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Research Article

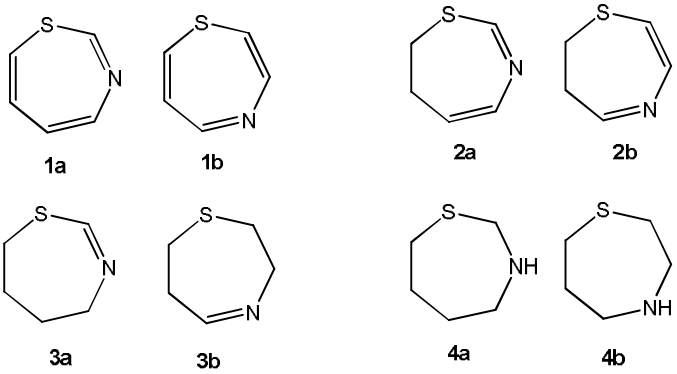
NEW INSIGHTS TO THE CHEMISTRY OF BENZOTHIAZEPINES-AN OVERVIEW

***Ajay Kumar K.[1], Renuka N.[1], Raghavendra K.R.[2], Vasanth Kumar G.[1] and Ranjitha B.K.[1]**
[1]Department of Chemistry, Yuvaraja College, University of Mysore, Mysore, India
[2]Department of Chemistry, Manasa Gangothri, University of Mysore, Mysore, India
**Author for Correspondence*

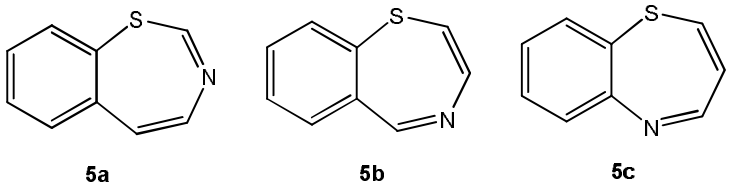
ABSTRACT
The compounds containing the benzothiazepine moiety are important targets in synthetic and medicinal chemistry. Benzothiazepines are widely found as the core structure in a large number of compounds that possess important pharmaceutical activities. These have been the recent target of numerous methodologies due to their prevalence as scaffolds in synthesis of bioactive compounds. The main objective of this review is to provide an up to date information about the synthetic methodologies developed, chemical transformation to bioactive molecules and pharmacological application associated with benzothiazepines with a more emphasis on 1,4-benzothiazepines and 1,5-benzothiazepines.

Keywords: *Benzothiazepines, Cyclocondensation, Microwave, Antimicrobial, Antioxidant, Anti-inflammatory*

INTRODUCTION
Thiazepines are the important members of seven membered heterocyclic compounds that contain nitrogen and sulfur atoms in a ring system. Depends upon the position of the nitrogen and sulfur atoms in a ring, these were categorized in to 1,3-thiazepine (**1a**) and 1,4-thiazepine (**1b**). The partially reduced forms of thiazepines are named as dihydrothiazepines (**2a-b**) and tetrahydrothiazepines (**3a-b**); while completely reduced forms are thiazapanes (**4a-b**).



Benzothiazepines are the fused heterocycles in which the thiazepine ring is fused to an aromatic ring. Depends upon the position of the nitrogen and sulfur atoms in a seven membered ring that fused to the benzene ring; Benzothiazepines are categorized in to 1,3-benzothiazepine (**5a**) and 1,4-benzothiazepine (**5b**) and 1,5-benzothiazepine (**5c**).



Research Article

Thiazepines are considered as lead molecules that occupy a prime position in medicinal chemistry for their enormous amount of diverse biological activities. They have been known to exhibit antiarrhythmic, antispasmodic, angiogenic, antimicrobial, analgesic, anticancer, anti-inflammatory, antidepressant, anticonvulsant, antihyperglycemic, antipyretic and antioxidant properties. The thiazepine moiety is present as the core in a variety of leading drugs. The thiazepine skeleton was found to be building block in organic synthesis for designing bioactive pharmaceuticals.

