ISSN 2231-0541

PHARMANEST

An International Journal of Advances in Pharmaceutical Sciences

Volume 4 | Issue 1 | January-February 2013 | Pages 84-93

Review Article

BENZOTHIAZOLE - A POTENT PHARMACOPHORE IN MEDICINAL CHEMISTRY: A REVIEW

[a]DESH DEEPAK PANDEY, [b]DILIPKUMAR PAL*

[a] Lucknow Institute of Pharmacy, Gosaiganj, Lucknow-227125, U.P., India

[b]Department of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya, Koni, Bilaspur-495 009, Chhatrisgarh, India

Author for Correspondence: drdilip2003@yahoo.co.in

Received: 11-02-2013 Revised: 16-02-2013

Accepted: 22-02-2013 Available online: 01-03-2013

ABSTRACT

Benzoheterocycles such as benzothiazoles, benzimidazoles and benzoxazoles can serve as unique and versatile scaffolds for experimental drug design. Among the all Benzoheterocycles, benzothiazole has considerable place in research area especially in synthetic as well as in pharmaceutical chemistry because of its potent and significant pharmacological activities. Since, a wide range of methods are available for synthesizing benzothiazole nucleus and its derivatives but a real need exists for new procedures that support many kinds of structural diversity and various substitution. The present review deals with the common methods adopted and reported to focus the synthesis as well as cyclisation of benzothiazole nucleus.

Key Words: Benzoheterocycles, Benzothiazole, Cyclization

INTRODUCTION

Benzothiazole is an important class of hetrocyclic compound that exhibit a wide range of biological properties such as antimicrobial, anticonvulsant, antitumor, antibiotic, antidepressant, anti-inflammatory, analgesic, antifungal, antitubercular and diuretic activities. Literature survey reveals that benzothiazole ring is present in various marine or terrestrial natural compounds which have useful biological activities[20-23] . Series of benzothiazole derivatives need to be prepared to improve the above properties [25]. It is a very important pharmacophore in drug discovery and its derivatives have significant activity against several viruses and have been demonstrated to be potent ant-parasitic agent, anti-tumor agents and inhibitors of hepatitis C virus RNA polymerase.

STRUCTURE AND PREPARATION

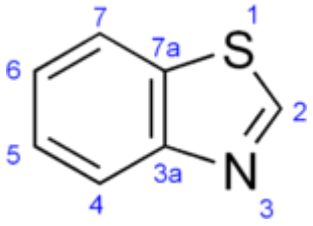


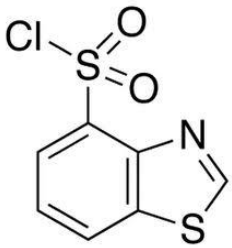
Fig.1.Structure of 1,3-Benzothiazole

Benzothiazoles consist of a 5-membered 1,3-thiazole ring fused to a benzene ring. The eight atoms of the bicycle and the attached substituents are coplanar [1].

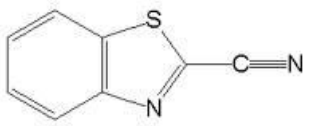
Benzothiazole are prepared by treatment of 2-aminobenzenethiol with acid chlorides.

$C_6H_4(NH_2)SH + RC(O)Cl \rightarrow C_6H_4(NH)SCR + HCl + H_2O$

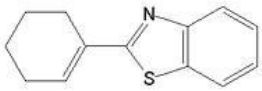
SAR:



