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1, 5-BENZOTHIAZEPINES: AN UPDATE

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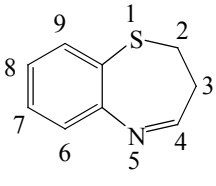
ABSTRACT

1, 5-Benzothiazepine, a heterocyclic compound involved in research aimed to evaluate new products that possess interesting biological activities. The present review article focuses on the various methods of synthesis, spectral properties and pharmacological profile of 1,5-benzothiazepines.

Keywords: 1, 5-Benzothiazepinen, Pharmacological profile.

INTRODUCTION:

The 1,5-benzothiazepines[1] **(1**and **2)** are important nitrogen- and sulfur-containing seven-membered heterocyclic compounds in drug research since they possess diverse bioactivities[2-9]. 1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine **(3)** and one of the three possible benzo-condensed derivatives, viz. 1,4-**(4)**, 4,1- **(5)** and 1,5-benzothiazepines[10-13].



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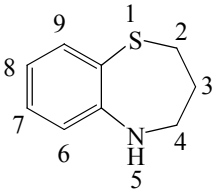

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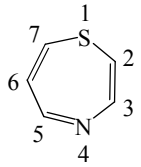
General structures of 1, 5-benzothiazepine



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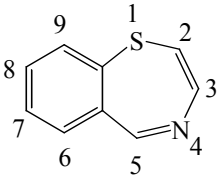

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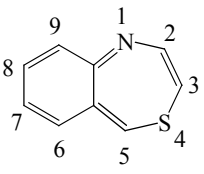

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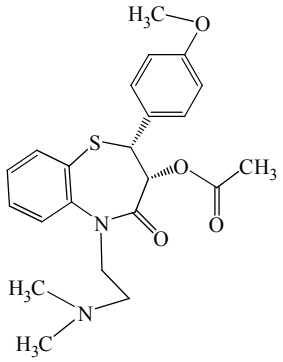
The 1, 5-benzothiazepine derivatives are of particular interest for lead discovery because they have been found active against different families of targets[14-24]. The first molecule of 1,5-benzothiazepine used clinically was diltiazem **(6)**, followed by clentiazem **(7)**, for their cardiovascular action. Some of the 1,5-benzothiazepine derivatives were also used clinically for CNS disorders which includes thiazesim **(8)**, clothiapine **(9)** and quetiapine **(10)**. 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[25-45].

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[46-56].



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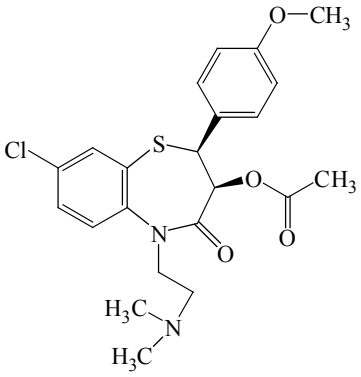

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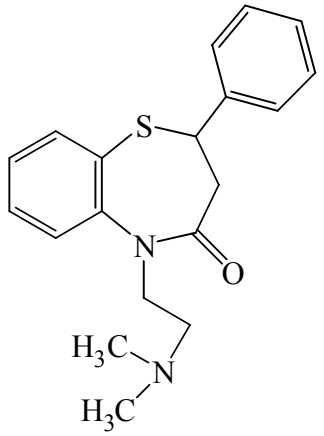

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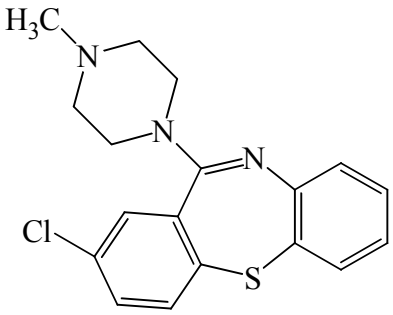

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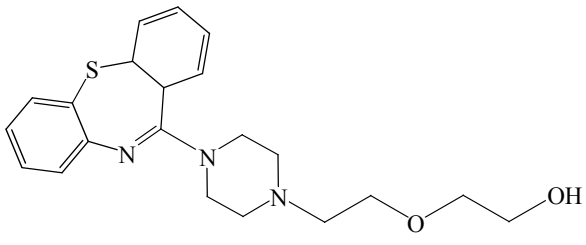

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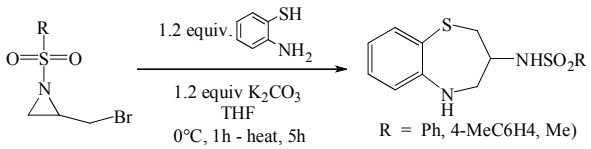
General methods of synthesis:

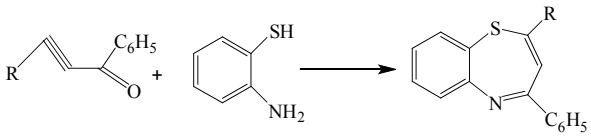
A number of established protocols are there for the synthesis of 1,5-benzothiazepine moiety, which can be well modified to prepare a number of differently substituted 1,5-benzothiazepines. Some of the conventional methods are given below.

