Chem. Biol. Lett. 2016, 3(1), 18-31 Article

Chemical Biology LETTERS

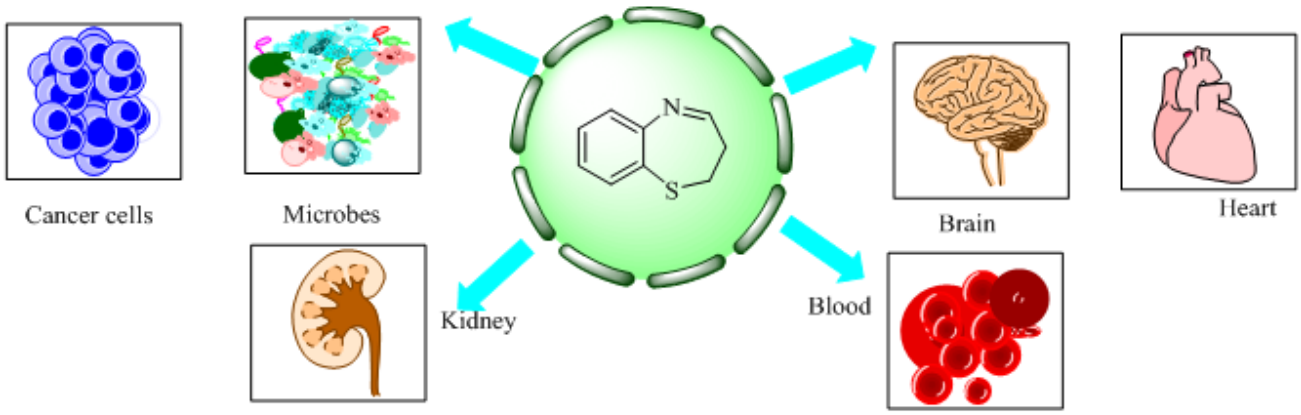
1,5-Benzothiazepine: Bioactivity and targets

Rajneesh Kaur, Kuldeep Singh,* Raman Singh*

Chemistry Department, MMEC, M. M. University, Mullana – 133207, India

Received on: 15-Apr-2016 Accepted and Published on: 04-June-2016

ABSTRACT



1,5-Benzothiazepine nucleus is present in a number of clinically used drugs such as diltiazem, clentiazem, thiazesim, quetiapine, and clothiapine. 1,5-Benzothiazepine can be easily introduced in the molecule having 2-aminothiophenol moiety. This article considers various targets for 1,5-benzothiazepine nucleus to establish structural activity relationship. It is an attempt to compile account of various structural modification in 1,5-benzothiazepine scaffold as reported for their versatile biological activities. This review would provide a platforms for selection of suitable moieties and development of specific chemical entities with desired features.

Keywords: 1,5-benzothiazepine, Vasodilator, Antiplatelet aggregation, Anticholinesterase inhibitor, Glycogen synthase kinase-3β inhibitors, Mitogen-Activated Protein kinase protein inhibitors.

INTRODUCTION

1,5-Benzothiazepines are well-known representatives of benzologs of 1,4-thiazepine and one of the three possible benzo-condensed derivatives, viz. 1,4-, 4,1- and 1,5-benzothiazepines (Figure 1).[1] Because of their ease of availability 2,4-disubstituted, 2,3-dihydro-1,5-benzothiazepines have received considerable attention. The procedures utilized for the synthesis of 1,5-benzothiazepines are mainly based on the reaction of 2-aminothiophenol with α, β- unsaturated ketones. Numerous derivatives of 1,5-benzothiazepines have already been synthesized and described in literature.[2]

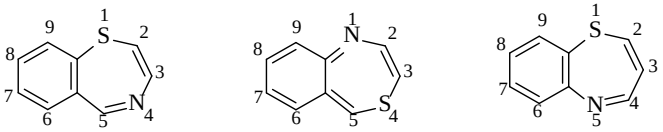


Figure 1:1,4-, 4,1- and 1,5-benzothiazepines

Dr. Kuldeep Singh
Tel: +918059930803
Email: drkuldeep@pundir.in

Dr. Raman Singh
Tel: +918059930802
Email: raman@pundir.in

Cite as: *Chem. Biol. Lett., 2016, 3(1), 18-31.*

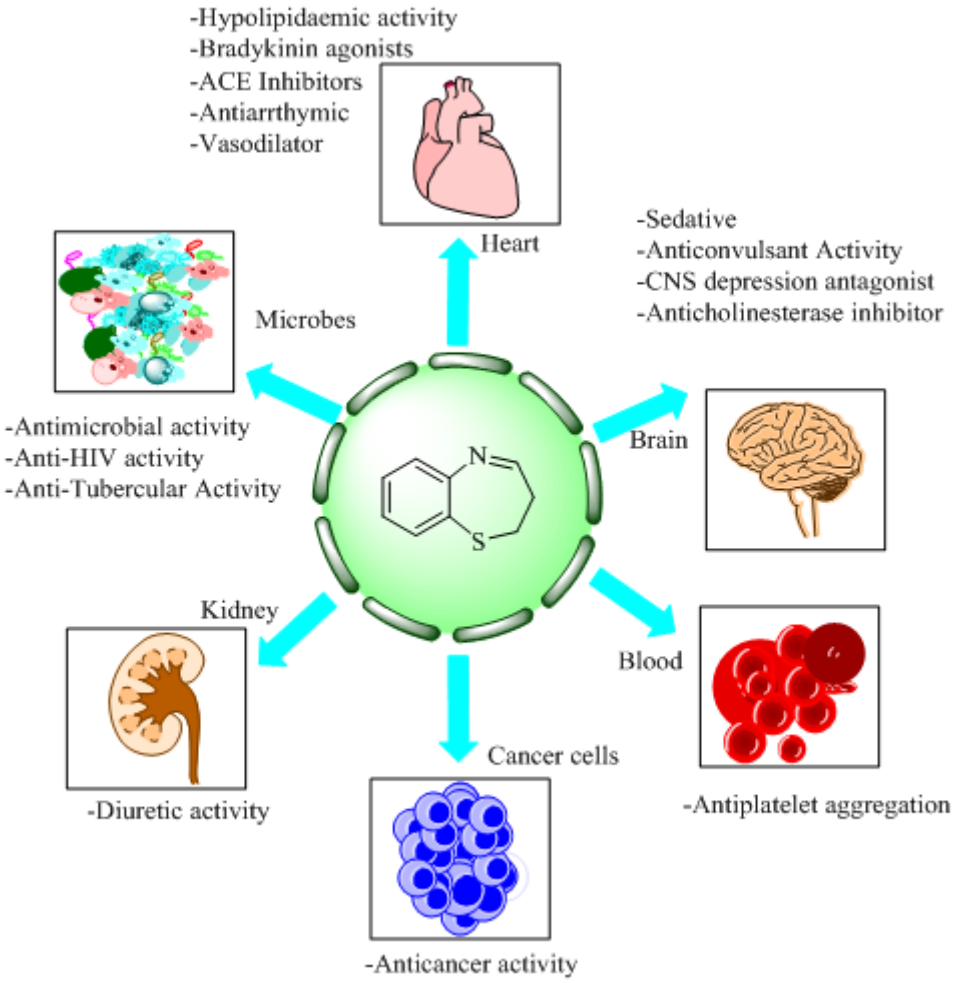
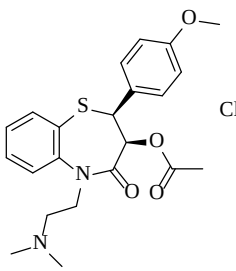
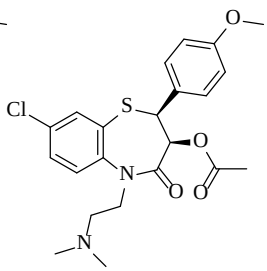


Figure 2

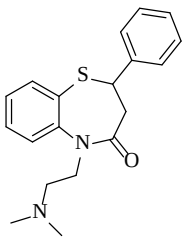
There is potential interest in the synthesis of new 1,5-benzothiazepine derivatives due to their biological potential (Figure 2).



4.Diltiazem



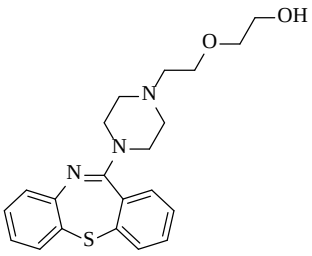
5.Clentiazem



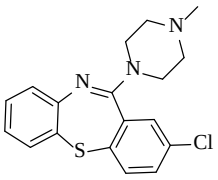
6.Thiazesim

2. Clinically Used Drugs

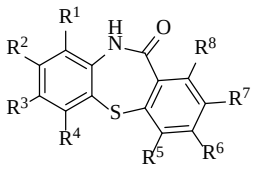
The 1,5-benzothiazepine nucleus, a biologically accepted pharmacophore in medicinal compounds, has versatile heterocyclic nucleus possessing wide spectrum of biological activities.[3] This nucleus has been featured in many drugs used as vasodilator, calcium channel antagonists (diltiazem **4**, clentiazem **5**) and also used in the treatment of depression (thiazesim **6**, quetiapine **7**, clothiapine **8**).



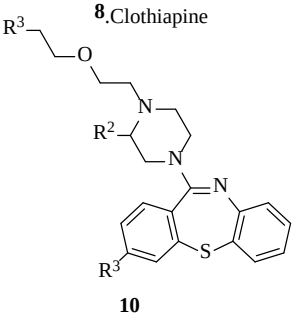
7.Quetiapine



8.Clothiapine



9

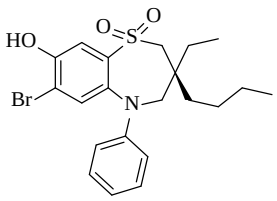


10

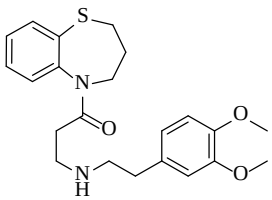
Recent patents deal with the synthesis and process improvement of theses scaffolds as dibenzothazepineone compounds **9** acts as the effective antipsychotic substance.[4] Some recent patents reported improved process for preparation of quetiapine **7**.[5,6] Donahue et al. reported synthesis of conjugates of quetiapine hapten.[7]

3. Drugs under preclinical trials

A number of compounds containing 1,5-benzothiazepine nucleus are under preclinical studies. 7-bromo-3(S)-butyl-3-ethyl-8-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepine-1,1-dioxide (GW-577) **11** is a candidate for the treatment of lipoprotein disorder and inhibition of transporter of ileal bile acids.