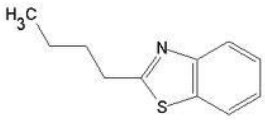
Benzothiazole-4-sulphonylchloride



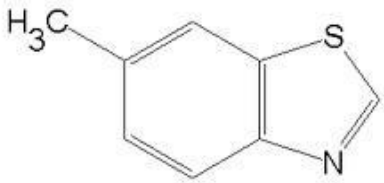
1,3 Benzothiazole-2carbonitrile



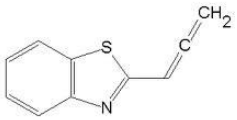
1-Cyclohexenylbenzothiazole



2-Butyl-1,3benzothiazole

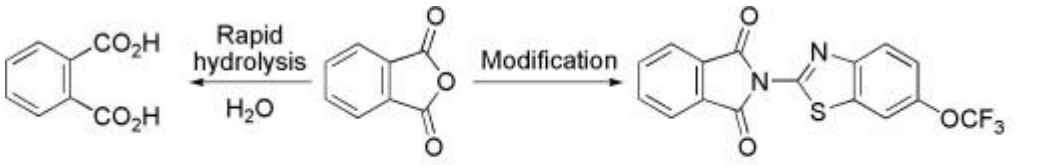


6-Methyl-1,3benzothiazole



Propa-1,2dienylbenzothiazole

1) Phthalic anhydride is a highly toxic substance, facing, however, the problem of hydrolysis. In fact, it is rapidly hydrolyzed in aqueous medium, generating phthalic acid as the final product, which is almost harmless to viable cells. Here we describe the 'one pot' condensation reaction for the synthesis of phthalic imide derivative (benzothiazole containing phthalimide), exhibiting in vitro cytotoxic potential on human cancer cell lines[8]. We further demonstrated that both caspase-dependent and -independent pathways are involved in our novel benzothiazole containing phthalimide induced apoptosis on cancer cells.



Non-cytotoxic | Cytotoxic | Cytotoxic towards human cancer cells lines with 50% inhibition 69μM(25μg/mL)

2) Condensation of *o*-aminothiophenol with aldehydes : Treatment of o-aminothiophenols with substituted aldehydes affords the synthesis of 2-substituted benzothiazoles using different catalysts and reaction conditions

Aldehydes Catalysts (a-f)

a.Montmorillonite,SiO2/Graphite; Microwave, p-TsOH

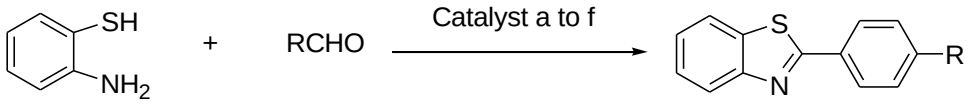
b.Diethyl bromophosphonate/*tert*-Butyl hypochlorite; acetonitrile

c.Cerium (IV) ammonium nitrate

d.H2O2/HCl system in ethanol

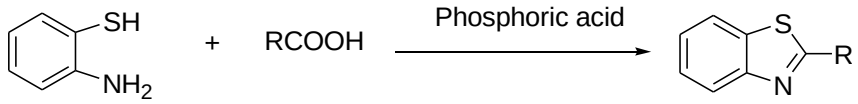
e.AcOH/Air; Microwave/ Thermal Heating

f.Baker's yeast, Dichloro methane



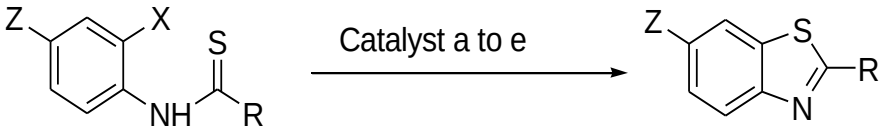
Condensation of o-aminothiophenol with aldehydes

3) Condensation of *o*-aminothiophenol with acids : Treatment of 2-aminothiophenol and substituted aromatic acids in presence of Polyphosphoric acid provides a good method to synthesize 2-substituted benzothiazoles and gives a good yield[5]



Condensation of o-aminothiophenol with acids

4) Cyclization of thioformanilides using different reagents: Substituted thioformanilides can be converted to 2-aminobenzothiazoles *via* intramolecular C-S bond formation/C-H functionalization utilizing various reagents and catalysts[6].