1) Treatment of 2-(bromomethyl)aziridines with 1.2 equiv of 2-aminothiophenol in THF in the presence of potassium carbonate provide an easy access to 3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines after reflux for 5 h[57]. **(Scheme-1).**



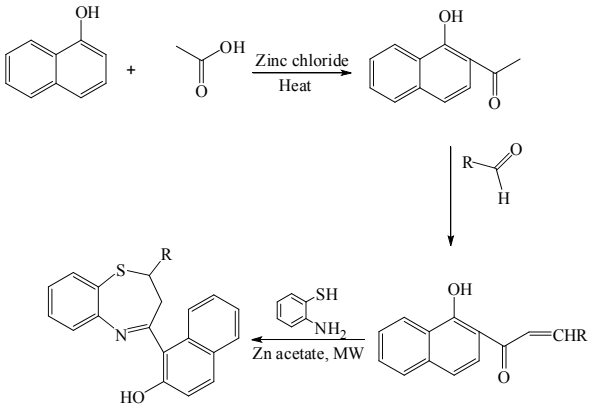
Scheme-1

2) The preparation of 2,4-disubstituted 1,5-benzothiazepines occurs by the reaction of 2-aminothiophenol with acetylinic ketones[58] **(Scheme-2)**.



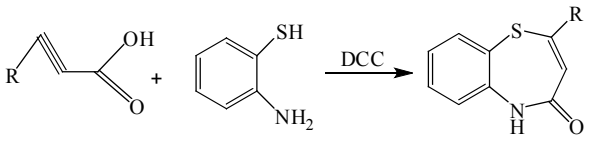
Scheme-2

3) Acetylation of α-naphthol with acetic acid and subsequent treatment of acetylated α-naphthol with aromatic aldehyde gives 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 gives 2,3-dihydro-2-substituted-4-(naphthalen-2-ol)-yl-1,5-benzothiazepines[59] **(Scheme-3)**.



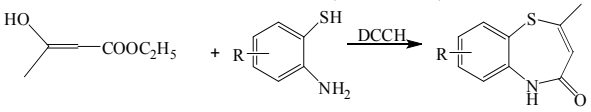
Scheme-3

4) The preparation of 1,5-benzothiazepin-4(5H)-ones occurs by the reaction of 2-aminothiophenol and propiolic acid with subsequent cyclisation of the addition product in the presence of dicyclohexylcarbodimide[60] **(Scheme-4)**.



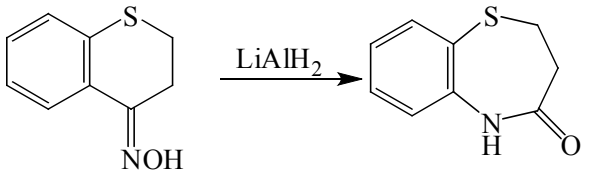
Scheme-4

5) 2-Methyl-1,5-benzothiazepines-4(5H) one derivatives can be obtained by the reaction of acetoacetic ester with substituted 2-aminothiohenols[61] **(Scheme-5)**.



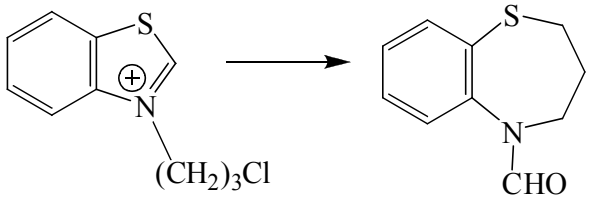
Scheme-5

6) 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[62] **(Scheme-6)**.



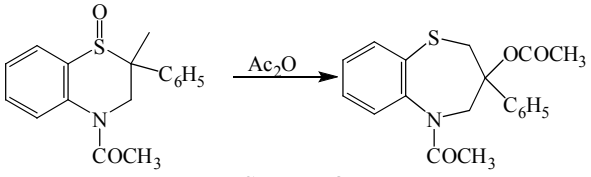
Scheme-6

7) In alkaline-catalytic reaction, quaternary salt of N-haloalkylbenzothiazole forms 2,3,4,5-tetrahydro-5-formyl-1,5-benzothiazepine[62] **(Scheme-7)**.



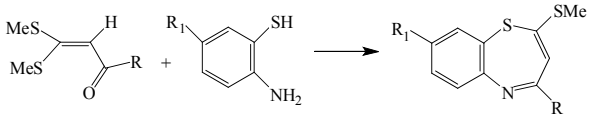
Scheme-7

8) It has been observed that benzothiazoline-S-oxide is capable of undergoing ring expansion, 2,3,4,5-tetrahydro-3-phenyl-3-acetoxy-5-acetyl-1,5-benzothiazepine is formed as one of the products when 4-acetyl-2-methyl-2-phenyl-2,3-dihydro-4H-1,4-benzothiazin-1-one is refluxed in acetic anhydride[62] **(Scheme-8)**.



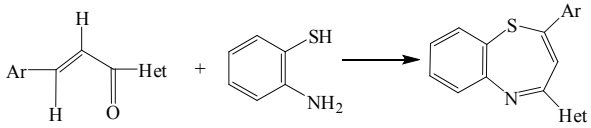
Scheme-8

9) Reaction of α-oxoketene-S,S-acetal with o-aminothiophenol gives the corresponding 1,5-benzothiazepines[63] **(Scheme-9)**.



