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AN OVERVIEW OF 1,5-BENZOTHIAZEPINES

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ABSTRACT

1,5-Benzothiazepine scaffold is an important class of heterocycles and has featured in a number of clinically used drugs. Compounds bearing 1,5-benzothiazepine moiety shows a broad spectrum of biological activities such as CNS-acting agents, anti-HIV and anticancer drugs, angiotensin converting enzyme inhibitors, antimicrobial, calmodulin antagonists, bradykinin receptor agonists, as well as Ca^{2+} blockers.

KEYWORDS: **1,5-Benzothiazepine, heterocycles, CNS-acting agents, anticancer, antimicrobial.**

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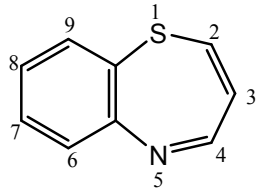
INTRODUCTION

The heterocyclic systems with seven atoms, once considered chemical oddities, are today just as easily obtained as five and six membered analogues, and these compounds no longer remain the esoteric species, they were once considered to be. Quite to the contrary, the pace of research and development in this area is accelerating due to the substantial advances that have been made in the synthesis of these materials in the last few decades. As a result of this there seems to be virtually no limit to the number of interesting ring systems that can be created in the laboratory today by the combination of ingenuity and perseverance. 1,5-Benzothiazepines are bicyclic heterocyclic compounds with one nitrogen and one sulphur atom at 1 and 5 positions in a seven membered ring fused to a benzene ring. Basically 1,5-benzothiazepines are the 2,3 benzo-annelated derivatives of 1,4-thiazepines. Benzothiazepines are numbered as shown in (1) Fig.1. The numbering of these benzothiazepines proceeds in the opposite direction to that used for the unannulated thiazepines. The position of the odd hydrogen atom (even if occupied by another mono or divalent substituent) is indicated by the term 1H, 2H, 3H etc. In dihydro and tetrahydro benzothiazepines the odd hydrogen is given the lowest possible number. This is however, complicated by the fact that, first consideration is given to the position of a functional group which is expressed as a suffix to the name of the compound.



1

Fig. 1

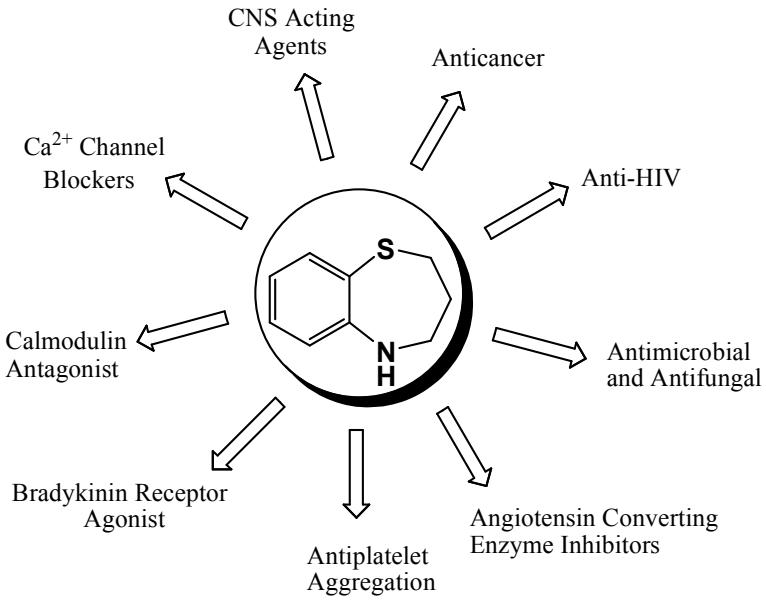
The development of privileged heterocyclic scaffolds is a rapidly emerging subject in medicinal chemistry. The chemical modification of privileged heterocyclic systems offers a continuous challenge to the medicinal chemists in search of compounds with bio-pharmacological activity[1]. In view of the interesting biological properties shown by privileged heterocyclic compounds, the study of this system provides a very fascinating field for exploration in drug research. 1, 5-Benzothiazepine is an important privileged seven membered heterocyclic ring system[2] that features in a number of clinically used drugs[3] due to their potential to provide an active pharmacophore for *de novo* exploration[4].

