MDR) bacteria and fungi resulting from the widespread use and misuse of classical antimicrobial agents[39]. Therefore, various approaches have been applied to modify different positions of [1,5]-benzothiazepines to divert their activity to inhibit the growth of microbes. Here, in this section we have selected some of the recent literature reports in this regards.

A series of methylene-bis-benzofuranyl[1,5]-benzothiazepines **9a-g** and methylene-bis[1,5]-benzothiazepines **10a-g** has been reported as potent antimicrobial and antifungal agent [40]. The new hybridized molecules possesses [1,5]-benzothiazepine and benzofuran in a single molecule and were evaluated against gram positive (*B. Subtilis*, *B. sphaericus* and *S. aureus*) and gram negative bacteria (*P. aeruginosa*, *Klebsiella aerogenes* and *Chromobacterium violaceum*). The newly synthesized compounds were also screened for activity against four fungal strains namely *Candida albicans*, *Aspergillus fumigatus*, *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Among these novel compounds, compound **10g**, **9f** and **9g** were found to be the most active against all bacterial and fungal strains. The MIC of these compounds was found to be 6.25µg/ml against *B. sphaericus*, *Klebsiella aerogenes*, *Aspergillus fumigates*. (Figure 2)

Further, a series of methylene bis(phenyl-[1,5]-benzothiazepines) **11** and methylene bis(benzofuryl-[1,5]-benzothiazepines) **12** has been reported and evaluated for their *in vitro* antibacterial and antifungal activity[41]. The dimeric compounds **11f**, **11g**, **12f** and **12g** were found to be most active against *Bacillus subtilis*, *Bacillus sphaericus*, *Staphylococcus aureus*, *Klebsiella aerogenes* and *Chromobacterium violaceum* as compared to the standard Streptomycin and Penicillin. Similarly, these

dimeric compounds showed potent antifungal activity for *Candida albicans*, *Aspergillus fumigatus*, *Trichophyton rubrum* and *Trichophyton mentagrophytes* compared with the standard Amphotericin B. It is interesting to note that the dimeric compounds in which heterocyclic rings are substituted at 4th position of thiazepine ring showed significant antibacterial and antifungal activity comparable to streptomycin and penicillin. The SAR studies revealed that, dimeric compounds containing benzothiazepine moiety (**11**) showed significant inhibition for *B. subtilis*, *B. sphaericus*, *S. aureus* and *P. aeruginosa*, while introduction of benzofuran moiety (**12**) reduced the antibacterial activity except for *C. violaceum*. However, in case of antifungal activity, dimeric compounds bearing both benzothiazepine and benzofuran moieties (**12**) showed higher activity towards *A. fumigatus*, *T. rubrum* and *T. mentagrophytes* than compounds containing only benzothiazepine moiety (**11**), but the activity towards *C. albicans* decreased due to the presence of benzofuran moiety. This indicates that the dimeric compound showed enhanced activity than their monomeric compounds. (Figure-3)

Similarly, a series of new methylene-bis-8-substituted[1,5]-benzothiazepines **13a-g** has been screened for antibacterial and antifungal activity against various strains of gram positive, gram negative bacteria[42]. In this series, the benzanoid part of the benzothiazepine was substituted with electron donating methyl group. Compound **13f** and **13g** were found to be most active against all the strains of microorganisms screened. All the new compounds were screened using streptomycin, penicillin and amphotericin-B as standard. (Figure 4)

Two new series of substituted[1,5]-benzothiazepines, **14a-r** and **15a-d**, has been

synthesized and tested against microbial strains like *C. albicans*, *S. aureus*, *S. epidermidis* and *E. coli* [17]. The compound **14c**, **14e** and **15e** were found to possess the highest antifungal activity compared to antibacterial activity. It may be observed that the acetyl group at C-3 is required for enhancing the antimicrobial activity whereas, compound **15e** was found to be most potent compound due to the presence of reactive imine function in the structure. Further, high solubility of the compound in agar medium, which may be assumed to be mediated by the hydroxyl group, plays an important role in antimicrobial activity. Fluconazole and Vancomycin were used as standard drugs in antifungal and antibacterial assays. (Figure 5)

Further, (2-oxo-2*H*-chromen-3-yl)-1,3-thiazol-2-yl-amino derivatives of [1,5]-benzothiazepines as 2,3-dihydro-2-aryl-4-[4-(2-oxo-2*H*-chromen-3-yl)-1,3-thiazol-2-ylamino]-[1,5]-benzothiazepine **16a-j** were found to be moderately active against a variety of gram positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*), gram negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) and also active against some fungal pathogens (*Candida albicans*, *Candida krusei*) and *Candida parapsilosis*) at a concentration of 100 µg/ml[43]. However, all compounds were found to be less active than standard drugs. (Figure 6)

Further, synthesis of C-2 and C-8 substituted analogues of [1,5]-benzothiazepines **17a-j** have been reported and screened for their antibacterial activity against gram positive (*Pseudomonas aeruginosa* and *Staphylococcus*), gram negative bacteria (*E. coli*) and antifungal activity against *Candida sp* [44]. Among all the screened compounds, **17e** was found to be most potent against gram positive bacteria *Staphylococcus*

aureus and showed moderate activity against *Candida sp.* (Figure 7)

Benzopyrano fused [1,5]-benzothiazepines **18a-f** have been reported for antimicrobial activity against bacteria *E. coli* and *GFC* (*Alteromonas tetraodonis*) and antifungal activity against some fungal sp. (*Aspergillus niger*, *A. flavus* and *Curvularia lunata*)[45]. Most of the compounds showed moderate bactericidal activity whereas, compound **18f** was found to be active against *E. coli* and *GFC* (index activity = 1.28). This indicates that the electron withdrawing fluoro group played a significant role in bioactivity of the [1,5]-benzothiazepine. (Figure 8)