Scheme-9

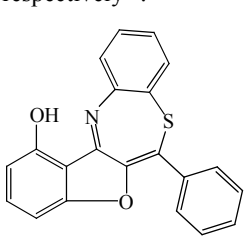
10) The reaction of chalcone with o-aminothiophenol in presence of 1-2 drop of piperidine in alcoholic solution of ethanol gives the corresponding 1,5-benzothiazepines[64] **(Scheme-10)**.



Scheme-10

Spectral properties of 1,5-benzothiazepines:

The UV-Visible spectra of several 1,5-benzothiazepine derivatives were characterized by electronic bands in 517-251 nm region. For example, **(11)** (UV-Visible (MeOH), λ_{max}(ε): 511 (56925), 323 (20780), 286 (21080), 253 (31300) nm; **(12)** and **(13)**: λ_{max}(ε x 10^{-3}; MeOH): 511 (50.60), 328 (17.40), 287 (17.70), 252 (24.50) and 517 (68.50), 353 (22.30), 297 (19.20), 252 (32.20) nm respectively[65].



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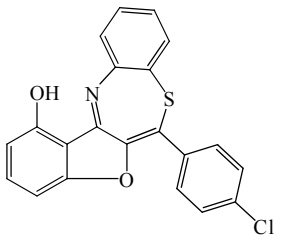

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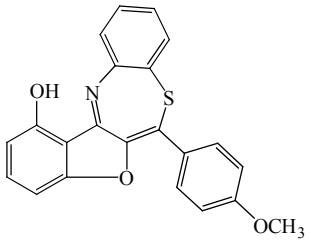
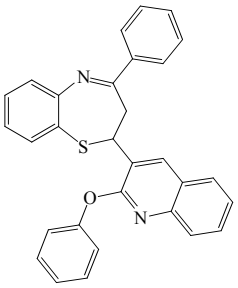


(13)

Infrared spectral studies of 1,5-benzothiazepines showed that the characteristic absorption band attribute to the (C=N) group occur at frequency range of 1600-1430 cm^{-1}. For example the infrared spectrum of 2-(2-phenoxyquinolin-3-yl)-4-phenyl-2,3-dihydrobenzo[1,5]thiazepine **(14)** and (*E*)-2-(2-(4-(phenylthio)phenyl)-2,3-dihydrobenzo[1,5]thiazepin-4-yl)phen-o1 **(15)** exhibit characteristic C=N absorption bands at 1596 and 1460 cm^{-1} respectively[66].



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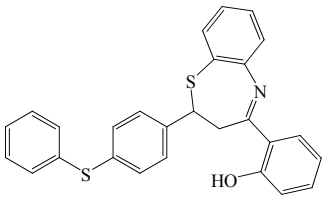
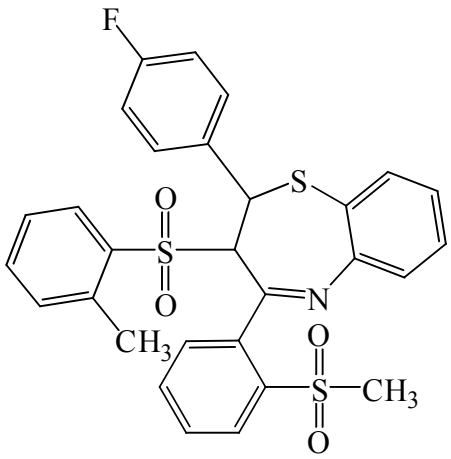


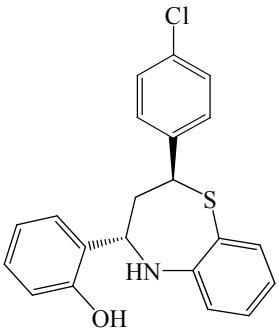
(15)

The ^{1}H NMR spectrum (DMSO-*d*6, 400 MHz) of (Z)-2-(4-fluorophenyl)- 4-(2-(methylsulfonyl) phenyl)-3-(*o*-tolylsulfonyl)-2,3-dihydrobenzo[1,5]thiazepine **(16)** displayed signals at δ : 2.50 (s, 3H, Ar-CH), 3.27 (s, 3H, SO2CH), 3.44–3.71 (two undiagonistic doublets, 2H, 2 methine protons) and 6.82-8.13 (m, overlap, 16H, Ar-H)[67].



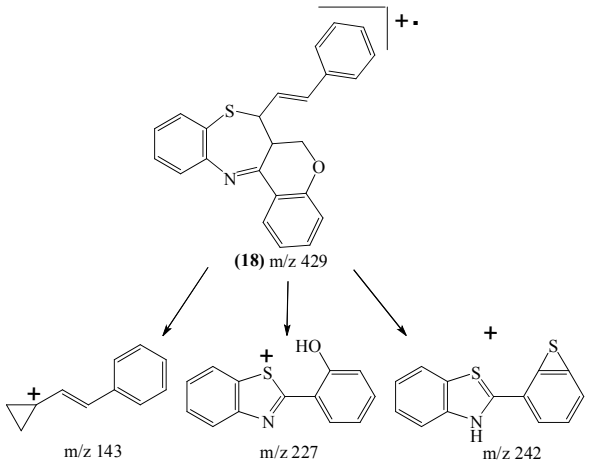
(16)

In the ^{13}C NMR ($CDCl_3$, 400MHz) of *trans*-2-(4-chlorophenyl)-4-(2-hydroxyphenyl)-2,3,4,5-tetrahydro-1,5-benzothiazepine **(17)**, the chemical shifts of the carbon atoms revealed signals at: 118.1, 120.3, 122.5 , 125.3, 125.5, 126.4, 128.7, 128.8, 129.2, 129.7, 129.8, 133.2, 134.2, 144.0, 146.4, and 159.6 ppm[68].



