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**ARTICLE**

**Benzothiazepines: Chemistry of a Privileged Scaffold**

Debasmita Saha, Garima Jain and Anuj Sharma*

Benzothiazepines is one such class of heterocyclic scaffolds with celebrated biological activities. The pharmaceutical market being flooded by the cardiovascular drugs like Diltiazem, Clentiazem and Siratiazem bearing the benzothiazepine core ascertains the biological importance of the core. This review presents a comprehensive vision of the various synthetic tactics adopted till now to afford benzothiazepine core.

**Introduction**

Medicinal chemistry is related to discovery, development, interpretation and identification of mechanism of action of biologically active compounds at the molecular level. Organic synthesis of new compounds plays a vital role in this tedious process of drug discovery. Particularly, development of privileged heterocyclic scaffolds is an ever burgeoning area of research in medicinal chemistry. The term ‘privileged structure’ being coined by Evans et al. in 1988 in relation to the heterocycle 1,4-benzodiazepine-2-one was defined as “a single molecular framework able to provide ligands for diverse receptors”. Molecular framework of ‘privileged structure’ has versatile binding extensions that enable to be projected as potent and selective ligands for a range of different biological targets.

Benzothiazepines is one such class of heterocyclic scaffolds with celebrated biological activities in the central nervous system and other therapeutic actions. Over years of thorough research in the area of this heterocyclic core, benzothiazepines have firmly stood as “drug prejudice core” due to its presence in a wide range of bioactive compounds like antimicrobial, antifungal, Ca²⁺ antagonist, CNS depressant, antiplatelet aggregation, anti-HIV, calmodulin antagonist and bradykinin receptor antagonist.

The therapeutic journey of benzothiazepines can be traced back by entry of the anti-depressent “Thiazesim” into the pharmaceutical market followed by Diltiazem, Clentiazem, and Siratiazem being the cardiovascular drugs of this family. Further optimization of substituents around the benzothiazepine nucleus resulted in many drugs like quetiapine fumarate and thiazesim for treating CNS disorders, 2164U90 as bile acid active transport system inhibitor and JMV1645 as bradikynin receptor antagonist (Figure 1).

The pharmaceutical prominence of thiazepines has encouraged some reviews to be documented in the literature. These reviews were primarily focused on compilation of reports on all activities associated with the benzothiazepine nucleus and few have been organized from a synthetic perspective. Limited compiled literature reports on synthetic advances towards various possible thiazepine nucleus motivated us to script this document.

Consequently, this review presents a systematic assemblage of more than 60 research articles and reviews to provide a comprehensive vision of the various synthetic tactics adopted till now to afford benzothiazepine core.

**2. Classification of Benzothiazepines**

Benzothiazepines are benzo-fused analogues of a seven membered thiazepine ring. The three structural isomers of thiazepines are as follows:

![Fig 1: Drugs with a thiazepine core](image-url)
Interestingly, several structures of this important seven-membered core involve three instead of two annulated rings in which the seven-membered thiazepine is commonly sandwiched between a benzene ring and another aromatic or heteroaromatic ring. The role of an additional ring to the bicyclic benzothiazepine core is to restrict inversion of the seven-membered ring which improves thermodynamic profile of the scaffold. Both bicyclic and tricyclic forms of thiazepines can exist in various isomeric forms. The ten possible structural isomers of benzothiazepines and six dibenzothiazepines are depicted as below:

Fig 2: Classification of thiazepine

Till date, most of the compounds have been reported from scaffold type III for the reasons of sheer abundance pharmacoprofiling of this class of compounds. The present review article summarizes the synthetic progress of all three types of scaffolds and their various subtypes.

3. Biological Activities of Benzothiazepines

As mentioned before, both benzothiazepines and tricyclic thiazepines have been reported in the domain of pharmacologically active compounds of profound biological activities. In several cases, the compounds have been known to cross the blood brain barrier with ease and subsequently used as psychoactive drug candidates. All pharmacologically active thiazepine scaffolds after the aforementioned work are shown in the Table 1 below.

<table>
<thead>
<tr>
<th>S No</th>
<th>Compound Name</th>
<th>Structure</th>
<th>Use</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2,4-diaryl-2,3-dihydro-1,5-benzothiazepine</td>
<td>Antifungal</td>
<td>9,10</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>1,1-dioxide-2,4-diaryl-2,3-dihydro-1,5-benzothiazepine</td>
<td>Antifungal</td>
<td>9,10</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>(±)-cis-2-[4-methoxyphenyl]-3hydroxy-7-chloro-8-methoxy-1,5-benzothiazepine-4-(5H)-one</td>
<td>Antimicrobial</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>6,9-dichloro-2,3-dihydro-1,5-benzothiazepine-4-(5H)-ones</td>
<td>Antimicrobial</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>(2S,3S)-5-(2-(dimethylamino)ethyl)-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]thiazepin-3-yl benzoate</td>
<td>Calmodulin Receptor</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>MB2</td>
<td>Antiplatelet Aggression</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>MB3</td>
<td>Antiplatelet Aggression</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>5-(4-bromophenyl)-1,3-diphenyl-4,5-dihydro-3H-benzol[b][1,2,4]oxadiazolo[4,5-d][1,4]thiazepine</td>
<td>CNS Depressant</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>
9. 4-chloro-7-[(diethylcarbomyl)oxy]-6-phenylpyrrolo[2,1-d]-[1,5]-benzothiazepine