In an another study, benzopyrano fused [1,5]-benzothiazepines as (10-substituted-6-(4-methoxyphenyl)-6*H*-6a, 7-dihydro-7-(4-methoxyphenyl/3,4-dimethoxyphenyl) benzopyrano-[3,4-*c*][1,5]-benzothiazepines) **19a-l** have been synthesized by reacting two flavindogenides, 2-(4-methoxyphenyl)-3-(4-methoxybenzylidene)-flavanone and 2-(4-methoxyphenyl)-3-(3,4-dimethoxybenzylidene)-flavanone with 5-substituted-2-aminobenzenethiols[46]. These compounds were screened for antimicrobial activity against the gram-positive bacteria (*Staphylococcus aureus*), gram-negative bacteria (*Pseudomonas aeruginosa*) and the fungal strains (*Candida albicans*). The compound **19k** was found to possess the maximum antifungal activity compared to fluconazole which is taken as reference standard. It may be noticed that electron donating methoxy group may be contributing positively for the antifungal activity as the compound **19k** bears the maximum number of methoxy groups. However, electron-withdrawing groups results in complete loss of activity as fluoro derivative **19a** and **19g** are completely inactive. (Figure-9)

Further, a series of fluorine containing azeto[2,1-*d*][1,5]-benzothiazepines (**20a-m**) has been reported and evaluated as antifungal agent against *Rhizoctonia solani*, *Fusarium oxysporum* and *Collectotrichum capsici*[47]. The maximum germination of 76-80% was found in compounds bearing alkoxy (**20e**) and trifluoromethyl (CF₃, **20i**) substitution through the pot trial experiment. “Baynate” and “Thiram” were used as standard fungicides as they are having -N-C-S linkage, similar to the synthesized compounds. The -N-C-S linkage is considered to be responsible for their antifungal activity. (Figure 10)

A new series of 2,5-dihydro-4-[1'-(*o*-chlorophenyl)-3'-methyl-5'-pyrazolidine azomethine]-2-(substituted phenyl)-[1,5]-benzothiazepines **21a-j** were synthesized and evaluated for their antimicrobial and antifungal activity against *E.coli*, *Staphylococcus aureus*, *Candida albicans*, *Candida krusei* [48]. The six compounds namely, **21b**, **21d**, **21e**, **21h**, **21i** and **21j** showed highest degree of inhibition against all the bacterial species and compound **21d**, **21e**, **21g** and **21j** showed good activity against fungal species. Therefore, concluded that chlorine, dimethylamine and *p*-methoxy group substitution increased the activity against the both bacterial and fungal species, while hydroxyl and trimethoxyl group displayed significant activity against only bacterial species. But, the activity results of the newly synthesized compounds showed that these compounds were less potent than the standard drug used in the assay, Streptomycin and Griseofulvin. (Figure 11)

Antibacterial and antifungal activity of a series of substituted [1,5]-benzothiazepines containing 2-COOC₂H₅/COONa (**22a-h**) has been reported against *S. aureus*, *S. epidermidis*, *E. coli* and *C. albicans* [49]. The compounds **22a**, **22b**, **22c**, and **22e**

showed moderate activities while **22d** and **22f** showed less activity against *S. aureus* and *S. epidermidis*. The sodium salts of [1,5]-benzothiazepine-2-carboxylic acid **22g-h** showed higher activity against *S. aureus* and *S. epidermidis* than **22a-f**. It has been found that all the compounds were inactive against *E. coli* as compared to the standard drug, vancomycin. The compound **22b** was found to be the best in all [1,5]-benzothiazepines against *C. albicans* compared with reference drug, fluconazole. However, the antifungal activity of the salts **22g-h** was found to be less than **22a-f**. This indicates that the presence of an ester group at the C(2)-position of the [1,5]-benzothiazepine ring played a crucial role for the antibacterial and antifungal activity. (Figure 12)

Further, a new series of [1,5]-benzothiazepines (**23a-f**) and [1,5]-benzodiazepines (**24a-f**) has been reported and screened for their antibacterial activity against *B-subtilis*, *E-coli*, and *S. typhi* compared to the standard Norfloxacin[50]. Chloro substituted compound **23e** displayed moderate activity against *B-subtilis*, while all other compounds were found to be weakly active against *E.coli*. (Figure 13)

Further, 8-substituted-2-(2-chlorophenyl)-4-(4-chlorophenyl/2-thienyl)-2,5-dihydro-[1,5]-benzothiazepines (**25a-l**) have been reported as potent antibacterial and antifungal agents[51]. The compound **25i** has shown the highest relative activity against the gram-positive bacteria *Staphylococcus aureus* and **25c** showed good activity against the gram-negative bacteria, *Pseudomonas aeruginosa* compared with gatifloxin and natilmicin as standard. Compounds **25b**, **25h** and **25j** showed high activity against the fungus *Candida albicans* whereas; compound **25l** showed significant activity compared to the

standard fluconazole. These observations indicates that the 4-(2-thienyl)-substituted 2-(2-chlorophenyl)-[1,5]-benzothiazepines (**25g-l**) are better in activity than the compounds 4-(4-chlorophenyl)-substituted 2-(2-chlorophenyl)-[1,5]-benzothiazepines (**25a-f**). (Figure-14)

In an another study, a series of tricyclic azeto[2,1-*d*][1,5]-benzothiazepine ring system (**26a-f**) has been synthesized by conventional as well microwave irradiation method and the compounds were reported for their antifungal and antibacterial activity [52]. Use of microwave irradiation give high purity of the products with less by products and reduce the overall reaction time. Among the synthesized compound, OCH₃ (**26a**) and CF₃ (**26e**) substituted compounds showed maximum antifungal activity against *Rhizoctonia solani*, *Fusarium oxysporum*, *Colletotrichum capsici* compared to standard. Compound **26a**, **26d**, and **26f** showed good activity against *S. aureus*. (Figure-15)

