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Benzothiazepines: Chemistry of a Privileged Scaffold

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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.[1] 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.[2]

Benzothiazepines is one such class of heterocyclic scaffolds with celebrated biological activities in the central nervous system and other therapeutic actions.[3] Over years of thorough research in the area of this heterocyclic core, benzothiazepines have firmly stood as a "drug prejudice core" due to its presence in a wide range of bioactive compounds like antimicrobial, antifungal, Ca^{+2} antagonist, CNS depressant, antiplatelet aggregation, anti-HIV, calmodulin antagonist and bradykinin receptor antagonist.[4]

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.[5] 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).[6] This seven membered ring system is also widely acclaimed as eminent cardiotherapeutic and psychotherapeutic scaffold.[7]

The pharmaceutical prominence of thiazepines has encouraged some reviews to be documented in the literature.[8] 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.

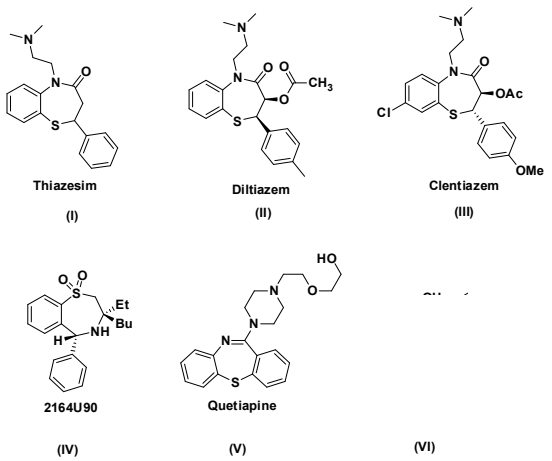

Fig 1: Drugs with a thiazepine core

2. Classification of Benzothiazepines

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

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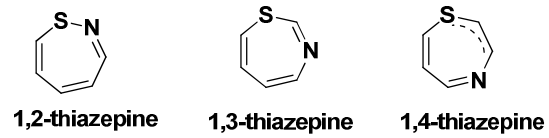


Fig 2: Classification of thiazepine

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:

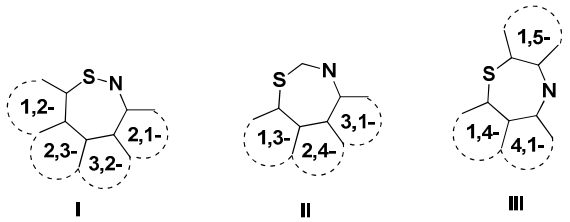
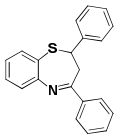
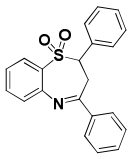
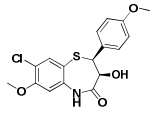
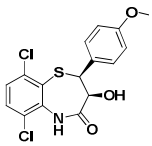
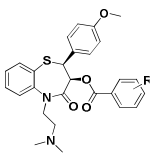
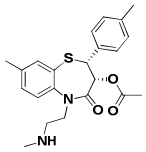
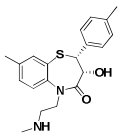
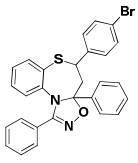


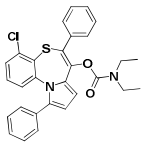
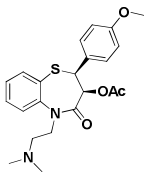
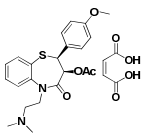
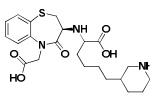
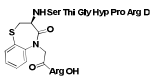
Fig 3: Structural isomers of thiazepine

Till date, most of the compounds have been reported from scaffold type III for the reasons of sheer abundance pharmaco-profiling 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 pharmaco-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 psycho-active drug candidates. All pharmacologically active thiazepine scaffolds after the aforementioned work are shown in the Table 1 below.

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

9.	4-chloro-7-[(diethylcarbomyl)oxy]-6-phenylpyrolo[2,1-*d*]-[1,5]-benzothiazepine		CNS Depressant	15
10.	**CRD-401** (+)-*cis*-3-(acetyloxy)-5-[[2,2-dimethylamino]ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepine-4(5*H*)-one		Ca^{+2} antagonists	16
11.	**TA-3090** (+)-(2S,3S)-3acetoxy-8-chloro-5-(2-(dimethylamino)ethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepine-4-(5*H*)-one		Ca^{+2} antagonists	16
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		ACE Inhibitor	17
13.	**JMV1116**		Bradikynin Receptor	18

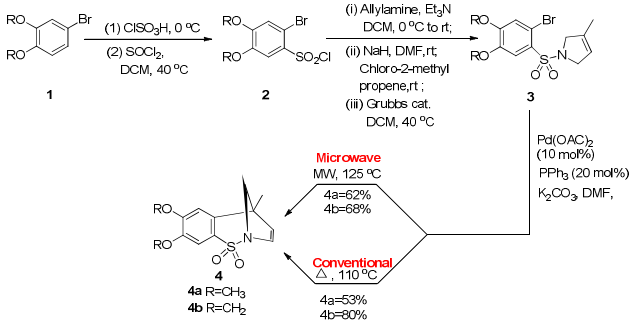
4. 1,2-benzothiazepines

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, Tianeptine (tradenames: Stablon, Coaxil, Tatinol) 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.[19] For instance, 2,3,4,5-tetrahydro-4-methyl-1,2-benzothiazepine 1,1- dioxide showed HIV-1 protease inhibitory activity. Dibenzo[*c,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.

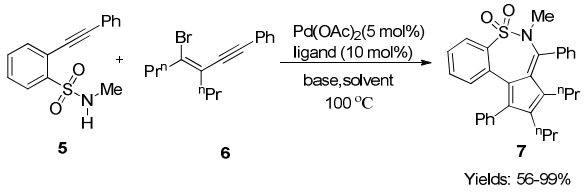
4.2 Synthesis of 1,2-Benzothiazepines

For example, Geoghegan *et al*. generated a series of regioisomeric 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 Grubb's catalyst promoted ring closing metathesis to generate intermediate **3** which is the key product to access tri or bi-cyclic 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 ring.[20]



Scheme 1: Synthesis of 1,2 benzothiazepine derivatives

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]



Scheme 2: Synthesis of 6*H*-benzo[*f*]cyclopenta[*d*]1,2-thiazepine-5,5-dioxides

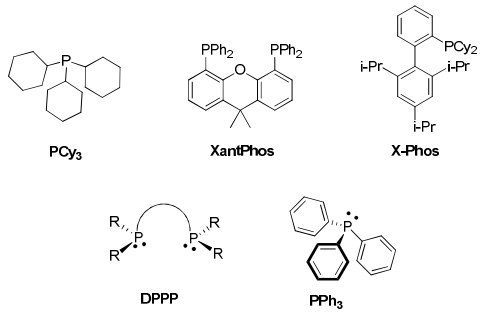
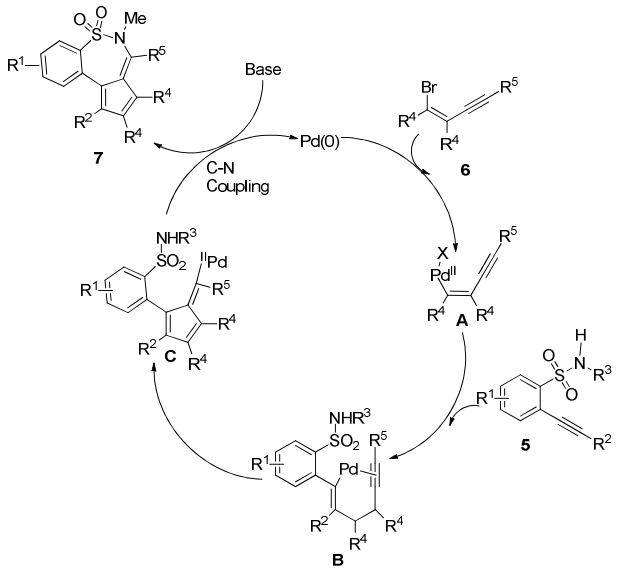


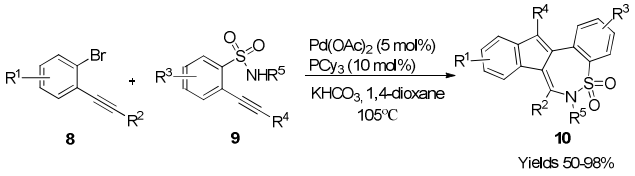
Fig 4: Phosphine ligands used in the reaction

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.



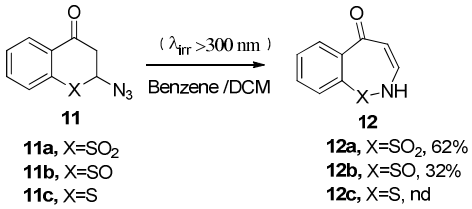
Scheme 3: Mechanistic pathway of formation of 6*H*-benzo[*f*]cyclopenta[*d*]1,2-thiazepine-5,5-dioxides

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 PCy_3 was used as the phosphine ligand along with $KHCO_3$ 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.



