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Review Article

Pharmacological and synthetic profile of benzothiazepine: A review

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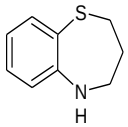
Abstract

The 1, 5-benzothiazepines are important nitrogen- and sulfur-containing seven-membered heterocyclic compounds in drug research since they possess diverse bioactivities. 1, 5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine and one of the three possible benzo-condensed derivatives, and 1,5-benzothiazepines. The 1, 5-benzothiazepine derivatives are of particular interest for lead discovery because they have been found active against different families of targets. Therefore, the 1,5-benzothiazepines are useful compounds in the drug research which has stimulated the invention of a wide range of synthetic methods for their preparation and chemical transformations. Benzothiazepine and its derivatives exhibit diverse biological activities such as coronary vasodilatory, tranquilizer, antidepressant, antihypertensive, calcium channel blocker. This review also discusses the structure-activity relationship of the most potent compounds. It can act as an important tool for medicinal chemists to develop newer compounds possessing 1, 5-benzothiazepines moiety that could be better agents in terms of efficacy and safety.

Keywords: Benzothiazepine, vasodilatory, antihypertensive

1. Introduction

The 1, 5-benzothiazepines are important nitrogen- and sulfur-containing seven-membered heterocyclic compounds. 1, 5-Benzothiazepines are the most well-known representatives of benzologs of 1, 4-thiazepine and one of the three possible benzo-condensed derivatives.



1,5-benzothiazepine

The 1,5-benzothiazepine derivatives are of particular interest for lead discovery because they have been found active against different families of targets. The first molecule of 1,5-benzothiazepine used clinically was diltiazem, followed by clentiazem, for their cardiovascular action. Some of the 1,5-benzothiazepine derivatives were also used clinically for CNS disorders which includes thiazesim, Clothiapine and quetiapine.

The common strategy for the construction of the 1,5-benzothiazepine moiety is the reaction of 1,3-diarylprop-2-enones with o-aminothiophenol. The various reported methodologies involve the use of inorganic solid supports such as alumina, silica gel and clay under microwave irradiation, acetic acid or trifluoroacetic acid, hydrochloric acid, piperidine etc.

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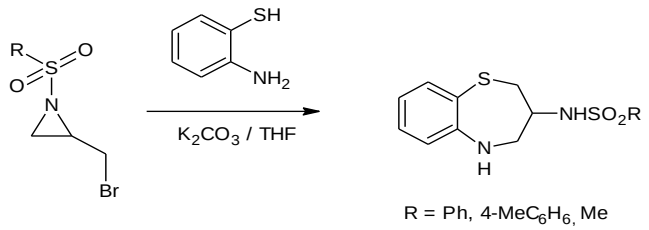
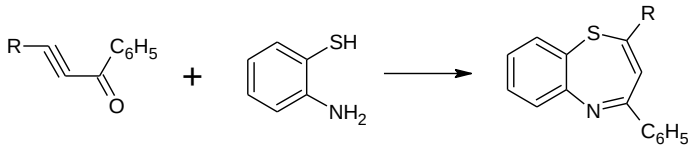
2. Method of synthesis

Michinori *et al*[1] in year 2008 had been reported the synthesis of 3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines Treatment of 2 (bromomethyl) aziridines with 1.2 equiv of 2-aminothiophenol in THF in the presence of potassium carbonate.

