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PHARMACOLOGICAL POTENTIAL OF 1,5-BENZOTHIAZEPINE DERIVATIVES: AN UPDATED REVIEW OF BIOLOGICAL ACTIVITIES, MOLECULAR TARGETS AND STRUCTURE–ACTIVITY RELATIONSHIPS

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ABSTRACT

1,5-Benzothiazepines represent an important class of heterocyclic compounds that have gained considerable attention in medicinal chemistry due to their broad spectrum of pharmacological activities. The unique fusion of benzene and thiazepine rings imparts remarkable biological versatility, making them valuable scaffolds in drug discovery. This review comprehensively highlights the chemistry, synthesis and diverse therapeutic potentials of 1,5-benzothiazepine derivatives with emphasis on their antimicrobial, anticonvulsant, anticancer, anti-inflammatory and antidiabetic properties. Various studies have demonstrated that structural modifications on the benzothiazepine nucleus, particularly the introduction of electron-withdrawing or hydrophilic substituents, significantly influence biological activity and selectivity. Halogenated and heteroaryl-substituted derivatives exhibit potent antimicrobial and antitubercular activity, while specific analogues show promising anticonvulsant efficacy through GABAergic modulation. Similarly, 1,5-benzothiazepines with tailored substitutions have revealed noteworthy cytotoxicity against several cancer cell lines and some derivatives demonstrate strong COX-2 inhibition and α-glucosidase inhibitory potential, indicating anti-inflammatory and antidiabetic relevance. The integration of in silico modeling, structure-activity relationship (SAR) analysis and green synthetic approaches has further advanced understanding of their pharmacological mechanisms. Collectively, these findings underline the importance of 1,5-benzothiazepine derivatives as versatile lead structures for the design of novel therapeutic agents.

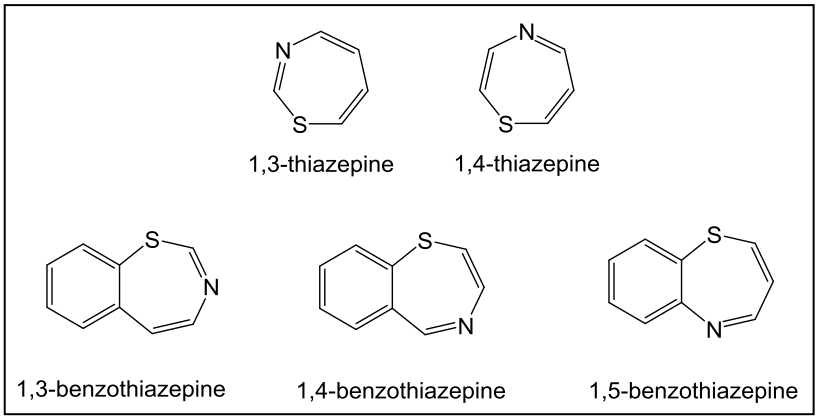
KEYWORDS: 1,5-Benzothiazepines, antimicrobial, anticonvulsant, anticancer, anti-inflammatory, antidiabetic.

1. INTRODUCTION

Medicinal chemistry is an interdependent mature science that is a combination of applied (medicine) and basic (chemistry) sciences including organic chemistry, physical chemistry, pharmacology, microbiology, biochemistry as well as computational chemistry. It includes the discovery, development, identification and interpretation of biologically active substances, molecular mechanism of action. Medicinal chemistry may viewed as melting pot of synthetic chemistry and molecular pharmacology that emphasizes the study of SAR of drug molecules; it therefore requires clear understanding of both chemical and pharmacological principles.[1]

In the pursuit of novel therapeutic agents, heterocyclic compounds have played a pivotal role, among which benzothiazepine derivatives have attracted significant attention due to their diverse pharmacological potential. Thiazepines are important members of the seven-membered heterocyclic chemical family, which has a ring system that incorporates sulfur and nitrogen. Benzene and seven-membered thiazepine rings fused together to form benzothiazepine analogues. They have been classified into three distinct classes named as 1,3-,

1,4- and 1,5-benzothiazepine out of which 1,5-benzothiazepines have been explored extensively for the development of new drug molecule.[2]



Owing to their unique structural framework and wide range of biological activities, benzothiazepines have emerged as valuable scaffolds in medicinal chemistry research. Various benzothiazepines have played major roles in the history of heterocyclic chemistry, serving as pharmacophores and synthons in organic chemistry and drug development.[3]

Among the different structural variants, 1,5-benzothiazepine derivatives have gained particular importance due to their remarkable therapeutic versatility and clinical relevance. One of the most prominent pharmacophores in pharmaceuticals is 1,5-benzothiazepine. 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 (Figure I). Thiazesim and quetiapine fumarate are another class of 1,5-benzothiazepine derivatives used as psychotropic medications to treat CNS problems (Figure I). Various interesting biological properties have also been explored, including anticonvulsants, anti-HIV, enzyme inhibitors and antibacterial activities.[4]

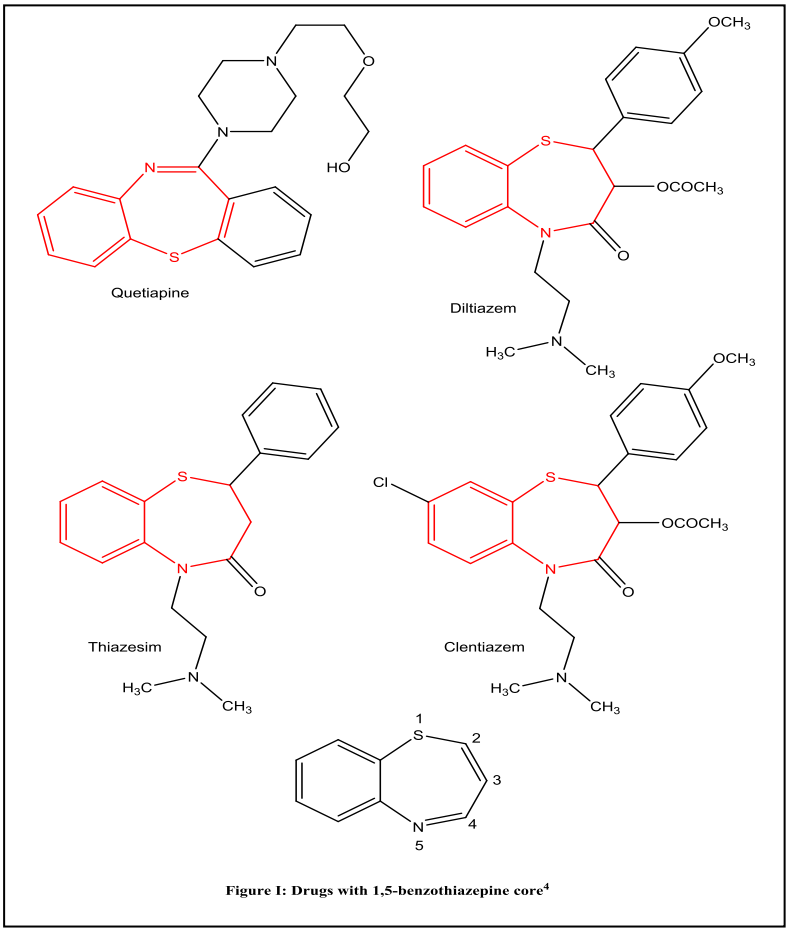
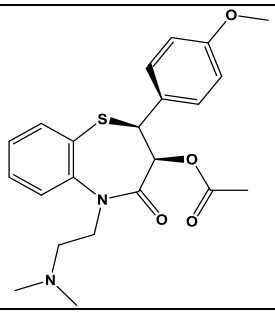
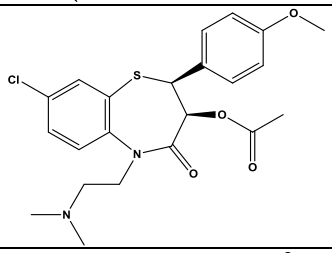
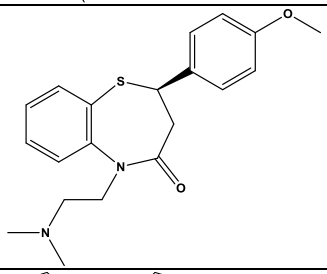
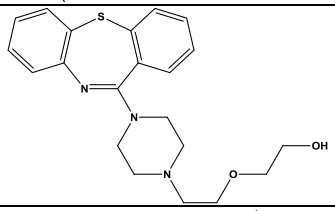
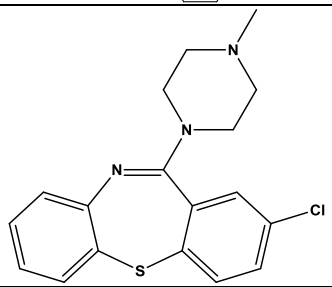