Scheme 4: Synthesis of 6*H*-benzo[*f*]cyclopenta[*d*]1,2-thiazepine-5,5-dioxides

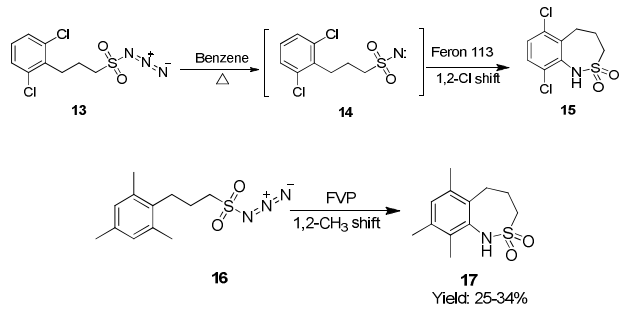
Earlier in 1980, Still *et al.* (Scheme 5) incorporated photolytic conditions (λ >300 nm) in benzene or DCM to synthesize 2*H*-benzo[*f*]-1,2-thiazepin-5-one-1,1-dioxide **12a** (62%) from 2-azido-4-thiochromanone-1,1-dioxide **11a** in good yields. This methodology turned out to be tricky to isolate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



Scheme 5: Synthesis of 2*H*-benzo[*f*]-1,2-thiazepin-5-one 1,1-dioxide

Abramovitch *et al.*, (Scheme 6) performed thermal decomposition of 3-(2,6-dichlorophenyl)propanesulfonylazide **13** to furnish 6,9-dichloro-1,3,4,5-tetrahydrobenzo[*c*][1,2]thiazepine 2,2-dioxide **15**. Also flash vacuum pyrolysis (FVP) of 3-(2-mesityl)propanesulfonylazide **16** followed by 1,2-methyl shift afforded 6,8,9-trimethyl-1,3,4,5-tetrahydrobenzo[*c*][1,2]thiazepine-2,2-dioxide **17** in lower yields (25-34%).

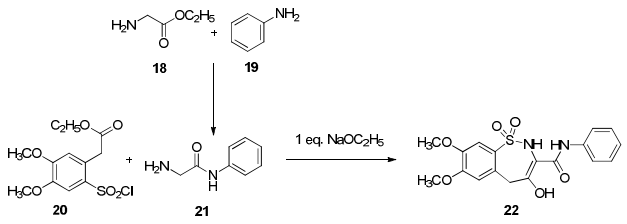
The mechanistic details point towards the formation of an intermediate 3-(2,6-dichlorophenyl)propanesulfonyl nitrene **14** which further undergoes intermolecular cyclisation followed by 1,2-Cl shift by Feron113 under inert atmosphere to afford 6,9-dichloro-1,3,4,5-tetrahydrobenzo[*c*][1,2]thiazepine-2,2-dioxide **15**.[24]



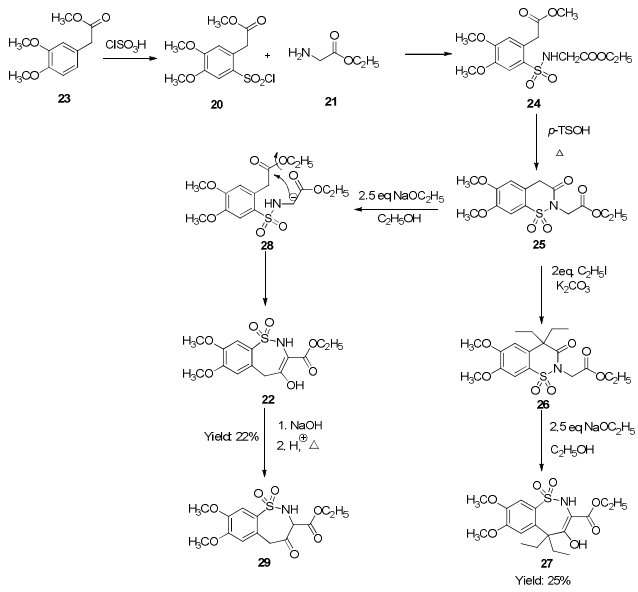
Scheme 6: Synthesis of 6,9-dichloro-1,3,4,5-tetrahydrobenzo[c][1,2]thiazepine -2,2-dioxide and 6,8,9-trimethyl-1,3,4,5-tetrahydrobenzo[c][1,2]thiazepine-2,2-dioxide

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-aminoacetate **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%).[25]



Scheme 7: Synthesis of 7,8-dimethoxy-4-hydroxy-2,5-dihydrobenzo[*f*][1,2]thiazepine-1,1-dioxide-3-carboxanilide



Scheme 8: Mechanistic details for synthesis of 1,4-benzothiazepine dioxide derivatives

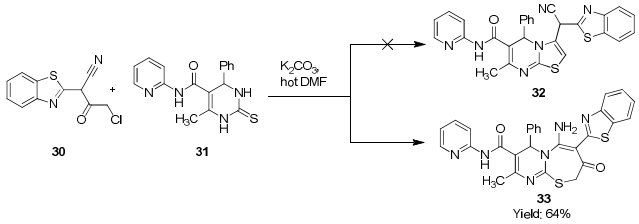
5. 1,3-benzothiazepines

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[26-29] such as nitric oxide synthase inhibitors. 1,3-thiazepine core is present in Omipatrilat 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]

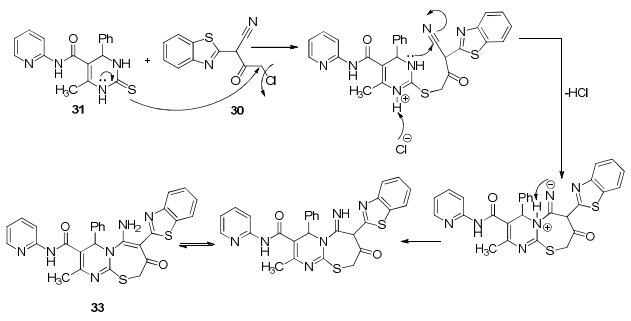
5.2 Synthesis of 1,3 Benzothiazepines

In an interesting example, Mohamed *et al*. attempted to synthesize pyridine and pyrimidine derivatives **32** 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_2CO_3/hot DMF to obtain the 15 title compounds in good yields (64%). [32]



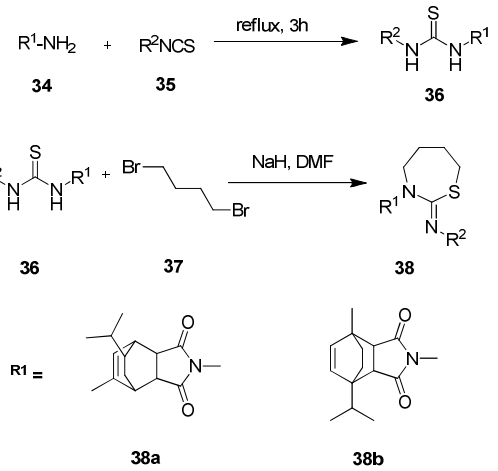
Scheme 9: Synthesis of [2,1-*b*][1,3]thiazepine-3-carboxamide

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**.



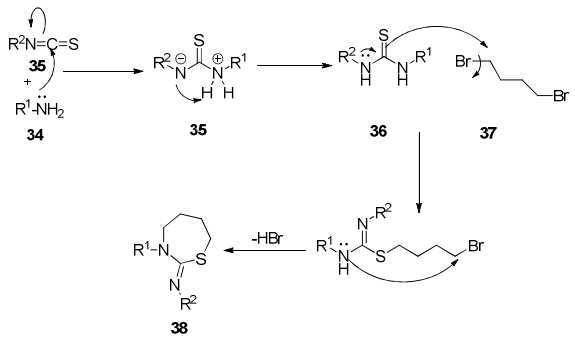
Scheme 10: Mechanistic aspects of formation of [2,1-*b*][1,3]thiazepine-3-carboxamide

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-thiazepine 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%).[33,34]



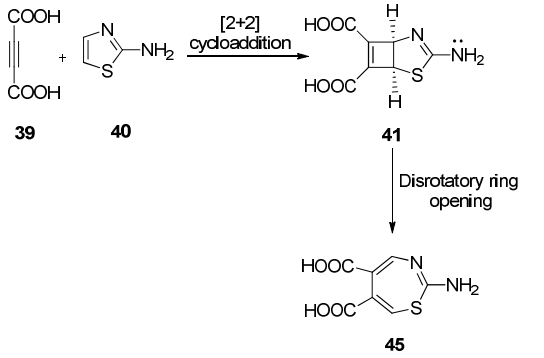
Scheme 11: Synthesis of 1,3 benzothiazepine derivatives

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



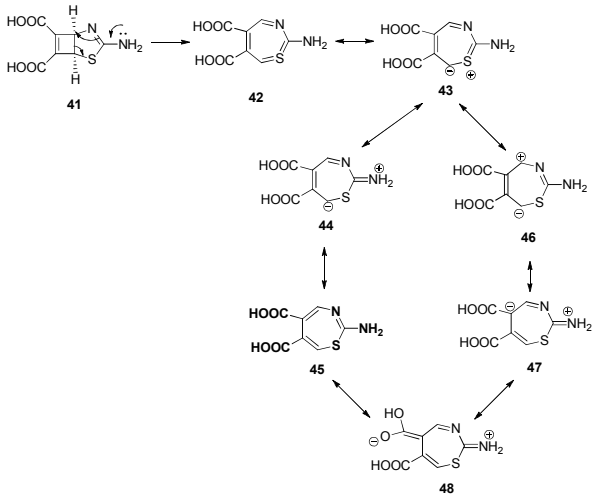
Scheme 12: Mechanistic aspects of formation of 10-isopropyl-8-methyl-4-aza tricyclo[5.2.2.02,6]undec-8-ene-3,5-dione-1,3 benzothiazepine derivatives

Alajarìn *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**.[35] (Scheme 13)