(17)

The molecular ion peak in the electron impact mass spectrum (EI-MS) 70 eV of 1,5-benzothiazepine derivative **(18)** was observed at *m/z* 429. The fragmentation pattern of **(18)** may be represented as in **(Scheme 11)** [69].



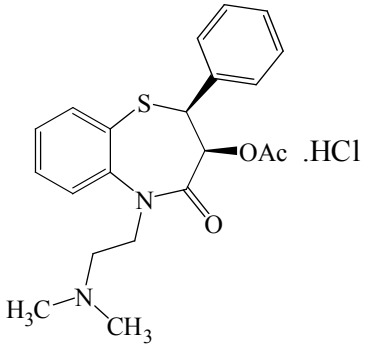
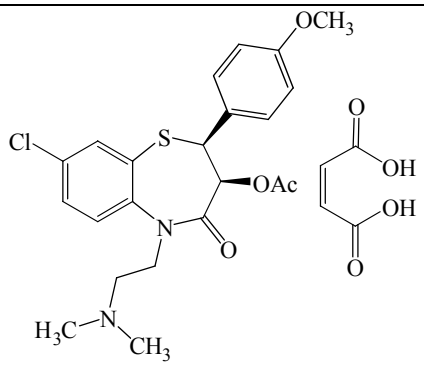
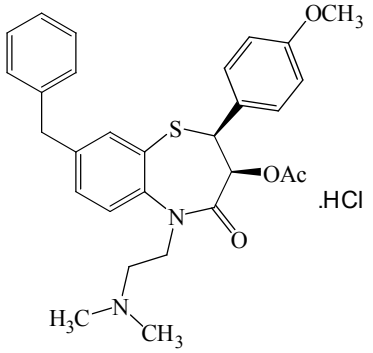
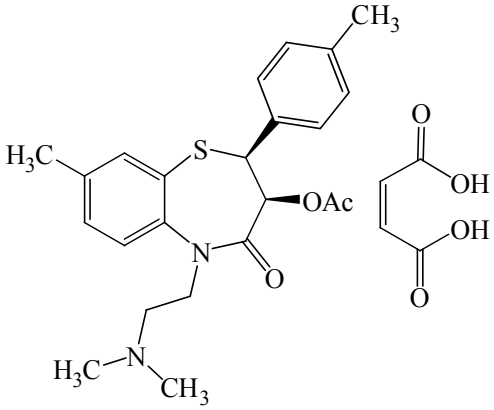
(18) m/z 429

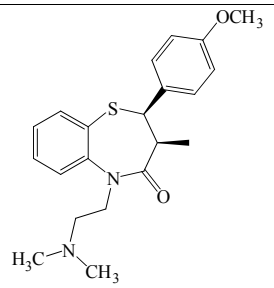
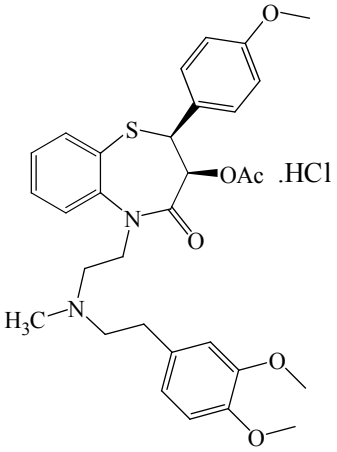
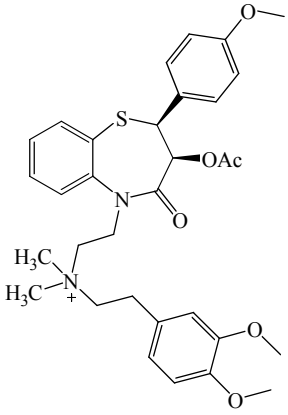
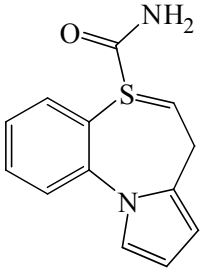
m/z 143 m/z 227 m/z 242