Cyclization of thioformanilides using detergent reagents

Cyclization of thioformanilides using different reagents

Catalysts (a-e):

a. CuI; 1, 10-Phenanthroline, CS2CO3, reflux 18

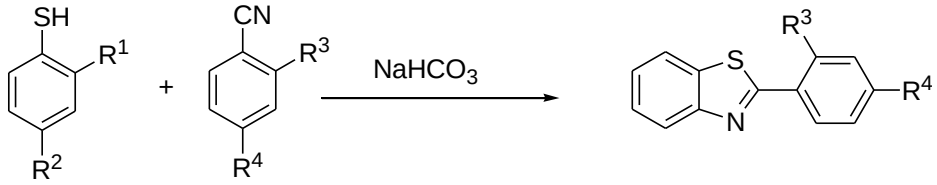
b. Manganese triacetate 20

c. CS2CO3, Dioxane 21

d. Photochemical cyclization induced by chloranil 19

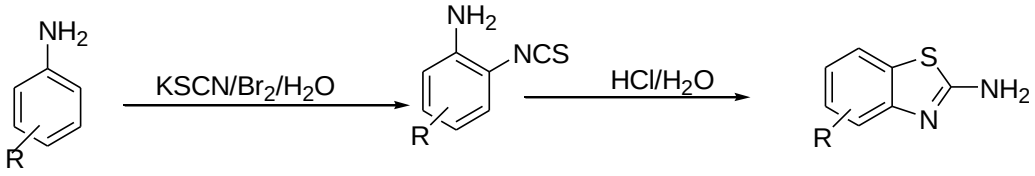
e. Pd(PPh3)4/MnO2 system under an oxygen atmosphere

5) Coupling between thiophenols and aromatic nitriles: Thiophenols when treated with aromatic nitriles to affords a smooth reaction mediated by Ceric ammonium nitrate to give corresponding 2-arylbenzothiazoles in excellent yield[8]



Coupling between thiophenols and aromatic nitriles

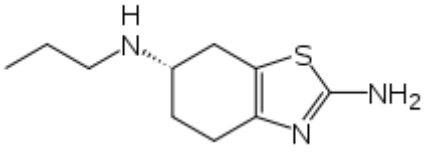
6) Synthesis using anilines: Different substituted anilines when treated with KSCN in presence of glacial acetic acid to synthesize 2-substituted benzothiazoles [10]



Synthesis using anilines

IMPORTANT BENZOTHIAZOLE BASED DRUGS: Pramipexole, Riluzole

PRAMIPEXOLE



(*S*)-*N*^{6}-propyl-4, 5, 6, 7-tetrahydro-1,3-benzothiazole-2,6-diamine

Pramipexole **(**Mirapex**,** Mirapexin**,** Sifrol**)** is a non-ergoline dopamine agonist indicated for treating early-stage Parkinson's disease (PD) and restless legs syndrome (RLS). It is also sometimes used off-label as a treatment for cluster headache and to counteract the problems with sexual dysfunction experienced by some users of the selective serotonin reuptake inhibitor (SSRI) antidepressants. Pramipexole has shown robust effects on pilot studies in a placebo-controlled proof of concept study in bipolar disorder. It is also being investigated for the treatment of clinical depression and fibromyalgia [4-6].

Pramipexole acts as a partial/full agonist at the following receptors:

- D_{2S} receptor (K_i = 3.9 nM; IA = 130%)
- D_{2L} receptor (K_i = 2.2 nM; IA = 70%)
- D_3 receptor (K_i = 0.5 nM; IA = 70%)
- D_4 receptor (K_i = 5.1 nM; IA = 42%)

Pramipexole also possesses low/insignificant affinity (500-10,000 nM) for the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and α_2-adrenergic receptors.[7][9] It has negligible affinity (>10,000 nM) for the D_1, D_5, 5-HT_2, α_1-adrenergic, β-adrenergic, H_1, and mACh receptors. All sites assayed were done using human tissues. Parkinson's disease is a neurodegenerative disease affecting the substantia nigra, component of the basal ganglia. The substantia nigra has a high quantity of dopaminergic neurons, which are nerve cells that release the neurotransmitter known as dopamine.