1.2 [1,5]-Benzothiazepines as Anticonvulsant

Epilepsy is a disorder characterized by synchronized discharges of large number of neurons that alters the brain's normal electrochemical balance [53-54]. Epileptic episodes are defined as seizures having manifestations ranging from brief lapses of lack of attention to limited motor, sensory, or psychological changes but in severe cases it includes prolonged losses of consciousness with convulsive motor activity [55]. Currently available antiepileptic drugs (AED) such as phenytoin, carbamazepine, diazepam, phenobarbital, ethosoximide, valproate, valroceamide, vigabatrin, gabapentin, zonisamide, topiramate, tiagabine, felbamate, retigabine, lamotrigine, and

levetiracetam are not effective for several epileptic episodes, and suffers from some undesirable side effects such as vertigo, ataxia, headache, hirsutism, hepatotoxicity, gastrointestinal, and cardiovascular side effects [56-61]. Some of these side-effects are appeared immediately after drug exposure [62] however, chronic side effects are detected only after a long treatment, and most of them are not dose-related [63-64].

It is difficult to provide a precise classification of AEDs according to their mode of action, due to the reason that they interact with more than one receptor and have not been linked with a specific binding site. But, some of the cellular mechanisms involved are:

- i) potentiation of GABA-ergic transmission[65],
- ii) blockade of voltage gated sodium channel (VGSC)[66],
- iii) attenuation of excitatory neurotransmission,[66-68] and/or
- iv) modulation of voltage sensitive calcium channels[69].

Therefore, two main strategies are employed to design new compounds having high potency and specificity, as well as low toxicity: compounds are investigated that cause modification of certain stage of the cellular mechanism (mechanism-based design) and the modification of already synthesized compounds (structure-based design).

A new series of 4-(4'-hydroxyphenyl)-2-(3-substitutedphenyl)-3-(4-substituted phenylamino methylene)-2,3-dihydro-[1,5]-benzothiazepines(**27a-3j**) has been reported as anticonvulsant agents[1]. From all the screened compounds, compound **27g** was found to possess most potent anticonvulsant activity with 90% inhibition and is more

than standard drug, phenytoin sodium. This compound exhibits maximum approximate lethal dose (ALD₅₀) 2000 mg/kg. It has been observed that the presence of electronegative atom on benzothiazepine ring and 2-chlorophenyl substitution at second position of benzothiazepine ring is optimal and play a significant role to increase the anticonvulsant activity. (Figure 16)

A new series of [1,5]-benzothiazepines integrated with 5-methyl-2-oxo-3-phenyl- Δ^4 -4-(1,3,4)-oxadiazoles (**28a-d**) has been reported by classical and microwave heating methods [70]. The microwave irradiation method provided the high yield (84-92%) compared to the classical heating method (49-62%). The newly synthesized compounds were screened for their antimicrobial, anticonvulsant, anti-inflammatory, and diuretic activities. Analysis of antibacterial and antifungal data revealed that chloro (**28b**) and bromo (**28d**) substituents on C2'-phenyl nucleus displayed higher activity than methyl substituted **28c** and unsubstituted **28a** compound, against *S. aureus*, *P. aeruginosa*, *A. flavus*, *F. oxysporium*. However, methyl **28c** and bromo **28d** substituted compounds showed significant anti-inflammatory and anti-convulsant activity compared to standard Ibuprofen and Phenytoin. However, these compounds showed less diuresis compared to furosemide. (Figure 17)

2.3 [1,5]-Benzothiazepine as Antidepressant

Depression is a disorder of the brain and is characterized by sadness, loss of interest or pleasure in activities in which individual normally used to enjoy [71]. Other symptoms include change in weight, feelings of guilt or low self-worth, disturbed sleep, energy loss, feelings of worthlessness *etc.*[72]. Due to the high prevalence of suicide in depressed patients added with the

problems arising from stress and its effect on the cardiovascular system, it has been suggested that it will become the second leading cause of premature death or disability worldwide by the year 2020 [72]. There are various causes for this disorders that includes genetic, environmental, psychological, and biochemical factors.

Antidepressant drugs employed for clinical therapy are classified as classical antidepressant drugs such as monoamine oxidase inhibitors (*e.g.*, tranylcypromine) and drugs that inhibit the reuptake of catecholamines (*e.g.*, imipramine) [73]. Second generation drugs include compounds such as the selective inhibitors of serotonin reuptake (*e.g.*, fluoxetine) and drugs with non-conventional mechanisms of action (*e.g.*, trazodone, nefazodone and mirtazapine). These drugs are very effective but with common complication and side effects such as anti-cholinergic, gastrointestinal distress, anxiety, insomnia and sexual dysfunction *etc.* apart from their slow onset of action [74]. These side effects demand a renewed effort seeking the development of new therapeutic agents, with fewer collateral effects and/or with novel mechanisms of action, which could reduce the delay in the onset of antidepressant therapy. In order to accomplish these goals, new compounds with antidepressant properties from [1,5]-benzothiazepins scaffold has been investigated in recent years.