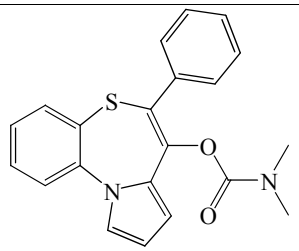
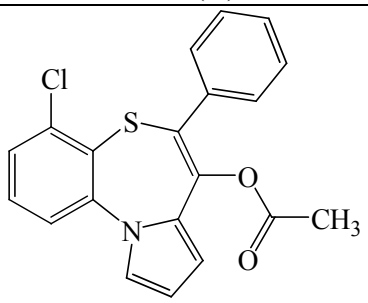
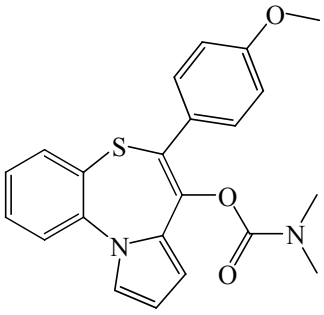
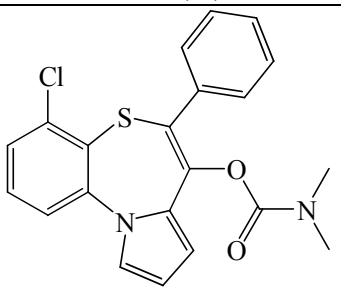
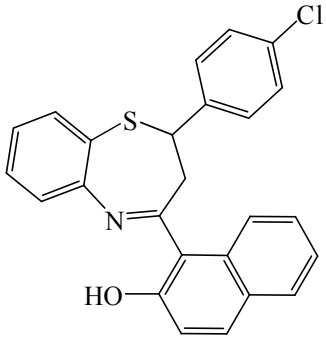
Scheme 11

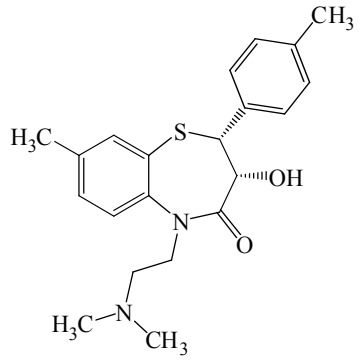
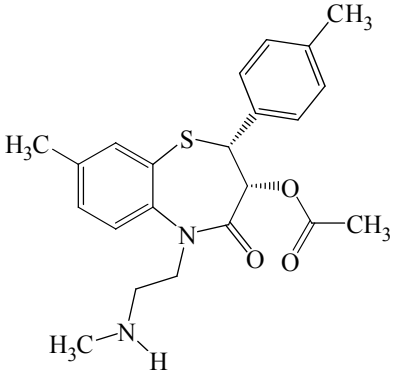
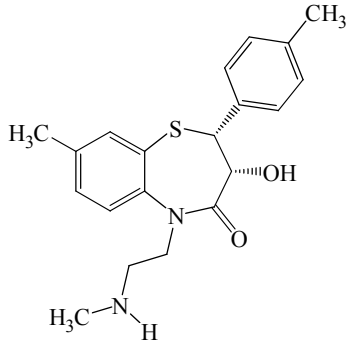
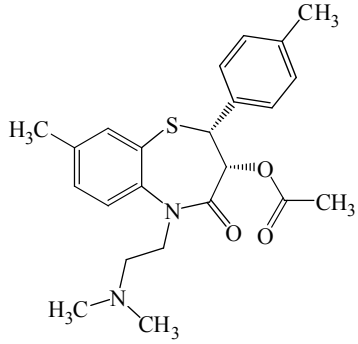
Therapeutic potential of 1,5-benzothiazepines:

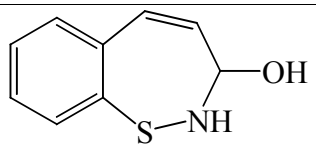
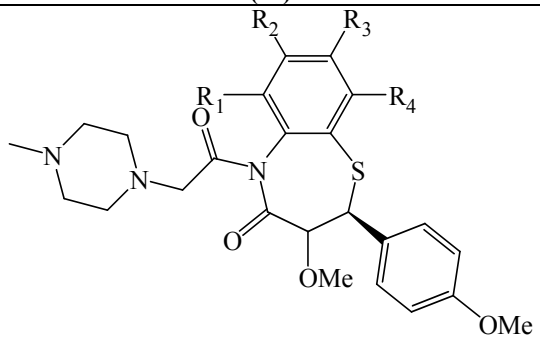
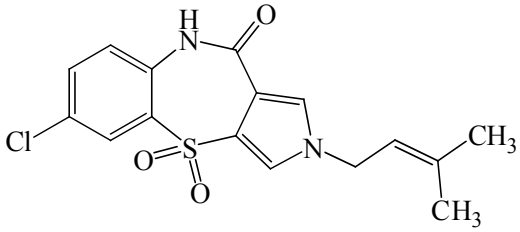
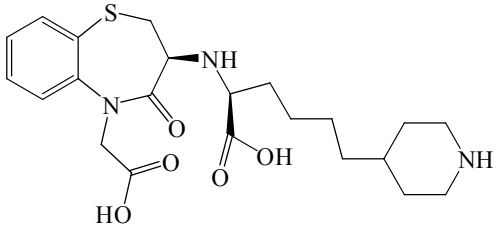
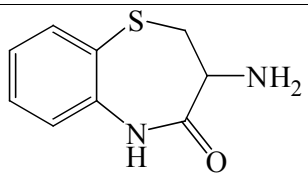
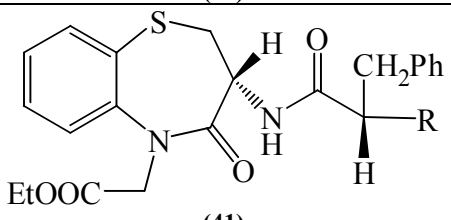
The importance of the l,5-benzothiazepine nucleus has been well established as illustrated by a large number of compounds which have been patented as chemotherapeutic agents.[70] A number of biological activities have been associated with it, such as antifeedant[71], coronary vasodilatory[72], tranquilizer[73], antidepressant[74], CNS stimulant[75], antihypertensive[76], calcium channel blocker[77], antiulcer[78], calcium antagonist[79], antimicrobial[80] and anticonvulsant agents[81]. l,5-Benzothiazepine molecules have been found to be useful in mucosal blood flow, as antiulcer and gastric secretion inhibitor. Recently, anticancer activities[82], hemodynamic effects[83], and spasmolytic activities[84] have also been reported.[85] Diltiazem has been used in the treatment of hypertension, angina pectoris, arrhythmias and other cardiac disorders. It also increases the supply of blood and oxygen to heart.[86-87] Thiazesim act as psychotopic agent, clentiazem have antiatherogenic effect[88], and clothiapine shows antimuscarinic potential.[89]