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

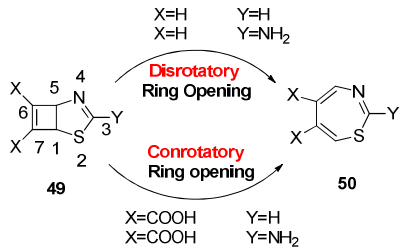
Six electron five centre thermally allowed electrocyclic disrotatory ring opening mechanism was proposed to produce *cis* 1,3- thiazepine **42** in good yield, started with fused cyclobutene with five membered ring **41** which contribute electronically and geometrically in polar disrotatory ring opening. Polar groups present in the ring reduce the energy barrier for the disrotation. The reaction did not perform well in the absence of trifluoroacetic acid and formed pyridine in the place of 1,3-thiazepine. (Scheme 14)



Scheme 14: Ring opening mechanism of the bicycle forming 2-amino-1,3-thiazepine-5,6-dicarboxylic acid

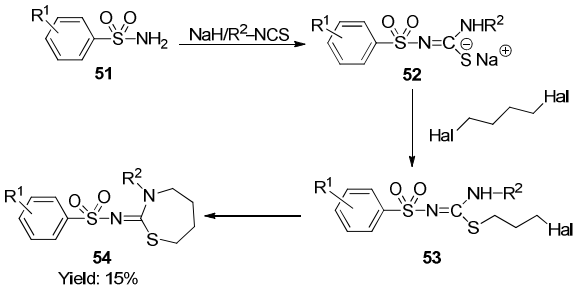
In continuation, Silva López *et al.* extended the above work in order to explain the mechanism more clearly (Scheme 15). Their aim was to notify a more favourable product between Woodward-Hoffman (W-H) and anti W-H. It explains that the mechanistic pathway strives between the disrotatory transition 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**.[36]



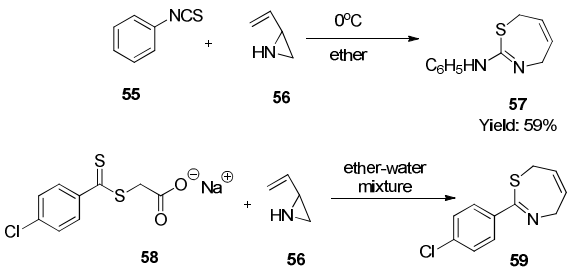
Scheme 15: Mechanistic alternatives for the ring-opening of *cis* bicyclo[4.2.0]oct-7-ene

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%).[37]



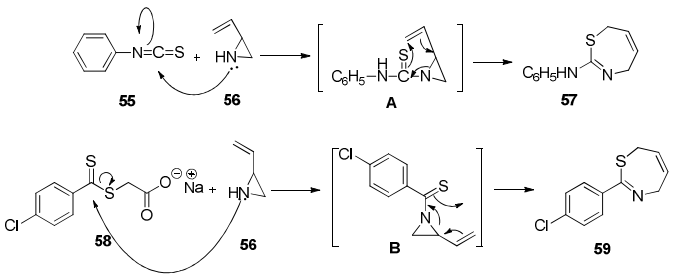
Scheme 16: Synthesis of 3-Phenyl-2-(*p*-toluenesulfonylimino)-perhydro-1,3-thiazepine

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.[38] (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.

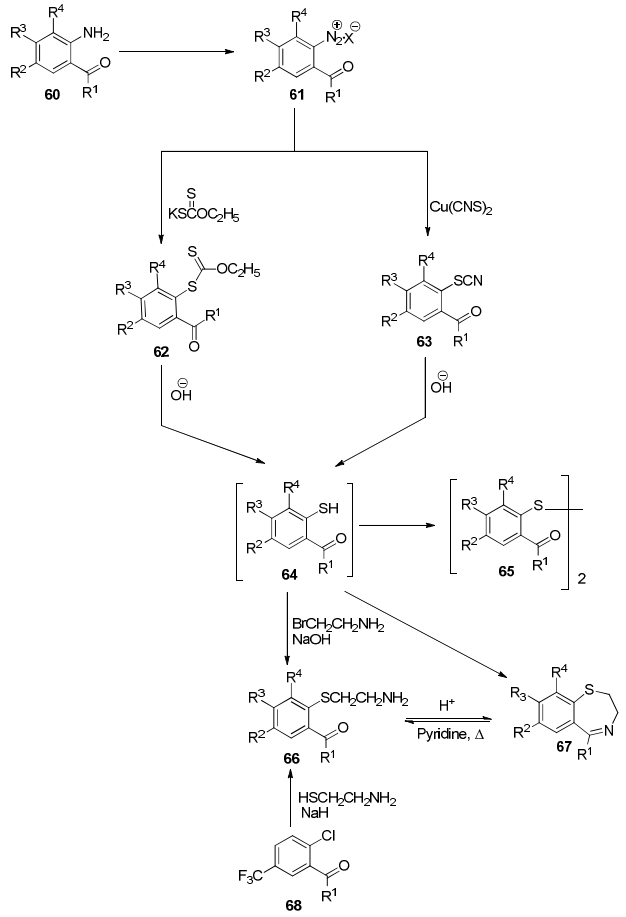
We have split this section into two parts based on the cyclic nature of the products:

a) Bicyclic Thiazepines

b) Tricyclic Thiazepines

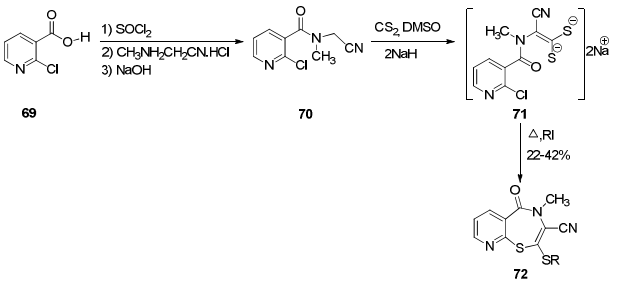
6.2 Synthesis of Bicyclic 1,4-Benzothiazepines

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*-mercapto ketones **66** which underwent ring closure in presence of pyridine to give 2,3-dihydro-l,4-benzothiazepines **67** in moderate yields (41%).[39]



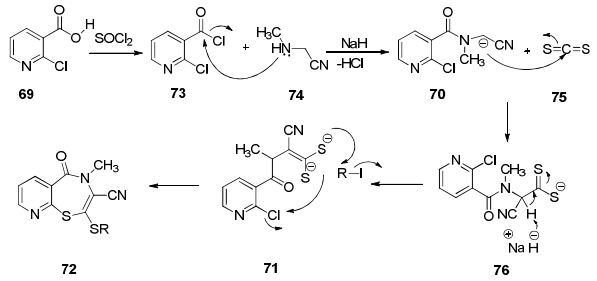
Scheme 19: Synthesis of 2,3-dihydro-1,4-benzothiazepine

Dölling *et al.,* devised a methodology to synthesize only two thiazepine derivatives **72** namely 4-methyl-2-methylthio-5(4*H*)-oxopyrido[3,2-*f*][1,4]thiazepine-3-carbonitrile and 2-ethylthio-4-methyl-5(4*H*)-oxopyrido[3,2-*f*][1,4]thiazepine-3-carbonitrile in 42% and 12% yields respectively *via* a multistep reaction sequence.[40] (Scheme 20)



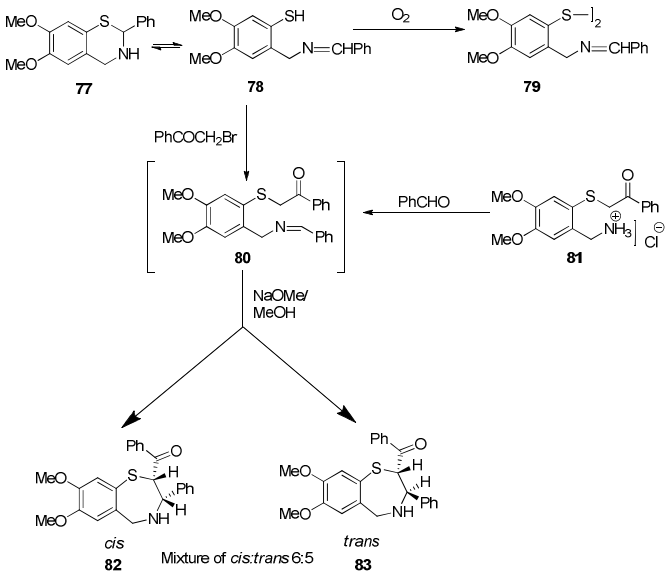
Scheme 20: Synthesis 1,4-benzothiazepine from 2-chloronicotinic acid

Mechanistically, 2-chloronicotinic acid **69** subsequently reacted with thionyl chloride and 2-(methylamino)acetonitrile 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)



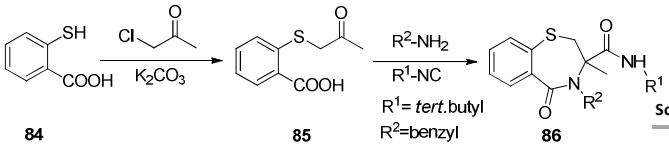
Scheme 21: Mechanistic aspects of 1,4-benzothiazepine from 2-chloronicotinic acid

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-l,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)



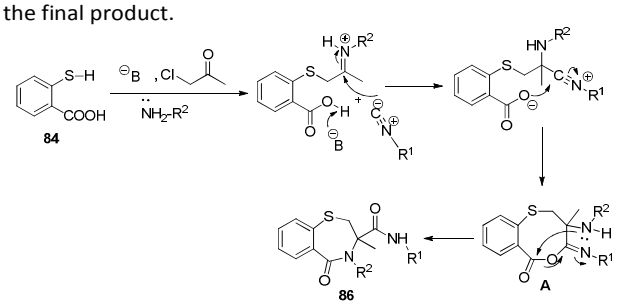
Scheme 22: Synthesis of diasteriomeric 1,4-benzothiazepines derivatives.