As discussed earlier, by our previous review thiazesim is the [1,5]-benzothiazepine derivative that act by binding with benzodiazepine receptor, most probably on mitochondrial benzodiazepine receptors (MBR). A new synthetic route for ($\pm$)-thiazesim **3** has been reported by minimizing the number of reaction steps using water as a solvent[75]. This green chemistry protocol

provides the good yield and purity of the target compound. ($\pm$)-Thiazesim **3** is well known GABA_A blocker and marketed as hydrochloride salt as an anti-depressant. (Figure 18)

2.4 [1,5]-Benzothiazepines as Antithrombotic agents

Synthesis, and biological evaluation of [1,5]-benzothiazepine-4-one derivatives targeting factor VIIa/tissue factor has been reported [76]. Compound **29** possesses the (*S*) configuration that showed micromolar inhibitory potency toward FVIIa/TF (IC_{50} = 2.16 μ M, a 10 times improvement compared to the activity of the (*R*) analogue **30**. Following the molecular modeling studies of compound **29**, a new series of protected 7- or 8-substituted [1,5]-benzothiazepine-4-ones have been synthesized. Among them, compound **31** having an acetic group at position 7 of D-BT displayed 15 times improvement in inhibitory potency against FXa (IC_{50} = 0.21 μ M) compared to the unsubstituted analogue **29**, rather making it a relatively selective inhibitor of FXa (IC_{50} 's ratios FVIIa/FXa = 14; FIIa/FXa = 150). Therefore, compared to unsubstituted compound **29**, derivatization of the D-BT moiety at positions 7 or 8 did not show the significant results. (Figure 19)

2.5 [1,5]-Benzothiazepines as Antitumour

Cancer is considered as one of the most intractable disease due to uncontrolled cell proliferation, diminished apoptosis, invasion, metastasis. It has been estimated that about 15% of all human deaths in the developed world is due to this severe disease [77]. In spite of increasing number of inhibitory compounds against several molecular targets, there is still a lack of clinically useful cytotoxic drugs selective for cancerous cells. Now, the application of

known anticancer agent is limited due to their cytotoxic effect on normal rapidly dividing cells (*i.e.*, the bone marrow cells, the epithelial cells in the gastrointestinal tract) and by side effects characteristic for given anticancer drugs [78]. Therefore, the development of novel synthetic anticancer agents that show a selective cytotoxicity for cancer cells over normal cells seems to be of great urgency.

A series of [1,5]-benzothiazepines **32a-f** were synthesized by utilizing LaY (Lanthanum) zeolite and screened for cytotoxic activity [79]. The more acidic LaY zeolite catalyst was found to be effective for the preparation of 2-carboxy-2,3-dihydroxy-[1,5]-benzothiazepines compared with CeY (cerium), NaY (sodium faujasites) and HY (acidic). Since the number and strength of acid site in zeolite increase with metal cation exchanged in the order of $H^+ < Na^+ < Ce^{2+} < La^{3+}$ which resulted into increase in the yield of the product and also suggested that acid sites on zeolite acts as active sites for this reaction. The phototoxicity of compounds was investigated first on a cell line of human tumor HL-60 (human pro-myelocytic leukemia). Compound **32e** and **32f** exhibited highest activity against HL-60 cell line and these compounds were also examined on a human intestinal adenocarcinoma cell line (LoVo) and one line of immortalized, not tumorigenic, human keratinocytes (NCTC 2544). The results indicate that the compound **32f** was very effective against the tumor cell lines in comparison to the normal ones (NCTC 2544) where doxorubicin was used as positive control. (Figure 20)

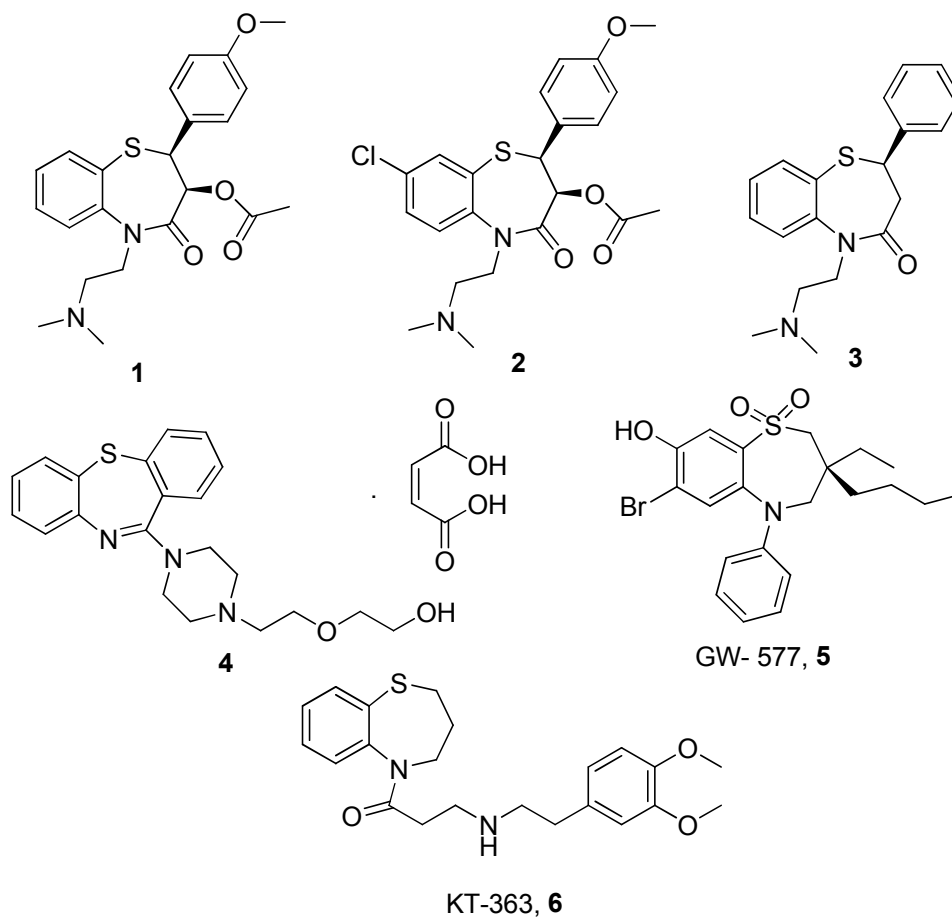
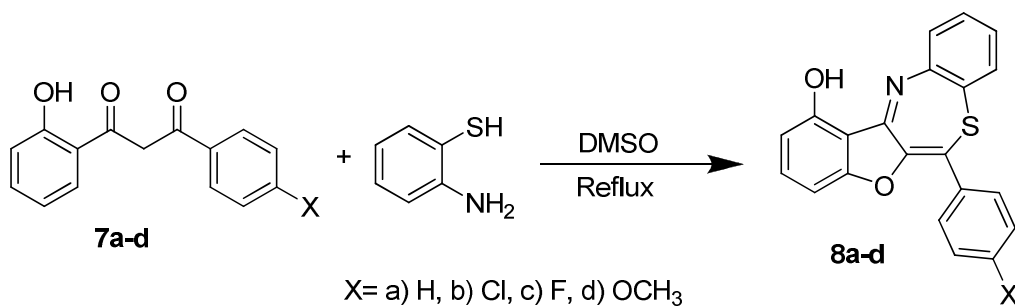
Further, a series of 3'-hydroxy-2,3-dihydro[1,5]-benzothiazepines have been synthesized through solid-phase synthesis by [4+3] annulations of α,β -unsaturated ketones with aminophenol utilizing Wang resin solid