1,4-Thiazepine is a privileged structure because of its presence in a number of pharmacologically important compounds. Several derivatives of 1,4-thiazepine fragments are present in a wide range of natural and synthetic biologically active agents. Among these, analogs of 1,4-thiazepines fused with aryl and heteroaryl moieties represent an important class of compounds with interesting pharmacological properties.

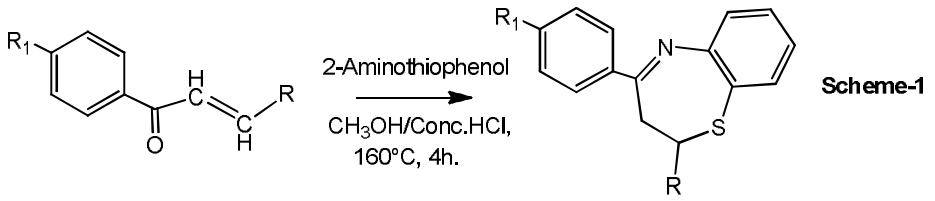
Among the classes of nitrogen and sulfur heterocycles, benzothiazepines plays a prominent role in synthetic and bioorganic chemistry for their greater susceptibility as building blocks in the construction of versatile biologically active molecules. 1, 4-Benzothiazepine derivatives are known to exhibit biological activities such as inhibitors of HIV-1 integrace, enzyme inhibitors, calcium channel blockers, antitumor agents, sedatives and hypnotics, antibiotics, anti histamine, anxiolytic and antioxidant activities. Herein, an attempt has made to sum up the recent developments in the field of benzothiazepines. This review article briefs survey on the developments in the field of benzothiazepines. The critical discussion has made on the strategies adopted for the synthesis, chemical application to transform them in to bioactive molecules and their pharmaceutical applications with a more emphasis on 1,4-benzothiazepines and 1,5-benzothiazepines in recent times.

1,4-Benzothiazepines

The broad spectrum of clinical importance and commercial success associated with pharmacologically active benzothiazepines has led to their recognition as lead molecules in medicinal field which has made them popular synthetic targets. Chalcones forms the central core for the synthesis variety of bioactive molecules. These are considered as key intermediates in the synthesis of medicinally important heterocycles such as 1,4-benzothiazepines (Manjula *et al.*, 2013) and pyrazolines (Manjula *et al.*, 2013), (Jayaroopa *et al.*, 2013).

Synthesis

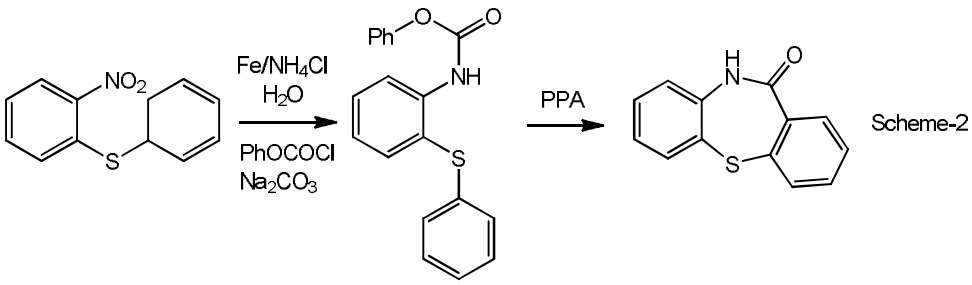
The 1,4-thiazepine ring is one of important moieties in nitrogen-and sulfur-containing heterocycles and has been widely used as key building block for pharmaceutical agents as well as biologically active compounds. Numerous methods have been developed for synthesis of 1,4-benzothiazepines, of them cyclocondensation reaction of α-amino thiophenol with α,β-unsaturated ketones (chalcones) in alkaline conditions was most commonly employed method. For instance, A series of 1,4-benzothiazepines were obtained by the reaction of chalcones and 2-aminothiophenol in the presence of 3-4 drops of conc. HCl in methanol at 160^{o}C in good yields (Scheme-1). The synthesized compounds have shown promising antimicrobial activities (Raghavendra *et al.*, 2014).