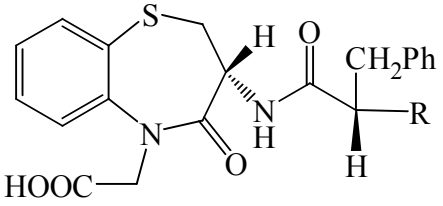
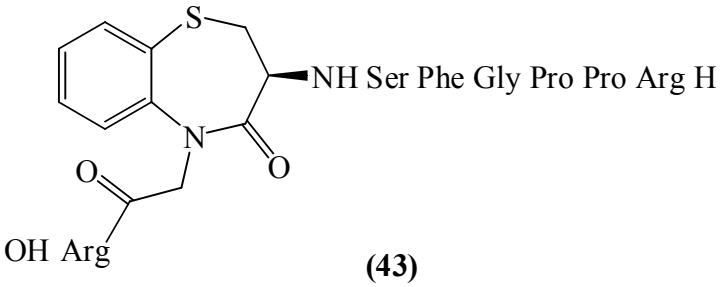
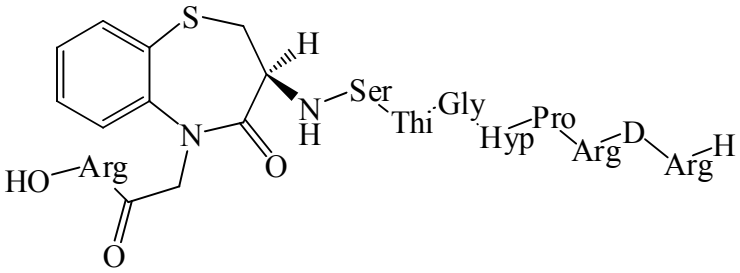
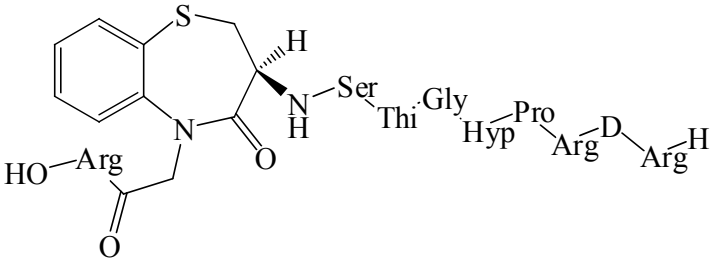
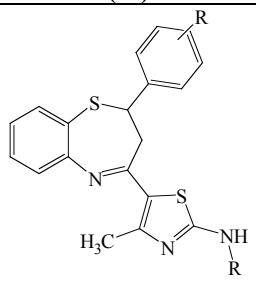
Compound	Pharmacological profile	Reference
 **(51)**	Ca^{2+} channel antagonistic activity	Ref.[90-94]
 **(52)**	Ca^{2+} channel antagonistic activity	Ref.[95]
 **(53)**	Ca^{2+} channel antagonistic activity	Ref.[96]
 **(54)**	Ca^{2+} channel antagonistic activity	Ref.[97]

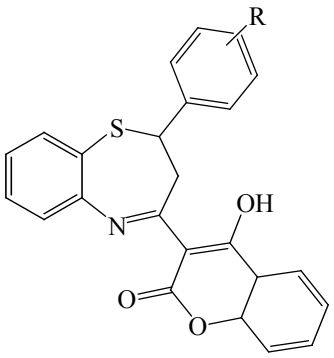
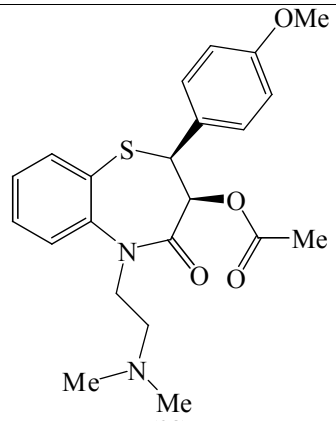
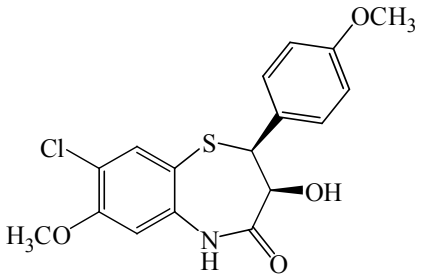
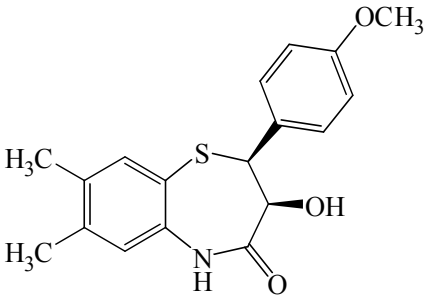
 **(55)**	Ca^{2+} channel antagonistic activity	Ref.[98]
 **(56)**	Ca^{2+} channel antagonistic activity	Ref.[99]
 **(57)**	Ca^{2+} channel antagonistic activity	Ref.[100]
 **(58)**	Ca^{2+} channel antagonistic activity	Ref.[101]