Biological aspects of 1,5-benzothiazepines

1,5-Benzothiazepine and 1,5-benzodiazepine are the two main seven-membered heterocyclic ring systems reported for their cardiac and psychotherapeutic activities. Successful introduction of diltiazem and clentiazem for angina pectoris, hypertension, arrhythmias and other related cardiac disorders proved potential of 1,5-benzothiazepine moiety[3]. The 1,5-benzothiazepine derivatives are of particular interest for lead discovery because they have been found active against different families of targets[5]. The 1,5-benzothiazepine scaffold has been used as cardiovascular modulator[6] such as vasodilator[7,8] and antiarrythmic[9], protease inhibitors, elastase[10]/ACE inhibitors[11], antagonists of several G-protein coupled receptors such as cholecystokinin (CCK) receptor as interleukin-1b converting enzyme inhibitors / the angiotensin II receptor (ACE) inhibitors[12]. Recently, anticancer activity[13], haemodynamic effects[14,15], antiulcer activity[16,17] and spasmolytic activities[18-20] have also been

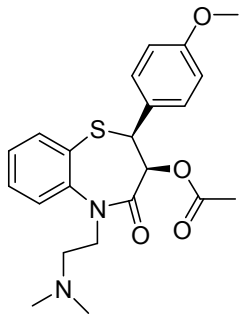
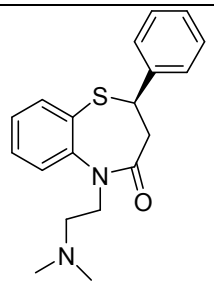
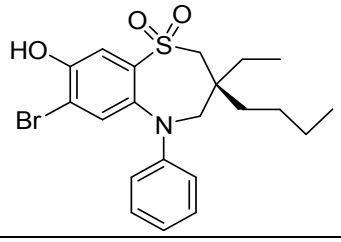
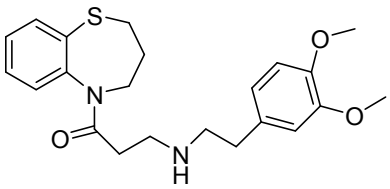
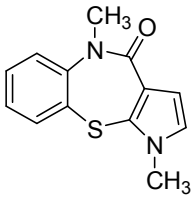
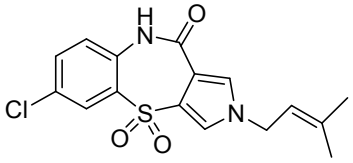
reported. First molecule used clinically was diltiazem, followed by clentiazem, for their cardiovascular action[21-23]. Some of the 1,5-benzothiazepine derivatives were also used clinically for CNS disorders which includes thiazesim, and quetiapine fumarate[24,25] . A literature survey reveals the enhanced bioactivity of annulated 1,5-benzothiazepines[26]. The recent demonstration that some of their derivatives can serve as potential agents in the control and treatment of AIDS has stimulated further interest in these compounds from yet another perspective[27]. The wide range of pharmacological profile shown by 1,5-benzothiazepine can be classified into the following categories.