Scheme-1

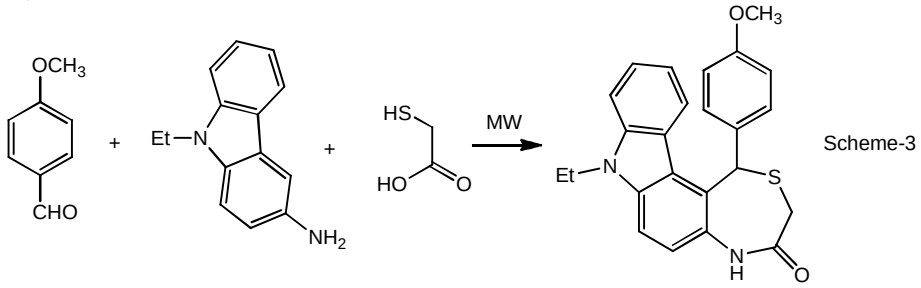
The intramolecular Ugi four-component condensation between 6-oxo-4-thiacarboxylic acids, benzylamines, and cyclohexyl isocyanide gave hexahydro-1,4-thiazepin-5-ones and 1,4-benzothiazepin-5-ones with high stereoselectivity. On the other hand the intramolecular Passerini three-component reaction in the presence of catalytic amine produced tetracyclic 1,4-benzothioxepin orthoamides (Stefano *et al.*, 2003). Dibenzo[b,f][l,4]thiazepine-l,l-(10H)-one is the key intermediate in the synthesis of antipsychotic

agent Quetiapine. A improved process was developed for synthesis of dibenzo[b,f](1,4)-thiazepine-11-(10H)-one (Scheme-2), which involves the reaction of 2-nitro diphenyl sulphide with an aqueous solution of Fe powder and NH_4Cl, followed by treatment with phenyl chloroformate in the presence of sodium carbonate. The resulting 2-(phenylthio)-phenylcarbamate on cyclisation using polyphosphoric acid afforded dibenzo[b, f](1,4)-thiazepine-11-(10H)-ones in excellent yields (Prasad *et al.*, 2013).



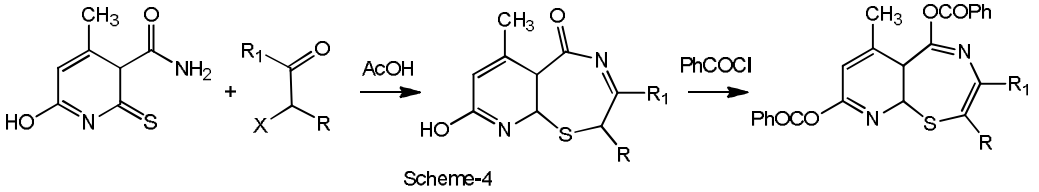
Scheme-2

The design and diversity-oriented synthesis of novel 1,4-thiazepine derivatives embedded with carbazole, pyrazole or isoxazole motif via microwave-assisted multicomponent reactions under solvent-free condition (Scheme-3). The methode provide a green and facile access to 1,4-thiazepine derivatives with prominent features of high structural diversity, short reaction time, high yields and environmental friendliness. These novel compounds have been subjected to the test of in vitro antioxidant and cytotoxic activities. The results of the study indicating that these 1,4-thiazepine derivatives not only have significant antioxidant activity, but also exhibit remarkably selective cytotoxicity to carcinoma cell line HCT 116 (Shi *et al.*, 2012).



Scheme-3

6-Hydroxy-4-methyl-2-thioxo-2,3-dihydropyridine-3-carboxamide reacts with α-haloketones to produce 2,3-disubstituted-8-hydroxy-6-methyl-2H,5H-pyrido[3,2-f]-[1,4]thiazepin-5-ones. These can be efficiently transformed to respective dibenzoate derivative by treating with excess of benzoyl chloride (Scheme-4) (Rasha *et al.*, 2011).