10. CRD-401
    (+)-cis-3-(acetoxy)-5-[[2,2-(dimethylamino)ethyl]-2,3-dihydro-2-[4-methoxyphenyl]-1,5-benzothiazepine-4(5H)-one

11. TA-3090
    (+)-(2S,3S)-3-acetoxy-8-chloro-5-(2-(dimethylamino)ethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepine-4-(5H)-one

12. CV-5975
    (R)-3-[(S)-1-carboxy-5-(4-piperidyl)pentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid

13. JMV1116
    Bradikynin Receptor

4. 1,2-benzothiazepines

4.1 Introduction
1,2-thiazepines are a class of privileged skeletons labelled as drug-like compounds. Among all, the core structure of benzo[f][1,2]thiazepine dioxide exhibit remarkable biological activities with the major antidepressants in their pouch. For example, Tianepine (tradenames: Stablon, Coaxil, Tatnil) has been a popular antidepressant drug. Benzo[f][1,2]thiazepine dioxide derivatives are marked as human immunodeficiency virus protease inhibitors, calcium sensing receptor agonists and farnesyltransferase inhibitors. For instance, 2,3,4,5-tetrahydro-4-methyl-1,2-benzothiazepine 1,1-dioxide showed HIV-1 protease inhibitory activity. Dibenzoc[f][1,2]thiazepine was revealed as the first LC-MS based metabolite for antidepressants. Several synthetic protocols have been reported in literature to access this biodynamic core, most of which has been taken into account in this document.

4.2 Synthesis of 1,2-Benzothiazepines
For example, Geoghegan et al. generated a series of regiosomeric cyclic sulphonamides by reacting 4-bromo-1,2-dialkoxybenzene 1 with chlorosulphonic acid resulting into corresponding sulfonic acid which transformed into 2-bromo-4,5-dialkoxybenzene-1-sulfonyl chloride 2 by reacting with thionyl chloride on amination and further incorporation of Grubbb’s catalyst promoted ring closing metathesis to generate intermediate 3 which is the key product to access tri or bicyclic sulfonamide 4 by intra molecular Mizoroki-Heck coupling reaction (Scheme 1). Both conventional and microwave conditions were explored and it was found that 4a was obtained in good yields under MW conditions whereas 4b provided better yields under conventional conditions. This method worked well for substrates having an electron donating group attached to benzene ring²⁰.

H. Wang et al., performed a one pot tandem reaction to synthesize 6H-benzo[f]cyclopenta[d][1,2-thiazepine-5,5-dioxides 7 using Pd(0) via double carbopalladation of 2-(2-alkynyl)benzenesulfonamide 5 and 2-alkynylvinyl bromide 6 (Scheme 2). This reaction takes place specifically in presence of a class of phosphine ligands shown in Fig 4. This method yielded fifteen thiazepine dioxide derivatives in good to excellent yields (56-99%).²¹
Mechanistically as depicted in Scheme 3, first oxidative addition of Pd(0) to 2-alkynylvinyl bromide generated the Pd(II) species A, which underwent coordination to the triple bond of 2-(2-alkynyl)benzenesulfonamide to afford intermediate B. Further intramolecular insertion of a triple bond produce intermediate C which then provided the expected benzo[f][1,2]thiazepine dioxide 7 via a C–N coupling.

Earlier in 1980, Still et al. (Scheme 5) incorporated photolytic conditions (λ >300 nm) in benzene or DCM to synthesize 2H-benzo[f]-1,2-thiazepin-5-one-1,1-dioxide 12a (62%) from 2-azido-4-thiochromanone-1,1-dioxide 11a in good yields. This methodology turned out to be tricky to isolate 2-azidothiochroman-4-one-1-oxide 12b from starting sulphoxide analogue 11b and a failure for sulphide analogues 11c.23

On similar lines, Xiao and coworkers (Scheme 4) also provided the synthesis of benzo[f][1,2]thiazepine dioxides 10 using 2-alkynylbromobenzene 8 as the starting substrate. Here PCy3 was used as the phosphine ligand along with KHCO3 as base in 1,4-dioxane. This methodology furnished twenty three derivatives in good to excellent yields (50%-98%).22 The reaction undergoes via an analogous mechanistic pathway similar to scheme 3.
Similarly, Khalaj & Adibpour via ring expansion converted 1,2-benzothiazines 25 to hydroxy 1,2-benzothiazepines 22, 27 (Scheme 7 & 8). These hydroxy 1,2-benzothiazepines were synthesized by reaction of ethyl methyl 2-(2-chlorosulfonyl-4,5-dimethoxyphenyl) acetate 20 with N-phenyl acetamide 21 which itself was prepared from the reaction of ethyl 2-aminocacetate 18 with aniline 19. A series of starting benzothiazines 25 were synthesized which when further treated with sodium ethoxide in ethanol for subsequent substitution of alkoxy group through nucleophilic substitution via anion generated by abstraction of benzylic hydrogen of the acetate group. This eventually led to the formation of 7,8-dimethoxy-4-hydroxy-2,5-dihydrobenzo[f][1,2]thiazepine-1,1-dioxide-3-carboxanilide 22. This approach produced only two derivatives 22 and 27 in lower yields (22% and 25%).