Figure I: Drugs with 1,5-benzothiazepine core[4]

The wide spectrum of pharmacological applications of 1,5-benzothiazepine derivatives underscores the significance of the benzothiazepine nucleus as a vital structural motif in drug discovery and development. Benzothiazepines are recognized as lead compounds, having a prominent position in medicinal chemistry due to their broad range of biological actions. They have been known to exhibit antimicrobial, anticancer, anticonvulsant, antipsychotic, antiangiogenic and antioxidant properties. Many popular medications contain the thiazepine moiety as their basic component. The benzothiazepine skeleton was discovered to be a building blocks in organic synthesis for developing bioactive pharmaceuticals. It is also present in the core structure of numerous commercially available drugs such as Diltiazem, Clentiazem, Thiazesim, Quetiapine-fumarate and Clothiapine as shown in Table I.[3]

Table I: Structures of clinically used benzothiazepine derivative.[3]

Sl No	Drug Name	Structure	Application
1	Diltiazem		Antihypertensive
2	Clentiazem		Antihypertensive
3	Thiazesim		Antidepressant
4	Quetiapine		Antidepressant
5	Clothiapine		Antipsychotic

Several synthetic methodologies have been developed for the preparation of 1,5-benzothiazepine derivatives employing various catalysts and reaction conditions, as illustrated in Figure II.

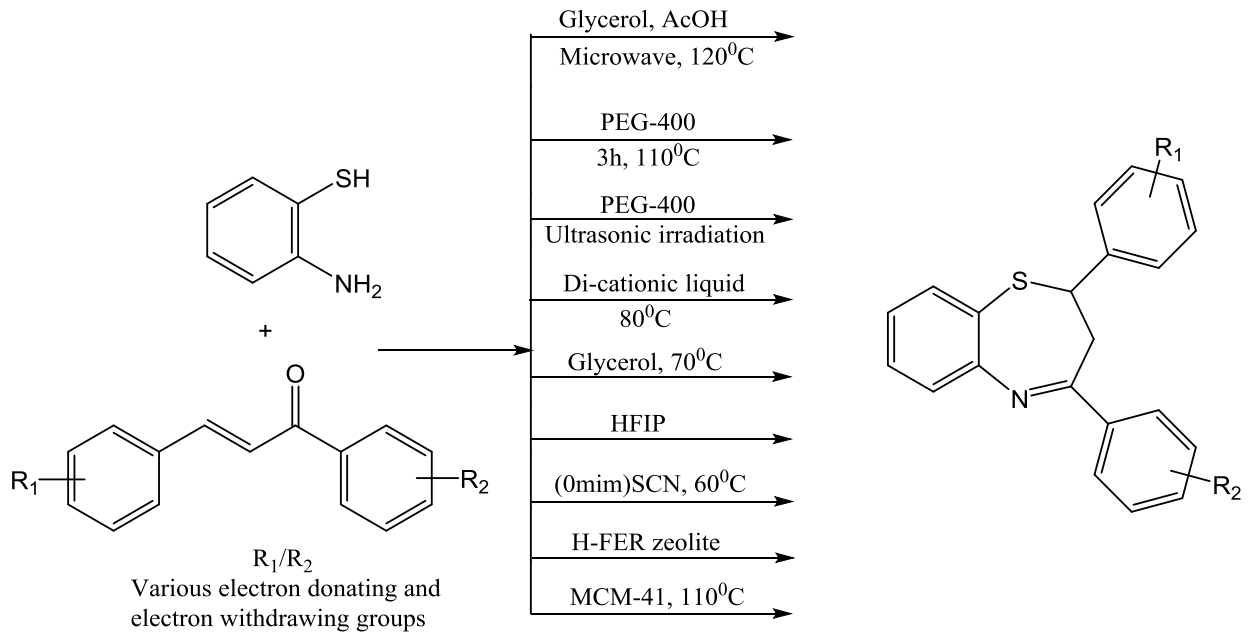


Figure II. Different synthetic routes of synthesis of 1,5-Benzothiazepines[3]

2. REVIEW

2.1 Antimicrobial

Antimicrobial agents

In recent years, the emergence and rapid spread of antimicrobial resistance have become a major global health concern, emphasizing the urgent need for novel and more effective antimicrobial agents. Antimicrobial medication is necessary to treat illness caused on by microorganisms. Antimicrobial medicines that are now in the market are insufficient to counteract the impact of microorganisms. Resistance to a variety of antimicrobial medications for clinically relevant bacteria species has arisen as a global issue. The issue that have led to this situation include systemic toxicity, hypersensitivity and a limited antibacterial spectrum. As a result, the growing clinical significance of drug-resistant microbial infections has made the creation of new antimicrobial medicines essential for mankind. Therefore, there is a larger need to design and develop potent antimicrobial medications with improved features, such as selectivity, potency, shorter treatment durations and less toxicity to tackle microbial infections.[5]

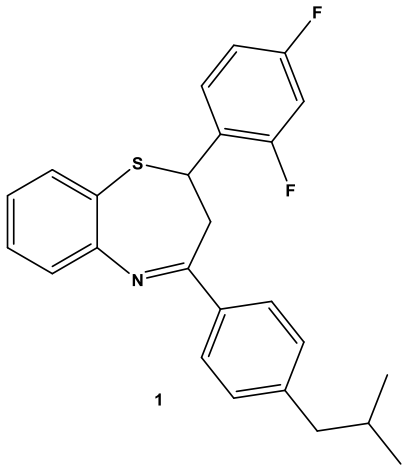
Antimicrobial activity

Among the various pharmacological activities exhibited by benzothiazepine derivatives, their antimicrobial potential has been of particular interest to researchers. 1,5-Benzothiazepines have demonstrated significant antimicrobial activity against a wide range of gram-positive and gram-negative bacteria, as well as various fungal strains. The incorporation of different substituents on the benzothiazepine ring system notably affects their potency, with certain electron-withdrawing or hydrophobic groups enhancing antimicrobial efficacy. The activity is likely due to interactions with microbial enzymes, membrane disruption or inhibition of nucleic acid synthesis. Studies suggest that these compounds can serve as valuable scaffolds for the development of new antimicrobial agents, especially in the context of rising drug resistance. However, further pharmacodynamic, pharmacokinetic and in vivo studies are needed to validate their therapeutic potential.[6]

In support of these findings, several studies have reported the synthesis and biological evaluation of 1,5-benzothiazepine derivatives, highlighting their notable antimicrobial potential.