When dopamine is released, it may activate dopamine receptors in the striatum, which is another component of the basal ganglia. When neurons of the substantia nigra deteriorate in Parkinson's disease, the striatum no longer properly receives dopamine signals. As a result, the basal ganglia can no longer regulate body movement effectively and motor function becomes impaired. By acting as an agonist for the D_2, D_3, and D_4 dopamine receptors, pramipexole may directly stimulate the under functioning dopamine receptors in the striatum, thereby restoring the dopamine signals needed for proper functioning of the basal ganglia[7-10].

SIDE EFFECTS

Common side effects of pramipexole may include: [11]

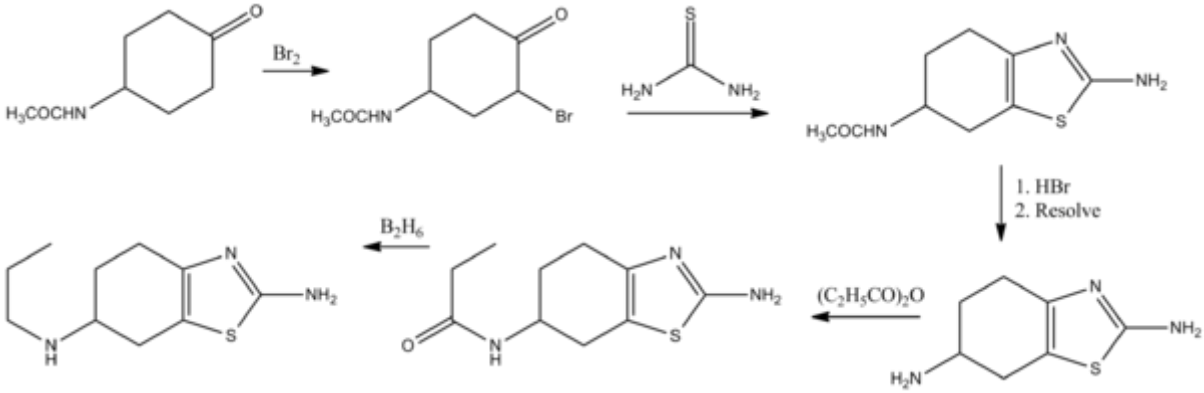
- Headache
- Hyperalgesia (body aches and pains)
- Nausea and vomiting
- Sedation and somnolence
- Decreased appetite and subsequent weight loss
- Orthostatic hypotension
- Insomnia
- Hallucinations
- Twitching, twisting, or other unusual body movements
- Unusual tiredness or weakness

Several unusual adverse effects of pramipexole (and related D_3-preferring

dopamine agonist medications such as ropinirole) may include compulsive gambling, hypersexuality, and overeating, even in patients without any prior history of these behaviours. These behaviors have been reported to manifest in almost 14% of patients on DA agonist therapies. Other compulsive behaviors, such as excessive shopping and compulsive cross-dressing, have been reported. L-DOPA is an indirect acting DA agonist with no specificity for any receptor subtypes. As it is the precursor for dopamine it is rarely associated with these disorders. These side effects are thought to be linked to the D_3 activity of pramipexole, as D_3 receptors are heavily expressed in brain regions involved in mood, behavior, and reward [12-13].