5. 1,3-benzothiazepines

5.1 Introduction

1,3-Thiazepines can be described as seven membered cyclic thiourea derivatives. These derivatives are an important class of compounds with triggered biological activities such as nitric oxide synthase inhibitors. 1,3-thiazepine core is present in Omapatrilat which is currently in the phase IV of clinical trials. Omapatrilat lowers blood pressure by inhibiting the activity of the angiotensin converting enzyme (ACE), which causes blood vessels to constrict. Added advantage of this drug is inhibition of neutral endopeptidase enzyme (NEP), which causes relaxation of blood vessels. 30,31

5.2 Synthesis of 1,3 Benzothiazepines

In an interesting example, Mohamed et al. attempted to synthesize pyridine and pyrimidine derivatives containing benzothiazole moiety but serendipitously formed the [2,1-b][1,3]thiazepine-3-carboxamide 33 (Scheme 9). They treated 1-(2-benzothiazolyl)-1-cyano-3-chloroacetone 30 with 6-methyl-4-phenyl-N-(pyridin-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide 31 in presence of anhydrous K$_2$CO$_3$/hot DMF to obtain the 15 title compounds in good yields (64%).

Mechanistic details as depicted in Scheme 10 explain the formation of a 7-membered ring proceeded by nucleophilic substitution of α-halo group 30 resulting in a C-S bond, where nitrogen further behaved as a nucleophile to attack on cyanide carbon resulting in the target molecules 33.
Afterwards, Struga et al. (Scheme 11) synthesized 14 thiourea derivatives 36 which were used as starting substrates to react with 1,4-dibromobutane 37 to obtain 1,3-thiazine derivatives 38 of 10-isopropyl-8-methyl-4-aza-tricyclo[5.2.2.0²,6]undec-8-ene-3,5-dione 38a in moderate to good yields (38% to 66%) and 1-isopropyl-7-methyl-4-aza-tricyclo[5.2.2.0²,6]undec-8-ene-3,5-dione 38b in good yields (62% to 85%).

Mechanism illustrated in Scheme 12 explains nucleophilic substitution of dihalo compound is the cause of formation of the target product.

Scheme 12: Mechanistic aspects of formation of 10-isopropyl-8-methyl-4-aza-tricyclo[5.2.2.0²,6]undec-8-ene-3,5-dione-1,3 benzothiazepine derivatives

Alajarín et al., carried out thermal transformation of (1S, 5R)-3-amino-2-thia-4-azabicyclo[3.2.0]hepta-3,6-diene-6,7-dicarboxylic acid 41 into 2-amino-1,3-thiazepine-5,6-dicarboxylic acid 42. Prior to this transformation, compound 41 was prepared by [2+2] cycloaddition of but-2-ynedioic acid 39 and thiazol-2-amine 40.  

Scheme 13: Synthesis of 2-amino-1,3-thiazepine-5,6-dicarboxylic acid

In continuation, Silva López et al. extended the above work in order to explain the mechanism more clearly (Scheme 15). Their aim was to notify a more favourable product between Woodward-Hoffman (W-H) and anti W-H. It explains that the mechanistic pathway strives between the disrotatory transition state and double-bond isomerization depending on the substituents around the bicyclic structure. They suggested that bicyclo[3.2.0]hepta-3,6-diene 49 moiety adorned with heteroatoms at 2 and 4 position, electron withdrawing group at cyclobutene core and electron donor amine forming an isothiourea group on the five membered ring enhanced energy.
profile of W-H conrotatory pathway ensuring the target moiety 50.

Scheme 15: Mechanistic alternatives for the ring-opening of cis bicyclo[4.2.0]oct-7-ene

Rudorf and Cleve described a thiocarbamoylation protocol of sulfonamides 51 with isothiocyanates allowing an access to 3-Phenyl-2-(p-toluenesulfonylimino)-perhydro-1,3-thiazepine 54. As depicted in Scheme 16, sulfonamide when treated with isothiocyanates in presence of NaH produced the corresponding sodium salt 52 which was further alkylated and cyclized by nucleophilic substitution with dihalobutane in very low yield (15%).

Scheme 16: Synthesis of 3-Phenyl-2-(p-toluenesulfonylimino)-perhydro-1,3-thiazepine

Mente and Heine, employed a reaction of 2-vinylaziridine 56 with phenyl isothiocyanate 55 in ether at 0°C to furnish 2-anilino-4,7-dihydro-1,3-thiazepine 57 in moderate yields (59%). Subsequently, applying same method with 2-vinyl aziridine 56 and sodium p-chlorothiobenzoylthioglycolate 58 in a stirred ether-water mixture gave low-melting 2-(p-chlorophenyl)-4,7-dihydro-1,3-thiazepine 59 which decomposed after sometime. (Scheme 17)

Scheme 17: Synthesis of 2-anilino-4,7-dihydro-1,3-thiazepine and 2-(p-chlorophenyl)-4,7-dihydro-1,3-thiazepine

Mechanistic pathway in Scheme 18 postulated nucleophilic attack of amine on carbon which shifted the electron density of double bond towards the nitrogen followed by cyclization to the 7-membered ring.