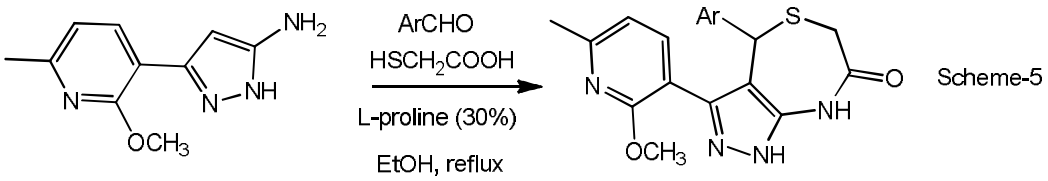


Scheme-4

Pyridothiazepines are important compounds that possess valuable biological activities. A series of 2-arylmethylene-8-hydroxy-6-methyl-2,3,4,5-tetrahydropyrido-[3,2-f][1,4]thiazepine-3,5-diones have been prepared from 6-hydroxy-4-methyl-2-thioxo-2,3-dihydropyridine-3-carboxamide both conventional chemical methods and modern microwave techniques (Ayman *et al.*, 2012). Reaction of ethyl-2-cyano-3,3-dimercaptoacrylate dipotassium salt with 2-chloroethylamine hydrochloride in water afforded the novel (4E,6E)-ethyl 5-amino-2,3-dihydro-7-mercapto-1,4-thiazepine-6-carboxylate. The molecular

geometry of the most stable tautomeric structure was investigated with DFT and AIM at the B3LYP level of theory using the 6-31G** and 6-311+G** basis sets (Bakavoli *et al.*, 2009).

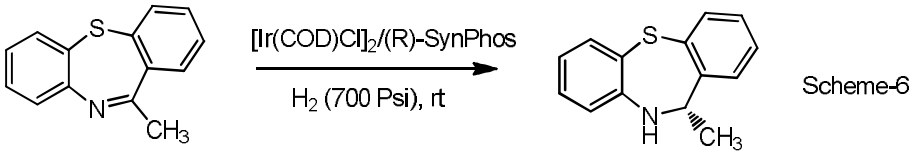
A mild and efficient synthesis of pyrazolo[3,4-e][1,4]thiazepine derivatives through an L-proline catalyzed multi-component reaction was developed (Scheme-5). The synthesized compounds were subjected to in vitro cytotoxicity studies toward pancreas (PANC1), renal (ACHN) and colon (HCT116), non-small cell lung (H460), lung (CALU1), and normal breast epithelium (MCF10A) cell lines. Study revealed that most of the compounds exhibit moderate activity (Srikanth *et al.*, 2015).



Scheme-5

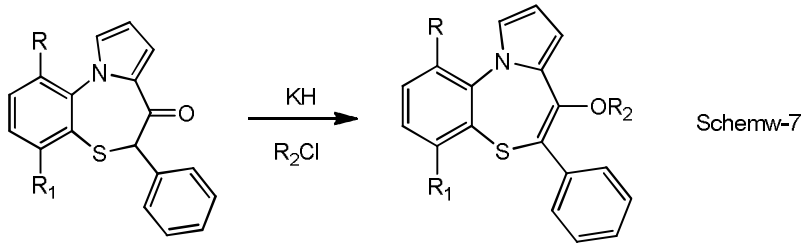
Synthetic Applications

Highly enantioselective hydrogenation of substituted dibenzo[*b,f*][1,4]thiazepines was achieved with up to 96 % ee (enantiomeric excess) using $[Ir(COD)Cl]_2$/(*R*)-SynPhos complex as catalyst in the presence of iodine (Scheme-6). This method proved to be an efficient access to optically active 11-substituted-10,11-dihydrodibenzo[*b,f*][1,4]thiazepines (Ran-Ning *et al.*, 2013).



Scheme-6

A number of new pyrrolobenzothiazepine derivatives and a pyrrolobenzothiazocine derivative have been synthesized (Scheme-7) and evaluated for their affinity towards the 'peripheral-type' benzodiazepine receptor (PBR). The compounds were tested in rat cortex, a tissue expressing a high density of mitochondrial PBR. Some of the pyrrolobenzothiazepines exhibited IC_{50} values in the low nanomolar range as measured by the displacement of [3^H]PK11195 binding. Structure affinity relationships (SARs) have been developed to elucidate the topology of the PBR binding site (Campiani 1997).