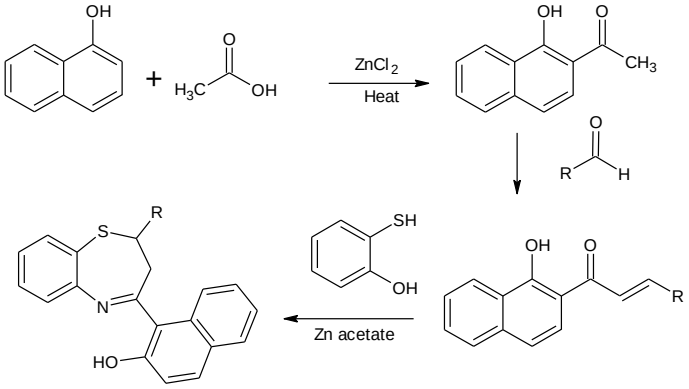


R = Ph, 4-MeC$_6$H$_6$, Me

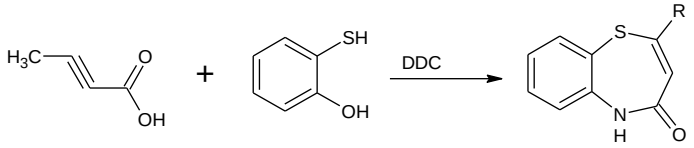
Masquelin *et al*[2] in the year 1997 had been reported 2,4-disubstituted 1,5- benzothiazepines occurs by the reaction of 2-aminothiophenol with acetylinic ketones.



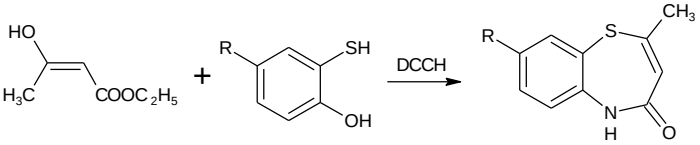
Vyawahare *et al*[3] in year 2010 had been reported 2,3-dihydro-2-substituted-4-(naphthalen-2-ol)-yl-1,5-benzothiazepines from 1,3-substituted-prop-2-en-1-one.Cyclocondensation of with 2-aminothiophenol in presence of ecofriendly catalyst zinc acetate in the solvent free condition under microwave irradiation.



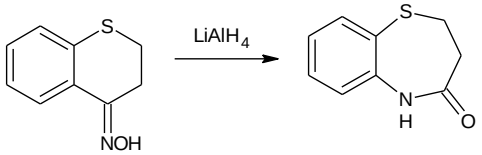
Krapcho *et al*[4] in year 1966 had been reported 1,5-benzothiazepin-4(5H)-ones occurs by the reaction of 2-aminothiophenol and propiolic acid with subsequent cyclisation.



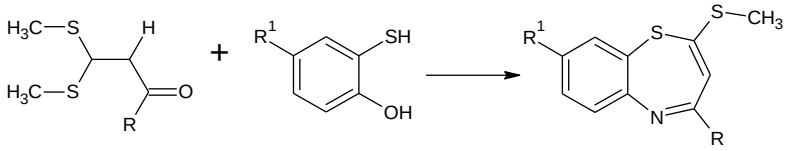
Gupta *et al*[5] in year l980 had been reported 2-Methyl-1,5-benzothiazepines-4(5H) one derivatives can be obtained by the reaction of acetoacetic ester with substituted 2-aminothiohenols.



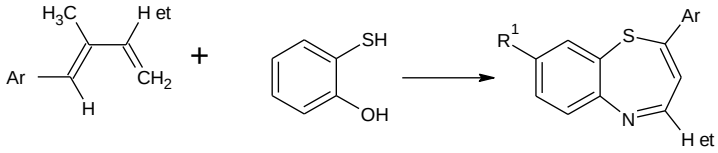
Levai *et al*[6] in the year 1986 had been reported 2,3,4,5-Tetrahydro-1,5-benzothiazepine has been obtained by reductive expansion of the ring of 1-thiochromanone oxime with lithium aluminum hydride.



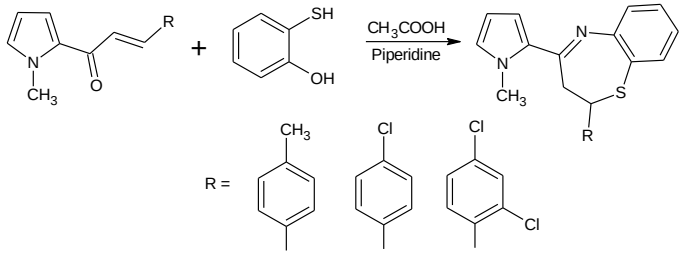
Junjappa *et al*[7] in year 1990 had been reported 1,5-benzothiazepines from Reaction of α-oxoketene-S,S-acetal with o-aminothiophenol.