support [80]. All the compounds were evaluated for antibacterial, anti-tumor as well as acetyl and butyryl cholinesterase inhibitory activity. Some of compounds namely compound **35**, **36** and **37** where benzothiazepine is substituted with a 4-pyridyl and a thiophene ring were found very active against crown gall which is a neoplastic plant disease caused by *Agrobacterium tumefaciens* with IC_{50} values 6.4, 4.8 and 11.2 ppm, respectively. On the other hand, the benzothiazepines **33** and **34** were found to be potent inhibitor of butyrylcholinesterase (BChE) with IC_{50} 4.07 and 4.65 ppm. The compound **36** was found to be active against for both AChE and BChE with IC_{50} = 5.9 and 3.97 ppm. It is important to observe that substitution of hydroxyl group at C-3 in ring A led to increased activity in comparison to unsubstituted and 2'-hydroxyl substituted benzothiazepines. (Figure 21)

Conclusion

Benzothiazepines belongs to privileged class of bicyclic heterocyclic compounds

having a wide range of pharmacological activities. Methylene-bis-benzofuranyl, methylene-bis-8-substituted[1,5]-benzothiazepines, C-2, C-4 and C-8 substituted analogues were found to be potent against various microbial and fungal strains. Attachment of [1,5]-benzothiazepines with other moiety such as chromen, benzopyrano, azeto, pyrazolidine azomethine, oxadiazoles have been proved beneficial in improving the antimicrobial and antifungal activity. For anticonvulsant activity, substituted aryl at C-4 and oxadiazole and hydroxyl amine at C-2 were explored. In thrombotic disorders, role of [1,5]-benzothiazepine is well established in our previous article. In this, protected 7- or 8-substituted [1,5]-benzothiazepine-4-one derivatives were found to exhibited improvement in inhibitory potency against FXa. The [1,5]-benzothiazepine is a promising scaffold for different molecular targets. Significant efforts will be made by the researchers to explore this wonderful moiety in future.