Scheme 18: Mechanistic routes to 2-anilino-4,7-dihydro-1,3-thiazepine and 2-anilino-4,7-dihydro-1,3-thiazepine

6. 1,4-benzothiazepines

6.1 Introduction

There have been several reports available for the synthesis of 1,4-benzothiazepine. We have split this section into two parts based on the cyclic nature of the products:

a) Bicyclic Thiazepines
b) Tricyclic Thiazepines

6.2 Synthesis of Bicyclic 1,4-Benzothiazepines

Sternbach et al., constructed 2,3-dihydro-1,4-benzothiazepine 67 through various transformations (Scheme 19). The multi-step synthesis started with diazotization of o-amino substituted aromatic compound 60 followed by Sandmeyer-type reaction using potassium xanthate or copper thiocyanate. Further, base hydrolysis and nucleophilic substitution with 2-bromoethanamine resulted into substituted o-mercaptop ketones 66 which underwent ring closure in presence of pyridine to give 2,3-dihydro-1,4-benzothiazepines 67 in moderate yields (41%).
Dölling et al., devised a methodology to synthesize only two thiazepine derivatives 72 namely 4-methyl-2-methylthio-5(4H)-oxopyrido[3,2-f][1,4]thiazepine-3-carbonitrile and 2-ethylthio-4-methyl-5(4H)-oxopyrido[3,2-f][1,4]thiazepine-3-carbonitrile in 42% and 12% yields respectively via a multistep reaction sequence. (Scheme 20)

Similarly, Fodor et al. reported two strategies for the formation of a mixture of two diastereomers of 2-benzoyl-3-phenyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1,4-benzothiazepine, 82 and 83. One of them include conversion of the methanolic solution of dihydro-1,3-thiazine 77 into disulphide 79 on exposure to air. The open ring tautomeric intermediate 78 on reaction with 2-bromoacetophenone formed a mixture of 1,4-benzothiazepine diastereomers via cyclisation of the intermediate 80 to yield cis isomer 82 slightly more than trans 83 (75%). On the other hand, reaction of 2-benzoylmethylthio-4,5-dimethoxybenzylamine hydrochloride 81 with benzaldehyde in the presence of NaOMe in MeOH, yielded the diastereomers in a cis:trans ratio of 6:5. 41 (Scheme 22)

Mechanistically, 2-chloronicotinic acid 69 subsequently reacted with thionyl chloride and 2-(methylamino)acetanonitrile resulting into 2-chloro-N-(cyanomethyl)-N-methylnicotinamide 70. Two equivalents of sodium hydride were used to abstract the more acidic proton to generate thiolate anion on reaction with carbon disulphide with succeeding cyclisation via intermolecular aromatic nucleophilic substitution into the desired 1,4-benzothiazepine 72. This reaction has been a failure for nitro substituted chloronicotinic acid as in this case intermediate 71 failed to undergo cyclisation into benzothiazepine instead forming benzothiazole derivative. (Scheme 21)
Nowadays, significance of multicomponent reactions is flourishing in current research scenario. Complete utilization of three or more components present in the reaction mixture, atom economy, efficiency, environmental friendliness and selectivity are some of the consequences of MCRs. Mironov et al., indulged benefits of MCR in a one-pot four component Ugi reaction in liquid phase synthesis of twelve 1,4-benzothiazepin-5-ones 86 in good yields (36%-90%) by condensing thiosalicylic acid 84, 1-chloropropan-2-one, tert-butyl isocyanide & benzylamine. In this reaction, bromoacetophenone as acetyl halide input did not work well despite chloroacetophenone being a success. Also use of methanol as polar solvent is the prime requirement of the reaction besides electron donating group substituted isocyanides providing incremental yields.\(^{42}\) (Scheme 23)

\[\text{Scheme 23: Synthesis of 1,4-benzothiazepin-5-ones}\]

A detailed mechanism of the Ugi reaction to afford 1,4-thiazepinone derivatives has been illustrated in Scheme 24. It first explains the base promoted proton abstraction followed by nucleophilic substitution with 1-chloropropan-2-one. Further condensation of the amine with the keto functionality generates the iminium ion on which attack of isocyanide forms a cyclic intermediate A which undergoes acyl transfer to afford the final product.

\[\text{Scheme 24: Ugi reaction mechanism to afford 1,4-benzothiazepine derivatives}\]

C. Spitz et al., anticipated two pathways for the synthesis of 1,4-Benzothiazepines. One pathway explains the formation of the target compounds being facilitated by simultaneous bond breaking and bond formation via ring expansion mechanism, in which cyclic sulfenamide 87 reacted with allenolate A derived from the Michael addition of neutral organic nucleophiles to methyl propionate. The second pathway involved trapping the cyclic sulfenamide 87 by an enamine B followed by an acid catalyzed condensation reaction to give 1,4-benzothiazepine 89 (Scheme 25). Electron withdrawing groups attached to the nitrogen atom of 87 favoured the product formation. Trapping intermediates A & B proved extremely troublesome, failure of which resulted in a side reaction to generate an acetylide C from the allenolate intermediate A which on reaction with cyclic sulfenamide 87 lead to 1,3-benzothiazine. This methodology provided 100% conversion with high efficiency and atom economy.\(^{43}\)

\[\text{Scheme 25: Synthesis of 1,4-benzothiazepine from cyclic sulfenamide}\]

