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A Review on 1,5-Benzothiazepines as a Versatile Pharmacophore

Dr. Ramchandra Deshmukh[1], Dr. Vishwambhar Shinde[2], Dr. Dhanaji Kanase[3]

[1]Assistant Professor, Department of Chemistry, Bharati Vidyapeeth's Dr. Patangrao Kadam Mahavidyalaya, Sangli, Maharashtra, India.

[2]Assistant Professor, Department of Chemistry, Bharati Vidyapeeth's Yashwantrao Mohite College, Pune, Maharashtra, India.

[3]Principal and Head of the Department, Department of Chemistry, Bharati Vidyapeeth's Dr. Patangrao Kadam Mahavidyalaya, Sangli, Maharashtra, India.

ABSTRACT: 1,5-benzothiazepine is an extremely versatile moiety and has wide range of pharmacological activities. A diverse number of 1,5-benzothiazepines have been synthesized by reacting chalcones, ketones, diketones with 2-aminobenzenethiol are used in the treatment of various diseases. Present review is focused on some potentially active 1,5-benzothiazepine derivatives having versatile pharmacological activities.

KEYWORDS: 1,5-benzothiazepine, chalcones, ketones, pharmacological

I. INTRODUCTION:

1,5-benzothiazepines are important nitrogen and sulfur containing seven-membered heterocyclic compounds. Literature survey reveals that 1,5-benzothiazepines and their derivatives are important heterocyclic compounds in the field of pharmaceutical research which were found to possess different pharmacological activities. [1] 1,5-Benzothiazepines are bicyclic heterocyclic compounds. In 1,5-benzothiazepine a benzene ring is fused with thiazepine. It is a seven

membered heterocycle with one sulfur and one nitrogen atom at 1st and 5th positions in a seven membered ring. [2] (Figure 1)

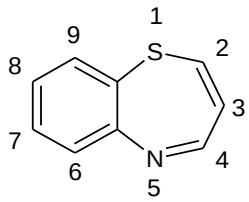

Figure 1 1,5-Benzothiazepine

Three possible benzocondesed derivatives of 1,5-Benzothiazepine are 1,4-, 4,1- and 1,5-benzothiazepines of the 1,4-thiazepine. According to IUPAC nomenclature (Figure 2) the benzo[1,5]thiazepine structures 1 or 2 may be named as (*z*)-2,3-dihydrobenzo[b][1,4]thiazepine or (*z*)-2,3-dihydro-substituted-benzo[b][1,4]thiazepine. The substituted-benzo[1,5]thiazepine structures 3 or 4 may be named as, 2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine or 2,3,4,5-tetrahydro-substituted-benzo[b][1,4] thiazepine.[3]

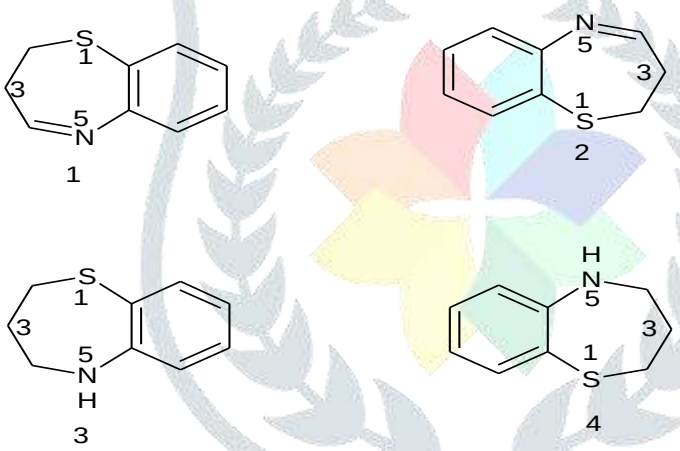

Figure 2 IUPAC nomenclature of 1, 5-benzothiazepines

II. Active derivatives of 1, 5-benzothiazepines

1,5-Benzothiazepine is a privileged heterocyclic ring system because of their broad and significant pharmacological properties.[4] 2,4-disubstituted derivatives of 1,5-Benzothiazepine and several hydrated derivatives have been synthesized by numerous research groups and the invented procedures have also been summarized in several review articles.[5-6] The significance of the 1,5-benzothiazepine nucleus has been well established as illustrated by a large number of compounds which have been patented as chemotherapeutic agents. 1,5-Benzothiazepine scaffold is extremely versatile and has been used as antibacterial,[7] antifungal,[8] antihypertensive,[9] antidepressant,[10] antiischemic,[11] antiarrythmic,[12] anticytotoxic,[13] antifeedant,[14] coronary vasodilatory,[15]

anticoagulant,[16] CNS stimulant,[17] calcium channel blocker[18] and anticonvulsant.[19] 1,5-Benzothiazepine molecules have been used as cardiovascular modulator,[20] and calcium antagonist.[21] It has been found to be helpful in mucosal blood flow, as antiulcer, gastric secretion inhibitor, antagonists of several G-protein coupled receptors such as chlolecystokinin (CCK) receptors as interleukin-1β converting enzyme inhibitors/angiotensin II receptor (ACE) inhibitors.[22] Anticancer activity,[23] haemodynamic effect of 1,5-benzothiazepine nucleus have also been reported.