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)



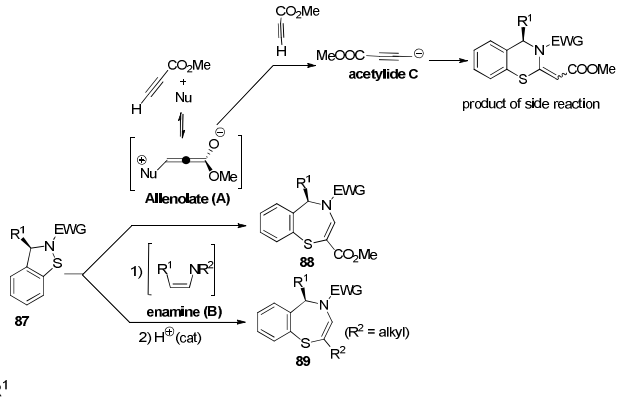
Scheme 23: Synthesis of 1,4-benzothiazepin-5-ones

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 nuleophilic 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.



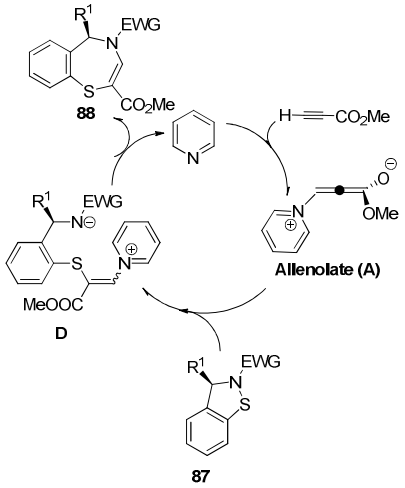
Scheme 24: Ugi reaction mechanism to afford 1,4-benzothiazepine derivatives

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 cylic 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]



Scheme 25: Synthesis of 1,4-benzothiazepine from cyclic sulfenamide

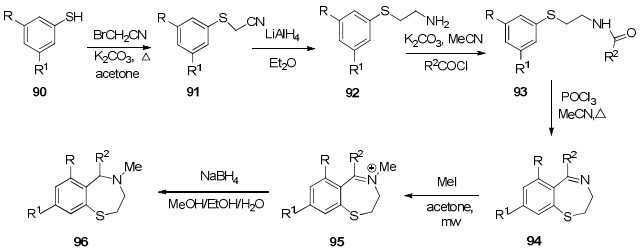
The plausible mechanism for the above reaction has been described in Scheme 26. It explains the initial formation of the zwitterionic allenolate **A** which attacks the electrophilic sulfur atom of sulfenamide **87** to form the corresponding zwitterion **D** which in turn cyclizes after an addition-elimination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



Scheme 26: Mechanistic detail for synthesis of 1,4-benzothiazepine from cyclic sulfenamide and allene.

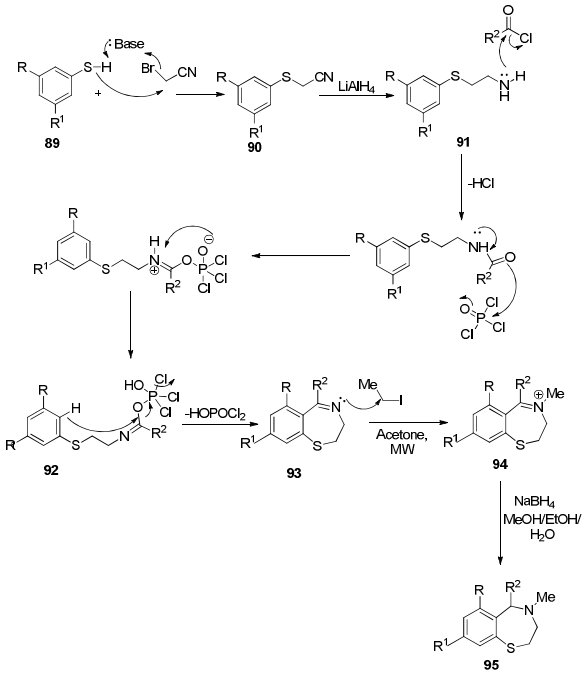
Voskressensky *et al.*, utilized tandem nucleophilic substitution and Bischler-Napieralski reaction to synthesise 2,3-dihydro 1,4-benzothiazepine **96**. In this multistep reaction, alkylation of substituted thiophenol **90** with bromoacetonitrile generated cyanomethylthioethers **91** followed by reduction, 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).



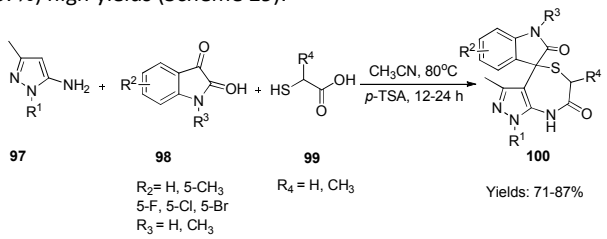
Scheme 27: Synthesis of 2,3-dihydro 1,4-benzothiazepine *via* a tandem Bischler-Napieralski protocol

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

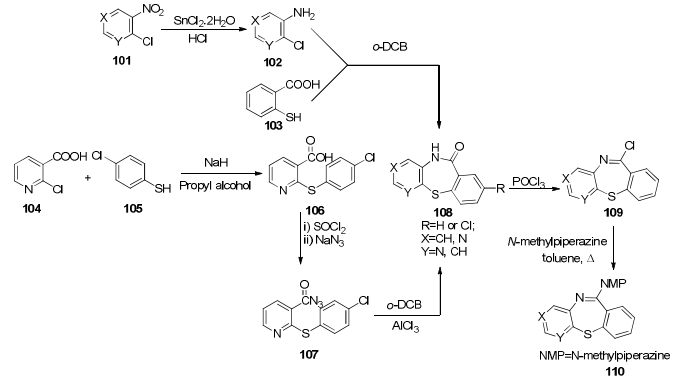
Shi *et al.,* reported a one-pot 3-CR of 5-amino-3-methylpyrazole **97**, isatin **98** and thioacid **99** through 3-(5-aminopyrazol-3-yl)-3-hydroxy-2-oxindoline intermediate (Baylis-Hillman type adduct) for the synthesis of spiro[indoline-3,4-pyrazolo[3,4-*e*][1,4]thiazepinedione derivatives **100** in (71-87%) high yields (Scheme 29).[45]



Scheme 29: Synthesis of spiro[indoline-3,4-pyrazolo[3,4-*e*][1,4]thiazepine-dione

6.3 Synthesis of Tricyclic 1,4-Benzothiazepines

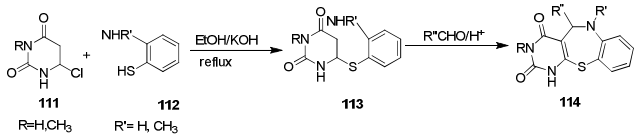
In 1994, Liegios *et al.,* synthesized nine *N*-methylpiperazinopyrido-[1,4]benzothiazepine derivatives **110** in good yields *via* a pyrido-[1,4]benzothiazepinone intermediate **108** which undergoes chlorination in presence of $POCl_3$ to form compound **109** which finally afford the target product **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)thiolnicotinic 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 5*H*-Pyrido[2,3-*b*][1,4]benzothiazepine

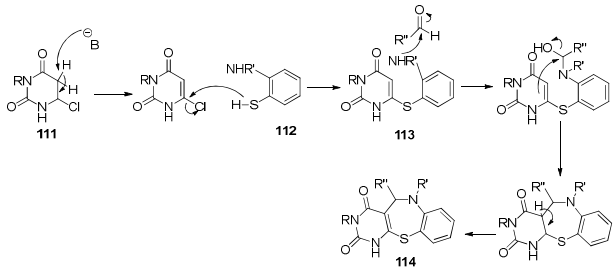
In 1995, Johnson and Maruendat performed reaction of 6-chlorouracils **111** with substituted 2-aminothiophenols **112** under refluxing conditions with KOH in ethanol to afford 6-(arylthio)uracils **113** which were further treated with appropriate aldehydes under acidic conditions to yield the desired 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.[47] (Scheme 31)



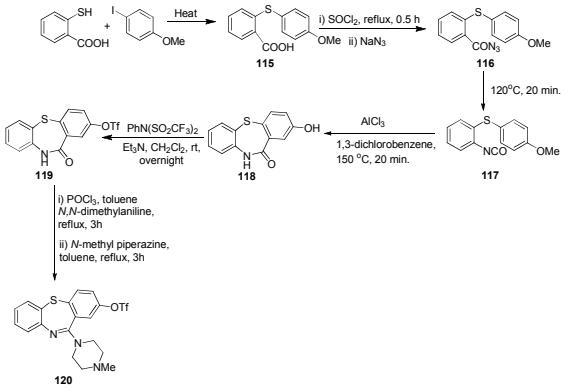
Scheme 31: Synthesis of Pyrimido[5,4-*f*]benzo[1,4]thiazepines

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.