The plausible mechanism for the above reaction has been described in Scheme 26. It explains the initial formation of the zwitterionic allenolate A which attacks the electrophilic sulfur atom of sulfenamide 87 to form the corresponding zwitterion D which in turn cyclizes after an addition-elimination reaction into the final 1,4-benzothiazepine.

\[\text{Scheme 26: Mechanistic detail for synthesis of 1,4-benzothiazepine from cyclic sulfenamide and allene.}\]

Voskressensky et al., utilized tandem nucleophilic substitution and Bischler-Napieralski reaction to synthesise 2,3-dihydro 1,4-benzothiazepine 96. In this multistep reaction, alkylation of substituted thiophenol 90 with bromoacetonitrile generated cyanomethylthioethers 91 followed by reduction, acylation and finally cyclization to afford 8-methoxy-5-phenyl-2,3-dihydro-1,4-benzothiazepine 94 in low yield (11%) and further reduction led to formation of 8-methoxy-4-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 96 in good yields (92%).\(^{44}\) This
reaction was facilitated by electron donating groups adorned to the backbone structure of starting material (Scheme 27).

Scheme 27: Synthesis of 2,3-dihydro 1,4-benzothiazepine via a tandem Bischler-Napieralski protocol

A mechanistic detail for the above reaction as depicted in Scheme 28 first describes alkylation of starting substituted thiophenol with bromoacetonitrile to the cyanomethylthioethers. Reduction of the nitrile group by lithium aluminum hydride gave the amines which were converted to the N-acyl derivatives using acyl chlorides. Cyclization of 92 under Bischler-Napieralski conditions gave dihydrobenzothiazepine. The dihydro derivatives were quaternized with methyl iodide under microwave irradiation to give the quaternary salts, reduction of which by sodium borohydride in methanol gave the 2,3,4,5-tetrahydro-1,4-benzothiazepine.

Scheme 28: Mechanistic aspects of synthesis of 2,3-dihydro 1,4-benzothiazepine

Shi et al., reported a one-pot 3-CR of 5-amino-3-methylpyrazole 97, isatin 98 and thioacid 99 through 3-(5-

aminopyrazol-3-yl)-3-hydroxy-2-oxindoline intermediate (Baylis-Hillman type adduct) for the synthesis of spiro[indole-3,4-pyrazolo[3,4-e][1,4]thiazepinedione derivatives 100 in (71-87%) high yields (Scheme 29).

Scheme 29: Synthesis of spiro[indole-3,4-pyrazolo[3,4-e][1,4]thiazepinedione

6.3 Synthesis of Tricyclic 1,4-Benzothiazepines

In 1994, Liegios et al., synthesized nine N-methylpiperazinopyrido-[1,4]benzothiazepine derivatives 110 in good yields via a pyrido-[1,4]benzothiazepinone intermediate 108 which undergoes chlorination in presence of POCl₃ to form compound 109 which finally afford the target product 110. The intermediary lactam 108 has been synthesized by two different methods. Reaction of 4-chloro-3-aminochloropyridine 102 with thiosalicylic acid 103 gave the lactam 108. On the other hand, 2-chloronicotinic acid 104 when treated with 4-chlorothiophenol 105 to provide (4-chlorophenyl)thiolicotinic acid 106 which got transformed to an acyl azide 107. Thermal decomposition of this azide yielded the corresponding isocyanate which in the presence of aluminum chloride yielded the lactam 108.46 (Scheme 30)

Scheme 30: Synthesis of 5H-Pyrido[2,3-b][1,4]benzothiazepine

In 1995, Johnson and Maruendat performed reaction of 6-chlorouracils 111 with substituted 2-aminothiophenols 112 under refluxing conditions with KOH in ethanol to afford 6-(arylthio)uracils 113 which were further treated with appropriate aldehydes under acidic conditions to yield the desired pyrimido[5,4-f]benzo[1,4]thiazepines 114 via an intramolecular Mannich-type cyclization. This synthetic route generated ten thiazepine derivatives in good to excellent yields (56-95%) and tolerated a wide variety of substituted
substrates such as methyl, phenyl and p-nitro phenyl benzaldehydes. 

(Scheme 31)

The mechanism of the above reaction is depicted in Scheme 32. It describes the initial base promoted proton abstraction followed by nucleophilic substitution with substituted 2-aminothiophenol to obtain the intermediate 113 which causes a nucleophilic attack on benzaldehyde followed by cyclisation to fabricate the final pyrimido benzothiazepine derivative.

(Scheme 32)

In 1999, Laio et al., synthesized 2-TfO-11-(4-methylpiperazinyl)-dibenzo[b,f][1,4]thiazepine 120 from 4-iodoanisole and 2-carboxythiophenol which was transformed into an acid intermediate 115 and then azide 116. This was then converted into the final product 120 via 2-hydroxylactum intermediate 118 and isocyanate intermediate 117. Triflate derivatives induce less oxidative metabolism in comparison to a hydroxy or methoxy group due to its electron-withdrawing and lipophilicity. So to enhance the pharmacological profile of this core, this group specially focussed on synthesis of triflate derivatives in moderate yields (45%). 