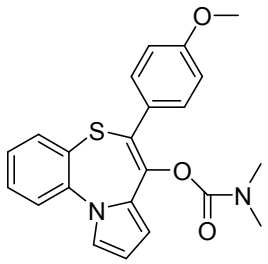
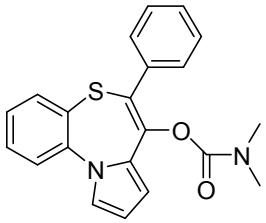
1. Ca^{2+} channel antagonist and vasodilator
2. CNS depressant/peripheral receptor antagonist
3. Antiplatelet aggregation
4. Anticancer
5. Anti-HIV
6. Angiotensin converting enzyme inhibitors
7. Bradykinin receptor agonist
8. Calmodulin antagonist
9. Antimicrobial and antifungal



2
Figure 2

Pharmacological properties of substituted derivatives of 1,5-benzothiazepines

S.No. I	Structure of the compound II	Trade name III	Pharmacological Properties IV	Reference V
1.		Diltiazem	Used in the treatment of hypertension, angina pectoris and some types of arrythmia	22
2.		Thiazesim	Acts as a heterocyclic antidepressant	24
3.		GW-577	Treatment of lipoprotein disorders	3
4.		KT-363	Shows antihypertensive, antiarrythmic, Ca^{2+} channel antagonist activity	28,29
5.		3H-pyrrolo[2,3-b][1,5]benzothiazepine derivative	Inhibited HIV-1 replication in the micromolar range	30
6.		2H-pyrrolo[3,4-b][1,5]-benzothiazepine derivatives	Exhibits reverse transcriptase inhibitory activity	31

7.		6-arylpyrrolo[2,1-d][1,5]benzothiazepine derivatives	Most potent ligands specific for mitochondrial benzodiazepine receptor (MBR)	32
8.		6-arylpyrrolo[2,1-d][1,5]benzothiazepine derivatives	Most potent ligands specific for mitochondrial benzodiazepine receptor (MBR)	32

Synthetic aspects of 1,5-benzothiazepines

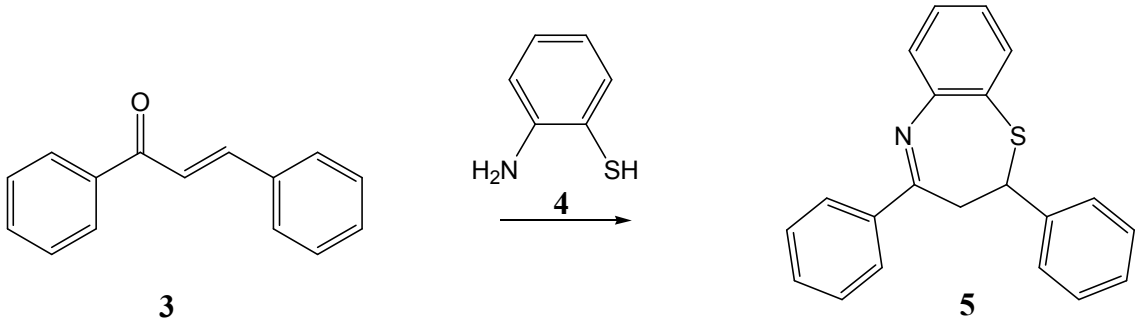
The broad spectrum of medicinal properties associated with these molecules has triggered the development of a variety of methods for the synthesis of these materials and has led to an impressive armoury of synthetic strategies to be devised in the literature for this class of compounds. In this context, it seems necessary to present in the discussion to follow a brief outline of some of the available literature methods, which have been employed to date for the synthesis of 1,5-benzothiazepines.

One pot synthesis of 1,5-benzothiazepines

1,5-Benzothiazepines are easily prepared by reacting the corresponding α, β-unsaturated ketones and o-aminothiophenol in the presence of a solvent and/or catalyst, in a one-pot reaction. Many experimental variations have been made in this broad procedural framework altering the substrate characteristics.