**Figure-1****Scheme 1**

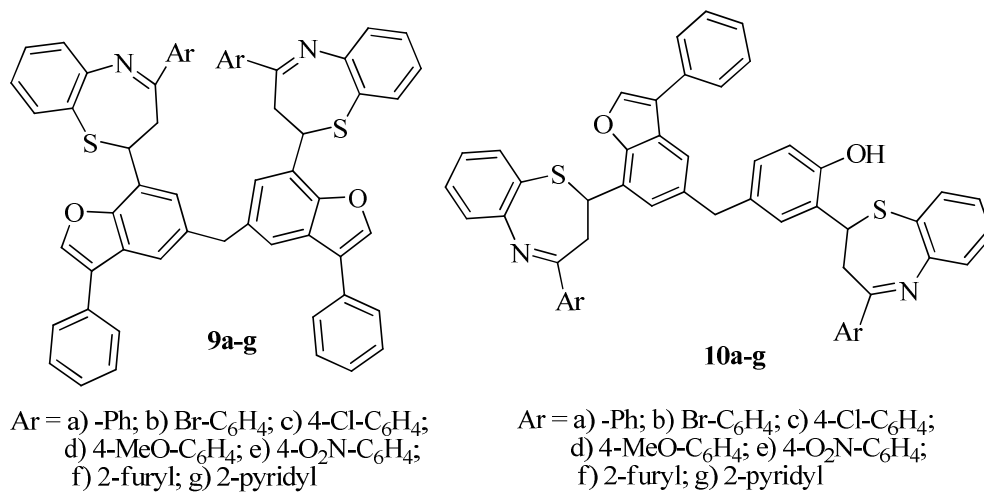


Figure-2

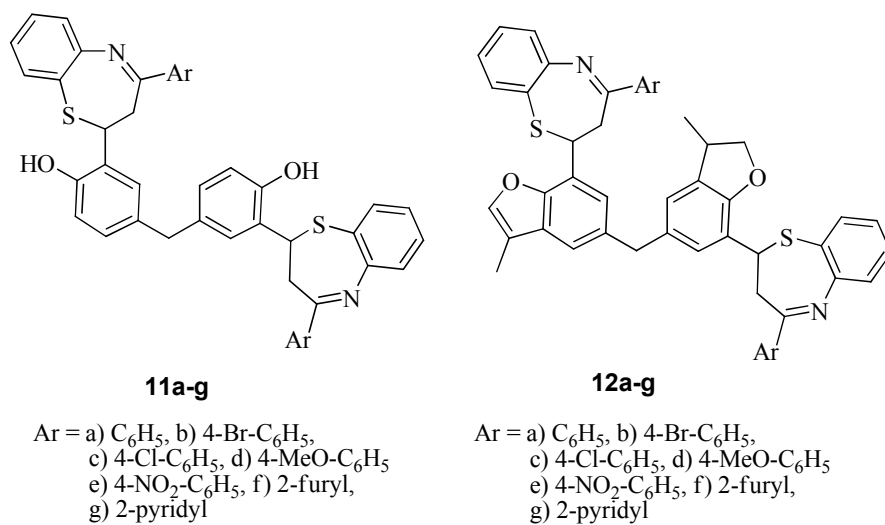
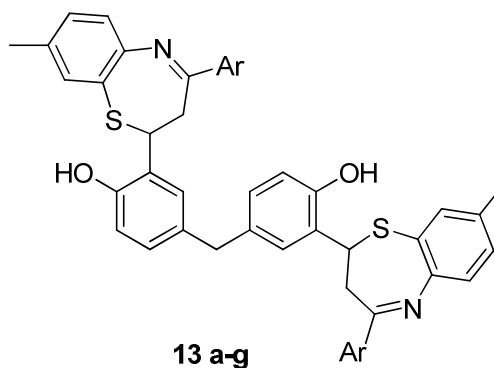
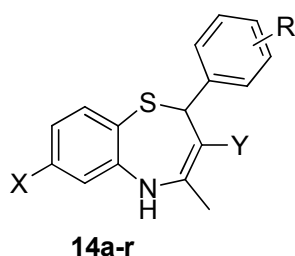


Figure-3

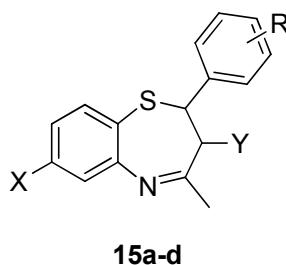


Ar = a) -Ph; b) Br-C₆H₄;
 c) 4-Cl-C₆H₄; d) 4-OCH₃-C₆H₄;
 e) 4-O₂N-C₆H₄; f) 2-furyl;
 g) 2-pyridyl;

Figure-4

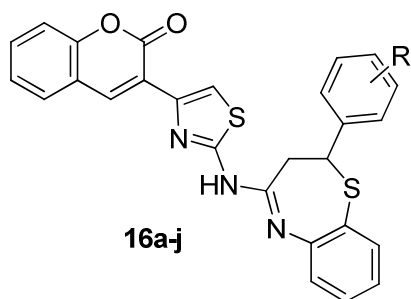


a: X = H, Y = COCH₃, R = *p*-NO₂,
 b: X = H, Y = COCH₃, R = *o*-NO₂,
 c: X = H, Y = COCH₃, R = *p*-Cl,
 d: X = H, Y = COCH₃, R = *o*-Cl,
 e: X = H, Y = COCH₃, R = *p*-CH₃,
 f: X = H, Y = COCH₃, R = *p*-OH,
 g: X = H, Y = COCH₃, R = H,
 h: X = H, Y = COCH₃, R = *p*-OCH₃,
 i: X = H, Y = COCH₃, R = *p*-F,
 j: X = H, Y = COCH₃, R = 2,4-di-Cl
 k: X = Cl, Y = COCH₃, R = *p*-NO₂,
 l: X = Cl, Y = COCH₃, R = *o*-NO₂,
 m: X = Cl, Y = COCH₃, R = *p*-Cl,
 n: X = Cl, Y = COCH₃, R = *o*-Cl,
 o: X = Cl, Y = COCH₃, R = H,
 p: X = Cl, Y = COCH₃, R = *p*-F,
 q: X = Cl, Y = COCH₃, R = *p*-Br,
 r: X = Cl, Y = COCH₃, R = 2,4-di-Cl



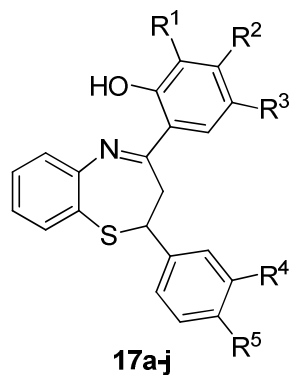
a: X = H, Y = COOCH₂CH₃, R = *p*-CH₃,
 b: X = H, Y = COOCH₂CH₃, R = *p*-F,
 c: X = H, Y = COOCH₂CH₃, R = *p*-NO₂,
 d: X = H, Y = COOCH₂CH₃, R = *o*-Cl

Figure-5



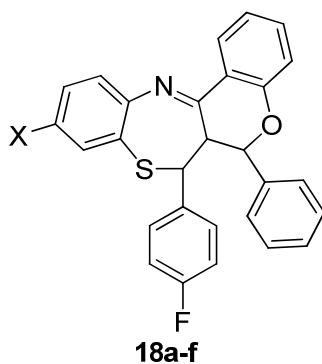
R= a) 3-CH₃, 4-OH; b) 4-CH₃;
c) 2-Cl; d) 4-(Cl)₂; f) 2-OCH₃;
g) 4-OCH₃; h) 3,4,5-(OCH₃)₃;
i) 4-N(CH₃)₂; j) 4-OH

Figure-6



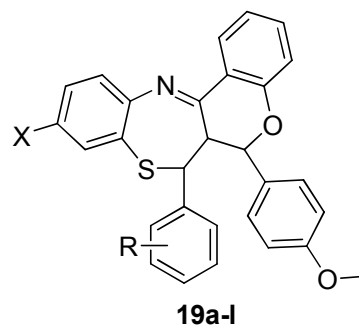
a: R¹= H, R²= H, R³= H, R⁴= H, R⁵= F
b: R¹= H, R²= H, R³= CH₃, R⁴= H, R⁵= F
c: R¹= H, R²= H, R³= Cl, R⁴= H, R⁵= F
d: R¹= H, R²= H, R³= CH₃, R⁴= H, R⁵= F
e: R¹= H, R²= CH₃, R³= Cl, R⁴= H, R⁵= F
f: R¹= H, R²= H, R³= H, R⁴= OCH₃, R⁵= OCH₃
g: R¹= H, R²= H, R³= CH₃, R⁴= OCH₃, R⁵= OCH₃
h: R¹= H, R²= H, R³= Cl, R⁴= OCH₃, R⁵= OCH₃
i: R¹= Cl, R²= H, R³= Cl, R⁴= OCH₃, R⁵= OCH₃
j: R¹= H, R²= CH₃, R³= Cl, R⁴= OCH₃, R⁵= OCH₃