GW-577
11



KT-363
12

Compound 5-[N-[2-(3,4-dimethoxypheny)ethyl]-b-alanyl]-2,3,4,5-tetrahydro-1,5-benzothiazepine (KT-363) **12**, is under the phase II clinical trials for the treatment of antihypertensive , antiarrhythmic, calcium (Ca^{+2}) channel antagonist activity.[8]

4. Therapeutic targets of 1,5-benzothiazepine nucleus

1,5-benzothiazepine derivatives have variety of activities. In this section we have grouped them according to their site of action. The moiety has shown effect on cardiac system, brain, liver, blood, cancer cells, kidney and microbes.

4.1. Effect on cardiac system

Cardiac effect of 1,5-benzothiazepine is due to the action on Ca^{+2} channel. Four types of Ca^{+2} channels are identified which have specific functions and location.

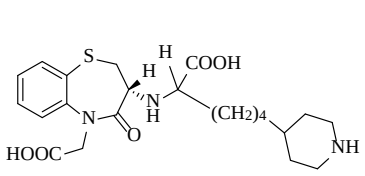
These include (i) L-type, located in skeletal, cardiac and smooth muscle cells, (ii) T-type, located in pacemaker's cells, (iii) N-type, found in neuronal cells and (iv) P-type, located in neuromuscular junction.[9,10]

1,5-benzothiazepine acts by blocking voltage-gated calcium channels (VGCCs).[11] Primarily 1,5-benzothiazepine derivatives block the calcium influx through calcium channels in excitable membranes. In cardiac muscle they act by decreasing intracellular calcium leading to a reduction in muscle contraction. In the heart, a decrease in calcium availability for each beat results in a decreased cardiac contractility. In blood vessels, a decrease in calcium results in less contraction of the vascular smooth muscle, which leads to an increase in arterial diameter (vasodilation). Vasodilation decreases total peripheral resistance, while a decrease in cardiac contractility decreases cardiac output. Since blood pressure is determined by cardiac output and peripheral resistance, blood pressure drops.

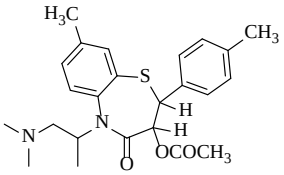
With a relatively low blood pressure, the afterload on the heart decreases; this decreases the amount of oxygen required by the heart, which can help ameliorate symptoms of ischemic heart disease such as angina pectoris.[12]

4.1.1. ACE Inhibitors

The renin angiotensin-aldosterone system (RAAS) plays an important role in regulating arterial blood pressure. Angiotensin II is responsible for increased total peripheral resistance via constriction of capillary arterioles through the activation AT1 receptors located on vascular smooth muscle cells.[13] A series of (R)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid derivatives were found to exhibit ACE inhibiting action, number of compounds in this series revealed potent ACE inhibiting activity in vivo and in vitro. To prove this fact, Inada et al. carried out the synthesis of (R)-3-[(S)-1-carboxy-5-(4-piperidyl)pentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid **13**, these synthesized compounds showed potency and long lasting ACE inhibitory activity.[14]

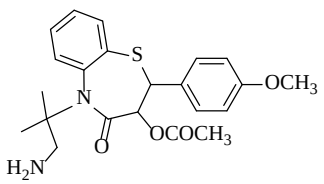


13



14

In another study 1,5-benzothiazepine derivatives such as (-)-cis-3-acetoxy-5-(2-(dimethylamino)ethyl)-2,3-dihydro-8-methyl-2-(4-methylphenyl)-1,5-benzothiazepin-4(5H)-one having l-cis configuration were evaluated for its cardiovascular effects and was found that Compound **14** increase cardiac output and limb blood flow, which was mediated by the sympathetic nervous system.[15]



15

16

17

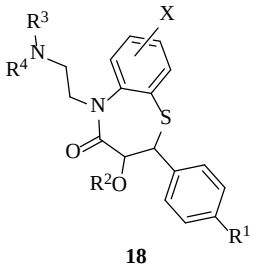
4.1.2. Antiarrthymic

Cardiac arrhythmia is a disturbance or irregularity in the heart rate, rhythm, or both.[16] A new series of benzothiazepine 3-acetoxy-cis-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one **15**, showed antiarrhythmic action comparable with that of propranolol and quinidine.[17]

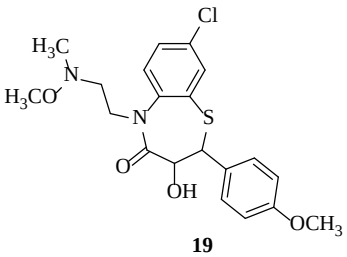
The mechanism of action of benzothiazepine class of compound was studied and found that compound **16** exhibit calcium channel blocking activity due to formation of related stability ternary complex because of intermolecular interactions of benzothiazepine drugs.[18] In search of new antiarrhythmic drugs Smith et al. synthesized compound **17** and found that synthesized compound inhibit store-overload induced calcium release (SOICR) through the RyR2 channel and showed antiarrhythmic effect.[19]

4.1.3. VASODILATOR

Vasodilation activity of 1,5-benzothiazepine derivatives having halogens substitution on the fused benzene ring (e.g.compound **18**) and the 8-chloro derivative **19** found to possess most potent cerebral vasodilating and antihypertensive activity among this series.[20]



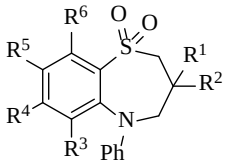
18



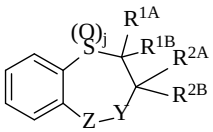
19

4.1.4. HYPOLIPIDAEMIC ACTIVITY

Starke et al. studied 1,5-benzothiazepine derivatives and reported that compound **20** possess ileal bile acid transport inhibitory activity and was found to decrease the risk of hyperlipidemia.[21] Whereas 1,5 -benzothiazepine derivative compound **21** is useful as apical sodium co-dependent bile acid transport inhibitor and is associated with Hypocholesterolemic Agents.[22]

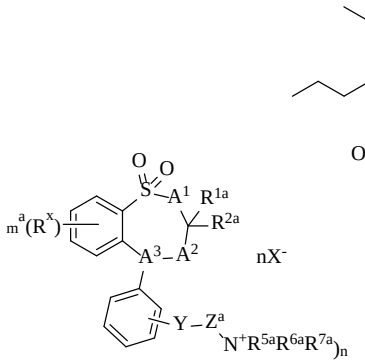


20

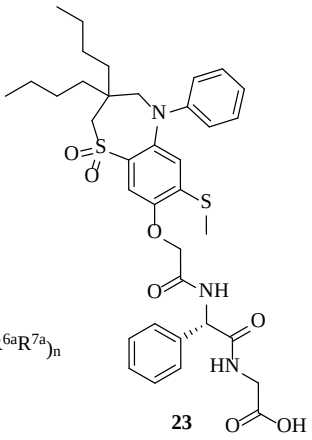


21

This invention led to the development of novel benzothiazepine or benzothiepine compound **22** having a thioamide bond and a quaternary ammonium substituent, used for prevention or treatment of coronary artery diseases.[23] Recently Starke et al. reported compound **23** with inhibitory activity against specific IBAT improved effect in prophylaxis, and treatment of metabolic syndrome, obesity, disorder of fatty acid metabolism, glucose utilization disorders, disorders in which insulin resistance is involved, diabetes mellitus, type 1 and type 2 diabetes.[24]



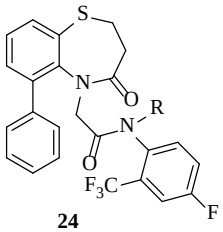
22



23

4.1.5. ACYL-COENZYME A CHOLESTEROL ACYLTRANSFERASE (ACAT) INHIBITORS

ACAT inhibitors have been clinical used in preventing both hypercholesterolemia and atherosclerosis by blocking cholesterol esterification. Tabata and coworkers reported synthesis of Compound **24** as an acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors.[25]

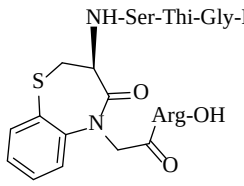


24

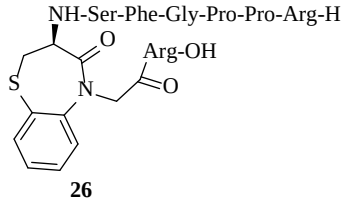
4.1.6. BRADYKININ AGONISTS

Bradykinin (BK), is a nonapeptide hormone which is involved in the induction of vascular, bronchial smooth muscle contraction, vasodilation and microvascular leakage.[26,27] The Cardio protective effect of ACE inhibitors is due to the metabolic protection of bradykinin.[28,29,30]

Amblard et al. reported the synthesis of fully bradykinin B_2 receptor antagonist compound **25** and **26**. **25** analogue was prepared by replacing D-BT to yield H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-BT-Arg-OH. These compounds were examined in vitro for their binding affinity toward bradykinin receptors (B1 and B2) as well as for their ability to interfere with bradykinin-induced contraction of both human umbilical vein and rat uterus.[31]



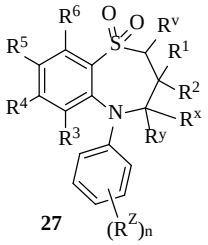
25



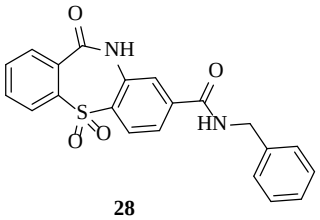
26

4.2. Effect on Liver

Hypercholemia and cholestatic liver diseases are associated with impaired bile secretion and often intracellular accumulation of bile acids/salts in hepatocyte. Derivative of compound **27** was found to show inhibitory action on bile recycling.[32] Guo et al. reported compound **28** useful as pregenomic RNA encapsidation inhibitors of Hepatitis B virus for treatment of Hepatitis B Virus infection and related conditions.[33]



27



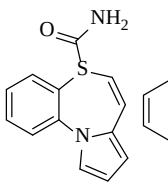
28

4.3. Effect on Brain

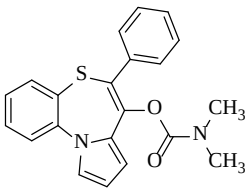
1,5-benzothiazepine acts by binding with benzodiazepine receptor, most probably on mitochondrial benzodiazepine receptors (MBR). It also causes the blocking of GABAA receptor.