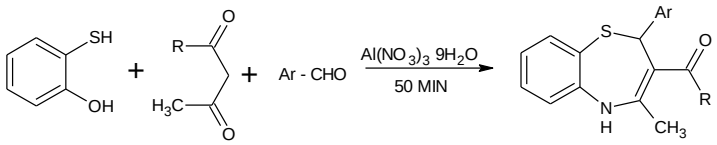
Prakash *et al*[8] in year 2005 had been reported 1,5-benzothiazepines from reaction of chalcone with o-aminothiophenol.



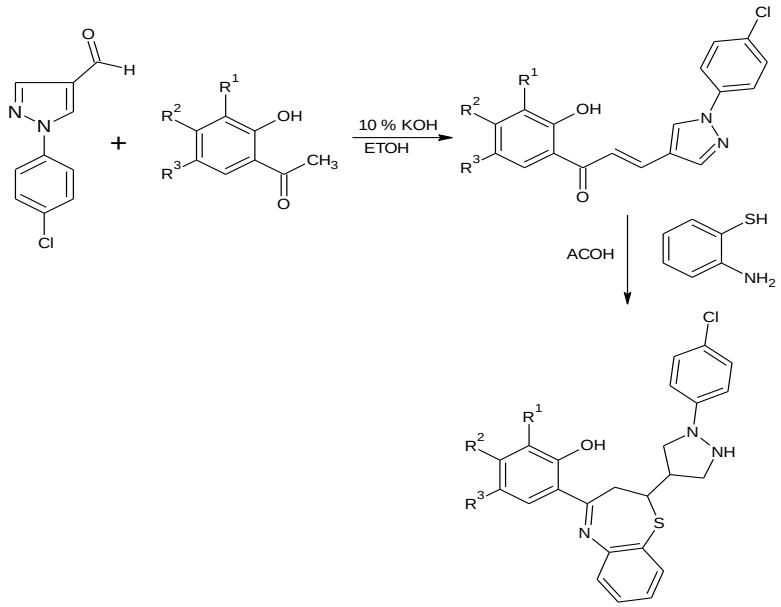
Ahmad *et al*[9] in year 2000 had been reported 1, 5-benzothiazepines from chalcones obtained from 2-acetyl-1-methylpyrrole.



Khan *et al*[10] in year 1987 had been reported 2,5-dihydro-4-methyl-2-phenyl-3-acetyl-1,5-benzothiazepine obtain from using aluminum nitrate as catalystwith equimolar mixture of 2-aminotiophenol,benzaldehydes and 2,4-pentanedione.

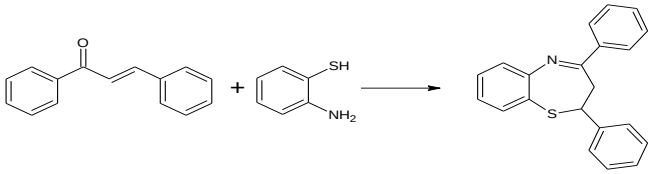


Mhaske *et al*[11] in year 2014 had been reported Novel 1, 5-benzothiazepine reaction of 1-(4-chlorophenyl)-1*H*-pyrazole-4-carbaldehyde, *o*-hydroxyacetophenones and chalcone.

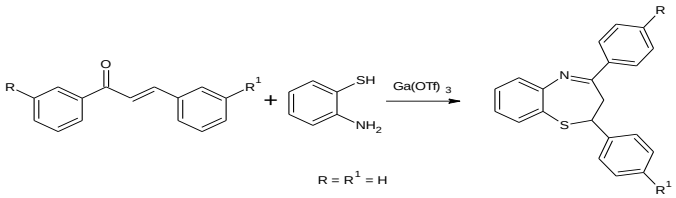


$R_1=R_2=R_3=$ H, CH_3

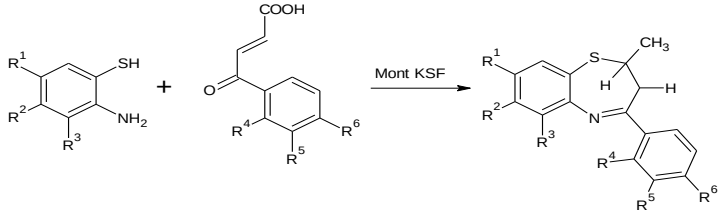
Arya *et al*[12] in year 2008 had been reported substituted 1,5-benzothiazepines from chalcones with o-aminothiophenol.