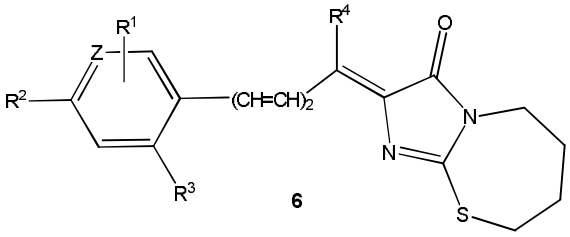
Schemw-7

Pharmaceutical Applications

Derivatives of benzothiazepines have played a crucial role in the history of heterocyclic chemistry and been used as important pharmacores and synthons in the field of organic chemistry and drug designing. A series of 1,4-benzothiazepines obtained by the reaction of chalcones and 2-aminothiophenol in the presence of 3-4 drops of conc. HCl in methanol have shown remarkable antioxidant activities (Renuka *et al.*, 2014).

A series of 5-substituted imidazo[2,1-*b*]thiazepines (**6**) were synthesized and investigated in radio ligand binding studies at the benzodiazepine binding site of GABA receptors in rat brain cortical membranes. Among ortho-substituted 5-arylidene-imidazo[2,1-*b*]thiazepines compounds could be identified which

exhibit affinity for the benzodiazepine binding site at low micromolar concentrations. The structure–activity relationships were studied by 3D models of all compounds using X-ray data (Katarzyna *et al.*, 2004).



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Several new tricyclic derivatives with structural analogy to TIBO were prepared starting from properly substituted 1,4-benzothiazines and 1,5-benzothiazepine. The synthesized compounds were submitted to screenings for in vitro anti-HIV-1 activity. The result revealed that only two compounds of the prepared showed moderate activity (Giuliano *et al.*, 2004). A series of monocyclic thiazepine inhibitors of interleukin-1β converting enzyme (ICE) were synthesized in eight steps. In vitro biological evaluation studies indicated that these thiazepines acts as moderately potent ICE inhibitors, with the most active compound exhibiting an IC_{50} value of 30 nM in an enzyme inhibition assay. Compounds of this class possessed good selectivity against the related enzymes caspase-3 and caspase-8 (Christopher *et al.*, 2006). A number of 2,5-disubstituted benzothiazepines were synthesized and screened for their ability to inhibit arginine vasopressin binding to the human V_2 and V_{1a} receptor subtypes. The more active compounds were subsequently analyzed for their antagonist activity in vitro functional assays. The SAR showed a preference for an acidic unit appended from the benzothiazepines scaffold. This substitution pattern afforded the most potent and selective analogues in the series. The carboxymethyl analogue, showed a 140-fold greater selectivity for the V_2 over the V_{1a} receptor in the binding assay (Maud *et al.*, 2003).

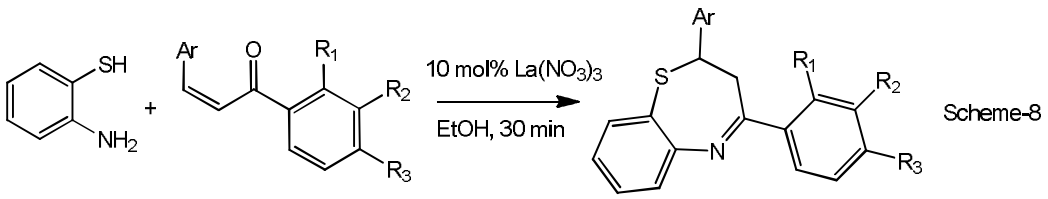
1,5-Benzothiazepines

1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine and one of the three possible benzo-condensed derivatives.

Synthesis

Of the numerous methods developed, the cyclocondensation reaction of α-amino thiophenol with chalcones in alkaline conditions was most commonly employed method for the synthesis of 1,5-benzothiazepines (Manjunath *et al.*, 2014). A series of methylene-bis-[1,5]-benzothiazepines and methylene-bis-benzofuranyl-[1,5]-benzothiazepines were prepared by the reaction of methylene-bis-chalcones with 2-aminothiophenol followed by the condensation with α-bromoacetophenone. The synthesized compounds were tested for their antimicrobial activity. Most of the compounds showed a moderate degree of antimicrobial activity. However, some among the series of the compounds were found to be the most active against *B. subtilis*, *B. sphaericus*, *S. aureus*, *K. aerogenes*, *C. violaceum*, *C. albicans*, *A. fumigatus*, *T. rubrum* and *T. mentagrophytes* species. It is noteworthy that the compounds with heterocyclic ring substituents at the 4th position of benzothiazepine system displayed notable antibacterial activity, almost equal to that of streptomycin and penicillin (Sanjeeva *et al.*, 2008).