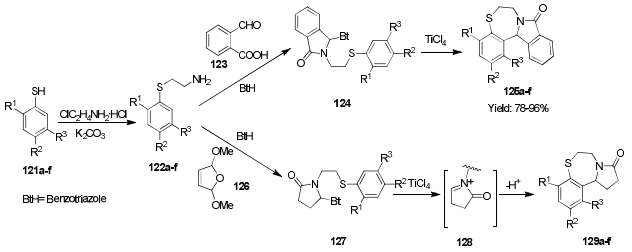
Scheme 32: Mechanistic aspects of formation of Pyrimido[5,4-*f*]benzo[1,4]thiazepine

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 effect and lipophilicity. So to enhance the pharmacological profile of this core, this group specially focussed on synthesis of triflate derivatives in moderate yields (45%).[48] (Scheme 33)



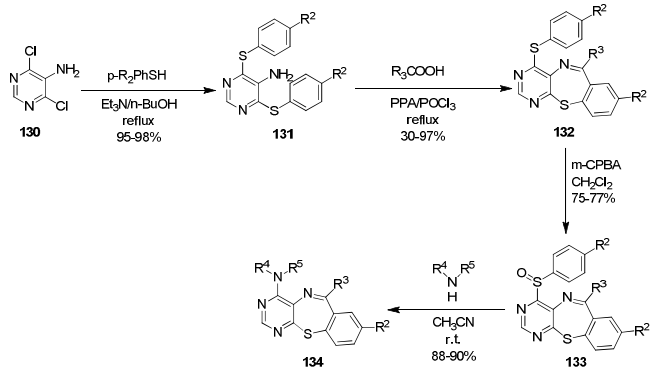
Scheme 33: Synthesis of 2-TfO-11-(4-methylpiperazinyl)-dibenzo[*b,f*][1,4]thiazepine

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**.[49](Scheme 34)



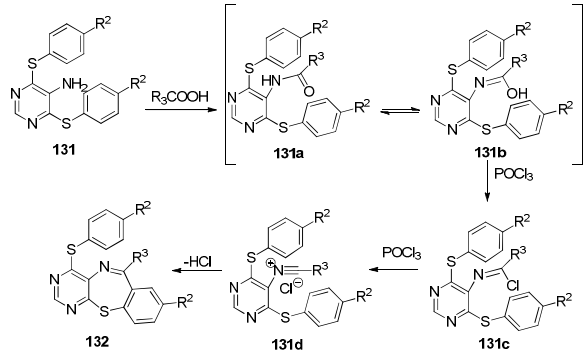
Scheme 34: Synthesis of 1,4- benzothiazepine derivatives

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-bisphenylthiopyrimidine **131** which under refluxing PPA/$POCl_3$ (Bishler-Napieralski conditions) gave the final benzothiazepine skeleton **132.** The aryl sulfide group of the resulting 4-arylthiopyrimido[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%).[50] Here, the bisphenylthio 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 (R^3) 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: Synthesis of 4-arylthiopyrimido[4,5-*b*][1,4]benzothiazepines

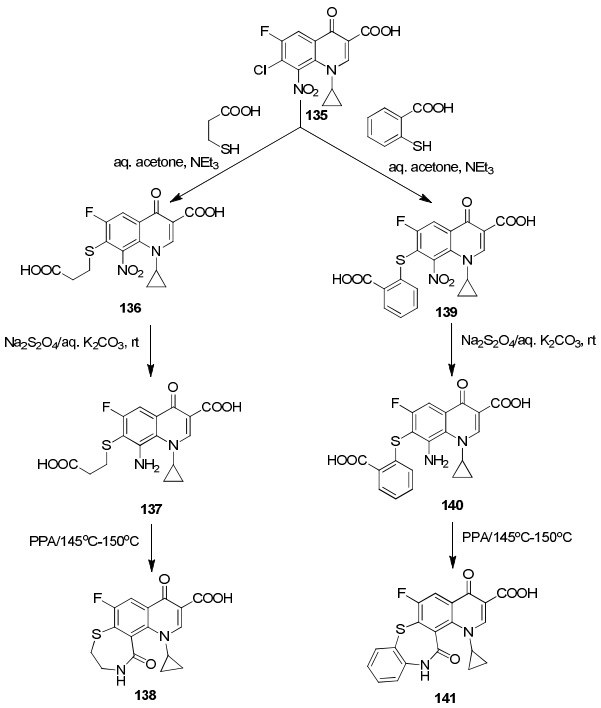
The mechanistic attributes in Scheme 36 portray acylation of bis-(phenylthio) compound **131** to give product **131a** which tautomerises to form **131b.** This was converted to imidoyl chloride **131c** when treated with $POCl_3$, which in turn transformed into corresponding nitrilium salt **131d**. 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.**



Scheme 36: Mechanistic details of Bischler-Napieralski cyclisation forming 4-arylthiopyrimido[4,5-*b*][1,4]benzothiazepines

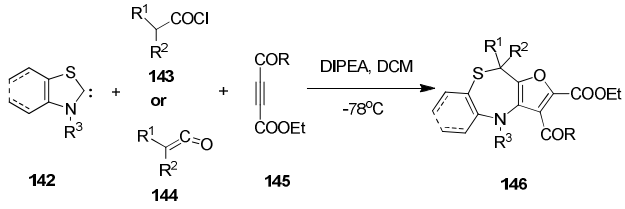
In 2007 Zahra *et al.*, synthesized substituted [1,4]thiazepino[2,3-*h*]quinolone carboxylic acid (**138** and **141)** by PPA-catalyzed thermal lactamization of the respective 8-amino-7-[(2-carboxyethyl)thio]-1,4-dihydroquinoline-3-carboxylic acid (**137** and **140**).[51]

Mechanistically, here 3-mercaptopropionic acid acts as 'sulfur' nucleophile which undergoes nucleophilic aromatic substitution S_NAr 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)



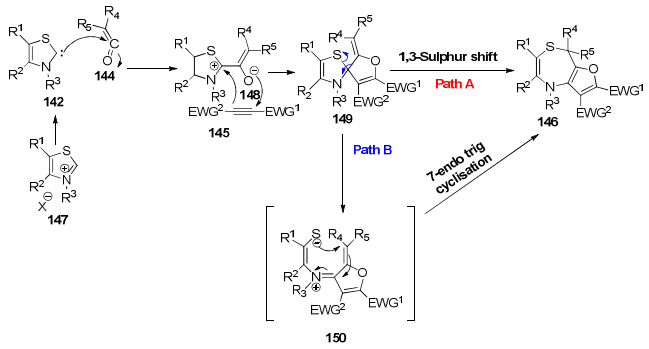
Scheme 37: Synthesis of substituted [1,4]thiazepino[2,3-*h*]quinolone carboxylic acid

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**.[52] (Scheme 38)



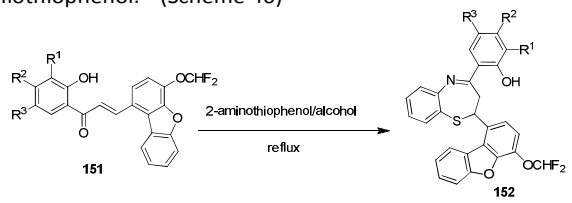
Scheme 38: Synthesis of furo[2,3-*c*][1,4]thiazepine

A plausible mechanistic pathway is depicted in Scheme 39. At first, thiazole carbene **142,** generated *in-situ* from thiazolium salt **147,** attacked the disubstituted ketene **144** to give zwitterion **148**, which underwent oxa-Michael addition with the activated alkyne **145** subsequently getting converted into the spirocycle intermediate **149** through intramolecular annulation. Ring-transformation of spirocycle **149** might take place *via* a concerted pathway **A** or a stepwise pathway **B**. Path **A** described the ring expansion of **148** proceeding to form furothiazepine **146** *via* a [1,3]-sigmatropic sulfur shift. On the other hand, path **B** illustrated the ring opening of **149** to a reactive thiolate **150**, which subsequently underwent a 7-endo-trig cyclization to produce thiazepine ring **146.**



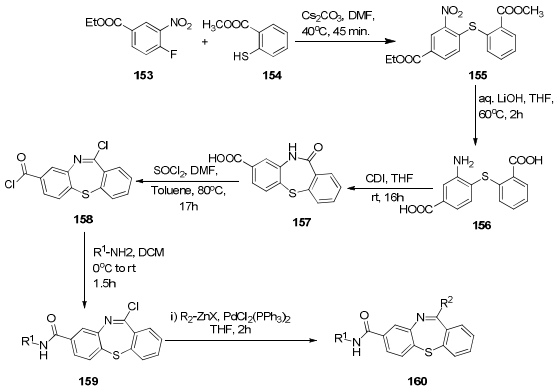
Scheme 39: Mechanistic aspects of formation of thiazepine ring

In 2009, Randhavane *et al.,* synthesized chalcones of 4-difluoromethoxy-dibenzofuran-1-carboxaldehyde **151** which were converted into corresponding dihydro-benzo[1,4]thiazepines **152** by refluxing with 2-amiothiophenol.[53] (Scheme 40)



Scheme 40: Synthesis of dihydrobenzo[1,4]thiazepines

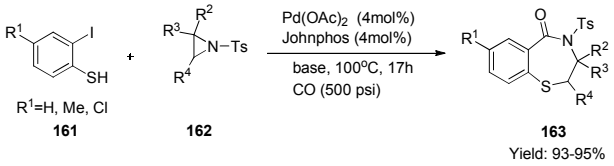
Later on, Olsson *et al.* synthesized lactam **157** from commercially available starting materials over three sequential steps. Subsequent diversification of lactam yielded the amide **159** and its further Negishi cross-coupling reaction afforded the final benzo[1,4]thiazepine-8-carboximide **160.**[54] 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 $SOCl_2$, 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).