First molecule of 1,5-benzothiazepines used clinically was diltiazem (Figure 3) followed by clentiazem (Figure 4) for their cardiovascular action. Diltiazem has been used in the treatment of hypertension, arrhythmias, angina pectoris and other cardiac disorders. It also increases the supply of oxygen and blood to heart.[24] Clentiazem is used as coronary vasodilatory, calcium antagonist.[25]

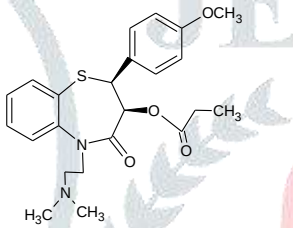

Figure 3 Diltiazem

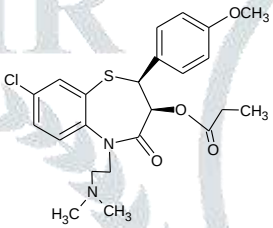

Figure 4 Clentiazem

1,5-Benzothiazepine derivatives were also used clinically for CNS disorders, psychotopic agent which include thiazesim and quetiapine fumarate. Thiazesim is used for CNS disorders, acts as a heterocyclic antidepressant[26] (Figure 5). Quetiapine fumarate used for antidepressant activities, CNS disorders.[27] (Figure 6)

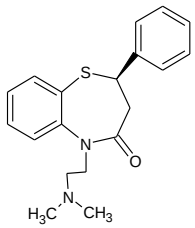

Figure 5 Thiazesim

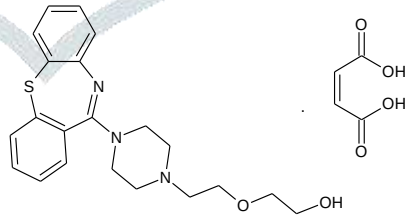

Figure 6 Quetiapine fumarate

Recently a number of 1,5-benzothiazepine derivatives can serve as potential agents in the control and treatment of AIDS.[28] 3H-pyrrolo [2,3-b] [1,5]benzothiazepine derivative-inhibited HIV-I replication in the micromolar range[29] (Figure 7), 8-metoxy-4-oxo-1H,4,5-dihydro-imidazo[3,4,5-d,e]-1,4-benzothiazin-2-thiones has moderate anti HIV activity.[30] (Figure 8)

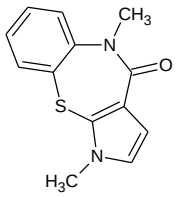

Figure 7

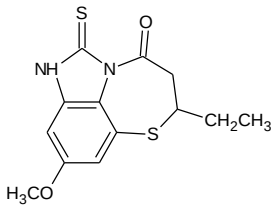

Figure 8

1,5-Benzothiazepines like GW-577 [31] (Figure 1.9) and KT-363 [32] (Figure 1.10) are used in the treatment of lipoprotein disorders and as antihypertensive, Ca^{++} channel antagonist, antiarrythmic respectively. Ameta and co-workers [33] have synthesized halogen substituted derivatives of 1,5-benzothiazepines with anti-lung cancer activity (Figure 1.11). Pant et al [34] demonstrated that incorporation of fluorine in the 1,5-benzothiazepine nucleus enhances the anti-fungal activity of compound. (Figure 1.12)

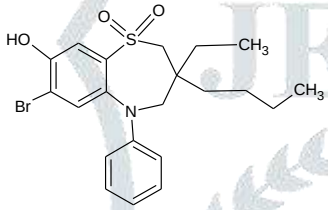

Figure 1.9

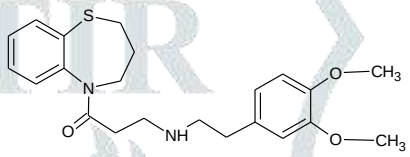

Figure 1.10

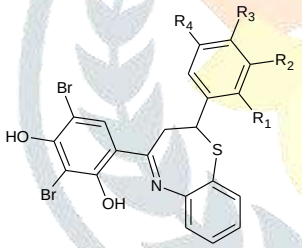

Figure 1.11

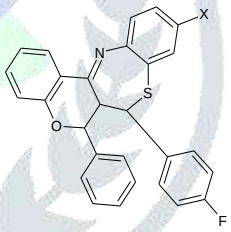

Figure 1.12

III. CONCLUSION

1,5-benzothiazepines have broad range of pharmacological profile and can be synthesized by using simple and easily accessible starting reagents like chalcones, ketones, diketones. A diverse range of 1,5-benzothiazepines can be synthesized using chalcones. The presence of α, β-unsaturated carbonyl moiety as well as of substituted aromatic rings render the chalcones biologically active. [35] Chalcones bear a reactive α, β-unsaturated carbonyl group so that different heterocyclic compounds with good pharmaceutical profile can be synthesized. Chalcones can be easily converted into biologically important heterocyclic compounds such as pyrazolines,[36-37] pyrimidines,[38-39] flavones,[40] isoxazoles,[41-42] 1,5-benzodiazepines,[43] 1,5-benzothiazepines.[42-50].

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