1. From α,β-unsaturated ketones or chalcones

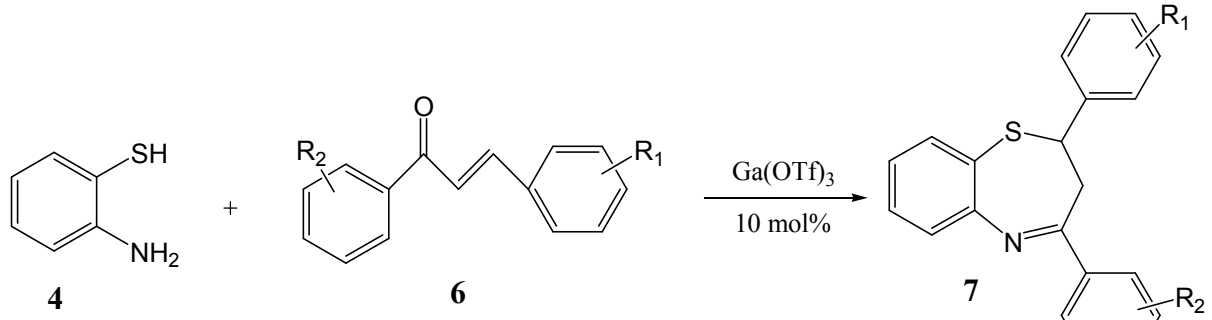
The cyclocondensation of chalcones 3 with o-aminothiophenol (4) give 1,5-benzothiazepines 5 in good yield[12] (Scheme 1).



3 **5**

Scheme: 1

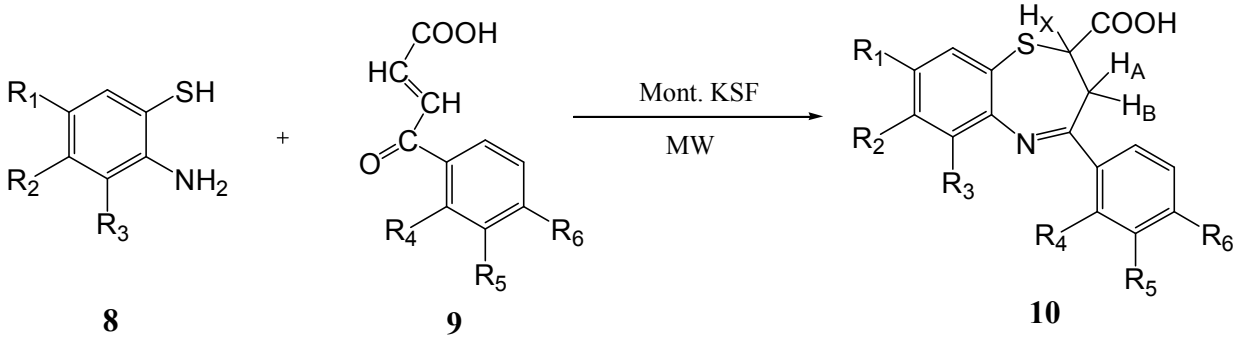
Condensation reactions of o-aminothiophenol (4) and chalcones 6 under gallium(III) triflate catalysis produce functionalized 1,5-benzothiazepines 7 in good to excellent yields[33]. The o-hydroxy group of chalcones is crucial for this unprecedented condensation process (Scheme 2).



R_1 = H, R_2 =H
R_1 = H, R_2 = 2'-OH
R_1 = 4-OMe, R_2 = 2'-OH
R_1 = 2-OH, R_2 = 2'-OH
R_1 = 4-OH, R_2 = 2'-OH
R_1 = H, R_2 = 4'-OH
R_1 = 2-OH, R_2 = H

Scheme: 2

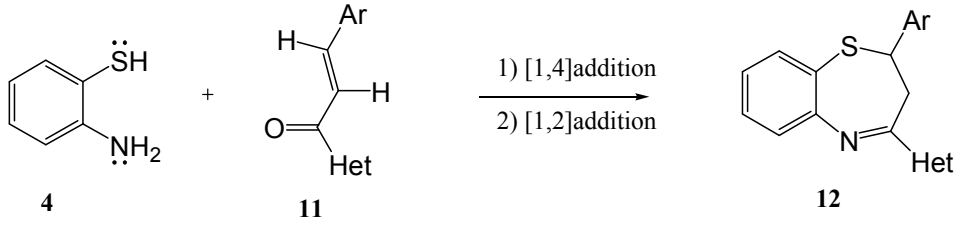
Microwave enhanced solvent-free synthesis of 2-carboxy-2,3-dihydro-1,5-benzothiazepines 10 was carried out by reacting substituted o-aminothiophenols 8 with α,β-unsaturated ketones 9 using montmorillonite clay[34] (Scheme 3).