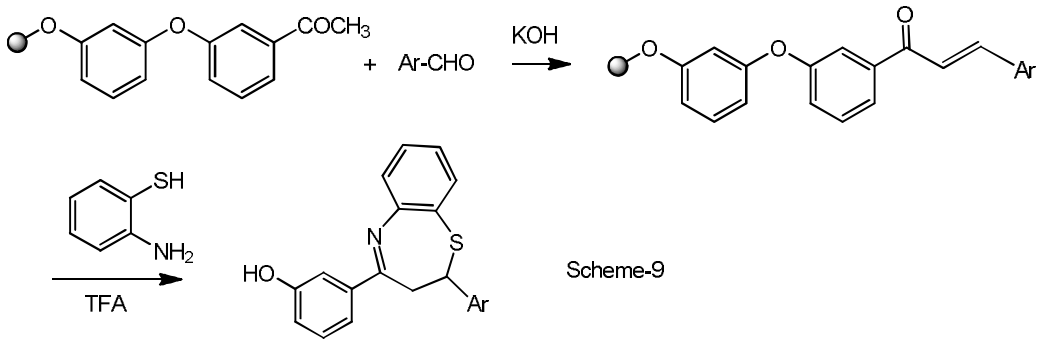
Simple and convenient procedure have been developed for the synthesis of optically active 1,5-benzothiazepine derivatives by reaction of 2-aminothiophenol with synthesized chalcones under mild conditions in the presence of catalytic amount of Lanthanum Nitrate was reported (Scheme-8) (Khan *et al.*, 2011). The reaction requires very short reaction time and produces the products with excellent yield.



Scheme-8

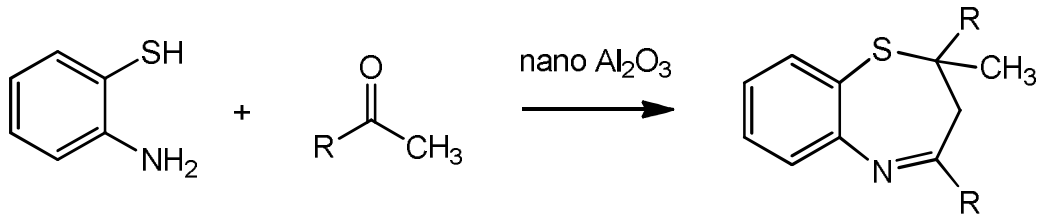
Research Article

Solid-phase synthesis of a parallel library of 30-hydroxy-2,3-dihydro-1,5-benzothiazepines has been carried out through [4+3] annulation of α,β-unsaturated ketones with aminothiophenol, using Wang resin as solid support (Scheme-9). The synthesized compounds were evaluated for their potential as antibacterial, tumor inhibitors as well as acetyl- and butyrylcholinesterase inhibitors. However, quite a few compounds showed significant potential as crown gall tumor inhibitors. These results reflect a strong exploratory potential in search of new benzothiazepines as source of anticancer agents. The results of the inhibition of cholinesterase revealed that benzothiazepines have a greater potential as butyrylcholinesterase inhibitors as compared to acetylcholinesterase. Moreover, the substitution of hydroxy group at C-3 in ring A led to increased activity when compared to unsubstituted- and 20-OH substituted benzothiazepines (Farzana *et al.*, 2008).