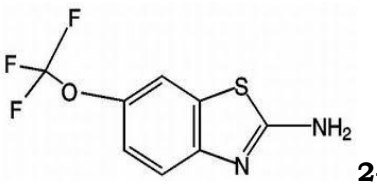
CHEMISTRY

Pramiprexole can be synthesized from a cyclohexanone derivative by the following route [14-15]:



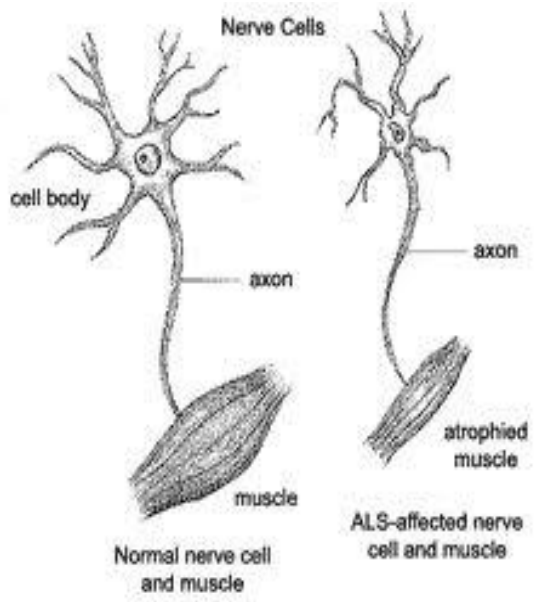
RILUZOLE : A benzothiazole derivative with neuroprotective and potential anti-depressant and anxiolytic activities. While the mechanism of action of riluzole is unknown, its pharmacological activities in motor neurons include the following, some of which may be related to its effect: 1) an inhibitory effect on glutamate release, 2) inactivation of voltage-dependent sodium channels, and 3) interference with intracellular events that follow transmitter binding at excitatory amino acid receptors.

In animal models, this agent has been shown to exhibit myorelaxant and sedative activities, apparently due to the blockade of glutamatergic neurotransmissin. Check for active clinical trials or closed clinical trials using this agent. (NCI Thesaurus) [16]



2-amino-6-(trifluoromethoxy)benzothiazole

IMPORTANCE OF BENZOTHIAZOLE NUCLEUS IN MEDICINAL CHEMISTRY: The small and simple benzothiazole nucleus is present in compounds involved in research aimed at evaluating new products that possess interesting biological activities like- antitumour, antimicrobial, antitubercular, antimalarial, anticonvulsant, anthelmintic,analgesic and anti-inflammatory activity[17-18]. The benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological activities. Heterocycles containing the thiazole moiety are present in many natural products such as bleomycin, epothilone A, lyngbyabellin A & dolastatin Benzothiazole is a privileged bicyclic ring system. Due to their important pharmaceutical utilities, the synthesis of these compounds is of considerable interests.[30]



Effect of riluzole on neurons

CHEMISTRY OF BENZOTHIAZOLE NUCLEUS: Being a heterocyclic compound, benzothiazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures[31]. Its aromaticity makes it relatively stable, although as a heterocycle, it has reactive sites, which allow for functionalization. Benzothiazole is a colorless, slightly viscous liquid with a melting point of 2°C, and a boiling point of 227-228 °C. The density of benzothiazole is 1.644 gm/ml, and molecular mass is 139.19 gmol. Benzothiazole has no household use. It is used in industry and research[32].

USES: This heterocyclic scaffold is readily substituted at the unique methyne centre in the thiazole ring. Its a thermally stable electron-withdrawing moiety with numerous applications in dyes such as thioflavin. Some drugs contain this group, an example being riluzole. The heterocycle is found in nature. Accelerators for the vulcanization of rubber are based on 2-mercaptobenzothiazole. This ring is a potential component in nonlinear optics (NLO). Benzothiazoles are related to thiazoles, which lack the fused benzene ring. Benzoxazoles, which substitute an oxygen for the sulfur atom[33].