4.3.1. Sedative

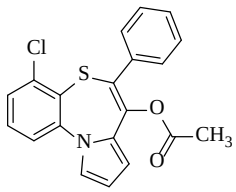
Some structural features are essential for CNS activity of this nucleus and it is observed that 4,5 fused pyrrolo ring essential for the development of CNS active molecules. Nacci et al. reported synthesis of a series of 1,5- benzothiazepines containing 4,5-fussed pyrrolo ring and found that NF-44 **29**, pyrrolo[2,1-d][1,5]benzothiazepine-5-carboxamides **30** exhibit potent sedative action comparable to diazepam.[34] Fiorini et al. reported Compounds 7-acetoxy-4-chloro-6-phenylpyrrolo[2,1-d][1,5]benzothiazepine **31** and 7-[(dimethylcarbamoyl) oxy]-6-(p-methoxyphenyl)pyrrolo[2,1-d][1,5]benzothiazepine **32** to be most potent and specific ligands for mitochondrial benzodiazepine receptor.[35] Greco et al. carried out Molecular modeling study (using CoMFA) of this series, and reported compound **33** having highest affinity for MBR.[36]



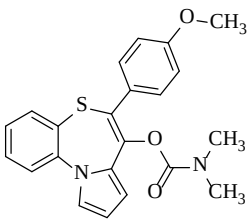
29



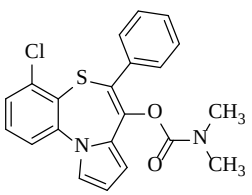
30



31



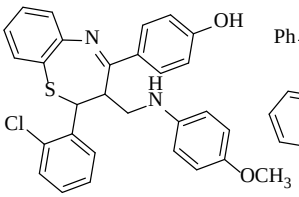
32



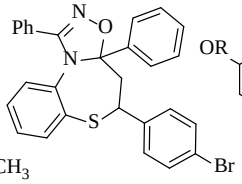
33

4.3.2. Anticonvulsant Activity

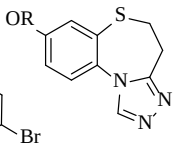
A periodic attack of disturbed cerebral function is defined as convulsion. It is an abnormal disturbance in electrical activity in one or more area of brain causing lack of attention or limited motor, sensory or psychological changes. In severe cases it may cause prolonged loss of consciousness.[37] Garg et al. reported synthesis and anticonvulsant activity of a new series of 4-(4'-Hydroxyphenyl)-2-(3-substituted phenyl)-3-(4-substituted phenyl amino methylene)-2,3-dihydro-1,5-benzothiazepines was synthesized.[38] The compound **34** was found to be most potent compound of this series. Likewise, Sarro et al. reported synthesis of 5H-[1,2,4]Oxadiazolo[5,4-d] [1,5]benzothiazepines and found that the 5-(4-bromophenyl)-1,3-diphenyl derivative **35** had potent anticonvulsant activity.[39]



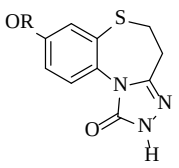
34



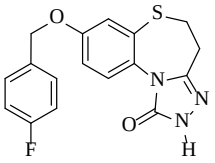
35



36

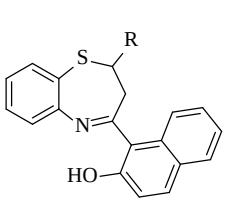


37

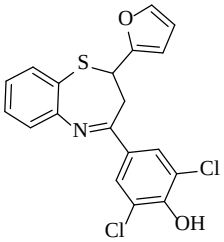


38

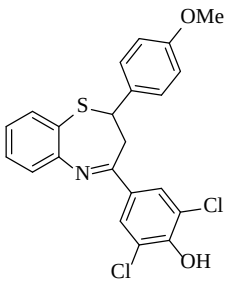
In an another study Deng et al. reported the synthesis of two series of 8-alkoxy-4,5-dihydrobenzo[b][1,2,4]triazolo[4,3-d][1,4]thiazepine derivatives **36**, **37** and evaluated for their anticonvulsant activity using the maximal electroshock (MES) method. Among these compounds **38** was considered as the most promising activity.[40]



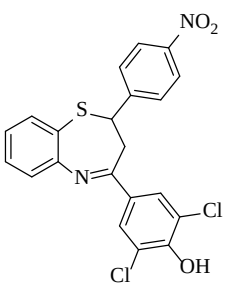
39



40



41



42

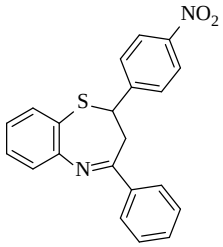
4.3.3. CNS DEPRESSION ANTAGONIST

Depression is one of the most common psychiatric disorders. It is characterized by feelings of intense sadness, helplessness, worthlessness, and impaired functioning. After the use of antidepressant drugs for several years it was thought that the antidepressants block the reuptake of the endogenous neurohormones norepinephrine and serotonin, which resulted in stimulation of the central nervous system (CNS). Therefore, new molecules which cause slower adaptive changes in norepinephrine and serotonin receptor systems may prove good antidepressants.[41]

For developing such antidepressants, Vyawahare et al. performed solvent free green synthesis of 2,3-dihydro-2-substituted-4-(naphthalen-2'-ol)-yl-1,5-benzothia zepines **39**.[42] These compounds exhibited excellent results against CNS depressant activity. Synthesis in similar lines, Nikalje et al., synthesized of 2, 4-substituted 2, 3-dihydro-1,5-benzothiazepine **40** derivatives as benzodiazepines bioisosters and study of CNS depressant activity of these compounds using sleep deprivation method revealed that compound **41** and **42** as excellent lead.[43]

4.3.4. ANTICHOLINESTERASE INHIBITOR

Acetylcholine, a natural chemical in the brain, is required for memory and thinking. Individuals with AD slowly lose this acetylcholine, and as the level of acetylcholine decreases, the patient experiences problems with memory and thinking. The cholinesterase inhibitors inhibits breakdown of acetylcholine and slows its neuronal destruction.[44]



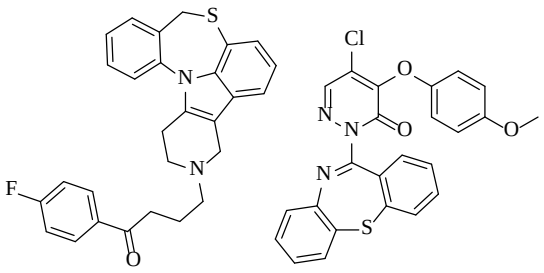
43

In this context Ansari et al. reported synthesis of different series of 1,5-benzothiazepine found benzothiazepine derivative **43** active against Brain Choline Esterases ChE with an IC50 value of 60 lM; and weakly active against AChE (IC50 = 102 lM).[45]

4.3.5. PSYCHIATRIC DISORDERS

In a recent work the synthesis of pyridolobenzothiazepine derivative done and compound **44** used for the treatment of schizophrenia and other central nervous system disorders.[46] Guerrero et al., reported that the compound **45** modulate the feeding behavior of mice by acting on neuropeptides.[47]

Neuropeptide W (NPW) and neuropeptide B (NPB) bind and activate two G-protein coupled receptors (GPCRs), namely NPBWR1 (GPR7) and NPBWR2 (GPR8).1 NPB mRNA is widely distributed throughout the mouse brain and is present in the hippocampus, hypothalamin nucleus, Edinger-Westphal nucleus (EW), locus coerulius, inferior olive and lateral parabrancheal nucleus. This neuropeptide system has been hypothesized to play an important role in modulating feeding behavior and developed adult-onset obesity.

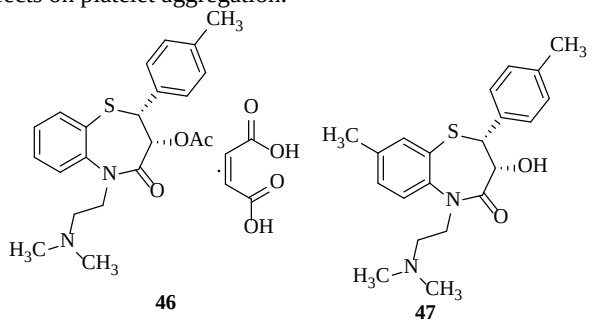


44 **45**

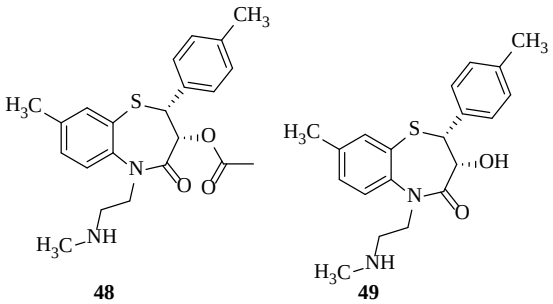
4.4. EFFECT ON BLOOD

4.4.1. ANTIPLATELET AGGREGATION

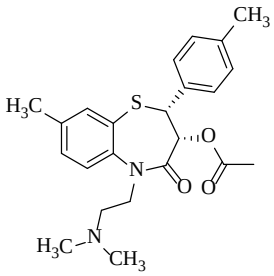
Platelets play a vital role in the progress and development of thrombotic disorder such as cerebral vascular diseases.[48,49] The inhibition of platelet function is thought to be therapeutically useful for prophylaxis and treatment of thrombotic diseases. In this context Mehta et al., found that diltiazem **4** showed antiplatelet aggregation action[50] and Ono et al found that its derivative clentiazem **5** and their metabolites have inhibitory effects on platelet aggregation.[51]



46 **47**



48 **49**



50

A number of 1,5-benzothiazepine derivatives are potent inhibitors of platelet aggregation induced by collagen, ADP, epinephrine, platelet activating effectors, arachidonic acid and U-46619, in vitro. TA-993 **46** and its metabolites (MB-1 **47**, MB-2 **48** and MB-3 **49**) were found to be potent inhibitors of platelet aggregation.[52] Among the two isomers, D-isomer of MB-3 was much more potent. The TA-993 **46** inhibits both primary and secondary phases of ADP-induced platelet aggregation, unlike acetylsalicylic acid (ASA).