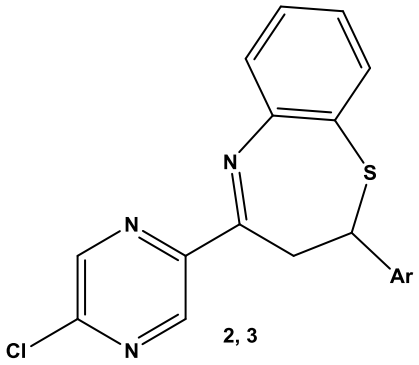
REVIEW

The development of new antimicrobial agents is crucial to combat the increasing resistance of pathogens to existing drugs. AB Shaik et al., were reported synthesis and antimicrobial evaluation of novel 1,5-benzothiazepine derivatives. In vitro antimicrobial activity of synthesized compounds were screened by serial tube dilution method and minimum inhibitory concentration method. The compounds with halogens showed very promising activity. Among the halogens, fluorine substituted compound 1 exhibited superior antimicrobial activity with MIC 0.4 µg/mL than the standard drugs amoxicillin and fluconazole against all the strains.[5]



1

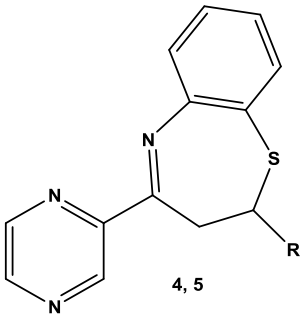
Benzothiazepine derivatives have emerged as promising scaffolds in medicinal chemistry due to their diverse biological activities, including antibacterial and antitubercular effects. AB Shaik et al., were reported synthesis and biological evaluation of chloropyrazine conjugated benzothiazepine derivatives as antibacterial, antitubercular and cytotoxic agents. Compounds 2 and 3 of benzothiazepines shown substantial antibacterial (MICs 38.02 µM, 19.01 µM) and antitubercular (MIC 18.10 µM) activity. Ciprofloxacin was used as positive control for antibacterial studies and fluconazole for antifungal activity.[7]



2, 3

Compound	Ar
2	2,4-dichlorophenyl
3	3,4,5-trimethoxyphenyl

The search for novel heterocyclic compounds with enhanced antimicrobial properties continues to be a key focus in drug discovery. KP SA et al., were synthesized design, characterization and antimicrobial activity of some novel substituted 1,5-benzothiazepine derivatives. All produced compounds shown good efficacy against the examined microorganisms. Among these, compounds bearing chlorine 4 and nitro 5 substitution has shown good activity against all the tested bacteria and fungi. Antibacterial and antifungal activity of the synthesized derivatives were done in comparison with ofloxacin and fluconazole as reference.[8]

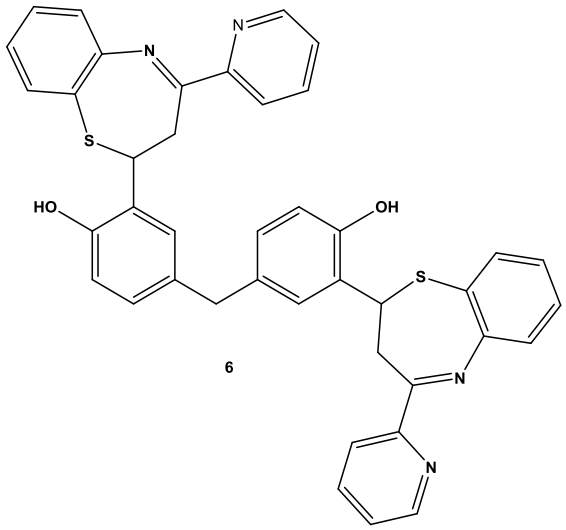


4, 5

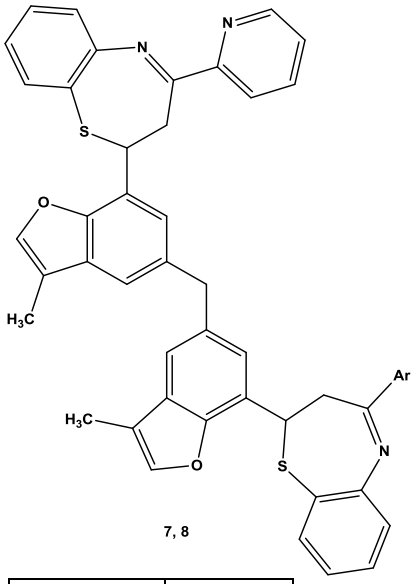
Compound	R
4	4-chlorophenyl
5	4-nitrophenyl

Dimeric and hybrid benzothiazepine derivatives have attracted attention due to their potential to enhance antimicrobial efficacy compared to their monomeric counterparts. C Sanjeeva Reddy et al., were reported synthesis and in vitro evaluation of novel methylenebis (phenyl-1,5-benzothiazepine) and methylenebis (benzofuryl-1,5-benzothiazepine) antimicrobial compounds. The antimicrobial activity and antifungal activity were done by broth dilution method. Among the compound tested, dimeric compounds 6, 7 and 8 were found to be most active against all the microorganisms employed both for antibacterial and antifungal activity.