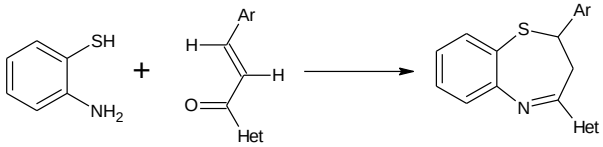
Dandia *et al*[13] in year 2007 had been reported 1,5-benzothiazepines from o-aminothiophenol and chalcones under gallium triflate catalysis.



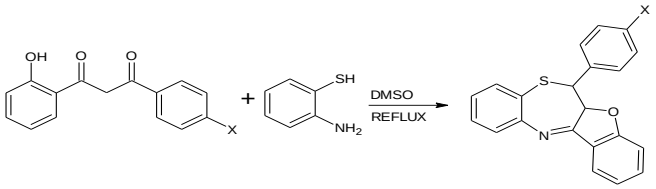
Press *et al*[14] in year 1980 had been reported 2-carboxy-2,3-dihydro-1,5-benzothiazepines was carried out by reacting from substituted o-aminothiophenols with α,β-unsaturated ketones using montmorillonite clay.



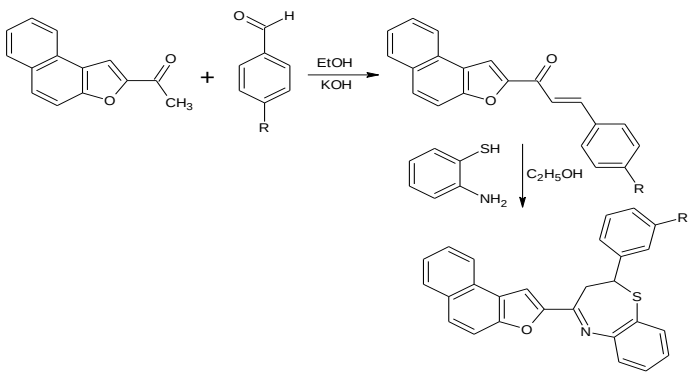
Ahmad *et al*[15] in year 2000 had been reported 1,5-benzothiazepines reaction of o-aminothiophenol with α,β-unsaturated ketones or chalcones.



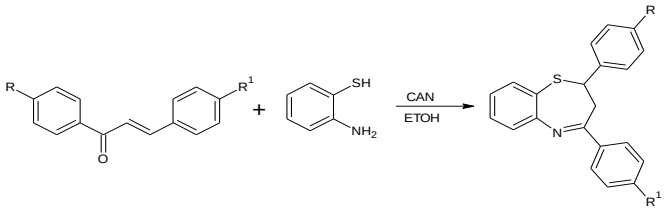
Balasubramaniyam *et al*[16] in year 1986 had been reported substituted 1,5-benzothiazepine derivatives β-diketones with o-aminothiophenol in DMSO.



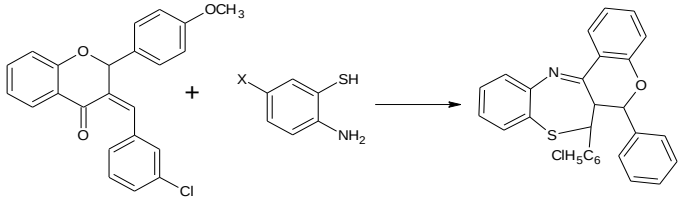
Gaikwad *et al*[17] in year 2013 had been reported novel 2, 3-diydro -4-(naphtho [2, 1-b] furan -2yl)-2-substitued [1,5] benzothiazepines mixture of 1-(naphtho [2,1-b] furan-2-yl)-3-penyl prop-2-en-1-one and o-amino thiophenol.