Scheme-9

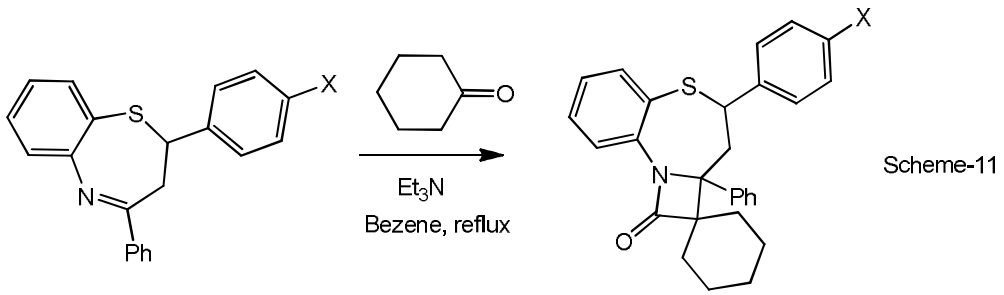
An efficient protocol associated with readily available starting materials, mild conditions, excellent yields, and a broad range of the products in synthetic chemistry was established for synthesis of 1,5-benzothiazepine derivatives in the presence of a catalytic amount of nanocrystalline aluminum oxide in water (Scheme-10) (Rahim *et al.*, 2009).



Scheme-10

Synthetic Applications

Several spiro-fused polycyclic β-lactam derivatives were synthesized in moderate to good yields by Staudinger reaction of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines with cyclohexanecarboxylic chloride in the presence of triethylamine in anhydrous benzene (Scheme-11). 1,5-Benzothiazepines gave rise to *trans*-diaryl-substituted fused spiro[1,2-*d*]benzo[*b*][1,4]thiazepine-2,1-cyclohexane]-1(2a*H*)-ones (Liu *et al.*, 2008).



Scheme-11

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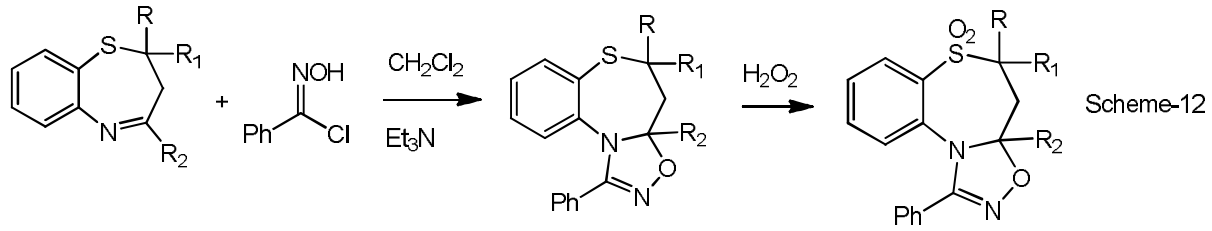
A series of 3a,4-dihydro-5H-[1,2,4loxadiazolo[5,4-d][l,5lbenzothiazepines have been synthesized by 1,3-dipolar cycloaddition reaction of benzonitriloxide to the C=N double bond of 1,5-benzothiazepine derivatives (Scheme-12). The stereochemical features have been determined by NMR spectroscopy. The results of evaluation of their activity in preventing seizures induced by audlogenic stimulation m DBA/2 mice are reported. The results revealed that the 5-(4-bromophenyl)-1,3-diphenyl derivative is the most active compound of the series and was found to be 20 times more active than the parent benzothiazepines (De Sarro *et al.*, 1995).

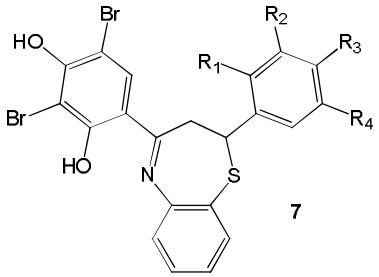


Scheme-12

Pharmaceutical Applications

Dibenzothiazepines were reported to show psychotherapeutic activities. Successful introduction of quetiapine, tianeptine, clotiapine for antipsychotic activity along with its evidence for other biological activity proved potential of dibenzothiazepine moiety. The discovery of quetiapine fumarate as psychotropic agents attracted much attention worldwide (Sarita *et al.*, 2013).