Amphotericin B, streptomycin and penicillin were used as standard for antimicrobial and antibacterial activity respectively.[9]



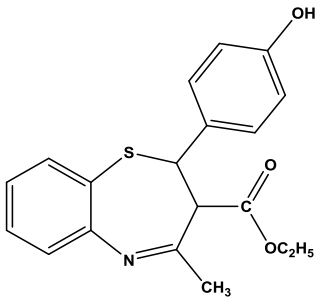
6



7, 8

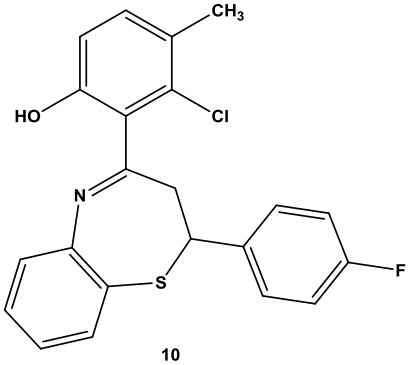
Compound	Ar
7	2-furyl
8	2-pyridyl

The exploration of novel 1,5-benzothiazepine derivatives continues to be an important strategy in developing effective antimicrobial agents. L Wang et al., were reported synthesis and biological evaluation of a novel series of 1,5-benzothiazepine derivatives as potential antimicrobial agents. The synthesized compounds were tasted for their antimicrobial (antibacterial and antifungal) activities by standardized disk diffusion methods. Compound 9 showed good biological activity against bacteria S. aureus and S. epidermidis and fungus C. albicans at 200 µg/disc. Fluconazole was used as a standard drug against fungi and vancomycin against bacteria.[10]



9

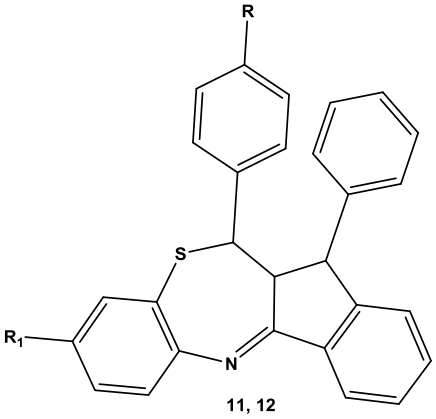
Fluorinated benzothiazepine derivatives have gained interest due to their enhanced antimicrobial and antifungal potential. D S Ghotekar et al., were reported synthesis of some biologically important fluorinated 3-chlorochromones and 1,5-benzothiazepines as antimicrobial and antifungal agents. All the newly synthesized compounds were screened for their in vitro antimicrobial activity against gram +ve organisms Pseudomonas aeruginosa and Staphylococcus aureus and gram -ve organism E. coli using paper disc diffusion method. Compound 10 has shown better activity for gram +ve bacteria Staphylococcus aureus. Antifungal activity is evaluated by using ketoconazole against Candida as standard. Gentamycin and cefixime were used as reference drugs.[11]



10

Indane-based benzothiazepine derivatives have emerged as promising candidates for antimicrobial drug development due to their structural diversity and biological potential. Mor et al., were reported synthesis of indane-based 1,5-benzothiazepines derived from 3-phenyl-2,3-dihydro-1H-indane-1-one and their antimicrobial studies and they carried out the in vitro antimicrobial screening of all the synthesized indane based 1,5-benzothiazepine against two gram-positive bacterial strains, namely, Bacillus subtilis and S. epidermidis; two gram-negative bacterial strains, E. coli and P. aeruginosa and two fungal strains, C. albicans and A. niger by using serial dilution method. The compounds 11 and 12 can be considered as potent antibacterial

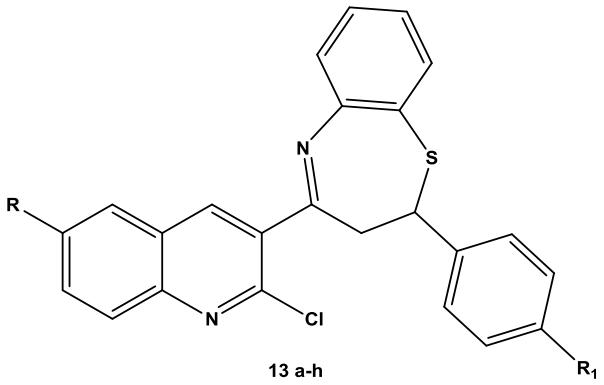
agents as compared with the standard ciprofloxacin and fluconazole.[12]



11, 12

Compound	R	R_1
11	F	Br
12	F	Cl

Quinoline-containing benzothiazepine derivatives have attracted attention for their potential antimicrobial properties, offering a promising approach in the search for new bioactive compounds. KM EI-Gaml et al., were reported synthesis and antimicrobial screening of new chalcones and 1,5-benzothiazepines containing quinoline nucleus. The cup plate agar diffusion method was employed for determining the antimicrobial activity of the newly synthesized compounds. 1,5-benzothiazepines 13 a-h showed moderate antimicrobial activity. The discussion and comparison of antibacterial activity were given with respect to ampicillin antibiotic and antifungal screening was compared with nystatin.[13]



13 a-h

Compound	R	R_1	Compound	R	R_1
13a	H	Cl	13e	NO_2	Cl
13b	H	OCH_3	13f	NO_2	OCH_3
13c	CH_3	Cl	13g	Br	Cl
13d	CH_3	OCH_3	13h	Br	OCH_3

2.2 Anticonvulsant

Anticonvulsant Agents

The search for novel heterocyclic compounds with central nervous system activity has highlighted 1,5-benzothiazepines as promising candidates for anticonvulsant drug development. 1,5-Benzothiazepines are a class of heterocyclic compounds that have attracted significant attention in medicinal chemistry due to their diverse pharmacological activities. Among these, their potential as anticonvulsant agents is particularly noteworthy. Epilepsy, a neurological disorder characterized by recurrent seizures, demands the development of novel agents with improved efficacy and reduced side effects. The 1,5-benzothiazepine scaffold allows for versatile structural modifications that can interact with central nervous system (CNS) targets, such as GABA receptors and ion channels, which play crucial roles in seizure generation and propagation. Various studies have shown that 1,5-benzothiazepine derivatives possess significant anticonvulsant activity in experimental models such as MES (Maximal Electroshock Seizure) and PTZ (Pentylenetetrazole-induced seizure) tests, suggesting their potential as leads for new antiepileptic drugs.[14]

Anticonvulsant Activity

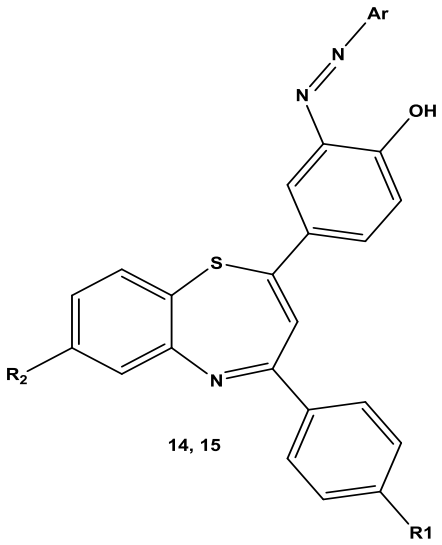
Recent research has increasingly focused on 1,5-benzothiazepine derivatives for their anticonvulsant potential, highlighting the importance of structural modifications in optimizing their efficacy. 1,5-Benzothiazepine have emerged as promising scaffolds for the development of new anticonvulsant agents due to

their favourable interaction with central nervous system targets, including GABAergic and glutamatergic systems. Various substituted derivatives of 1,5-benzothiazepines have exhibited significant anticonvulsant activity in animal models such as the maximal electroshock seizure (MES) and pentylenetetrazole (PTZ) induced seizure tests. Structure-activity relationship (SAR) studies suggest that electron-donating or electron-withdrawing substituents at specific positions on the benzothiazepine ring can modulate the potency and spectrum of anticonvulsant effects. These findings support the potential of 1,5-benzothiazepines as lead compounds for the development of novel antiepileptic drugs, although further pharmacokinetic and clinical investigations are necessary to confirm their therapeutic viability.[15]

Building on this pharmacological potential, several studies have focused on the synthesis of novel 1,5-benzothiazepine derivatives to evaluate their anticonvulsant efficacy in experimental models.