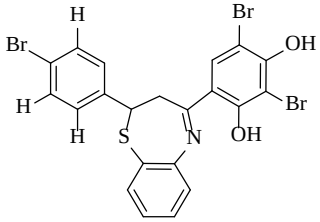
The TA-993 46 and ASA showed synergistic effect possibly due to the difference in mechanism for their antiplatelet action.[53] Inoue et al., synthesized and evaluated the compound, (-)-cis-3-acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-8-methyl-2-(4-methylphenyl)-1,5-benzothiazepin-4 (5H)-one, **50** and reported potent platelet aggregation inhibitory property among 2,3-dihydro-1,5-benzothiazepine-4(5H)-one derivatives substituted with alkyl, alkyloxy, alkylthio, hydroxyl or amino substitution on the fused benzene ring of the 1,5-benothiazepine skeleton.[54]

4.4. Effect on Cancer Cells

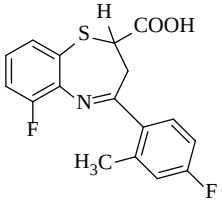
4.4.1 Anticancer Activity

Development of multidrug resistance (MDR) is a major obstacle for successful chemotherapy of many human cancers. Many mechanisms are involved in resistance to cancer chemotherapy, including decreased drug accumulation (decreased drug uptake and/or increased drug efflux), altered intracellular drug distribution, increased detoxification, diminished drug-target interaction, increased DNA repair, altered cell-cycle regulation, uncoupling of the pathways linking cellular damage with apoptosis, etc. Of these factors, over expression of P-glycoprotein (P-gp) and multidrug resistance protein 1 (MRP1) are main mechanisms of MDR.[55]

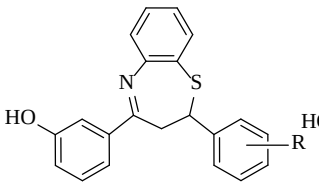
The 1,5-benzothiazepine derivatives are of particular interest for lead discovery because they have been found to be active against different families of targets and One of the target of this scaffold is to inhibit growth of cancer cells. Ameta et al. synthesized some new compounds and evaluated them for their cytotoxicity effect against the human breast cancer cell line MDA-MB-435.[56]



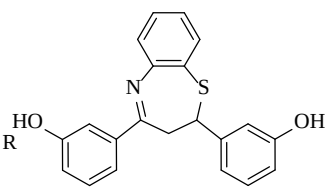
51



52

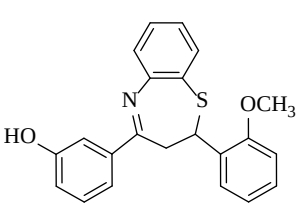


53

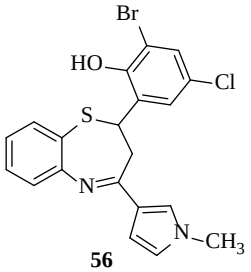


54

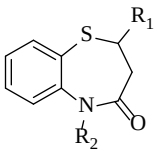
The compound 51 showed maximum GI50 in vitro study of cancer. In an another study by Arya et al., 8-substituted-2-carboxy-2,3-dihydro-1,5-benzothiazepines were synthesized and screened for phototoxicity on a cell line of human tumor HL-60 (human promyelocytic leukemia); the compound **52** was found to be most active among all tested compounds.[57] Experiment on solid phase synthesis of 2,3-dihydro-1,5-benzothiazepines was carried out and the synthesized compounds were subjected to potato disk tumor inhibitory activity. The compound **53**, **54** and **55** showed good activity against potato disk tumor.[58]



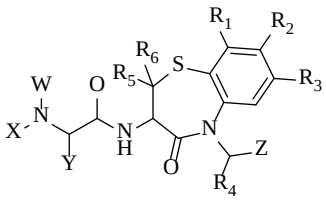
55



56



57

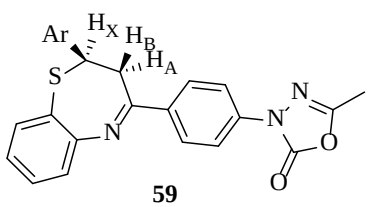


58

Yenupuri et al. reported the synthesis of a series of 2,3-dihydro-2-(susbtituted)-4-(1-methyl-1H-pyrrol-2-yl)-1,5-benzothiazepines demonstrated their in vitro cytotoxic activity using Brine shrimp lethality assay. Compound **56** showed significant cytotoxic activity.[59] Similarly Zhang et al. reported synthesis of benzothiazepinone derivatives **57** and their anticancer activity.[60]. Donnell et al., reported synthesis of substituted hetero-azepinones **58** and their use to inhibit SMAC protein binding to inhibitor of apoptosis proteins and inhibit activated caspase protein binding to IAPs.[61]

4.5. Effect on Kidney (Diuretic Activity)

1,5-benzothiazepine had shown diuretic effect Kamble et al. prepared 1,5-benzothiazepine derivatives and evaluated diuretic activity by studying the effect of drugs on water and electrolyte excretion in rats.[62] Furosemide was taken as standard drug for activity. The compound **59** showed highest diuretic activity in this study.



59

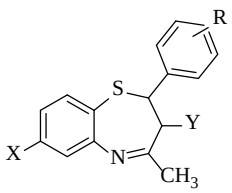
4.6. EFFECT ON MICROBES

4.6.1. ANTIMICROBIAL ACTIVITY

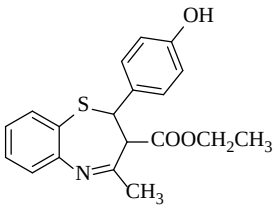
The emergence of bacterial resistance to β-lactam antibiotics, macrolides, quinolones and vancomycin is becoming a major worldwide health problem; so researchers are paying great attention on this topic.[63] Recent works on some of 1,5-benzothiazepine derivatives demonstrate that these compounds serve as potential agents in the control and treatment of microbial infection and it had stimulated further interest in these compounds.

In an attempt to obtain antimicrobial agent, synthesis and antibacterial antifungal screening of novel series of 1, 5-benzothiazepine derivatives of **60** was carried out by Wang et al., Compound **61** exhibited the greatest antimicrobial activity.[64] Structural activity relationship studies indicated that substituents in phenyl rings had a great effect on the antimicrobial activity of these compounds.

Optically active forms of 2,3-dihydro-1,5-benzothiazepine derivatives of **62** were synthesized by Khan et al. and tested against Gram positive (*Bacillus subtilis, Staphylococcus aureus*), Gram negative (*Pseudomonas aeruginosa, Escherichia coli*), and fungus (*Aspergillus niger, Aspergillus Flavus, Curvularia and Alternaria*). All compounds of this series exhibited good to excellent activity against bacteria and fungi.[65]

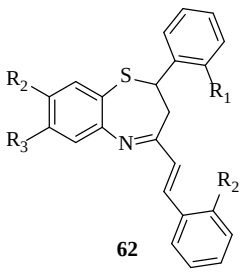


60



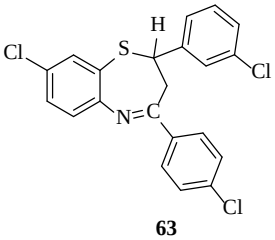
61

Due to antimicrobial resistance, latest generation of antibiotics virtually ineffective. The development of antimicrobial resistance by bacteria is inevitable and considered as major problem in the treatment of bacterial infections.[66] To avoid antimicrobial resistance there is a need to develop new lead molecules. Pant et al., reported the synthesis of various 4-(2-thienyl)-substituted 2-(2-chloro phenyl)-1,5- benzothiazepine derivatives and found that these derivatives are more active.

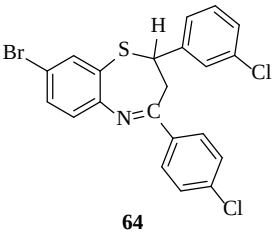


62

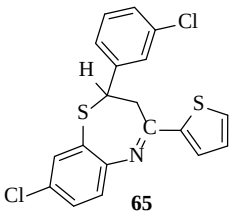
Compound **63** showed the highest relative activity against the Gram positive bacteria *Staphylococcus aureus*; whereas, compound **64** showed meaningful activity index against the Gram negative bacteria, *Pseudomonas aeruginosa*. Compounds **65**, **66**, and **67** showed high activity against the fungus, *Candida albicans*.[67]



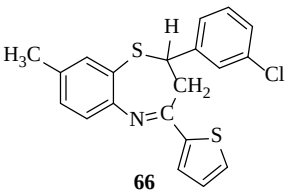
63



64

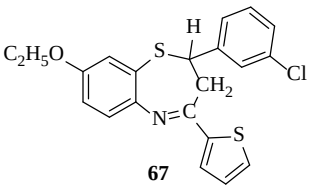


65

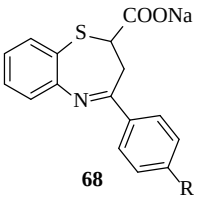


66

In this regard Zhang et al. synthesized a series of novel 1,5-benzothiazepine derivatives **68** containing $COOC_2H_5$/COONa groups at the C(2)-position and evaluated their antifungal and antibacterial activities. Most of the compounds were found to have moderate to good antibacterial activity against *S.aureus*, *S.epidermidis* and excellent antifungal activity against *C. albicans*.[68]

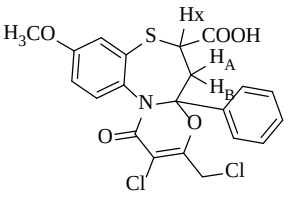


67

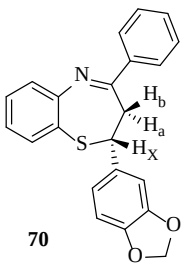


68

Similarly, Dandia et al. also carried out the synthesis of azeto[2,1-d][1,5]benzothiazepines and the screened for antimicrobial activity using the cup-plate method, Compound **69** showed a good activity against *S. aureus*.[69] In this context Saini et al. carried out an efficient and convenient synthesis of 1, 5-benzothiazepines and 1,5-benzodiazepines and screened them for their antibacterial activity against β-subtilis, *E. coli, S. typhis* and compound **70** showed excellent activity against the tested strains.[70]

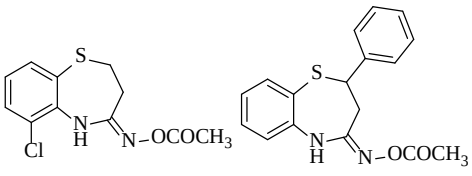


69

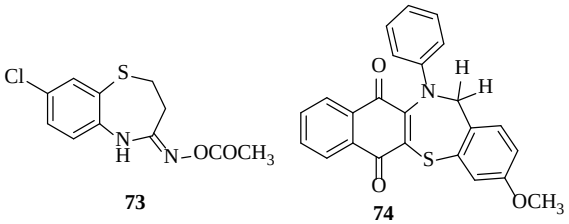


70

In search of new molecules to avoid antimicrobial resistance synthesis of the benzo-, naphtho- and quinolino-1,4-thiazine and l,5-thiazepine derivatives were carried out by Ambrogi et al.[71] All the compounds were tested in vitro for their antimicrobial activity against Gram-positive and Gram negative bacteria and fungi. The results indicated that compound **71**, **72**, **73** possessed antimycotic effects against fungal species.