CONCLUSION

The reviewed new class of 2-substituted aminobenzothiazoles has shown a wide spectrum of biological activities[34].
The substituted benzothiazolylimino

dithiazolidines and the 2-(2'-aryl-1,3, 4-oxadiazol-5-yl)mercaptomethyl benzothiazoles are having significant antibacterial activity. Significant antiinflammatory activity is displayed by some new 2-(4'-butyl-3'-5'dimethylpyrazol-1-yl)-6-substituted benzothiazoles and 4-butyl-1-(6'-substituted-2'-benzothiazolyl)-3-methylpyrazol-5-ones.

In search of new anticonvulsants[35], riluzole and benzothiazolylguanidines are found to have potent activity. Potent antitumor activity was demonstrated by a number of 2-(4-aminophenyl) benzothiazoles.

The 2-(4-acetamido-2-bromo-5-methylphenyl sulfonamide) benzothiazole is found to be effective as antituberculor agents, whereas ethoxazolamide and o-acyl derivatives of 6-hydroxybenzothiazole-2-sulfonamides are found to show the carbonic anhydrase inhibitory action[36]. The biological profiles of these new generations of benzothiazoles represent much progress with regard to the older compounds.

REFERENCES

1. Christopher LL, Moody J, Naturally occurring nitrogen sulphur compounds. The benzothiazole alkaloids, Aust J Chem 2008; 62 :639-47.
2. Engels HW, Weidenhaupt HJ, Pieroth M, Hofmann W, Menting KH, Chemicals and additive, Ullmann's encyclopedia of Indust.Chem 2004;12:1002.
3. Hrobarik P, Sigmundova I, Zahradnik P, Kasak P, Arion V, Franz E, Molecular engineering of benzothiazolium salts with large quadratic hyperpolarizabilities, J.Phy.Chem.2009;114:22289–302.
4. Debattista C, Solvason HB, Breen JA, Schatzberg AF, J. Clin Psychopharmacol.2000; 20 : 274–75.
5. Zarate CA, Payne JL, Singh J, Quiroz J, Pramipexole for bipolar II depression; a placebo-controlled proof of concept study. Biol psychiatry 2004; 56:54-60.
6. Lattanzi L, Dell'Osso L, Cassano P, Pini S, Rucci P, Houck PR, et al. Pramipexole in treatment- resistant depression: a 16-week naturalistic study. Bipolar Disord. J Clin Psychopharmacol.2002; 4 : 307–14.
7. Cassano P, Lattanzi L, Soldani F, Navari S, Battistini G, Gemignani A, Cassano GB. Pramipexole in treatment-resistant depression: an extended follow-up Depress anxiety, J. Clin Psychopharmacol, 2004; 20 (3): 131–38.
8. Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of pramipexole, arthritis rheum, J. Clin Psychopharmacol, 2005; 52 (8): 2495–2505.
9. Kvernmo T, Härtter S, Burger E, A review of the receptor-binding and pharmacokinetic properties of dopamine agonists, Clinical therapeutics, J. Clin Psychopharmacol,2006, 28 (8): 1065–78.
10. Millan MJ, Maiofiss L, Cussac D, Audinot V, Boutin JA, et al. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. J. Pharmacol. and experimental Therap,2002, 303 (2); 791–804.
11. Millan MJ, Maiofiss L, Cussac D, Audinot V, Boutin JA, NewmanT, Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor, J.Biol.Chem 2002; 303 : 815–22.
12. Wolters E, Vander W, Vanden H, Parkinson's disease-related disorders in the impulsive-compulsive spectrum. J. Neurol. 2008, 5:48-56.
13. Bostwick JM, Hecksel KA, Stevens SR, Bower JH, et.al. Frequency of new-onset pathologic compulsive gambling or hypersexuality after drug treatment of idiopathic Parkinson