REVIEW

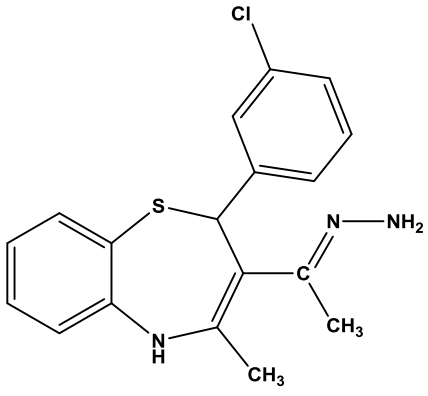
1,5-Benzothiazepine derivatives have been explored not only for their antimicrobial potential but also for central nervous system activities, including anticonvulsant effects. SK Parjane et al., were reported synthesis of certain new 1,5-benzothiazepine derivatives and biological testing for anticonvulsant potency. The anticonvulsant activity was determined using MES (maximal Electroshock Method). Compound 14 and 15 showed significant anti-seizure activity in the MES model compared to the standard phenytoin sodium.[16]



14, 15

Compound	R_1	R_2
14	NH_2	H
15	CH_3	H

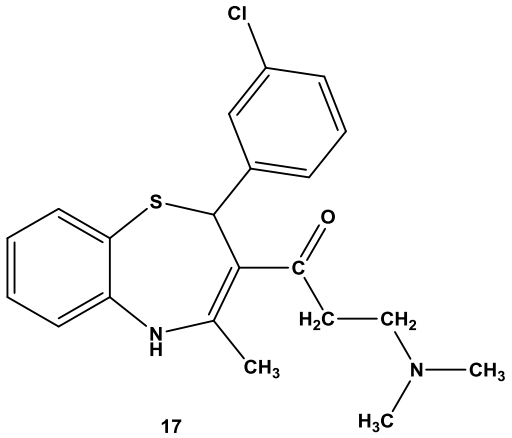
Substituted 1,5-benzothiazepine derivatives continue to be investigated for their anticonvulsant activity, with structural modifications aimed at enhancing efficacy and reducing toxicity. VK Chaudhari et al., were reported synthesis, preliminary anticonvulsant and toxicity screening of substituted {1-[4-Methyl-2-substitutedphenyl-2,5-dihydro-1,5-benzothiazepin-3-yl]-ethylidene}-hydrazide. The preliminary evaluation of newly synthesized molecules anticonvulsant efficacy using the maximal electroshock model. Based on anticonvulsant screening result, the most potent derivative was found 16 and phenytoin was used as standard.[17]



16

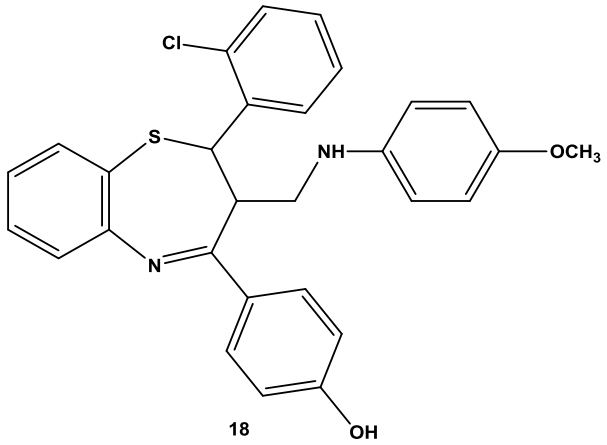
Recent studies have focused on modifying 1,5-benzothiazepine derivatives to improve anticonvulsant efficacy while minimizing neurotoxicity. VK Chaudhari et al., were reported synthesis, preliminary

anticonvulsant and toxicity screening of substituted 3-(Dimethyl/Diethylamino)-{1-[4-methyl-2-substitutedphenyl-2,5-dihydro-1,5 benzothiazepin-3-yl]}propane-1-one. All new synthesized compounds were evaluated for anticonvulsant activity using maximum electroshock induced seizure. The best significant synthesized compound 17 found as a primary class of anticonvulsants that have shown practically identical anticonvulsant action with uniquely lower neurotoxicity. Phenytoin was used as standard drug.[18]



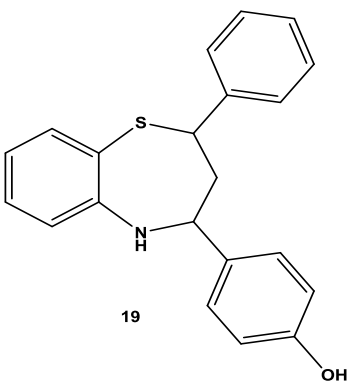
17

Benzothiazepine and benzoxazepine derivatives have been widely investigated for their potential as anticonvulsant agents due to their structural versatility and promising pharmacological profiles. N Garg et al., were reported synthesis and evaluation of some new substituted benzothiazepine and benzoxazepine derivatives as anticonvulsant agents. All of these drugs were tested in vivo for their anticonvulsant efficacy and acute toxicity. Compound 18 was found to be most potent compound of this series and was compared with the reference drug phenytoin sodium.[19]



18

In silico approaches, such as molecular docking, have become valuable tools for predicting the anticonvulsant potential of novel 1,5-benzothiazepine derivatives. MP Smita et al., were reported in silico design of potential 1,5-benzothiazepine derivatives as anticonvulsant agent by molecular docking studies. Atu2422-GABA receptor was used as target. The binding scores for all the compounds ranged from -82.61 to -118.25 kcal/mol. Most active compounds form hydrogen bond interactions with LEU282B. Protein indicated hydrogen bonding with all produced compounds, indicating potential against epilepsy via GABA nergic pathway. It was noted that the docking score of 19 and 20 was almost same as that of selected reference phenytoin sodium.[20]



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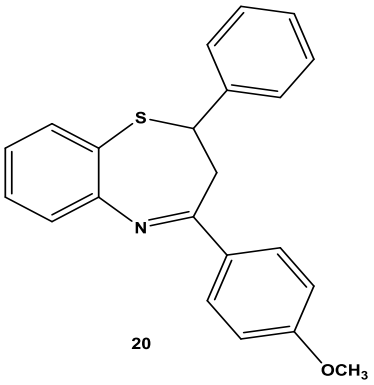


20

2.3 Anticancer

Anticancer agents

The search for novel heterocyclic scaffolds with potent anticancer activity has highlighted 1,5-benzothiazepines as promising candidates for drug development. 1,5-Benzothiazepines are a class of heterocyclic compounds characterized by a seven-membered diazepine ring fused to a benzene and thiazole moiety. Their unique chemical structure offers versatile sites for substitution, which enables fine-tuning of biological activity. In recent years, 1,5-benzothiazepines have garnered attention in medicinal chemistry for their broad spectrum of pharmacological properties, including anticancer potential. These compounds exhibit antiproliferative effects through various mechanisms such as tubulin polymerization inhibition, apoptosis induction and kinase modulation. As cancer remains a major global health burden, 1,5-benzothiazepines provide a promising scaffold for the development of novel chemotherapeutic agents with improved efficacy and reduced toxicity.[21]