(Scheme 33)

In 2001, Katrizky et al., synthesized six 1,4-benzothiazepines via a multistep reaction sequence in good yields (78-96%). Treatment of substituted thiophenols 121a-f with 2-chloroethylaminehydrochloride and excess potassium carbonate in DCM provided 2-(arylsulfanyl)ethylamines 122a-f. This series of amine 122a-f when treated with 2-carboxybenzaldehyde 123 and 2,5-dimethoxy-2,5-dihydrofuran 126 in presence of the nucleophile benzotriazole gave intermediate compounds 124 and 127 respectively. These intermediates in presence of a Lewis acid underwent cyclisation with elimination of benzotriazole to afford two series of 1,4-benzothiazepine derivatives 125a-f and 129a-f.

(Scheme 34)

Fu and co-workers described the synthesis of tricyclic pyrimido[4,5-b][1,4]benzothiazepines from 5-amino-4,6-bis(arylthio)pyrimidines and carboxylic acids via Bischler-Napieralski-type reactions (Scheme 35). Substitution of pyrimidine 130 with a thiophenol yielded 5-amino-4,6-bisphenylthio pyrimidine 131 which under refluxing PPA/POCl3 (Bishler-Napieralski conditions) gave the final benzothiazepine skeleton 132. The aryl sulfide group of the resulting 4-arylthio pyrimido[4,5-b][1,4]benzothiazepines was subjected to selective oxidation and subsequent nucleophilic substitution to produce derivatives of 134 in good yields (88-90%). Here, the bifensylthio product 131 could be obtained in substantial amounts due to high nucleophility of the thio group. The reaction yields were more sensitive to carboxylic acid (R3) compared to substitution on the thiophenol ring. Aromatic carboxylic acids provided higher yields compared to aliphatic ones. Improvement in yields was observed in presence of electron-donating group on the aromatic acid ring whereas electron-withdrawing group proved detrimental to the yields.

(Scheme 35)
The mechanistic attributes in Scheme 36 portray acylation of bis-(phenylthio) compound 131 to give product 131a which tautomerises to form 131b. This was converted to imidoyl chloride 131c when treated with POCl₃, which in turn transformed into corresponding nitrilium salt 131d. This nitrilium salt underwent an intramolecular electrophilic substitution on the phenyl ring and subsequent elimination of hydrogen chloride to yield the final thiazepine skeleton 132.

In 2007 Zahra et al., synthesized substituted [1,4]thiazepino[2,3-h]quinolone carboxylic acid (138 and 141) by PPA-catalyzed thermal lactamization of the respective 8-amino-7-[2-carboxyethyl]thio]-1,4-dihydroquinoline-3-carboxylic acid (137 and 140). Mechanistically, here 3-mercaptopropionic acid acts as 'sulfur' nucleophile which undergoes nucleophilic aromatic substitution S₂Ar facilitated by the presence of the electron withdrawing fluoro, keto and nitro groups. Further, compound 137 or 140 underwent lactamization upon heating with polyphosphoric acid (PPA) to afford a tricyclic system. (Scheme 37)

In 2007 Chen Ma et al., developed a highly efficient synthetic strategy to furo[2,3-c][1,4]thiazepine core 146 via a three component reaction between thiazole or benzothiazole carbenes 142, disubstituted ketenes 144 and activated alkynes 145. (Scheme 38)
In 2009, Randhavane et al., synthesized chalcones of 4-difluoromethoxy-dibenzofuran-1-carboxaldehyde 151 which were converted into corresponding dihydrobenzo[1,4]thiazepines 152 by refluxing with 2-aminothiophenol.153

Later on, Olsson et al. synthesized lactam 157 from commercially available starting materials over three sequential steps. Subsequent diversification of lactam yielded amide 159 and its further Negishi cross-coupling reaction afforded the final benzo[1,4]thiazepine-8-carboximide 160. Detailed description of the mechanism revealed an initial nucleophilic substitution of methyl 2-mercaptobenzoate with ethyl 4-fluoro-3-nitrobenzoate to generate bisphenylmonothio product 155. Further reduction of the nitro group followed by cyclisation in the presence of CDI in THF gave the lactam 157. Further chlorination in the presence of SOCl2 yielded the imidoyl chloride 158 and subsequent nucleophilic substitution of an amine provided the compound 159. Palladium-catalysed Negishi cross-coupling of imidoyl chloride 159 with Grignard’s reagent produce the final titled compound 160 (Scheme 41).

Similarly, Zeng et al., devised an efficient domino procedure for the synthesis of 1,4-benzothiazepin-5-ones 163 from simple and readily accessible N-tosyl aziridines 162 and o-iodothiophenols 161.156 (Scheme 42)

Newton et al. in 2011 carried out SNAr nucleophilic substitution of thiol 164, with aryl fluoride afforded 165, which upon further reduction via a three step process was converted to methyl 10-(3-chlorobenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylate 168 which on further N-alkylation gave the final product 169. (Scheme 43)
In continuation, Mahale et al. designed a reaction sequence involving hydrogenation of 2-nitrodiphenylsulphide 170 which formed the carbamate 172 on reaction with phenylchloroformate in presence of a base. This carbamate 172 underwent cyclisation into 173 which upon treatment with POCl₃ formed imino chloride 174. Here the reaction proceeded via formation of the iminium ion generated insitu by removal of chloride ion. This chloride ion is scavenged by acid scavengers to drive the reaction forward and obtain the final product dibenzo[b,f][1,4]thiazepines 175. This reaction accounted for sufficient versatility to generate 1,4-dibenzothiazepines in good yields (82-93%). (Scheme 44)