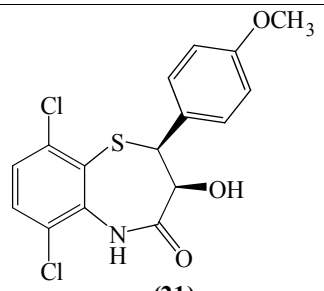
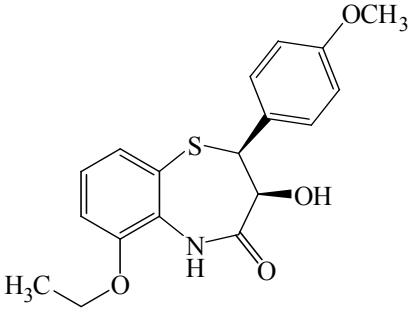
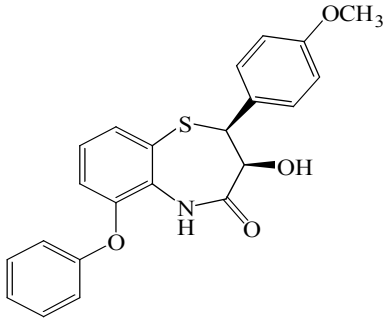
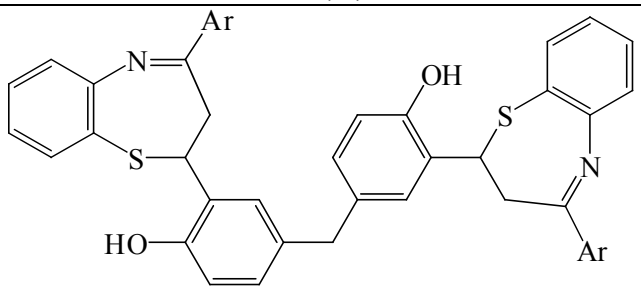
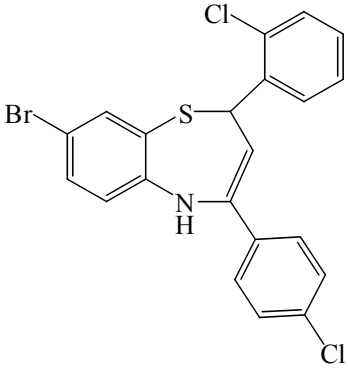
 **(59)**	Ca^{2+} channel antagonistic activity	Ref.[102]
 **(60)**	Ca^{2+} channel antagonistic activity	Ref.[103]
 **(61)**	Ca^{2+} channel antagonistic activity	Ref.[104]
 **(62)**	Ca^{2+} channel antagonistic activity	Ref.[105]
 **(49)**	CNS depressant activity	Ref.[106-112]

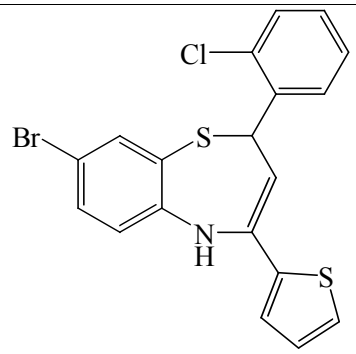
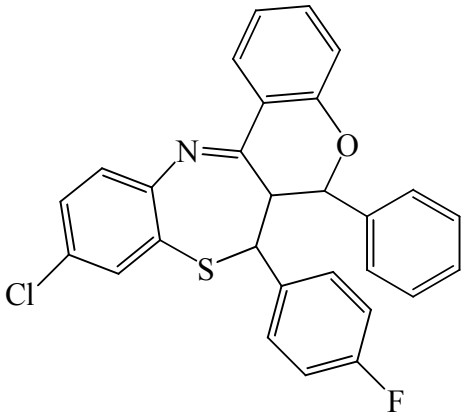
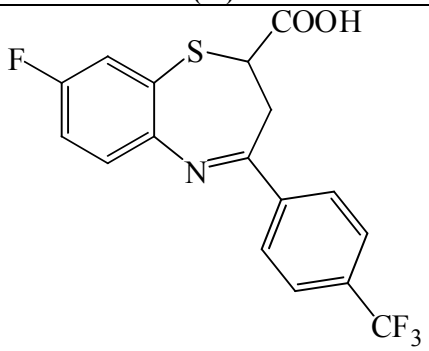
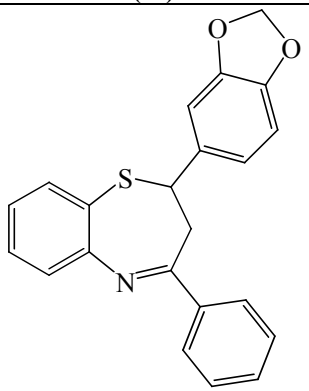
 **(63)**	Antiplatelet aggregator activity	Ref.[67-70]
 **(64)**	Antiplatelet aggregator activity	Ref.[71]
 **(65)**	Antiplatelet aggregator activity	Ref.[72]
 **(66)**	Antiplatelet aggregator activity	Ref.[73]