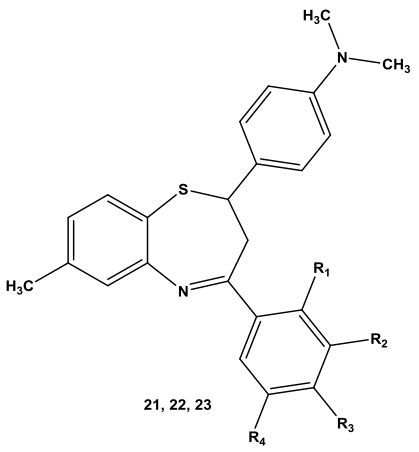
Anticancer activity

In the ongoing search for effective chemotherapeutic agents, heterocyclic scaffolds like 1,5-benzothiazepines have emerged as promising candidates due to their versatile biological activities. 1,5-Benzothiazepines are a class of heterocyclic compounds that have attracted significant attention in medicinal chemistry due to their diverse biological activities, including anticancer potential. The benzothiazepine scaffold allows for structural modifications, making it suitable for interaction with various cellular targets involved in cancer progression, such as kinases, microtubules and topoisomerases. These compounds have been reported to exhibit cytotoxic effects against a variety of human cancer cell lines, including breast, lung and colon cancers. The anticancer activity of 1,5-benzothiazepines is attributed to their ability to induce apoptosis, inhibit cell proliferation and disrupt the cell cycle. Their promising pharmacological profile makes them valuable leads in the development of novel anticancer agents.[22]

Building on their recognized anticancer potential, several studies have focused on the synthesis and evaluation of novel 1,5-benzothiazepine derivatives to assess cytotoxic activity against various cancer cell lines.

REVIEW

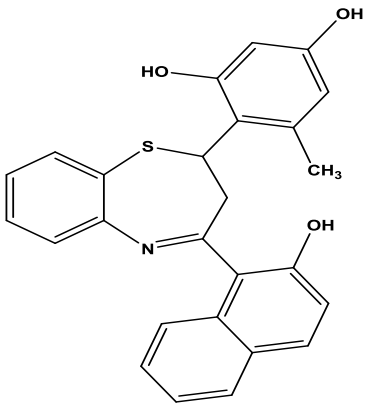
1,5-Benzothiazepine derivatives have also been explored for their anticancer potential, combining green synthesis approaches with in silico and in vitro evaluations. M Haroun et al., were reported 1,5-benzothiazepine derivatives: green synthesis, in silico and in vitro evaluation as anticancer agents. The synthesized pure benzothiazepine derivatives were tested for in vitro cytotoxicity using the MTT assay in two human cancer cell lines, liver (Hep-2) and prostate (DU-145) as well as human embryonic liver cell lines (L02), for selectivity toxicity. Three molecules 21, 22 and 23 of the present series of benzothiazepine presented promising cytotoxic activities against the tested cancer cell lines in comparison with the standard drug methotrexate.[23]



21, 22, 23

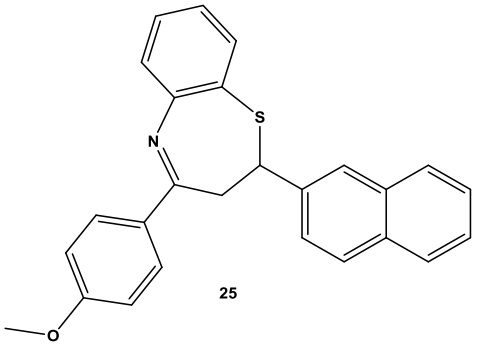
Compound	R_1	R_2	R_3	R_4
21	OH	Cl	H	Cl
22	OH	Br	H	Cl
23	OH	H	H	Br

Substituted 1,5-benzothiazepine derivatives have been investigated for their cytotoxic potential against various cancer cell lines, aiming to identify compounds with enhanced anticancer activity. PK Borra et al., were reported synthesis, characterization and cytotoxicity studies of novel 2,4-substituted-1,5-benzothiazepines using MTT assay. The compound 24 was the most active against the HT-29, MCF-7 and DU-145 cell lines, with IC_{50} values of 68 g/mL, 89 g/mL and 43 g/mL respectively. Methotrexate was used as standard drug.[24]



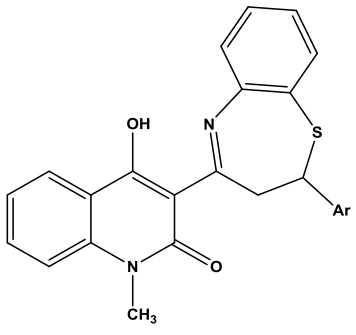
24

Chalcone-based 1,5-benzothiazepine derivatives have attracted attention for their potential as breast cancer inhibitors, with combined in silico and in vitro studies guiding their evaluation. N Frimayanti et al., were reported insight on the in silico study and biological activity assay of chalcone-based 1,5-benzothiazepines as potential inhibitor for breast cancer MCF-7. MTT assay were performed for compounds. Docking results reported that compound 25 with binding free energy of -11.2 kcal/mol can interact through hydrogen bonds with amino acids Cys788 on 1T46 protein active site. 25 is also shown to have drug likeness properties based on ADME prediction. Compound 25 with the best calculated anticancer properties revealed the best inhibition against MCF-7 cell line in vitro. Doxorubicin was used as reference drug.[25]



25

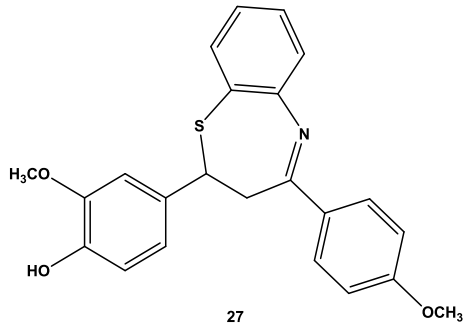
Quinoline-based hybrid 1,5-benzothiazepine derivatives have been investigated for their anticancer potential, integrating in vitro cytotoxic assays with ADMET and molecular docking studies to identify promising candidates. DN Toan et al., were reported synthesis, cytotoxic activity, ADMET and molecular docking study of quinoline-based hybrid compounds of 1,5-benzothiazepines. All synthesized compounds 26 a-g were evaluated for in vitro anticancer activity against two cancer cell lines, human squamous cell carcinoma (KB) and hepatocellular carcinoma (HepG2). Compounds 26c and 26g exhibited remarkable inhibitory activity against the tested cancer cell lines with MIC values of 0.25-0.27 and 0.26-0.28 µm, respectively. Docking results indicated that residues GLN778(A), DA12(F) and DG13(F) in the binding pocket as potential ligand binding hot-spot residues for compounds 26c and 26g. Ellipticine was used as standard drug.[26]