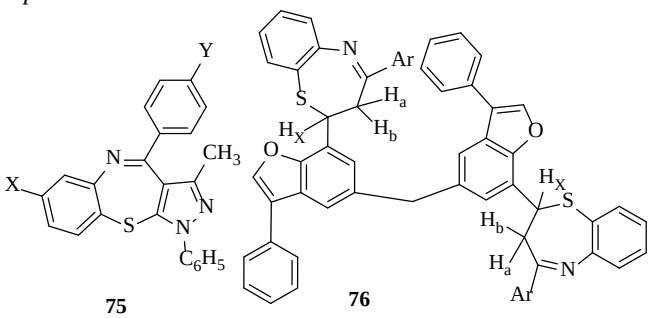


71 **72**



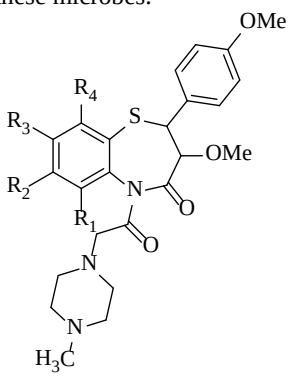
73 **74**

Tandon et al. synthesized a series of 1,5-benzothiazepine derivatives and the compound 3-Methyl-6H-benzo[b]phenothiazine-6,11(12H)-dione antifungal and antibacterial studies indicated that compound **74** had potent antifungal activity.[72] In an another study diltiazem analogue pyrazolo[4,3-c][1,5]benzothiazepines **75** were synthesized and found to have good activity against three pathogenic fungi, viz. as *Rhizoctonia solani*, *Fusariumoxysporum*, and *Colletotrichum capsici*.[73]

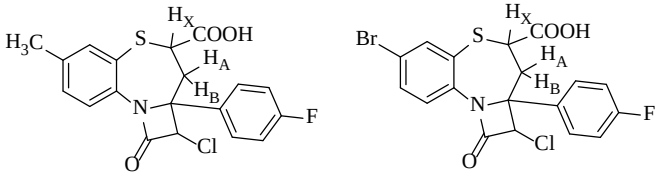


75 **76**

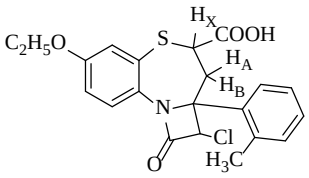
A series of novel methylene-bis-[1,5]-benzothiazepines and methylenebis- benzofuranyl-[1,5]benzothiazepines were synthesized by Reddy et al. and were evaluated for antimicrobial activity against various Gram-positive, Gram-negative bacteria and fungi. Among them, compounds **76** showed maximum activity.[74] Sharma et al. reported synthesis and antimicrobial activity of substituted 1,5-benzothiazepine derivatives of **77** against the bacteria (*S.aureus*, *E. coli*) and fungi (*Aspergillus niger*, *Aspergillusflavus*, *Curvularia lunata* and *Fusarium moniliformae*). These derivatives were found to be active against these microbes.[75]



77



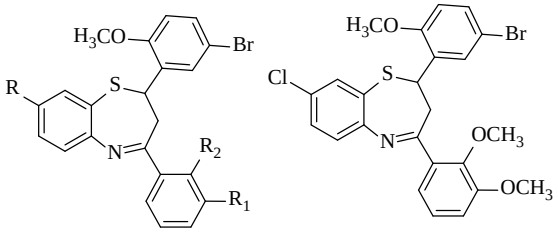
78 **79**



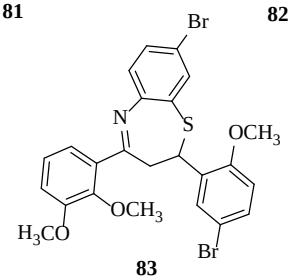
80

Synthesis of fluorine containing azeto[2,1-d][1,5]benzothiazepine derivatives carried out by Dandia et al. and tested them for antifungal activity against Rhizoctonia solani, Fusarium oxysporum and Collectotrichum capsici. Compounds **78, 79, 80** exhibited potent activity against these pathogens.[76]

In attempt to overcome antimicrobial resistance Kumar et al. reported the synthesis of a new series of structurally diverse 2,3-dihydro-1,5-benzothiazepines with substituted phenyl groups at C(2) and C(4) and all the synthesized compounds were evaluated for antibacterial and antifungal activity against a variety of bacterial and fungal strains. Compounds **81**, **82**, **83** showed antibacterial and antifungal activity comparable to ciprofloxacin and fluconazole.[77]



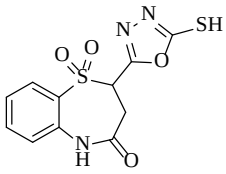
81 **82**



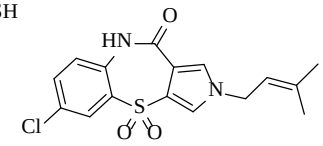
83

4.6.2. ANTI-HIV ACTIVITY

The discovery of the exceedingly high anti-HIV potency-enhancing effect of the pyridine nucleus in 'Nevirapine' provided the idea to Gupta et al. to club it into the 1,5-benzothiazepine nucleus. The idea behind using versatility of the oxoketene dithioacetal substituent in the 1,5-benzothiazepine nucleus was to devise an elegant plan for its annulation on to the pyridine ring. The biological evaluation of compound **84** showed good anti HIV activity.[78]



84

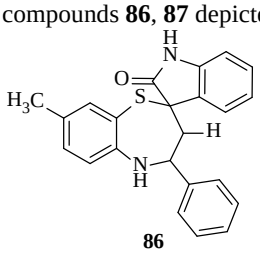


85

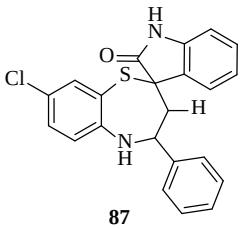
In this context Santo et al. evaluated a series of 2H-pyrrolo [3,4-b][1,5]-benzothiazepine, derivatives for their activity against reverse transcriptase. Majority of the tested compounds were active against HIV-1-induced cytopathicity in MT-4 cells. In this series, compound **85**, 6-chloro-2-(3-methyl-2-butenyl)-2H-pyrrolo[3,4-b][1,5]benzothiazepin-10(9H)-one 4,4-dioxide was the most potent comparable to nevirapine.[79] A series of thiazolothiazepines were prepared and tested against purified human immunodeficiency virus type-1 integrase (HIV-1 IN) and viral replication; compounds showed excellent activity.[80]

4.6.3. Anti-Tubercular Activity

Tuberculosis is caused by the Mycobacterium tuberculosis bacillus and it is a major health problem throughout the world.[81]In this context, Dandia et al. synthesized the spiro [1,5]-benzothiazepin-2,39[39H]indol-2[19H]-ones. These compounds were screened for their antitubercular activities. The synthesized compounds **86**, **87** depicted significant antitubercular activity.[82]



86

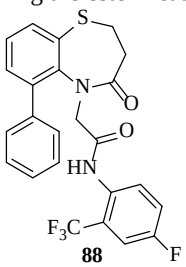


87

4.7. Miscellaneous

4.7.1. Acyl-coenzyme A cholesterol acyltransferase inhibitors

Acyl-coenzyme A cholesterol acyltransferase inhibitors play an important role to inhibit hypercholesterolemia and atherosclerosis by blocking the esterification of cholesterol.

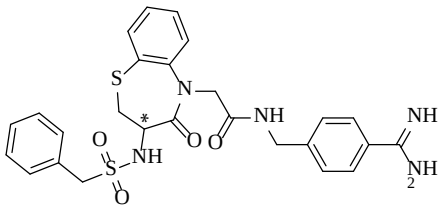


88

To prove this fact, Tabata et al. prepared the 1,5-benzothiazepin-2-one and found that compound **88** showed excellent activity against acyl-coenzyme A cholesterol acyltransferase.[25]

4.7.2. Factor VIIa/tissue factor inhibitors

1,5-benzothiazepine-4-one scaffold **89** showed efficient protease inhibitor activity and excellent factor VIIa/tissue factor inhibitory activity.[83]



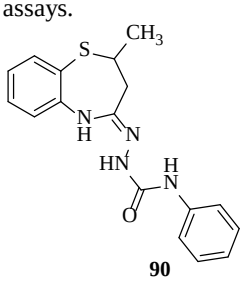
89

4.7.3. Antioxidant property

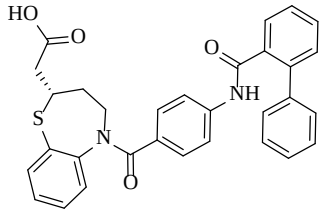
DPPH radical scavenge assay is a non-enzymatic method currently used to provide basic information about the ability of compounds to scavenge free radicals. Jafri et al., reported synthesis of scavenge free radical. The compound **90** found to be excellent antioxidant activity.[84]

4.7.4. V_2 Antagonist

Urbanski et al., synthesized a number of 2,5-disubstituted benzothiazepines and screened them for their ability to inhibit arginine vasopressin binding to the human V_2 and V_{1a} receptor subtypes. The more active compounds were subsequently analyzed for their antagonist activity for in vitro functional assays.



90

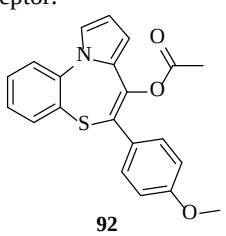


91

The carboxymethyl analogue **91**, showed a 140-fold greater selectivity for the V_2 over the V_{1a} receptor in the binding assay. In the cell-based functional assays this analogue proves to be more potent and selective antagonist of the V_2 receptor.[85]

4.7.5. Constitutive androstane receptor (CAR) and pregnane X receptor (PXR) agonist activity

Stonera et al., reported that NF49 benzothiazepine **92** is an agonist ligand of constitutive androstane receptor CAR1 and partial agonist of PXR pregnane X receptor, CAR1 and PXR regulates xenobiotic sensing and metabolism through interactions with multiple exogenous and endogenous which are related to nuclear receptor.[86]



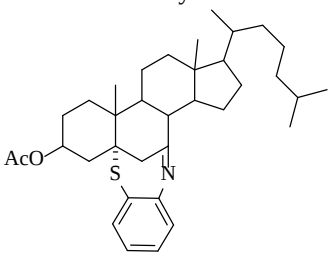
92

5. Docking studies on 1,5-Benzothiazepine

In silico studies of 1,5-benzothiazepines has been carried out as potential are discussed further.