Scheme 41: Synthesis of benzo[1,4]thiazepine-8-carboximide

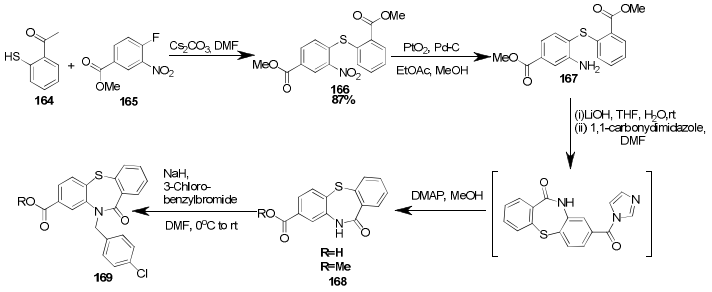
Similarly, Zeng *et al.,* devised an efficient domino procedure for the synthesis of 1,4-benzothiazepin-5-ones **163** from simple and readily accessible *N*-tosyl aziridines **162** and *o*-iodothiophenols **161**.[55] (Scheme 42)

The reaction of *N*-tosyl aziridine derivative with substituted 2-iodothiophenol furnished the corresponding 1,4-thiazepinones in excellent yields (93-95%). The versatility of the used starting materials demonstrated that this transformation could tolerate both electron donating (*p*-Me) and electron-withdrawing (*p*-Cl) groups on the phenyl ring of thiophenol.



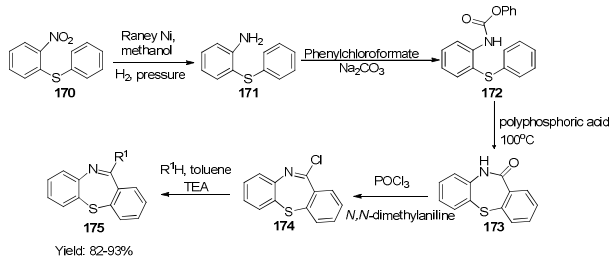
Scheme 42: Synthesis of 1,4-benzothiazepin-5-ones

Newton *et al.* in 2011 carried out S_NAr nucleophilic substitution of thiol **164**, with arylflouride 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.**[56](Scheme 43)



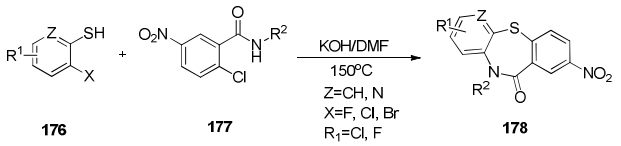
Scheme 43: Synthesis of Methyl 10-(3-chlorobenzyl)-11-oxo 10,11dihydrodibenzo[*b,f*][1,4]thiazepine-8-carboxylate

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 $POCl_3$ 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**.[57] This reaction accounted for sufficient versatality to generate 1,4-dibenzothiazepines in good yields (82-93%). (Scheme 44)



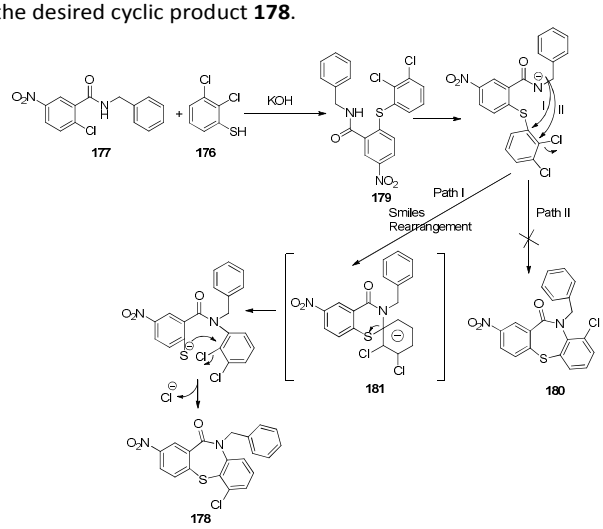
Scheme 44: Synthesis of dibenzo[*b,f*][1,4]thiazepines from 2-nitrodiphenylsulphide thiazepine ring.

Remarkably, Zhao *et al.* established an efficient metal free method for the synthesis of a library of dibenzo[*b,f*][1,4]thiazepin-11(10*H*)-ones **178** *via* Smiles rearrangement in excellent isolated yields (Scheme 45 and 46).[58] 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.



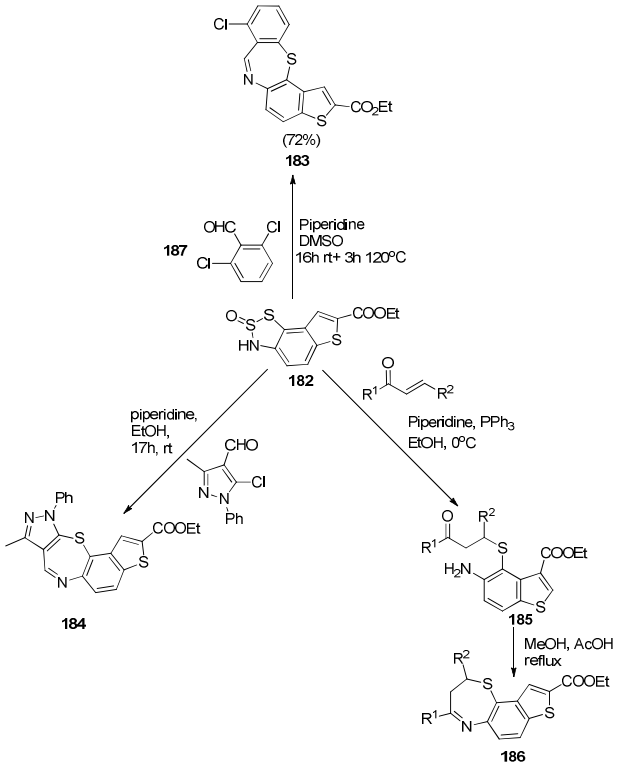
Scheme 45: Synthesis of dibenzo[*b,f*][1,4]thiazepin-11(10*H*)-ones *via* Smiles rearrangement

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**.



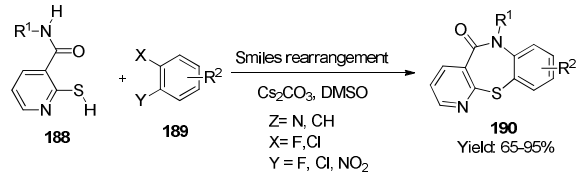
Scheme 46: Mechanistic aspects of Smiles Rearrangement

Interestingly, W. Van Snick *et al.* used 3*H*-thienobenzodithiazole-2-oxide **182** as 2-aminothiophenol precursor in synthesis of benzothiazepines (Scheme 47). Similarly reaction of 3*H*-thienobenzodithiazole-2-oxide **182** with 2,6-dichlorobenzaldehyde **187** resulted in the formation of thienobenzothiazepine derivative **183**[59] by intramolecular nucleophilic aromatic substitution reaction of the sulfur atom to the 2-position of the intermediate imine. Also reaction of chalcones with 3*H*-thienobenzodithiazole-2-oxide **182** produced dihydrothienobenzothiazepine **186**. Similarly, reaction of chloroformylpyrazole with precursor **182** generated new benzothiazepines **184**.



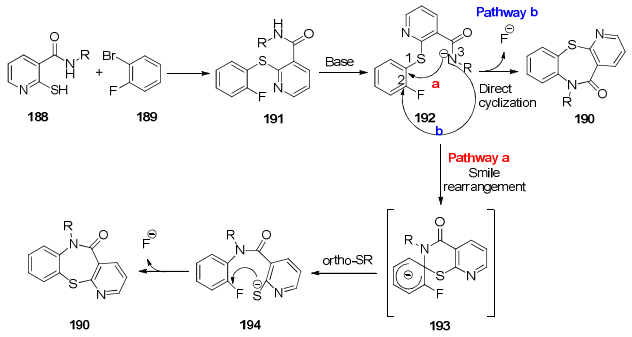
Scheme 47: Synthesis of thienobenzothiazepine derivatives

Recently, Yang *et al*. synthesized a series of twenty five 1,4-thiazepin-5(4*H*)-one **190** derivatives *via* a transition metal-free one-pot Smiles rearrangement process at room temperature.[60] Here, thiazepine scaffolds were obtained through the reaction of *N*-substituted 2-mercaptonicotinamides **188** and substituted benzenes **189** at room temperature in good to excellent yields (65-95%).(Scheme 48).



Scheme 48: Synthesis of 1,4-thiazepin-5(4*H*)-ones

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**.



Scheme 49: Competitive mechanistic details of the corresponding 1,4-dibenzothiazepinones

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:

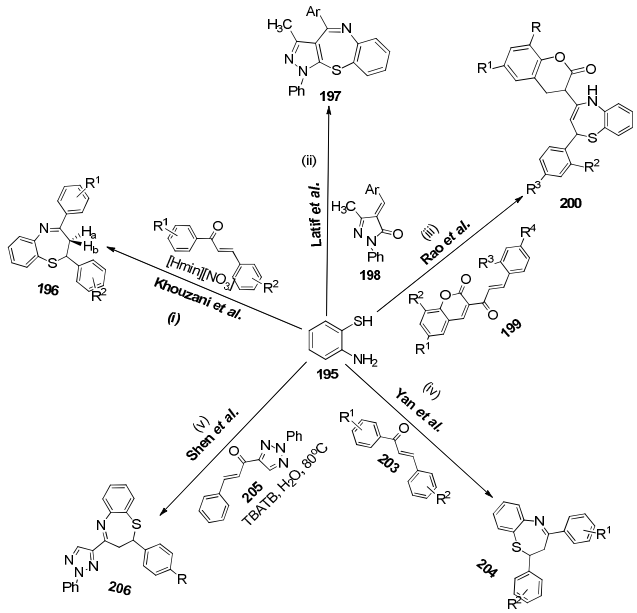
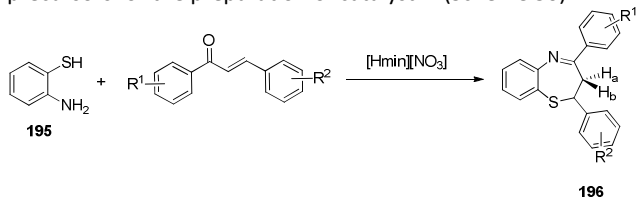