26c, 26g

Compound	Ar
26c	4’’-$MeOC_6H_4$
26g	2”-Thienyl

Vanillin-derived benzothiazepine and benzodiazepine derivatives have been explored for their dual potential as anticancer and antioxidant agents. BS Kittur et al., were reported synthesis, investigation of anticancer and antioxidant activity of certain 2,4-diaryl substituted benzodiazepine and benzothiazepines derived from vanillin. The title compounds were tested for anticancer activity against A549 (a lung carcinoma cell line) using MTT and antioxidant activity using DPPH radical scavenging tests. Among the compounds evaluated in the series, compound 27 emerged showing highly active anticancer and antioxidant activity with IC_{50} value of 19.20µM and 0.023µM respectively. 5-Fluorouracil and ascorbic acid were used as standard drugs.[27]



27

2.4 Anti-inflammatory

Anti-inflammatory agents

Chronic inflammation is a major contributor to the development and progression of numerous diseases, highlighting the need for therapeutic interventions that can effectively control inflammatory responses. Inflammation is a complex biological response of body tissues to harmful stimuli such as pathogens, damaged cells and it plays a crucial role in the progression of various chronic diseases including arthritis, cardiovascular disorders and cancer. Despite the widespread use of non-steroidal anti-inflammatory drugs (NSAIDs), their long-term use is often associated with adverse effects such as gastrointestinal irritation and cardiovascular risks. Therefore, the search for safer and more effective anti-inflammatory agents continues to be an active area of medicinal chemistry research.

In this context, 1,5-benzothiazepine derivatives have attracted attention as potential anti-inflammatory agents due to their ability to modulate key mediators of inflammation while offering opportunities for structural optimization. Heterocyclic compounds, especially those containing sulfur and nitrogen atoms, have garnered significant interest due to their diverse biological activities. Among them, 1,5-benzothiazepines have emerged as a promising class of compounds with potential anti-inflammatory properties. Their unique tricyclic structure allows for versatile modifications, which can enhance their interaction with key targets in the inflammatory pathway, such as cyclooxygenase (COX) enzymes, lipoxygenase and inflammatory cytokines. Several studies have reported that derivatives of 1,5-benzothiazepines exhibit notable anti-inflammatory effects in in vivo and in vitro models, making them attractive scaffolds for drug development.[28]

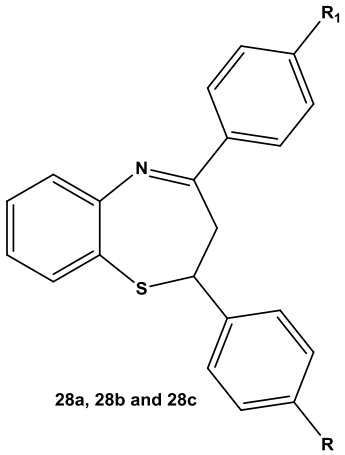
Anti-inflammatory activity

In recent years, heterocyclic scaffolds have gained attention for their potential to provide safer and more effective alternatives to conventional anti-inflammatory drugs. 1,5-Benzothiazepines have demonstrated noteworthy anti-inflammatory activity in both in vitro and in vivo models. These compounds are believed to exert their effects through inhibition of pro-inflammatory mediators such as prostaglandins (via COX-2 inhibition), cytokines (e.g., TNF-α, IL-6) and reactive oxygen species. Structure activity relationship (SAR) studies indicate that substitution at specific positions on the benzothiazepine ring significantly enhances anti-inflammatory potential. Compared to standard NSAIDs, some benzothiazepine derivatives show comparable or superior efficacy with potentially lower gastrointestinal toxicity. These findings support their further development as potential therapeutic agents for inflammatory diseases.[29]

Building on these promising pharmacological properties, several studies have focused on the synthesis and evaluation of specific 1,5-benzothiazepine derivatives to assess their anti-inflammatory and antioxidant activities.

Review

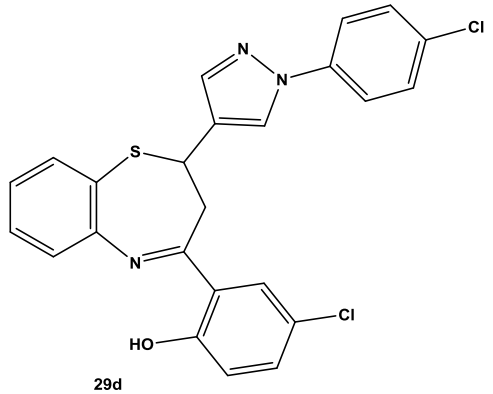
Benzothiazepine derivatives derived from substituted chalcones have been investigated for their potential anti-inflammatory and antioxidant activities. PN Balaji et al., were reported approach on design, synthesis and evaluation of pharmacophore benzothiazepine from substituted chalcones. In vitro anti-inflammatory activity was done by inhibition of protein denaturation method. Compound 28a, 28b and 28c shows significant activity studies on anti-inflammatory and antioxidant activity as compared with in vitro standard drug diclofenac sodium.[30]



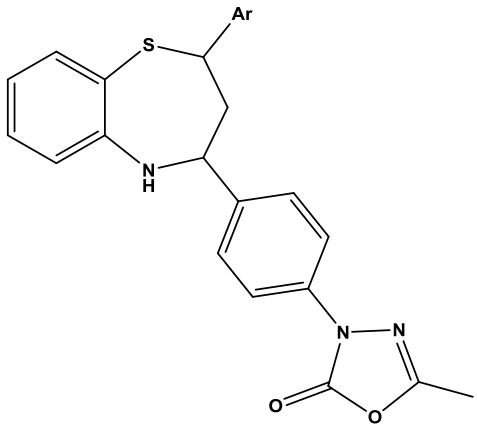
28a, 28b and 28c

Compound	R	R_1
28a	m-OH, p-OCH_3	p-Cl
28b	3,4,5-tri OCH_3	P-OH
28c	m-Cl	p-OH

1,5-Benzothiazepine derivatives have been extensively studied for their anti-inflammatory potential, with structural modifications aimed at enhancing efficacy. GR Mhaske et al., were reported synthesis and evaluation of novel 1,5-benzothiazepine derivatives as anti-inflammatory agents. All the newly synthesized benzothiazepines 29 a-g were screened for their in vivo anti-inflammatory activity by paw edema method. Among all tested compounds, chloro-substituted benzothiazepine derivative 29d showed the highest anti-inflammatory activity (10.89% inhibition) that was comparable to diclofenac (14.21% inhibition).[31]



29d



30 a-d

The development of novel 1,5-benzothiazepine derivatives continues to focus on their potential as effective anti-inflammatory agents. RR Kamble et al., were reported synthesis and pharmacological evaluation of 1,5-benzothiazepine derivatives. Anti-inflammatory activity was measured using the carrageenan induced paw edema test in rats. Compounds 30 a-d showed good anti-inflammatory activity. Ibuprofen was used as standard drug.[32]

Compound	Ar
30a	C_6H_5
30b	p-BrC_6H_4
30c	p-$CH_3C_6H_4$
30d	C_6H_4

2.5 Antidiabetic

Antidiabetic Agents

The global prevalence of type 2 diabetes and its associated complications has driven ongoing research into novel antidiabetic agents. Diabetes mellitus, specifically type 2 diabetes, is a chronic metabolic condition marked by insulin resistance and poor glucose metabolism. The search of new therapeutic agents with better efficacy and fewer side effects remains a significant challenge. Heterocyclic compounds, especially those containing sulphur and nitrogen, have shown great potential in drug discovery due to their broad spectrum of biological activities.