5.1. CHOLINESTERASES INHIBITORS

The inhibition of cholinesterases by 2,3-dihydro-1,5-benzothiazepines has been reported and considered as promising inhibitors for the cure of Alzheimer's disease. Cholinesterases (ChEs) have been classified into two types, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), on the basis of distinct substrate specificities and inhibitor sensitivities. Due to the increased activity of butyrylcholinesterase; the genesis of fibrils by β-amyloid plaques occurs. Formation of β-amyloid plaques is associated with Alzheimer's disease. Substituted 1,5-benzothiazepine derivatives with a hydroxy group at C-3 in ring A and 2-thienyl moiety as ring B, showed greater activity against butyrylcholinesterase than to acetylcholinesterase.[87]

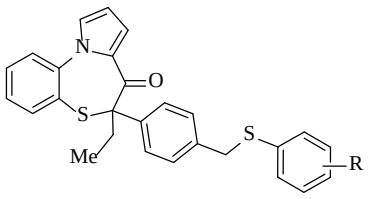


93

Similarly, Khana et al., performed the green synthesis of 1,5-benzothiazepine derivatives and all the synthesized compounds were screened for their acetylcholinesterase (AChE)inhibition activity. The AChE inhibition activity of the compound **93** was investigated with the help of in silico docking study to predict the active sites.[88]

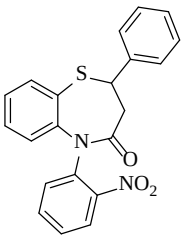
5.2. ADENOSINE KINASE INHIBITORS

Adenosine kinase inhibitors have shown to provide antinociceptive, anti-inflammatory, and anticonvulsant activity in animal models, thus suggesting their potential therapeutic utility for pain, inflammation, epilepsy, and possibly other CNS and PNS diseases associated with cellular trauma and inflammation. The reports of Ado-induced apoptosis have suggested a potential role for AK inhibitors in cancer therapy. So Butini et al. did the synthesis and molecular modeling of pyrrolobenzoxa(thia)zepinones and identified compound **94** as a non-nucleoside prototype hAK inhibitor human adenosine kinase inhibitor.

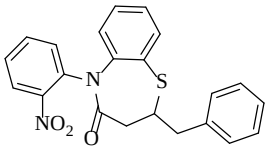


94

This compound possessed proapoptotic efficacy, slight inhibition of short-term RNA synthesis, and cytostatic activity on tumor cell lines while showing low cytotoxicity and no significant adverse effects on short-term DNA synthesis in cells.[89]



95



96

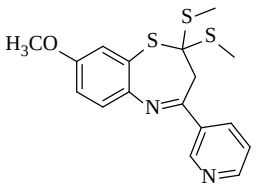
5.3. GLYCOGEN SYNTHASE KINASE-3B INHIBITORS

Glycogen synthase kinase-3β (GSK-3β) plays an important role in the neurodegenerative diseases and diabetes. BTZ compounds showed useful results in treatment of Alzheimer's disease and diabetes mellitus as novel GSK-3b inhibitors. Keeping in this mind Zhang et al performed In silico studies on Glycogen synthase kinase-3β inhibitors and after virtual screening the compound **95** gave highest activity against Glycogen synthase kinase-3β.[90]

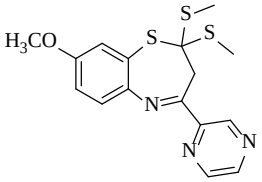
In an another study Zhang et al., synthesize and proposed docking study the benzothiazepinones compound 96 showed excellent activity.[60]

5.4. MAP KINASE PROTEIN INHIBITORS

Parthasarathy et al., synthesized hetrocyclic 1,5-benzothiazepines compounds and compounds were screened for their activity against MAP kinase protein.

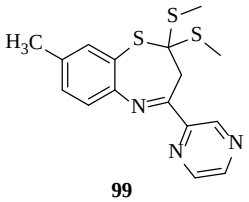


97



98

Compounds BTZ-6b **97**, BTZ-16 **98** and BTZ-17 **99** showed the specific binding with active site of amino acid residues of TYR35, LYS53 other amino acids present in the active site were found to possessed Vander waals interaction with protein with good dock score.[91]



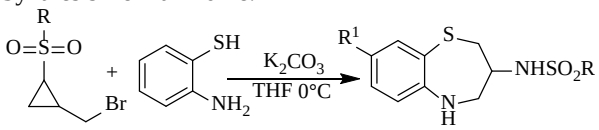
99

6. SYNTHETIC METHODS

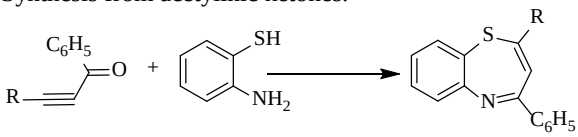
1,5- benzothiazepine nucleus can be prepared by condensing 2-aminophenol with the reaction of aziridine[92], acetylinic ketone[93], α,β-unsaturated ketone[42], chalcone[94], propiolic acid [95], acetoacetic ester[96], α-oxoketeone-s,s-acetone[97] followed by cyclization using a suitable base.by choosing proper substitution at 2-aminothiophenol and condensing partner a large number of

substituted 1,5-benzothiazepine derivatives have been reported in the literature.

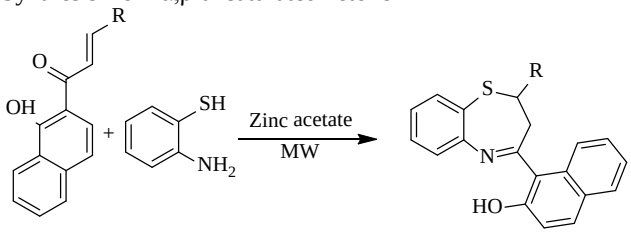
Synthesis from aziridine:



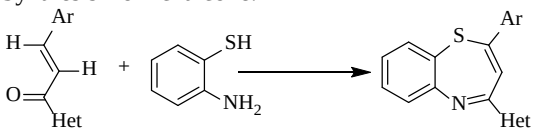
Synthesis from acetylinic ketones.



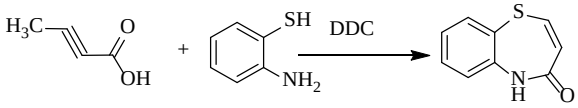
Synthesis from α,β-unsaturated ketone



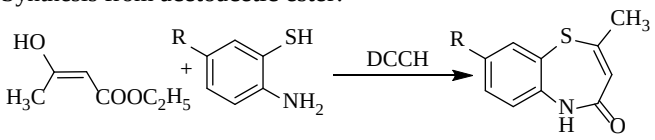
Synthesis from chalcone:



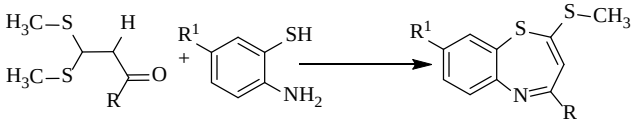
Synthesis from propiolic acid:



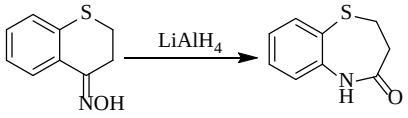
Synthesis from acetoacetic ester:



Synthesis from α-oxoketene-S,Sacetal:



Substituted nucleus is also synthesized by reductive ring expansion of 1-thiochromanone oxime in presence of $LiAlH_4$.[1]Quatanary salt of N-Haloalkyl benzothiazole has been converted into 1,5-benzothiazepine derivatives in presence of alkali.[1]



7. Conclusion

We have reviewed various 1,5-benzothiazepine derivatives with different pharmacological effects. The 1,5-benzothiazepine nucleus has high potential to be substitute systematically to produce desired biological activity.

Acknowledgments

Authors acknowledge support from MMU Mullana

References and Notes

1. A. Levai. Synthesis of Benzothiazepines. Chemistry of Heterocyclic compounds.**1986**, 22, 1161-1170.
2. A. Levai. Synthesis And Chemical Transformations of 1,5-benzothiazepines. *Heterocyclic Communication*. **2011**, 8, 375-380.
3. R. Dalpozzo, G. Bartoli, L. Sambri, P. Melchiorre. Perchloric Acid and Its Salts: Very powerful catalysts in organic chemistry. *Chemical reviews*. **2010**, 110, 3501-3551.
4. K. Nagarajan, R. Gupta, K. Pasupathy, S. Vijaikumar, P. Pradeep Process for preparation of dibenzothaizepinone comounds. (**2011**) WO patent WO 2011/121602A1.
5. S. Serafini, F. Tomasi, M. Galvagni (**2011**) Process for the synthesis of quetiapine US 2011/0118460A1.
6. V.V. Durvasula, Rathod P.D., R. C. Aryan, C. H. Khanduri. (**2012**) Process for the preparation of quetiapine fumarate. US 2012/0071649A1.
7. M.G. Donahue, Y. Gong, R. Salter, E. Hryhorenko, T. R. Decory, B. M. Remmerie, B. Sankaran (**2014**) Haptens of quetiapine for use in immunoassays WO Patent WO2014/031600A1.
8. J. B. Bariwal, K.D. Upadhyay, A.T. Manvar, J. C. Trivedi, J.S. Singh, K.S. Jain, A.K. Shah. 1,5-Benzothiazepine, a versatile pharmacophore: A review. *Eur. J. Med. Chem.*.**2008**, 43, 2279-2290.
9. O. Krizanova, R. Diebold, P. Lory, A. Schwartz. Molecular aspects and diversity of voltage dependent calcium channels. *Circulation*.**1993**, 87S VII44-VII48.
10. D. Pelzer, S. Pelzer, T.F. Macdonald. Properties and regulation of calcium channels in muscle cells *Reviews of Physiology, Biochemistry and Pharmacology* **1990**, 114, 107-207.
11. W. M. Yousef, A. H. Omar, M.D. Morsy, M. M. Abd El-Wahed, N.M. Ghanayem. The mechanism of action of calcium channel blockers in the treatment of diabetic nephropathy. *Int. J. Diabet. Metabol*. **2005**, 13, 76-82.
12. K.D. Tripathi (**2008**) Essentials of Medical Pharmacology, Jaypee Brothers Medical Publishers (LTD) 465.
13. E.K. Jackson (**2001**) Renin, Angiotensin, in: J.G. Hardman, L.E. Limbird (Eds.) Goodman and Gilman's The Pharmacological Basis of Therapeutics 809-821.
14. Y. Inada, M. Tanabe, K. Itoh, H. Sugihara and K. Nishikawa. Inhibition of angiotensin converting enzyme by (R)-3-(S)-1-carboxy-5-(4-piperidyl) pentyl amino-4-oxo-2,3,4,5-tetra- hydro-1,5-benzothiazepine-6-acetic acid (CV-5975), a non-sulfhydryl compound. *Japanese J. Pharmacology*.**1988**, 48, 323-330.
15. M. Kaburaki, H. Yabana, H. Doi, K. Nagata, H. Narita, and S. Murata The Mechanism of the Increasing Action of TA-993, a New 1,5-Benzothiazepine Derivative, on Limb Blood Flow in Anesthetized Dogs: Selective Suppression of Sympathetic Nerve Activity. *J. Pharmacology and Experimental Therapeutics*. **1999**, 288, 1167–1173.
16. S. M. Ford, S.Roach. Lippincott's Introductory Clinical Pharmacology-1, Lippincott Williams and Wilkins. **2008**, 367-379.
17. K. Yamada, T. Shimamura and H. Nakajima. Studies on a new 1,5-benzothiazepine derivative(CRD-401). *Japanese J. Pharmacology*.**1973**, 23, 321-328.
18. A.Yadav, A. Awasthi, N.K. Rao. Mechanistic aspects of benzothiazepines:A class of antiarrhythmic drugs. *Eur. J. Med. Chem.* **2009**, 44, 1-6.
19. C.D. Smith, A. Wang, K. Vembaiyan, J. Zhang, C. Xie, Q. Zhou, G. Wu, S. R. W. Chen and T. G. Back () Novel Carvedilol Analogues That Suppress Store-Overload-Induced Ca^{2+} Release. *J Med Chem.* **2013**, 56, 8626−8655.
20. H. Inoue, M. Konda, T. Hashiyama, H. Otsuka, K.Takahashi, M. Gaino, T. Date,K. Aoe, M. Takeda, S. Murata,H. Narita andT. Nagaoi. Synthesis