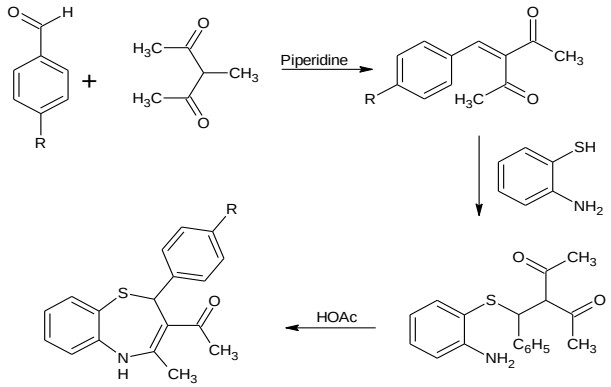
Chate *et al*[18] in year 2011 had been reported Synthesis of 1,5-Benzothiazepines Using from chalcones and o-aminothiophenol using Ceric Ammonium Nitrate as a catalysts under ultrasonic irradiation.



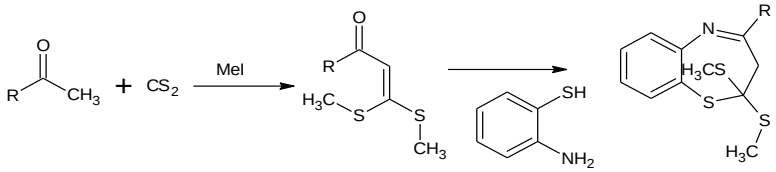
Jain *et al*[19] in year 2013 had been reported 10-fluoro- 6a, 7-dihydro-6H-7-(3-chlorophenyl)- 6-(4-methoxyphenyl)- [1] benzopyrano [3,4-c][1,5]- benzothiazepine 3-(3-chlorobenzylidine)flavanone and 5-substituted-2-aminothiophenols in dry toluene containing trifluoroacetic acid as catalyst.



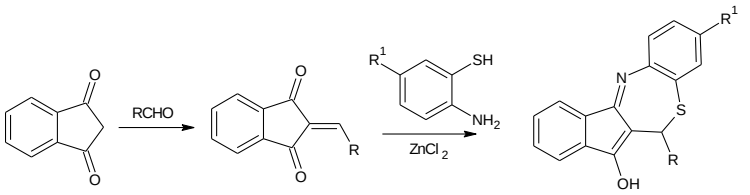
Wang *et al*[20] in year 2009 had been reported 1,5-benzothiazepine derivatives condensation of aromatic aldehydes with 2,4-pentandione in dry benzene catalyzed by piperidine gave compound 3. Then Michael addition of o-aminothiophenol to compound 3 yielded the corresponding pentandione derivatives 4.Finally, the intramolecular cyclisation of 4, followed by dehydration in acetic acid.



Parthasarathy *et al*[21] in year 2013 had been reported 1,5-benzothiazepines mixture of 2-aminothiophenol and a-oxoketene dithioacetals, adsorbed onto silica gel subjected to the 20 ml Microwave reactor and mixture was irrigated at 70^0C.

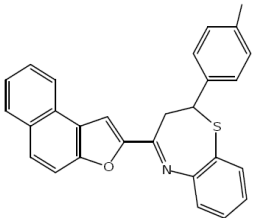


Carolyn *et al*[22] in year 2013 had been reported tetracyclic benzothiazepines(BTZs) from 1,3-indandione, 1 mmol of aldehyde, 0.2 mmol of the catalyst L-Proline, and then MeOH (2 ml). The reaction mixture was stirred at room temperature until the LC/MS analysis showed the completion of the reaction (30 min–1 hr). Intermediate, 2-arylidene-1,3-indandione, was used in the next step with 2-aminothiophenol and anhydrous ZnCl2 in anhydrous THF. The reaction mixture was heated in a microwave reactor at 100^0C for 1 hr.

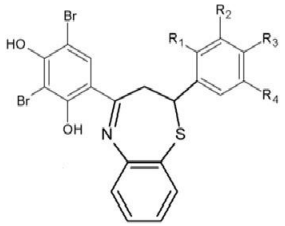


3. Pharmacological Profile

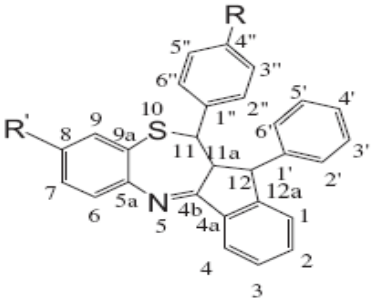
Gaikwad *et al*[23] in the year 2013 had been reported Synthesis and antimicrobial study of novel 2, 3-diydro -4-(naphtho [2, 1-b] furan -2yl)-2-substitued [1, 5]benzothiazepines.