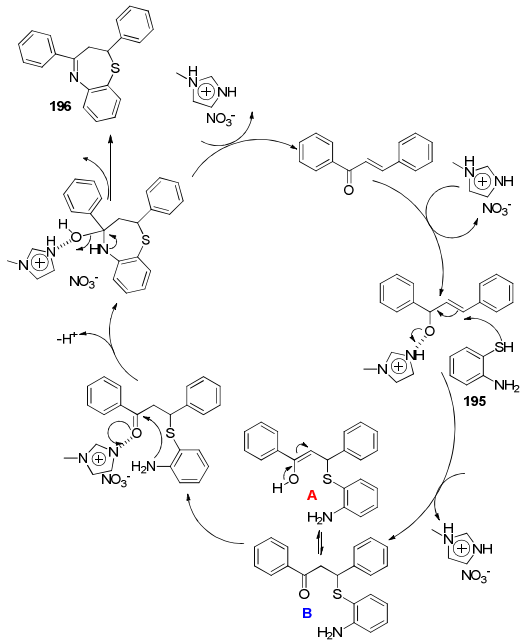
Figure 5: Reaction of 2-aminothiophenol with α,β-unsaturated carbonyl compounds to afford 1,5-benzothiazepine derivatives

(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][NO_3] as a brönsted 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)



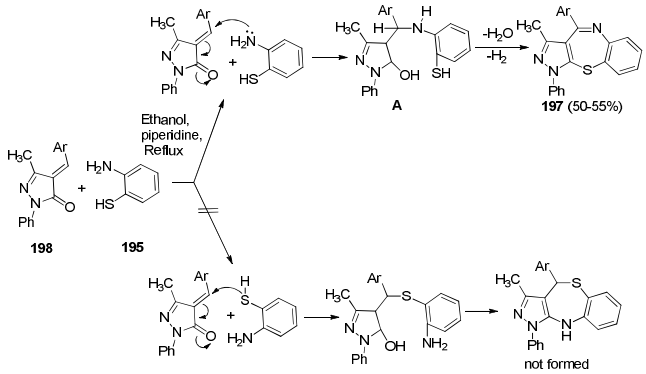
Scheme 50: Synthesis of 1,5 benzothiazepine derivatives

Mechanistically, the reaction proceeded initially by the intermolecular hydrogen bonding promoted by [Hmim][NO_3] 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)



Scheme 51: Mechanistic aspects of 1,5 benzothiazepine derivatives

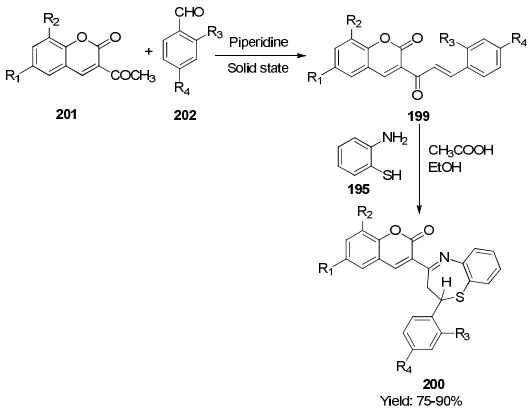
(ii) In 2004, Latif *et al.* reported the synthesis *of* 4-aryl-3-methyl-1-phenylpyrazolo[3,4-*b*][1,5]benzothiazepines **197** from 4-Arylidene-3-methyl-1-phenylpyrazole-5-one **198** and 2-aminobenzenethiol **195**. The products obtained were in moderate yields (50-55%).[62] (Scheme 52)



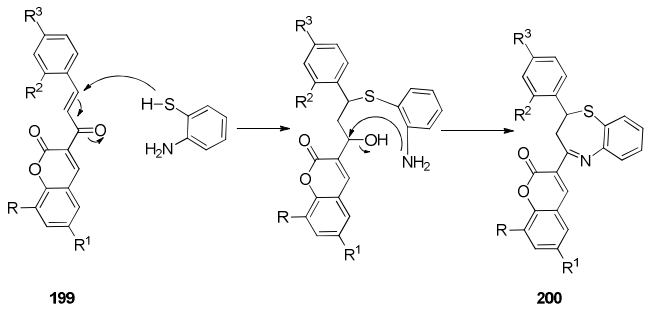
Scheme 52: Mechanistic pathway to form of 4-aryl-3-methyl-1-phenylpyrazolo[3,4-*b*][1,5]benzothiazepines

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-aminothiphenol to generate 2-aryl-4-[2*H*-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]

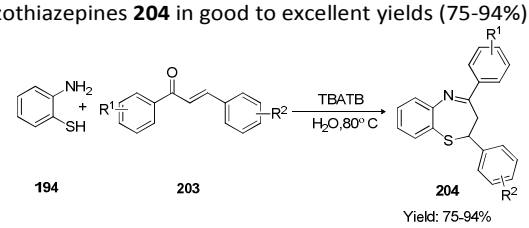


Scheme 53: Synthesis of and 2,5-dihydro-1,5-benzothiazepines



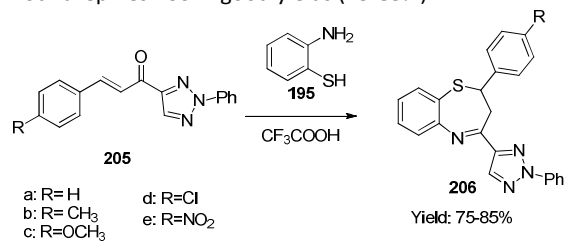
Scheme 54: Mechanistic pathways of 2,5-dihydro-1,5-benzothiazepines

(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%).[64]



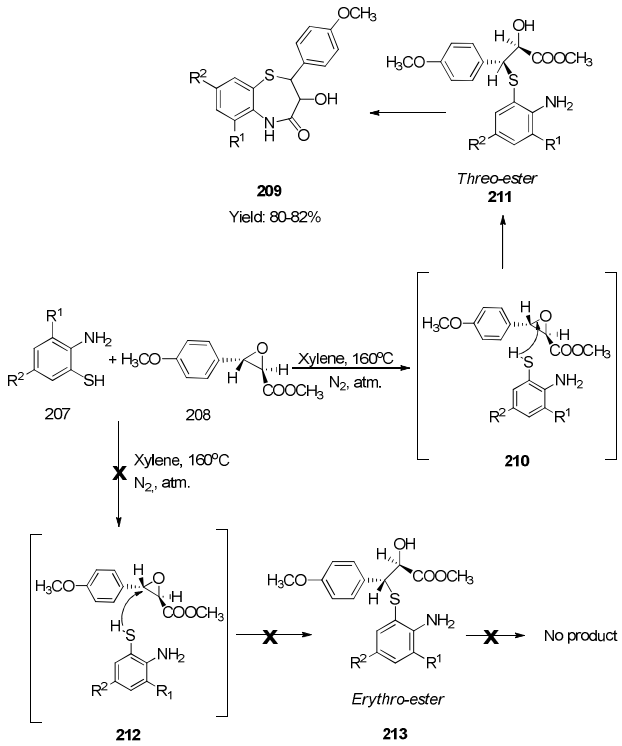
Scheme 55: Synthesis of 1,5 benzothiazepine derivatives

(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%).[65]



Scheme 56: Synthesis of 1,5-benzothiazepines

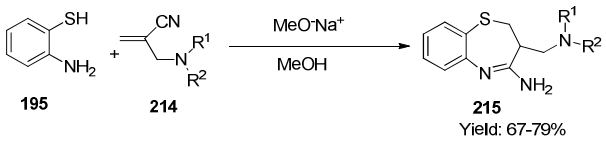
Similarly, Singh and co-workers described the synthesis of (±)-*cis*-2(4-Methoxyphenyl)-3-hydroxy-1,5-benzothiazepinones **209** by the condensation of chloro substituted 2-amino benzenethiol **207** with methyl-(±)-*trans*-3(4-methoxyphenyl)glycidate **208** in xylene under inert atmosphere in good yields (80-82%).[66] (Scheme 57)



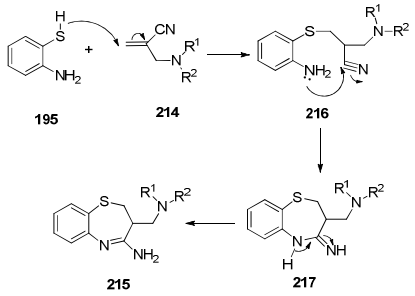
Scheme 57: Synthesis of (±)-*cis*-2(4-Methoxyphenyl)-3-hydroxy-1,5-benzothiazepinones

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**.[67]

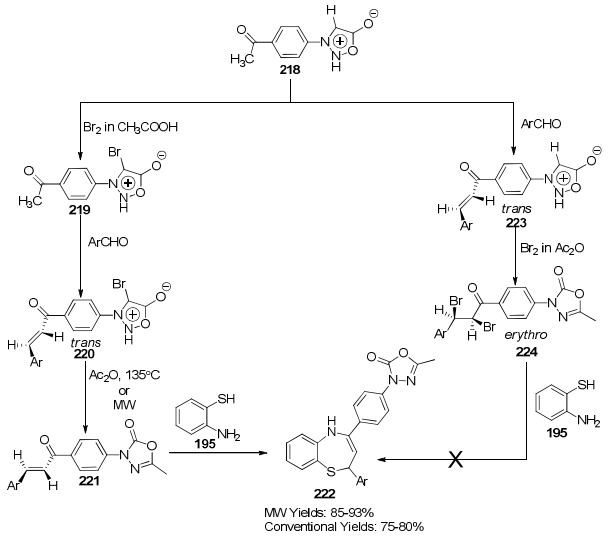


Scheme 58: Synthesis of 1,5-benzothiazepines



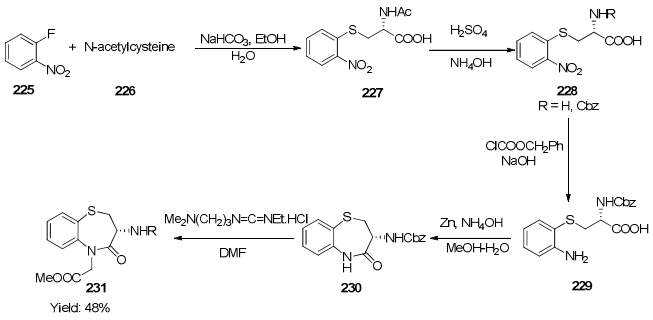
Scheme 59: Mechanistic pathway of 1,5-benzothiazepines