of halogen-substituted 1,5-benzothiazepine derivatives and their vasodilating and hypotensive activities. *J. Med. Chem.* **1991**, 34, 675-687.
21. I. Starke, M. Dahlstrom, D.Blomberg.1,5-Benzothiazepines and their use as hypolipidaemics.2005WO01/66533Al.
22. S.J. Tremont, St. Louis, J.K. Kevin, L. Neumann, William, St. Louis. Novel 1,4-benzothiazepine and 1,5-benzothiazepine compounds as inhibitors of apical sodium codependent bile acid transport abd taurocholate uptake **2004US** 2004/0077625 A1.
23. Sasahara T., ShiZuoka, M.M. ShiZuoka, K.I. Kasahara, ShiZuoka (**2012**) Novel benzothiazepine and benzothiepine compounds US 2012/0015925 A1.
24. Starke I., Graffner H, Gillberg P G, Lindqvist A M, Angelin B (**2012**) IBAT Inhibitors for treatment of metabolic disorders and related conditions US2012/0114588A1.
25. H.Tabata, H.Wada, N.Takada,Y. Nakagomi, J. Miike,T. Shirahase, H. Oshitari,T.Takahashi, H. Natsugari, Hideaki, Active Conformation of Seven-Membered-Ring Benzolactams as New ACAT Inhibitors: Latent Chirality at N5 in the 1,5-Benzodiazepin-2-one Nucleus. *Chem.-A Eur. J.* **2012**, 18, 1572-1576.
26. D. Regoli, J. Barabe.Pharmacology of bradykinin and related kinins. *Pharmacological Reviews.* **1980**, 32, 1-46.
27.K.D. Bhoola, C.D.Figueroa, K. Worthy. Bioregulation of kinins: kallikreins, kininogens, and kininases. *Pharmacol.l Rev.* **1992**, 44, 1-80.
28. G. Bao, P. Gohlke, T. Unger. Role of bradykinin in chronic antihypertensive actions of ramipril in different hypertension models. *J. cardiovascular pharmacology*, **1992**, 20, S96-S99.
29. P. A.Martorana, B. Kettenbach, G. Breipol,W. Linz, B. A. Scholkens Reduction of infarct size by local angiotensin-converting enzyme inhibition is abolished by a bradykinin antagonist. *Eur. J. Pharmacology* **1990**, 182, 395-396.
30. K. M. McDonald, J. Mock,M. D'Ajoia, T. Parrish,K. Hauer, G. Francis, A. Stillman, J.N. Cohn. Bradykinin antagonism negates the anti-remodeling action of converting enzyme inhibition. *Circulation*.**1995**, 91, 2043-2048.
31. M. Amblard, I. Daffix, P. Bedos et.al. Design and Synthesis of Potent Bradykinin Agonists Containing a Benzothiazepine Moiety. *J. Med. Chem.* **1999**, 42,4185-4192.
32. B. Gedulin, M. Grey, N. O'Donnell. Bile acid recycling inhibitors for treatment of hypercholemia and cholestatic liver disease. **2013**. US Patent US2013/0108573A1.
33. Guo, Ju-Tao, Xu, Xiaodong, M. Block Timothy (2013) Sulfamoylbenzamide derivatives as antiviral agents against HBV infection WO2013/006394A1.
34.V. Nacci, I. Fiorini, S. Vomero, I. Taddei,E. Taddei. Compounds with psychotropic activity. VIII. Synthesis and sedative activity of various 9-substituted derivatives of 5-phenylpyrrolo2,1-d1,5 benzothiazepine and cis-4,5-dihydro-4-hydroxy-5-phenylpyrrolo2,1-d1,5benzothiazepine. *Farmaco*. **1984**, 39, 289-304.
35. I. Fiorini, V. Nacci, S.M. Ciani, A. Garofalo, G. Campiani, S. Savini, E. Novellino, G. Greco, P. Bernasconi, T. Mennini. Novel ligands specific for mitochondrial benzodiazepine receptors-6-Arylpyrrolo2,1-D1,5benzothiazepine derivatives- Synthesis, structure-activity-relationships, and molecular modeling studies *J. Med. Chem.*.**1994**, 37, 1427-1438.
36. G. Greco, E. Novellino, I. Fiorini et.al. A comparative molecular-field analysis model for 6-Arylpyrrolo2,1-d1,5benzothiazepines binding selectively to the mitochondrial benzodiazepine receptor *J. Med. Chem.* **1994**, 37, 4100-4108.
37. S. M. Ford,S. Roach Lippincott's Introductory Clinical Pharmacology-1, Lippincott Williams and Wilkins. 2008, 253-263.
38. N.Garg, T. Chandra, A. Jain, A. B. Kumar. Synthesis and evaluation of some new substituted benzothiazepine and benzoxazepine derivatives as anticonvulsant agents. *Eur. J. Med. Chem.* **2010**, 45, 1529-1535.
39. G. D. Sarro, A. Chimirri, A. D. Sarro, R. Gitto, S. Grasso,M. Zappalh. 5H-1,2,4Oxadiazolo5,4-d 1,5benzothiazepines as anticonvulsant agents in DBA/2 mice. *Eur. J. Med. Chem.* **1995**, 30, 925 929.
40.X. Q. Deng,M. X. Song, S. B. Wang and Z. S. Quan. Synthesis and evaluation of the anticonvulsant activity of 8-alkoxy-4,5-dihydrobenzob1,2,4triazolo4,3-d1,4thiazepine derivatives. *J Enzyme Inhib Med Chem*. **2014**, 29(2), 272–280.
41. S. M. Ford, S.Roach Lippincott's Introductory Clinical Pharmacology-1, Lippincott Williams and Wilkins.**2008**, 281-293.
42. D. Vyawahare, M. Ghodke and A. P. Nikalje. Green synthesis and pharmacological screening of novel 1,5-benzothiazepines as CNS agents. *Int. J. Pharmacy Pharmaceutical Sci.* **2010**, 2, 27-29.
43. A. P. Nikalje, D. Vyawahare. Facile green synthesis of 2, 4-substituted -2, 3-dihydro-1, 5 benzothiazepine derivatives as novel anticonvulsant and central nervous system (CNS) depressant agents. *African J. Pure Appl. Chem*. **2011**, 5, 422-428.
44. S. M. Ford, S. Roach. Lippincott's Introductory Clinical Pharmacology-1. **2008**, 304-309.
45. F. L. Ansari, S. Kalsoom, Z. U. Haq, Z. F. Ali, Jabeen. In silico studies on 2,3-dihydro-1,5-benzothiazepines as cholinesterase inhibitors. *Medicinal Chemistry Research*. **2011**, DOI 10.1007/s00044-011-9754-6.
46.R. Parthasarati.Pyridoindolobenzox- and thiazepine derivatives and uses thereof US patent. **2011**, US2011/0003840A1.
47. M. Guerrero, M. Urbano, M. T. Schaeffer, S. Brown, H. Rosen, E. Roberts. SAR analysis of novel non-peptidic NPBWR1 (GPR7) antagonists. *Bioorg. Med. Chem. Lett*. **2013**, 23, 614–619.
48.E. Genton, H. J. Barnett,W. S. Fields,M. Gent, J. C. Hoak, Cerebral ischemia: the role of thrombosis and of antithrombotic therapy. Study group on antithrombotic therapy. *Stroke*. **1977**, 8, 150-175.
49. J.F. Mustard, M. A. Packham, R. L. Kinlouthbone. Platelets and thrombosis in the development of atherosclerosis and its complications. *Advances in Experimental Medicine and Biology*, **1978**,102, 7-30.
50. P. Mehta, J. Mehta, N. Ostrowski, L. J. Brigmon. Inhibitory effects of diltiazem on platelet activation caused by ionophore A 23187 plus ADP or epinephrine in subthreshold concentrations. *J. Lab. Clin. Med.* **1983**, 102, 332-339.
51. H. Ono, M. Kimura. Effect of Ca^{2+}-antagonistic vasodilators, diltiazem, nifedipine, perhexiline and verapamil, on platelet aggregation in vitro *Arzneim Forsch (Drug Res)*. **1981**, 31, 1131-1134.
52. A. Odawara, M. Katoh, T. Karasawa, et. al. Inhibitory effect of clentiazem (ta-3090) on platelet-aggregation - alone and in combination with aspirin or ticlopidine. *Thrombosis Res.* **1994**, 75, 109-119.
53.A. Odawara, K. Kikkawa, M. Katoh, et.al. Inhibitory effects of TA-993, a new 1,5-benzothiazepine derivative, on platelet-aggregation. *Circulation Research*.**1996**, 78, 643-649.
54. H. Inoue, M. Konda, T. Hashiyama, H. Otsuka, A. Watanabe, M. Gaino,K. Takahashi, T. Date, Okamura, M. Takeda, H. Narita, S. Murata, A. Odawara, H. Sasaki, T. Nagao. Synthesis and biological evaluation of alkyl, alkoxy, alkylthio, or amino-substituted 2,3-dihydro-1,5-benzothiazepin-4(5H)-one. *Chem. Pharma. Bull*. **1997**, 45, 1008-1026.
55.X. F. Hea, Y. Nakajimaa, T. Sumizawaa, et.al. Reversal of p-glycoprotein mediated multidrug resistance by a newly synthesized 1,4-benzothiazipine derivative, JTV-519. *Cancer Lett.*. **2002**, 187, 111–119.
56. K. L. Ameta, N. S. Rathore B. Kumar. Synthesis and in vitro anti breast cancer activity of some novel 1, 5-benzothiazepine derivatives. *J. Serb. Chem. Soc*., **2012**, 77, 725-731.
57. K. Arya, A. Dandia. The expedient synthesis of 1,5-benzothiazepines as a family of cytotoxic drugs. *Bioorg. Med. Chem. Lett.*. **2008**, 18, 114–119.
58. F. L. Ansari, F. Iftikhar, I. U. Haq et.al. Solid-phase synthesis and biological evaluation of a parallel library of 2,3-dihydro-1,5-benzothiazepine. *Bioorg. Med. Chem.* **2008**, 16, 7691-7697.
59.S. Yenupuri, A. Venkata, L. N. S .H. Hariharan, B. K. Bugataand, D. L. S. Nori. Microwave assisted synthesis.and biological evaluation of a series of.1,5-benzothiazepines as potential cytotoxic and antimicrobial agents. *European Journal of Chemistry*. **2014**, 5, 138-143.
60.P.Zhang, H. R.Hub,S. H. Bian, Z. H. Huang, Y. Chu, D. Y.Ye. Design, synthesis and biological evaluation of benzothiazepinones (BTZs) as novel non-ATP competitive inhibitors of glycogen synthase kinase-3β (GSK-3β). *European Journal of Medicinal Chemistry*. **2013**,61, 95-103.