In this context, 1,5-benzothiazepine derivatives have emerged as promising scaffolds for the development of antidiabetic agents due to their ability to target multiple pathways involved in glucose homeostasis. Among these, 1,5-benzothiazepines have attracted considerable attention owing to their versatile pharmacological properties, including antihypertensive, anti-inflammatory, anticancer and antidiabetic activities. The unique structural motif of 1,5-benzothiazepines enables interactions with various biological targets involved in glucose regulation. Recent studies have reported that certain derivatives of 1,5-benzothiazepines exhibit promising antidiabetic activity through mechanisms such as α-glucosidase inhibition, enhancement of insulin sensitivity and modulation of peroxisome proliferator-

activated receptors (PPARs), making them potential candidates for the development of novel antidiabetic agents.[33]

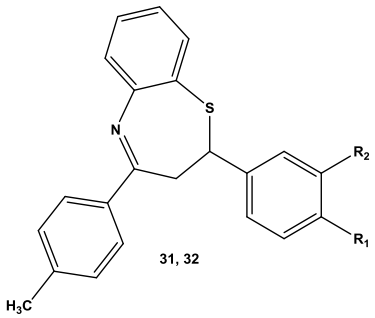
Antidiabetic Activity

Recent research has increasingly focused on exploring 1,5-benzothiazepine derivatives for their potential to regulate blood glucose levels and improve metabolic outcomes in diabetes. 1,5-Benzothiazepines have shown promising antidiabetic activity, primarily through mechanisms such as enhancement of insulin sensitivity, inhibition of α-glucosidase and stimulation of glucose uptake. Structural modifications on the benzothiazepine ring especially the introduction of electron-withdrawing or hydrophilic substituents can significantly influence their biological activity. Some derivatives have demonstrated significant blood glucose-lowering effects in diabetic animal models, comparable to standard antidiabetic agents like metformin or glibenclamide. These findings suggest that 1,5-benzothiazepine are valuable lead compounds for the development of new oral antidiabetic drugs, through further pharmacological and clinical studies are needed to confirm their therapeutic potential.[34]

To further explore their antidiabetic potential, several studies have focused on the synthesis and evaluation of 1,5-benzothiazepine derivatives as α-glucosidase inhibitors and other modulators of glucose metabolism.

Review

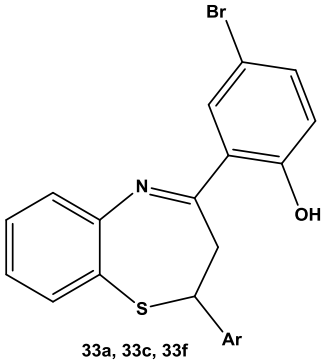
1,5-Benzothiazepine derivatives have been explored for their potential as α-glucosidase inhibitors, offering promising strategies for the management of diabetes. R Mehmood et al., were reported synthesis of novel 2,3-dihydro-1,5-benzothiazepines as α-glucosidase inhibitors: in vitro, in vivo, kinetic, SAR, molecular docking and QSAR studies. Compounds 31 and 32 showed potency with IC_{50} values of 2.62 ± 0.30 and 3.01 ± 0.29 µM respectively, as compared to standard acarbose.[35]



31, 32

Compound	R_1	R_2
31	OCH_3	OCH_3
32	OCH_3	H

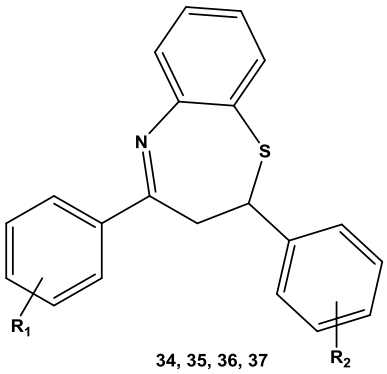
Recent studies have focused on 2-aryl-substituted benzothiazepine derivatives for their potential as α-glucosidase and α-amylase inhibitors in the management of diabetes. JK Nkoana et al., were reported synthesis, conformational analysis and evaluation of the 2-aryl-4-(4-bromo-2-hydroxyphenyl)benzo[1,5] thiazepines as potential α-glucosidase and α-amylase inhibitors compounds 33a, 33c and 33f exhibited increased inhibitory activity against α-glucosidase compared to acarbose(IC_{50} = 7.56 ± 0.42 µM) with IC_{50} values of 6.70 ± 0.15 µM, 2.69 ± 0.27 µM and 6.54 ± 0.11 µM respectively.[36]



33a, 33c, 33f

Compound	Ar
33a	C_6H_5
33c	C_6H_4 (4-Cl)
33f	C_6H_4 (4-isopropyl)

Chalcone-based 1,5-benzothiazepine derivatives have gained attention for their potential as multifunctional bioactive agents, including α-glucosidase inhibition and antioxidant activity. FL Ansari et al., were reported synthesis and biological activities of chalcone and 1,5-benzothiazepine derivatives: promising new free-radical scavengers and esterase, urease and α-glucosidase inhibitors. Compound 34, 35, 36 and 37 were found to be potent inhibitors of α-glucosidase with their IC_{50} values 12.8 ± 2.01, 12 ± 2.2, 11.9 ± 2.66 and 12 ± 1.2 µM respectively, as compared to standard deoxynojirimycin.[37]



34, 35, 36, 37

Compound	R_1	R_2
34	2-OH	H
35	2-OH	4-F
36	2-OH	4-OCH_3
37	2-OH	4-CH_3

CONCLUSION

1,5-Benzothiazepine derivatives have emerged as one of the most versatile heterocyclic scaffolds in medicinal chemistry, exhibiting an extensive range of biological activities that include antimicrobial, anticonvulsant, anticancer, anti-inflammatory and antidiabetic properties. The diversity in pharmacological potential is primarily attributed to the structural flexibility of the benzothiazepine ring, which allows fine-tuning of activity through strategic substitution with various electron-withdrawing and hydrophilic groups. Numerous studies have demonstrated that halogenated, heteroaryl and fused analogues significantly enhance potency and selectivity toward specific therapeutic targets.

Advances in synthetic methodologies, coupled with computational modeling, molecular docking and structure-activity relationship (SAR) studies, have facilitated the rational design of 1,5-benzothiazepine derivatives with improved pharmacodynamic and pharmacokinetic profiles. Moreover, green and sustainable synthesis approaches have expanded the accessibility of these derivatives for large-scale applications.In conclusion, 1,5-benzothiazepines represent a privileged chemical framework capable of addressing multiple pharmacological targets. Their continued exploration offers substantial opportunities for the discovery and development of next-generation therapeutic agents with enhanced efficacy and reduced toxicity.

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