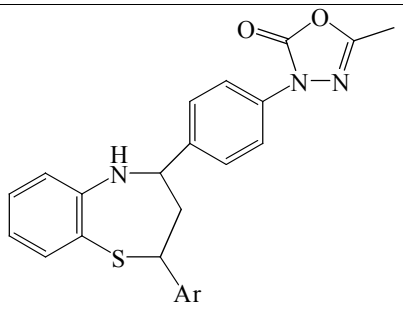
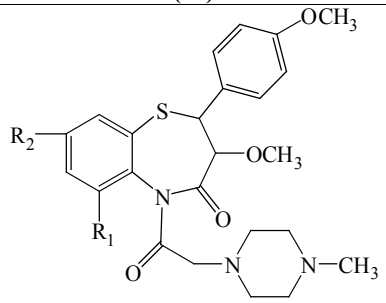
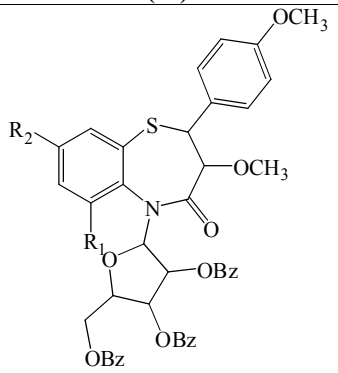
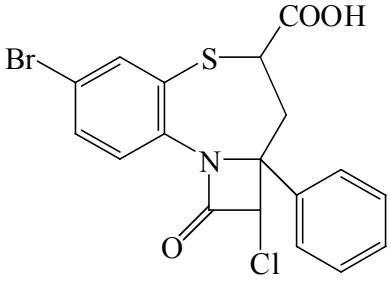
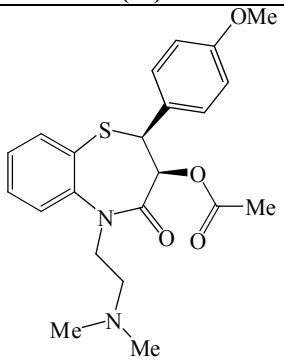
 **(47)**	Anticancer activity	Ref.[74-77]
 **(48)**	Anticancer activity	Ref.[78-80]
 **(67)**	Anti-HIV activity	Ref.[81]
 **(39)**	ACE inhibitory activity	Ref.[128]
 **(40)**	ACE inhibitory activity	Ref.[129]
 **(41)**	ACE inhibitory activity	Ref.[130]

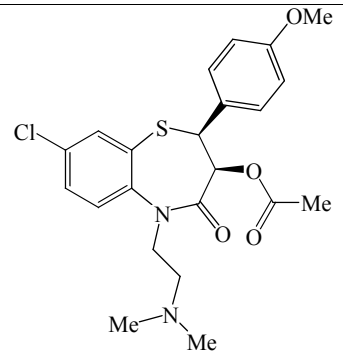
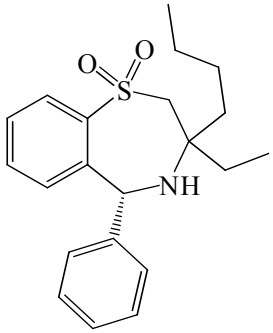
 **(42)**	ACE inhibitory activity	Ref.[131]
 **(43)**	Bradykinin agonistic activity	Ref.[132]
 **(44)**	Bradykinin agonistic activity	Ref.[133]
 **(45)**	Bradykinin agonistic activity	Ref.[134-139]
 **(36)**	Calmodulin antagonistic activity	Ref.[140]

 **(37)**	Calmodulin antagonistic activity	Ref.[141]
 **(38)**	Calmodulin antagonistic activity	Ref.[141]
 **(19)**	Antimicrobial activity	Ref.[142]
 **(20)**	Antimicrobial activity	Ref.[143]

 **(21)**	Antimicrobial activity	Ref.[143]
 **(22)**	Antimicrobial activity	Ref.[144]
 **(23)**	Antimicrobial activity	Ref.[145]
 **(24)**	Antimicrobial activity	Ref.[146]
 **(25)**	Antimicrobial activity	Ref.[147]

 **(26)**	Antimicrobial activity	Ref.[148]
 **(27)**	Antimicrobial activity	Ref.[149]
 **(28)**	Antimicrobial activity	Ref.[150]
 **(29)**	Antimicrobial activity	Ref.[151]

 **(30)**	Antimicrobial activity	Ref.[152]
 **(31)**	Antimicrobial activity	Ref.[153]
 **(32)**	Antimicrobial activity	Ref.[154]
 **(33)**	Antimicrobial activity	Ref.[155]
 **(34)**	Cardiovascular activity	Ref.[156]

 **(35)**	Cardiovascular activity	Ref.[156]
 **(46)**	Antihyperlipidemic activity	Ref.[156]

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