Kamble *et al.,* devised a synthesis of 1,5-benzothiazepines integrated with 5-methyl-2-oxo-3-phenyl-4-1,3,4-oxadiazoles using 4-acetylphenylsydnone **218** and 2-aminothiophenol **195** 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).[68] (Scheme 60)



Scheme 60: Synthesis of 1,5-benzothiazepines derivatives

Slade and co-workers devised a synthetic strategy to synthesize chiral 1,5-benzothiazepinones **231** using *o*-fluoronitrobenzene **225** and *N*-acetylcysteine **226** as the starting precursors (Scheme 61).[69] Initial nucleophillic substitution of *o*-fluoronitrobenzene with *N*-acetylcysteine affords S-(*o*-nitropheny1)-N-acetylcysteine which is further deacetylated and converted to Cbz derivative. It then undergoes ring closure to lactum using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimidehydrohloride in DMF to afford the title compound **231** in moderate yield (48%).



Scheme 61: Synthesis of chiral 1,5-benzothiazepines

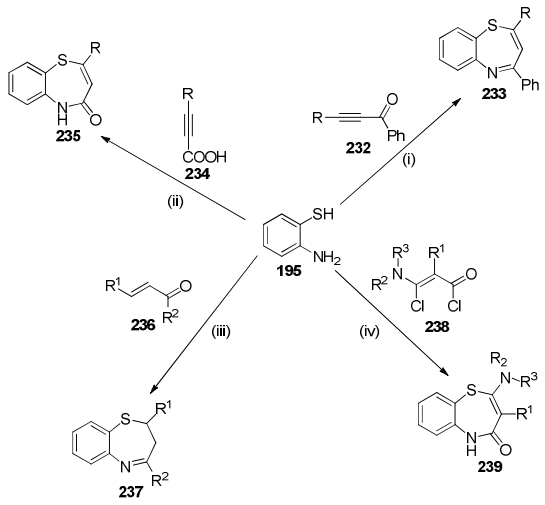
Conclusively, Scheme 62 summarizes reaction of 2-aminothiophenol with various unsaturated ketones to afford diverse substituted benzothiazepines. The reactions are described as follows:-

(i) 2-aminothiphenol react with alkynones **232** in a mixture of hot methanol and acetic acid to obtain 2,4- disubstituted 1,5-benzothiazepines **233**.[70,71]

(ii) Also, 1,5-benzothiazepin-4(5*H*)-ones were synthesized by heating 2-aminothiophenol with either propiolic acid **234** or its β-substituted derivatives to yield the appropriate 1,5-benzothiazepines **235**.[72,73,74]

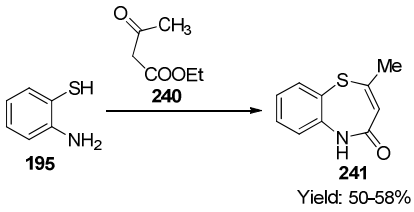
(iii) Reaction of 2- aminothiophenol and α,β- unsaturated ketones **236** gives 2,3-disubstituted 2,3-dihydro-1,5-benzothiazepine **237**.[75]

(iv) Reaction of 2-aminothiophenol with α-chloro-β-chlorocarbonyl enamines **238** in the presence of pyridine produced 2,3-disubstituted 1,5-benzothiazepin-4(5H)-ones **239**.[76]



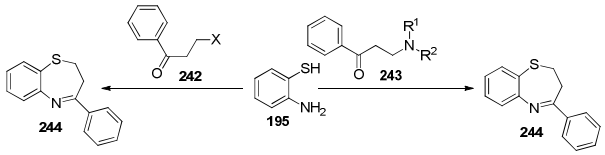
Scheme 62: Synthesis of 1,5-benzothiazepine derivatives *via* Michael addition of 2-aminothiphenol with α,β-unsaturated ketones

Also, 2-methyl-1,5-benzothiazepin-4(5*H*)-one **241** was synthesized in moderate yields (50-58%) by reaction of 2-aminothiophenol with ethylacetoacetate **240** in xylene at refluxing temperature (Scheme 63).[75,77]



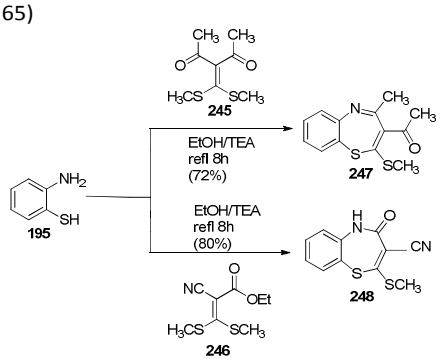
Scheme 63: Synthesis of 2-methyl-1,5-benzothiazepin-4(5*H*)-one

A series of 4-aryl-2,3-dihydro-1,5-benzothiazepines **244** has been synthesized by reaction of 2-aminothiophenol with either *N,N*-disubstituted (2-aminoethyl)aryl ketone **243**[78] or β-haloketone **242**.[79](Scheme 64)



Scheme 64: Synthesis of 4-aryl-2,3-dihydro-1,5-benzothiazepines from *N,N*-disubstituted (2-aminoethyl)aryl ketone

Likewise, Benzo[*b*][1,5]thiazepines **(247, 248)** were prepared *via* reaction of *o*-aminothiophenol **195** with 3-(bis(methylthio)methylene)-pentane-2,4-dione **245** or 2-(bis(methylthio)methylene)-3- carbonitrile **246** respectively.[80] (Scheme 65)



Scheme 65: Synthesis of Benzo[*b*][1,5]thiazepines from 3-(bis(methylthio)methylene)-pentane-2,4-dione

Conclusion

Over the past years the privileged structure concept has emerged as a rewarding approach in arena of drug discovery and development. Along this review, benzothiazepines have been showcased as a growing and increasingly important class of heterocyclic ring system with celebrated drug-like properties and versatile binding properties. Early developments in the arena of benzothiazepines were subjected to synthesis of various derivatives and their biological evaluation. This stemmed into discovery of some potent drugs such as Thiazesim, Dilteazem and Quetipine 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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Biographical Sketch

Debasmita Saha was born in New Delhi, India. She completed her Bachelors and Masters in Organic Chemistry from University of Delhi in 2009 and 2011 respectively. In 2012, she joined the research group of Dr. Anuj Sharma in the Department of Chemistry at Indian Institute of Technology, Roorkee. Her present research is focused on the design and synthesis of novel organic therapeutic frameworks, metal mediated coupling reactions and development of new isocyanide based multicomponent reactions.

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Benzothiazepines: Chemistry of a Privileged Scaffold

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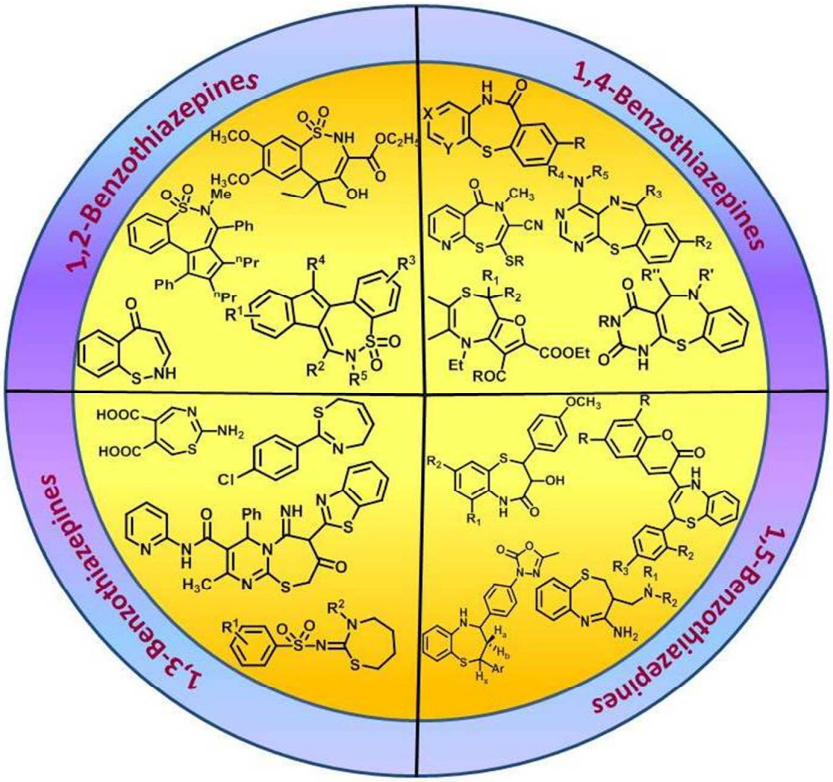
Graphical Abstract



Keywords

Dibenzothiazepine, Heterocycles, Anti-psychotics, Antimicrobial and Antifungal.