![Scheme 44: Synthesis of dibenzo[b,f][1,4]thiazepines from 2-nitrodiphenylsulphide thiazepine ring.](image)

Remarkably, Zhao et al. established an efficient metal free method for the synthesis of a library of dibenzo[b,f][1,4]thiazepin-11(10H)-ones 178 via Smiles rearrangement in excellent isolated yields (Scheme 45 and 46). Here substituted 2-halobenzenethiols 176 and N-alkyl-2-chloro-5-nitro benzamide 177 were reacted upon by KOH in DMF to effortlessly obtain the title compounds.

![Scheme 45: Synthesis of dibenzo[b,f][1,4]thiazepin-11(10H)-ones via Smiles rearrangement](image)

The probable mechanism for the above reaction could be described as in Scheme 44. The reaction of 2,3-dichlorobenzenethiol with N-benzyl-2-chloro-5-nitro benzamide yielded the compound 180 which may proceed towards completion via two paths. Path II afforded the direct intramolecular nucleophilic substitution product 179. By contrast, path I could lead to the intermediate 181 via Smiles rearrangement. The imido nitrogen underwent intramolecular nucleophilic attack on the carbonium ion followed by further migration of the spiro-sulfur, proceeding through the “Meisenheimer Complex” 181, with intramolecular nucleophilic displacement of chlorine by sulfur anion yielded the desired cyclic product 178.

Interestingly, W. Van Snick et al. used 3H-thienobenzodithiazole-2-oxide 182 as 2-aminothiphenol precursor in synthesis of benzothiazepines (Scheme 47). Similarly reaction of 3H-thienobenzodithiazole-2-oxide 182 with 2,6-dichlorobenzaldehyde 187 resulted in the formation of thienobenzothiazepine derivative 183 by intramolecular nucleophilic aromatic substitution reaction of the sulfur atom to the 2-position of the intermediate imine. Also reaction of chalcones with 3H-thienobenzodithiazole-2-oxide 182 produced dihydrothienobenzothiazepine 186. Similarly, reaction of chloroformylpyrazole with precursor 182 generated new benzothiazepines 184.
Recently, Yang et al. synthesized a series of twenty-five 1,4-thiazepin-5(4H)-one derivatives via a transition metal-free one-pot Smiles rearrangement process at room temperature. Here, thiazepine scaffolds were obtained through the reaction of N-substituted 2-mercaptonicotinamides and substituted benzenes at room temperature in good to excellent yields (65-95%). (Scheme 48).

On the basis of previous literature on Smiles rearrangement, a plausible reaction mechanism is depicted in Scheme 49. Reaction of the substrates 188 and 189 produced the intermediate 191 by nucleophilic substitution reaction. The carboxamide anion 192 then resulted in the target compounds by two ways. Pathway a formed intermediate 193 via Smiles rearrangement followed by an intramolecular nucleophilic substitution with a loss of fluorine atom, leading to the corresponding product 190. On the other hand, pathway b led to direct intramolecular cyclization to form the product 190.

7. 1,5-benzothiazepines

7.1 Introduction

Exclusively, 1,5-benzothiazepines have been the object of immense importance and investigation in the field of medicinal chemistry. Currently, some of the 1,5 benzothiazepines are amongst the most widely used drugs in the treatment of cardiovascular disorders such as Diltiazem, Thiazesim and Clentiazem.

7.2 Synthesis of 1,5-Benzothiazepines

A very typical method to construct 1,5-benzothiazepine skeleton is via reaction of 2-aminothiophenol with α,β-unsaturated carbonyl compounds. The generality and scope of this approach has been represented in Figure 5. Some of the schemes have been explained in detail as follows:

Figure 5: Reaction of 2-aminothiophenol with α,β-unsaturated carbonyl compounds to afford 1,5-benzothiazepine derivatives
(i) Initially, Khouzani et al. carried out an eco-friendly synthesis of thirty-six 1,5-benzothiazepine derivatives 196 in good yields via a one-pot cyclocondensation reaction of o-aminothiophenol 195 with α,β-unsaturated carbonyl compounds through a [4+3] annulation reaction in the presence of N-methylimidazolium nitrate [Hmim][NO₃] as a Brønsted acidic ionic liquid. Comparative studies proved this catalytic system is superior to the ones previously reported in terms of the amount of catalyst, cost and availability of the precursors for the preparation of catalyst. 61 (Scheme 50)

Mechanistically, the reaction proceeded initially by the intermolecular hydrogen bonding promoted by [Hmim][NO₃] ionic liquid that activated chalcone towards nucleophilic attack by sulfur of 2-aminothiophenol to afford the intermediate A. Further 1,3-H shift on intermediate A occurs to give an isomeric keto form B that cyclized to give the seven-membered ring product. (Scheme 51)

(ii) In 2004, Latif et al. reported the synthesis of 4-aryl-3-methyl-1-phenylpyrazolo[3,4-b][1,5]benzothiazepines 197 from 4-Arylidene-3-methyl-1-phenylpyrazole-5-one 198 and 2-aminobenzenethiol 195. The products obtained were in moderate yields (50-55%). 62 (Scheme 52)

The mechanistic pathway proceeded via Michael addition of anilinic nitrogen to the α,β-unsaturated ketone resulting in the formation of intermediate A which subsequently loses a water molecule to form the target compound 197. Alternatively, if the thiol functionality underwent Michael addition first, it subsequently resulted in a different product whose formation has not been confirmed through characterization techniques.