Novel 1, 5-benzothiazepine derivatives synthesized were screened for in vivo anti-inflammatory activity at a dose of 10 mg/kg BW. Among those tested, some of the compounds exhibited significant anti-inflammatory activity in models of acute inflammation such as rat paw edema (Ganesh *et al.*, 2014). A series of novel 1, 5-benzothiazepine derivatives (**7**) were synthesized by the condensation of substituted chalcones with 2-aminothiophenol using conventional as well as non-conventional methods. The synthesized compounds were evaluated for their *in vitro* anticancer activity against human lung cancer cell line (A549) using Adriamycin as a reference drug. The procedure represents a convenient, economic and environmentally friendly process for the synthesis of 1,5-benzothiazepines. The results showed that most of the tested compounds showed some anti-lung cancer activity (Ameta *et al.*, 2013).



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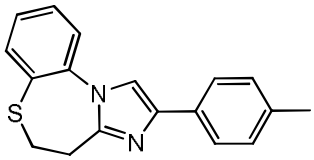
2-{4'-[(4''-methylpiperazinyl)diazenyl]phenyl}-4-(substitutedphenyl)-1,5-benzothiazepine derivatives were synthesized from 1-{4'-[(4''-methylpiperazinyl)diazenyl]phenyl}-3-(substitutedphenyl)prop-2-en-1-one with 2-mercaptoaniline. The compounds have exhibited antimicrobial activities against different microorganisms at 128µg/mL, 256 µg/mL and 512 µg/mL (Shailesh *et al.*, 2013). 1,5-benzothiazepine derivatives (**6**) approaches its binding domain within the cardiac L-type Ca^{2+} channel from inside or outside of the membrane. The effects of 1,5-benzothiazepine derivative (DTZ323) and its quaternary ammonium derivative (DTZ417) on guinea pig ventricular myocytes by using the whole-cell patch-clamp technique was studied. The results revealed that the extracellular application of DTZ417 suppressed the L-type Ca^{2+} channel currents ($I_{Ca(L)}$) with an IC_{50} value of 1.2 ± 0.02 µM, which was close to the IC_{50} value of diltiazem (0.63 ± 0.01 µM) (Junko *et al.*, 1997).

Research Article

The synthesis of three series of 1- and 2-substituted imidazo[2,1-d][1,5]benzothiazepines is accomplished starting from 1,5-benzothiazepin-4-ones. The synthesized compounds were evaluated for their affinity for the benzodiazepine receptor, testing their ability to displace [^{3}H]Flunitrazepam from bovine brain membrane protein. A few of the tested compounds showed good affinity, in particular compound (**8**) (Ki = 43.00 nM). The GABA-ratio of the active compounds suggests an antagonist or partial agonist activity. The data obtained allow us to draw some comments on the structure-activity relationships. imidazo[2,1-a][l,5lbenzothiazepine/benzodiazepine receptor affinity/structure-activity relations (Ambrogil *et al.*, 1995).



8

A series of 4-(40-Hydroxyphenyl)-2-(3-substitutedphenyl)-3-(4-substitutedphenylamino methylene)-2,3-dihydro-1,5-benzothiazepines and 4-(40-Hydroxyphenyl)-2-(3-substituted phenyl)-3-(4-substitutedphenylaminomethylene)-2,3-dihydro-1,5-benzoxazepins synthesized were evaluated in vivo for their anticonvulsant activity and acute toxicity. Some of the series were found to be most potent compared with the reference drug phenytion sodium (Neha *et al.*, 2010). A series of thiosemicarbazone, phenylthiosemicarbazone, oxime and oxime O-ester derivatives of l,5-benzothiazepines prepared were tested in vitro for their antimicrobial activity. Some of the series exhibited promising antifungal activity (Ambrogi *et al.*, 1990).

CONCLUSION

1,4-Benzothiazepines and 1,5-benzothiazepines were treated as potent molecules both chemically and pharmacologically for their diverse applications, as useful scaffolds for the synthesis of bioactive molecules and varied pharmacological properties. This article mainly focused on the synthetic strategies and biological activities associated with 1,4-benzothiazepines and 1,5-benzothiazepines. In context to the biological potency associated with benzothiazepines, this review expected to help and become a basis for researchers to device a new synthetic approach, study the new molecules for their bioactivity.

Authors Contributions: All authors involved in collection of data, manuscript preparation and read and approved the article.

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