61. A F. Donnell, H. Xiaochun, K. R. Francis, etal. Substituted hetero-azepinones.2014 WO patent WO2014/023708A1.
62. R. R.Kamble B. S.Sudha Synthesis and pharmacological evaluation of 1,5-benzothiazepine derivatives *Phosphorus, Sulfur, and Silicon*, **2008**, 183, 1691-1709.
63.D. Sharma, B. Narasimhan, P. Kumar et.al. Synthesis, antimicrobial and antiviral evaluation of substituted imidazole derivatives. *Eur. J. Med. Chem.* **2009**, 44, 2347–2353.
64.L.Wang, P. Zhang, X. Zhang,Y. Zhang, Y. Li, Y. Wang. Synthesis and biological evaluation of a novel series of 1,5-benzothiazepine derivatives as potential antimicrobial agents. *Eur. J. Med. Chem.* **2009**, 44, 2815-2821.
65.A. J. Khan,M. A. Baseer, J. M. Dhole, S. Shah. Synthesis, experimental studies of the antimicrobial potential of some novel 1, 5- benzothiazepine derivative. *Int. J. pharma. Sci. Res.*, **2011**, 2, 2619-2622.
66. K. Bockstael, A.V. Aerschot. Antimicrobial resistance in bacteria. *Central European Journal of Medicines*. **2009**,4, 141-155.
67. S. Pant, P. Sharma, U.C. Pant. Syntheses and antimicrobial evaluation of 2-(2- Chlorophenyl)-4-(4-chlorophenyl/2-thienyl)-2,5-dihydro-8-substituted-1,5-benzothiazepines. *Phosph., Sulf., Silicon* **2008**, 183, 2974-2983.
68.Zhang P., Wang L. Z., Wu H. S., Lan J. M., Li Y., Wang Y. X. The synthesis and biological evaluation of a series of novel 2-$COOC_2H_5$/COONa substituted 1,5-benzothiazepine derivatives as antimicrobial agents. *Chinese Chemical Letters*. **2009**, 20, 660-662.
69. A.Dandia, R.Singh, R. Sharma, D. Singh. Investigation of the Reaction of Chloroacetyl Chloride with 1,5-Benzothiazepines: Selective Synthesis of Azeto2,1-d1,5benzothiazepines by green chemical methods and their biological activity. *Phosphorus, Sulfur Silicon*. **2008**,183, 3116-3126.
70.Saini R. K., Joshi Y. C. and Joshi P.Solvent-free synthesis of some 1,5-benzothiazepines and benzodiazepines and their antibacterial activity. *Phosphorus, Sulfur, Silicon*, **2008**, 183 2181-2190.
71.Ambrogi V., Grandolini G., Perioli L., Ricci M., Rossi C., Tuttobello L. Synthesis, antibacterial and antifungal activities of several new benzo-naphtho- and quinolino-1,4-thiazine and 1,5-thiazepine derivatives. *Eur. J. Med. Chem.***1990**, 25, 403-411.
72.V. K. Tandon, H. K. Maurya, N. N. Mishra, P. K. Shukla. Design, synthesis and biological evaluation of novel nitrogen and sulfur containing hetero-1, 4-naphthoquinones as potent antifungal and antibacterial agents. *Eur. J. Med. Chem* **2009**, 44, 3130-3137.
73. A. Dandia, R. Singh, D. Singh, A. Laxkar and A. Sivpuri Regioselective Synthesis of Diltiazem Analogue Pyrazolo4,3-c1,5benzothiazepines and antifungal activity. *Phosphorus, Sulfur, Silicon*.**2010**, 185, 2472-2479.
74. C.S. Reddy, G.P. Reddy, A. Nagaraj. Synthesis and In-vitro study of novel methylenebis(phenyl- 1,5-benzothiazepine)s and methylene bis(benzofuryl-1,5-benzothiazepine)s as antimicrobial agents. *Chinese Journal of Chemistry*. **2009**, 27.
75. A. K.Sharma, G. Singh, A. K. Yadav and L. Prakash. Improved method for the synthesis of new 1,5-benzothiazepine derivatives as analogues of anticancer drugs. *Molecules*, **1997**, 2,129-134.
76. A.Dandia, R. Singh, S. Khaturia. Efficient microwave enhanced solvent-free synthesis of potent antifungal agents: Fluorinated benzothiazepine fused β-lactam derivatives. *J. Fluorine Chem.* **2007**,128, 524-529.
77.M. Kumar, K. Sharma, A.K. Fogla, K. Sharma, M. Rathore. Synthesis and antimicrobial activity of 2,4-diaryl-2,3-dihydrobenzob1,4thiazepines. *Res Chem Intermed*. **2013**, 39, 2555–2564.
78. J. Singh, B.S. Chhikara. Comparative global epidemiology of HIV infections and status of current progress in treatment. *Chem. Biol. Lett.*, **2014**, 1(1), 14-32.
79. R.D. Santo, C. Roberta.2H-Pyrrolo3,4-b 1,5benzothiazepine derivatives as potential inhibitors of HIV-1 reverse transcriptase. II *Farmaco*. **2005**, 60, 385-392.
80. N. Neamati, J.A. Turpin, H.E.Winslow et.al. Thiazolothiazepine Inhibitors of HIV-1 Integrase. *J. Med. Chem.* **1999**, 42, 3334-3341.
81. S.M. Ford, S. Roach Lippincott's Introductory Clinical Pharmacology-1, Lippincott Williams and Wilkins, **2008**, 108-115.
82. A. Dandia, M. Sati, K. Arya, R.Sharma and A. Loupy. Facile one pot microwave induced solvent-free synthesis and antifungal, antitubercular screening of spiro 1, 5-benzothiazepin-2, 3'3'H indol-2 1'H-ones. *Chemical & Pharmaceutical Bulletin*. **2003**, 51,1137-1141.
83. E. Ayral, E. Gloanec, P. Berge et.a;. Design, synthesis, and biological evaluation of 1,5-benzothiazepine-4-one derivatives targeting factor VIIa/tissue factor. *Bioorg. Med. Chem. Lett*. **2009**, 19, 1386-1391.
84. L. Jafri, L. Ansari, F.L. Jamil, M. Kalsoom, S. Qureishi, S. Mirza, Bushra. Microwave-assisted synthesis and bioevaluation of some semicarbazones. *Chemical Biology & Drug Design*. **2012**, 79, 950-959.
85. M.J. Urbanski, R.H. Chen, K.T. Demarest et.al. 2,5-Disubstituted 3,4-dihydro-2H-benzob1,4thiazepines as potent and selective V_2arginine vasopressinreceptor antagonists. *Bioorg. Med. Chem. Lett*. **2003**, 13, 4031-4034.
86. L.E. Andersona, A.M. Dringa, L.D. Hamela, M.A. Stonera. Modulation of constitutive androstane receptor (CAR) and pregnane X receptor (PXR) by 6-arylpyrrolo2,1-d1,5benzothiazepine derivatives, ligands of peripheral benzodiazepine receptor (PBR). *Toxicology Letters*. **2011**, 202, 148–154.
87. Z. Ul-Haq, W. Khan, S. Kalsoomand, F.L. Ansari.In silico modeling of the specific inhibitory potential of thiophene-2,3-dihydro-1,5-benzothiazepine against BChE in the formation of beta-amyloid plaques associated with Alzheimer's disease. *Theoretical Biol. Med. Modelling*. **2010**, 7, 22.
88. A.U. Khana, N. Malika, M. Alamb, D.U. Lee. Ultrasound-assisted synthesis of benzothiazepines and assessment of their in vitro acetylcholinesterase inhibition activity. *Green Chemistry Letters and Reviews*. **2014**, 7, 158–166.
89. S. Butini, S. Gemma, M. Brindisi et.al. Non-Nucleoside Inhibitors of Human Adenosine Kinase: Synthesis, Molecular Modeling, and Biological Studies. *J. Med. Chem.* **2011**, 54, 401–1420.
90. P. Zhang, H.R. Hub, Z.H. Huang, J.Y. Lei, Y. Chu, D. Y.Ye. Identification of novel scaffold of benzothiazepinones as non-ATP competitive glycogen synthase kinase-3β inhibitors through virtual screening. *Bioorg. Med. Chem. Lett*. **2012**, 22, 7232–7236.
91.M. Parthasarathy, C. Suresh kumar, S. Dhivya, S. Narasimhan. Virtual screening and evaluation of heterocyclic 1, 5-benzothiazepines compounds against MAP kinase protein *J. Pharmacy Research* **2013**, 6, 84-87.
92. M. Karikomi, M. D'hooghe, G. Verniest and N. De Kimpe. Regio- and stereocontrolled synthesis of novel 3-sulfonamido-2,3,4,5-tetrahydro-1,5-benzothiazepines from 2-(bromomethyl)- or 2-(sulfonyloxymethyl)aziridines. *Org. Biomol. Chem.* **2008**, 6, 1902-1904.
93.T. Masquelin, and D. Obrecht. A Novel Access to 2, 4-Substituted Quinolines from Acetylenic Ketones. *Tetrahedron*, **1997**, 53(2), 641.
94. O. Prakash, A. Kumar, A. Sadana et.al. Study of the reaction of chalcone analogs of dehydroacetic acid and o-aminothiophenol: synthesis and structure of 1,5-benzothiazepines and 1,4-benzothiazines. *Tetrahedron*. **2005**,61, 6642-6651.
95. J. Krapcho, C. F.Turk. Substituted 2,3-Dihydro-1,5-benzothiazepin-4(5H)-one and Related Compounds. II. A New Class of Antidepressants. *J. Med. Chem*. **1966**, 9(2), 191-195.
96. A.K. Gupta, and U. C. Pant. *Ind. J. Chem*. **l980**, 20B, l57.
97. H. Junjappa, H. Ila, and C. V Asokan. α-Oxoketene-S,S-, N,S- and N,N-acetals: Versatile intermediates in organic synthesis. *Tetrahedron* **1990**, 46(16), 5423-5506.