R_1=H,CH_3,F,Cl,Br,OCH_3,OC_2H_5,C_2H_5,CF_3
R_2=H,CF_3,CH_3
R_3=H,Cl,Br,CH_3,CF_3
R_4=H,CH_3
R_5=H,Cl,CF_3
R_6=H,F,OH

Scheme: 3

One of the most widely methods employed for the preparation of 1,5-benzothiazepines 12 involves the reaction of o-aminothiophenol (4) with α,β-unsaturated ketones or chalcones 11 both under acidic and basic conditions[35].(Scheme 4)

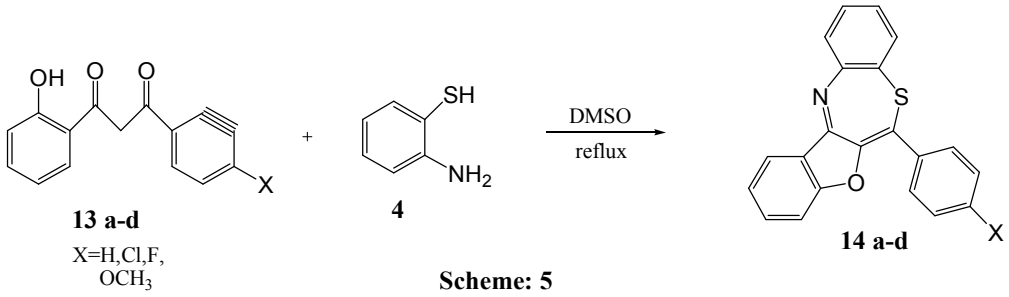


4 11 12

Scheme: 4

1. From β-diketones

Oxidative cyclocondensation of phenolic β-diketones 13 a-d with o-aminothiophenol (4) in DMSO give benzofuro-annelated-2-phenyl-1,5-benzothiazepine derivatives 14 a-d in reasonable yields[36] (Scheme 5).



13 a-d
X=H,Cl,F, OCH_3

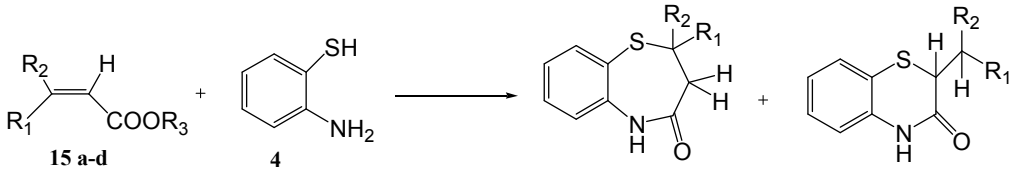
4

14 a-d

Scheme: 5

2. From β,β-dimethyl-acrylic acid and its ester

The reaction of β,β-dimethyl-acrylic acid and its ester 15 a-d with o-aminothiophenol (4) give exclusively the benzothiazepines[37] 16 (Scheme 6).



15 a-d

a $R_1=R_3=H, R_2=Me$
b $R_1=R_3=H, R_2=Ph$
c $R_1=R_2=Me, R_3=H$
d $R_1=R_2=Me, R_3=Et$

4

16
(major)

17

Scheme: 6

CONCLUSION

This promising moiety has much scope as a number of different molecular targets are available for 1,5-benzothiazepines.

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