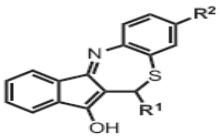
Ameta *et al*[24] in the year 2013 had been reported synthesis and preliminary evaluation of novel 1, 5-benzothiazepine derivatives as anti-lung cancer agents.



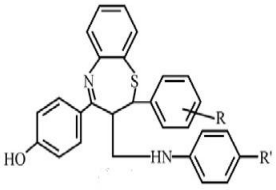
Mor *et al*[25] in the year 2012 had been reported 1, 5-benzothiazepine derivatives as anti-microbial activity.



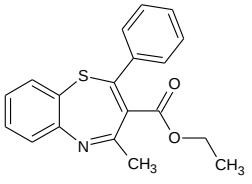
Dong *et al*[26] in the year 2011 had been reported Identification and Validation of Tetracyclic Benzothiazepines as Plasmodium falciparum Cytochrome bc1 Inhibitors.



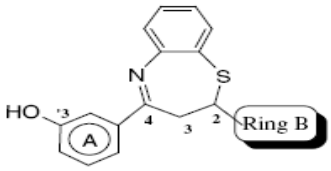
Garg *et al*[27] in the year 2010 had been reported Synthesis and evaluation of some new substituted benzothiazepine and benzoxazepine derivatives as anticonvulsant agents.



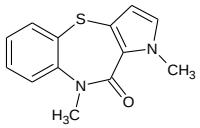
Wang *et al*[28] in the year 2009 had been reported Synthesis and biological evaluation of a novel series of 1,5-benzothiazepine derivatives as potential antimicrobial agents.



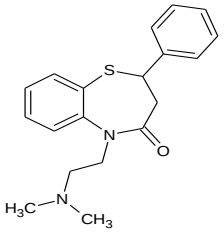
Ansari *et al*[29] In the year 2008 had been reported Solid-phase synthesis and biological evaluation of a parallel library of 2,3-dihydro-1,5-benzothiazepines.



Gee *et al*[30] in year 2005 had been reported 3H-pyrrolo[2,3- b][1,5]benzothiazepine Derivative Inhibited HIV-1 replication in the micromolar range.

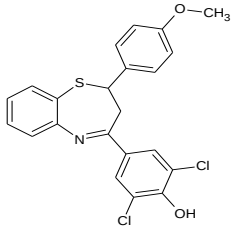


Hopenwasser *et al*[31] in year (2004) had been reported "Postmortem distribution of the novel antipsychotic drug quetiapine", Acts as a heterocyclic antidepressant.

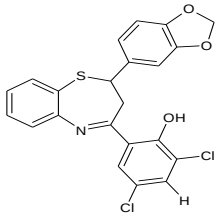


4. SAR Study

Nikalje *et al*[32] in the year 2011 had been reported SAR study of 2, 4-substituted -2, 3- dihydro-1, 5 Benzothiazepine derivatives as novel anticonvulsant and central nervous system (CNS) depressant agents. Generally, the anticonvulsant activity of organic compound may be increased after the introduction of halogen atom. Therefore, we selected 2, 6-dichlorophenol as starting material to obtain 2, 6- dichloro acetophenone so there must be two chloro substituents in the 1,5-benzothiazepine derivatives. Electron- donor derivatives were also prepared, compound containing p-methoxy and p-hydroxy group, respectively and have shown better anticonvulsant activity as compared to other derivatives. Compound containing phenyl group and compound containing para methoxy phenyl group have shown better CNS depression as compared to other derivatives. The mechanism of action of these molecules may be the same as that for benzodiazepines; which act on allosteric site of benzodiazepine which facilitates the GABA mediated Cl channel opening.



Bajod *et al*[33] in the year 2013 had been reported SAR study of 1, 5 Benzothiazepine derivatives. From the bioactivity results, we concluded that the newly synthesized benzothiazepine derivatives containing chlorine as a substitute are able to show the highest anti-microbial activity, whereas those compounds containing hydrogen as a substitute show the lowest anti-microbial activity.



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