Figure-7



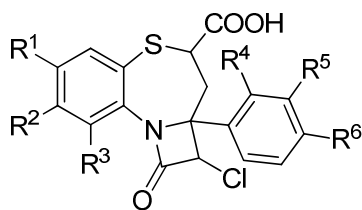
X= a) F, b) Cl, c) Br, d) CH₃,
e) OCH₃, f) OC₂H₅

Figure-8

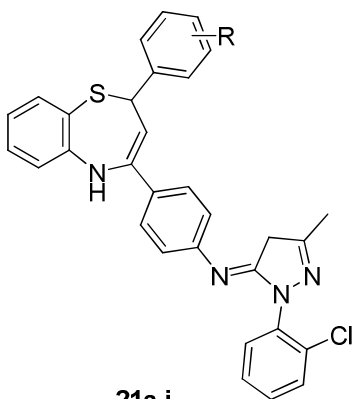


a: R = 4-OCH₃, X = F
b: R = 4-OCH₃, X = Cl
c: R = 4-OCH₃, X = Br
d: R = 4-OCH₃, X = CH₃
e: R = 4-OCH₃, X = OCH₃
f: R = 4-OCH₃, X = OC₂H₅
g: R = 3,4-(OCH₃)₂, X = F
h: R = 3,4-(OCH₃)₂, X = Cl
i: R = 3,4-(OCH₃)₂, X = Br
j: R = 3,4-(OCH₃)₂, X = CH₃
k: R = 3,4-(OCH₃)₂, X = OCH₃
l: R = 3,4-(OCH₃)₂, X = OC₂H₅

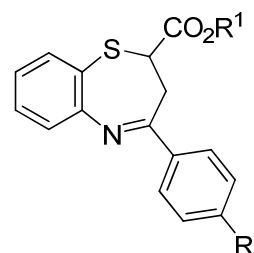
Figure-9

**20a-m**

- a:** $R^1 = \text{CH}_3$, $R^2 = \text{H}$, $R^3 = \text{H}$, $R^4 = \text{H}$, $R^5 = \text{H}$, $R^6 = \text{F}$
b: $R^1 = \text{F}$, $R^2 = \text{H}$, $R^3 = \text{H}$, $R^4 = \text{H}$, $R^5 = \text{H}$, $R^6 = \text{F}$
c: $R^1 = \text{Cl}$, $R^2 = \text{H}$, $R^3 = \text{H}$, $R^4 = \text{H}$, $R^5 = \text{H}$, $R^6 = \text{F}$
d: $R^1 = \text{Br}$, $R^2 = \text{H}$, $R^3 = \text{H}$, $R^4 = \text{H}$, $R^5 = \text{H}$, $R^6 = \text{F}$
e: $R^1 = \text{OCH}_3$, $R^2 = \text{H}$, $R^3 = \text{H}$, $R^4 = \text{H}$, $R^5 = \text{H}$, $R^6 = \text{F}$
f: $R^1 = \text{OC}_2\text{H}_5$, $R^2 = \text{H}$, $R^3 = \text{H}$, $R^4 = \text{CH}_3$, $R^5 = \text{H}$, $R^6 = \text{F}$
g: $R^1 = \text{C}_2\text{H}_5$, $R^2 = \text{H}$, $R^3 = \text{H}$, $R^4 = \text{CH}_3$, $R^5 = \text{H}$, $R^6 = \text{F}$
h: $R^1 = \text{H}$, $R^2 = \text{CF}_3$, $R^3 = \text{H}$, $R^4 = \text{H}$, $R^5 = \text{Cl}$, $R^6 = \text{H}$
i: $R^1 = \text{H}$, $R^2 = \text{H}$, $R^3 = \text{Br}$, $R^4 = \text{H}$, $R^5 = \text{CF}_3$, $R^6 = \text{H}$
j: $R^1 = \text{CF}_3$, $R^2 = \text{H}$, $R^3 = \text{H}$, $R^4 = \text{H}$, $R^5 = \text{H}$, $R^6 = \text{OH}$
k: $R^1 = \text{H}$, $R^2 = \text{H}$, $R^3 = \text{Cl}$, $R^4 = \text{H}$, $R^5 = \text{Cl}$, $R^6 = \text{F}$
l: $R^1 = \text{H}$, $R^2 = \text{H}$, $R^3 = \text{CF}_3$, $R^4 = \text{CH}_3$, $R^5 = \text{H}$, $R^6 = \text{F}$
m: $R^1 = \text{H}$, $R^2 = \text{CH}_3$, $R^3 = \text{CH}_3$, $R^4 = \text{H}$, $R^5 = \text{CF}_3$, $R^6 = \text{H}$

Figure-10**21a-j**

- R = a)** H, **b)** 2-OH, **c)** 3-NO₂
d) 2-Cl, **e)** 4-Cl, **f)** 4-N(CH₃)₂
g) 4-OCH₃, **h)** 3,4,5-tri-OCH₃
i) 3-OC₆H₅, **j)** 4-OCH₃

Figure-11**22a-h;**

- a:** $R^1 = \text{C}_2\text{H}_5$, $R = \text{H}$
b: $R^1 = \text{C}_2\text{H}_5$, $R = \text{F}$
c: $R^1 = \text{C}_2\text{H}_5$, $R = \text{Cl}$
d: $R^1 = \text{C}_2\text{H}_5$, $R = \text{Br}$
e: $R^1 = \text{C}_2\text{H}_5$, $R = \text{OCH}_3$
f: $R^1 = \text{C}_2\text{H}_5$, $R = \text{CH}_3$
g: $R^1 = \text{Na}$, $R = \text{H}$
h: $R^1 = \text{Na}$, $R = \text{F}$