(iii) On the similar lines, Rao and his co-workers successfully generated chalcones 199 by condensation of 3-acetyl coumarins 201 with various aromatic aldehydes 202 (Scheme 53 and 54). These chalcones 199 were utilised in-situ to react with 2-aminophenol to generate 2-aryl-4-[2H-2-oxo[1]benzopyran-3-yl]-2,3-dihydro and 2,5-dihydro-1,5-benzothiazepines 200 in a one pot manner in excellent yields (75-90%). 63

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(iv) Yan et al. performed the reaction of 2-aminothiophenol 195 with chalcone 203 into water as solvent using TBATB as the phase transfer catalyst (Scheme 55) to afford the final 1,5-benzothiazepines 204 in good to excellent yields (75-94%).

(v) In 2010, Shen and co-workers synthesized ten azeto[2,1-d][1,5]benzothiazepinone derivatives (Scheme 56) using 4-acetyl-2-phenyl-1,2,3-triazole as the starting substrate. Condensation with varied aromatic aldehydes produced 2-Phenyl-1,2,3-triazole-4-yl-α,β-unsaturated ketones 205 which subsequently underwent cyclisation with 2-aminothiophenol 195 to afford the corresponding 2,4-disubstituted-1,5-benzothiazepines 206 in good yields (75-85%).

Mechanistic interventions as in Scheme 57 were derived by performing control experiments. This method exclusively preferred the cis product over trans product. The formation of the cis product took place via threo-ester which upon cyclization yielded the desired compound 209. Whereas the trans-isomer did not form via erythro-ester under similar conditions.

In 2002, Yaccoubi et al. performed reaction of 2-aminothiophenol 195 with 2-dialkylaminomethylpropenenitriles 213 to afford corresponding benzothiazepines 214 (Scheme 58) in good yields (67-79%). Mechanistic pathway for this reaction has been determined by isolating some intermediates as depicted in Scheme 59. Firstly, michael addition of 2-aminothiol with dialkylpropenenitrile 213 formed the intermediate 215 which underwent intramolecular cyclisation to form the final product 214.
Kamble et al., devised a synthesis of 1,5-benzothiazepines integrated with 5-methyl-2-oxo-3-phenyl-1,3,4-oxadiazoles using 4-acetylphenylsydnone and 2-aminothiophenol as the starting substrates. Microwave and conventional synthetic aspect of this method has also been explored to infer that microwave (85-93% yield) fostered better results in comparison to conventional conditions (75-80% yield).

Slade and co-workers devised a synthetic strategy to synthesize chiral 1,5-benzothiazepinones using o-fluoronitrobenzene and N-acetylcysteine as the starting precursors. Initial nucelophilic substitution of o-fluoronitrobenzene with N-acetylcysteine affords 5-(o-nitrophenyl)-N-acetylcysteine which is further deacetylated and converted to Cbz derivative. It then undergoes ring closure to lactum using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimidehydrochloride in DMF to afford the title compound in moderate yield (48%).

Conclusively, Scheme 62 summarizes reaction of 2-aminothiophenol with various unsaturated ketones to afford diverse substituted benzothiazepines. The reactions are described as follows:

(i) 2-aminothiophenol react with alkyrones in a mixture of hot methanol and acetic acid to obtain 2,4-disubstituted 1,5-benzothiazepines.

(ii) Also, 1,5-benzothiazepin-4(5H)-ones were synthesized by heating 2-aminothiophenol with either propiolic acid or its β-substituted derivatives to yield the appropriate 1,5-benzothiazepines.

(iii) Reaction of 2-aminothiophenol and α,β-unsaturated ketones gives 2,3-disubstituted 2,3-dihydro-1,5-benzothiazepine.

(iv) Reaction of 2-aminothiophenol with α-chloro-β-chlorocarbonyl enamines in the presence of pyridine produced 2,3-disubstituted 1,5-benzothiazepin-4(5H)-ones.

Also, 2-methyl-1,5-benzothiazepin-4(5H)-one was synthesized in moderate yields (50-58%) by reaction of 2-aminothiophenol with ethylacetoacetate in xylene at refluxing temperature.
potent drugs such as Thiazen, Dilteazem and Quetiapine fumerate as the mainstays of anti-psychotic therapeutics. Remarkably, the last decade has witnessed substantial developments in the chemistry of benzothiazepines resulting in a variety of innovative and interesting reactions to construct this core. The present survey evidently unites the scattered synthetic links to provide a comprehensive outlook of all the synthetic tactics implemented till now. Yet many efficient synthetic procedures providing an access to the benzothiazepine core are already known, it is expected that research to be performed in the coming years will uncover interesting aspects of the fields discussed in this review.

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References

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Benzothiazepines: Chemistry of a Privileged Scaffold

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