Figure-12

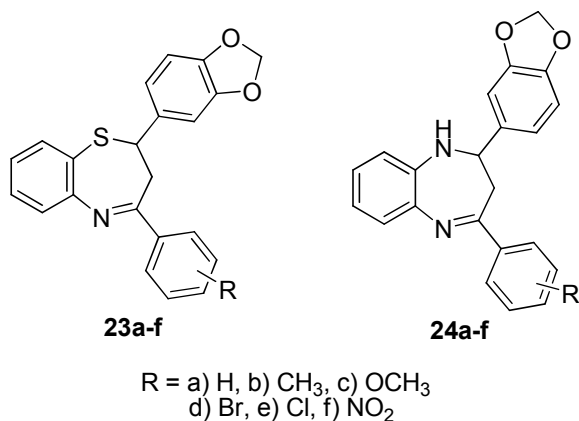


Figure-13

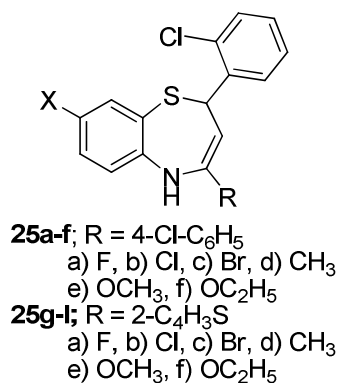


Figure-14

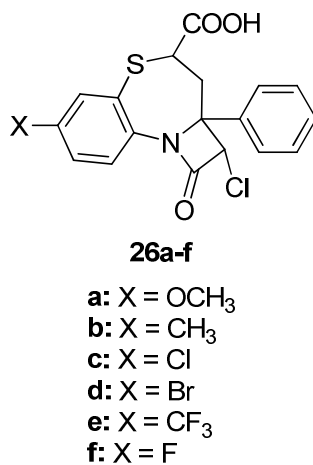


Figure-15

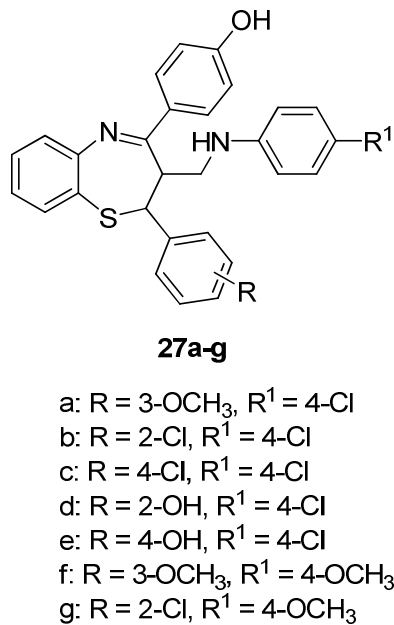
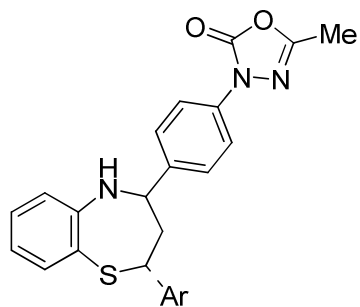
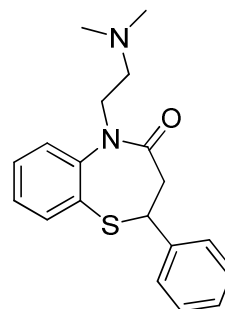
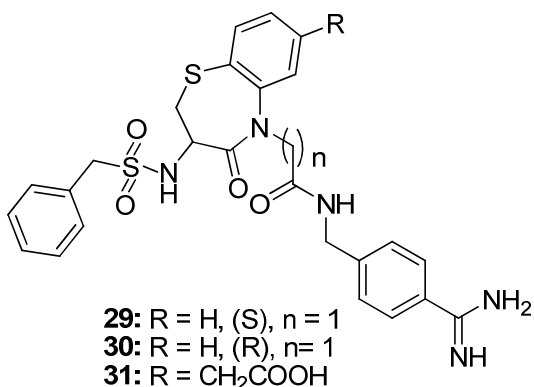


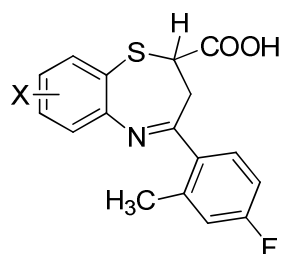
Figure-16

**28a-d**

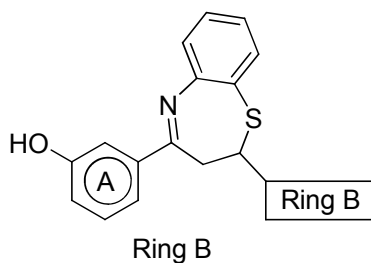
Ar = a) C₆H₅, b) 4-Br-C₆H₅,
c) 4-CH₃-C₆H₅, d) 4-Cl-C₆H₅

Figure-17**(±)- thiazesim, 3****Figure-18**

29: R = H, (S), n = 1
30: R = H, (R), n = 1
31: R = CH₂COOH

Figure-19**32a-f**

X = a) 8-OCH₃, b) 8-CH₃, c) 8-Cl,
d) 6-Cl, e) 8-Br, f) 8-F

Figure-20

Ring B

33: 3-OHC₆H₄
34: 2-OMeC₆H₄
35: 4-Pyridyl
36: 2-Thienyl
37: 2-Thienyl-5-Br

Figure-21

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