disease. J. Clin Psychopharmacol. 2009, 84:310-6.
14. Dodd ML, Klos KJ, Bower JH, Geda YE, Josephs KA, Pathological gambling caused by drugs used to treat Parkinson disease. Arch. Neurol.2005, 62 :1377–81.
15. Schneider, Claus S.; Mierau, Joachim Dopamine autoreceptor agonists: resolution and pharmacological activity of 2,6-diaminotetrahydrobenzothiazole and an aminothiazole analog of apomorphine. J. Med. Chem. 1987; 30 : 494–8.
16. Gunawardana GP, Kohmoto S, Unesakara S.P.G, Connel OJ,Alkaloid:chemical and biological prospective, J. Am. Chem. Soc., 1988,10: 4856-58.
17. Gunawardana GP, Kohmoto S, New cytotoxic acridine alkaloids from two deep water marine sponges of the family, Tetrahedron letter,1989, 30: 4359-62.
18. Demiryak S, Taha M, Synthesis of some 2-[(benzazole-2-yl)thioacetylamino]thiazole derivative and their antimicrobial activity and toxicity, Eur.J. Med. Chem, 2004, 39: 267-72.
19. Carol AR, Scheurer PJ, Synthesis and biological evaluation of benzothiazole J. of Org.Chem. 1990, 55: 4426-31.
20. Fajkusova D, Pazdera P, Unexpected formation of benzothiazole in the synthesis of new heterocycles:Benzo-1,2,4 dithiazine, J. Syn..Org.Chem.,2008 33, 1297-1305.
21. Bhusari KP, Amenerkar ND, Khedekar PB, Kele MK, Antimicrobial activity of of some benzothiazole derivatives . Asian J of Reasr Chem2010 ; 12 :53-58.
22. Patel NB, Agravat SN, Saudi J,synthesi and antimicrobial activity of some pyridine derivatives, chem. of heterocycle Comp 2006; 45 : 1343-53.
23. Mase T, arima H, Tomioka K,Pharmacological evaluation of benzothiazole derivatives Eur.J.of Pharm.Sci.1988; 23: 335-36.
24. Barchecath SD, Tawato R, Corr M, Carson DA, Benzothiazole salt as a potent inhibitor of apoptosis,Bioorg Med Chem Lett 2005;10:1785-88.
25. Guryn K, Zuiderveld R, Timmerman OP, Some benzothiazol derivatives have shown to be antagonist of histamine H3-Receptor. Eur J Pharm..Sci.,1999, 54, 684 -94.
26. Fridkin SK, Gaynes RP,Impact of fluconazole prophylaxis on cortisol level in critically III surgical patients, Antimicrob. agent and chemother 2004 ;20: 303 -16.
27. Oren IY, Isamail Y, Synthesis and structure activity relationship of new antimicrobial benzazole derivatives, Eur.J.of Med.Chem. 2004, 39, 291-98.
28. Bhusare SR, Pawar RP, Vibhute YP, Synthesis and antibacterial activity of some benzothiazole derivatives,Ind.J.of Het.Chem., 2001, 11, 79-80.
29. Patel NB, Agravat SN, Saudi J, Preperation of 2-aminobenzothiazole derivatives. Orient J Chem 2008;10:375.
30. Zitoni GT, Kapalancikili ZA,syntheis of 2-[1(4-pieronoyl)piperazinyl benzothiazole. Eur J Med Chem 2003; 39: 267-72.
31. Bhusari KP, Khedekar PB,A new profile of biological activity of benzothiazole Ind J of Het Chem 2000;9:257-78.
32. Racane L, TralicV, Pharmacological activity of benzothiazole. Ind J Het Chem 2001; 11:2085-98.
33. Jennings A, Stevens J. Synthesis antibacerial activity of benzothiazole derivatives, J Med Chem 2002; 45:745-746.
34. Rana A, Siddiqui N, Khan SA. Benzothiazoles: A new profile of biological activities. Indian J Pharm Sci 2007;69:10-17.
35. Pal DK,Sahoo M,Mishra AK,Analgesic and anticonvulsant effects of Saponin isolated from the Stems of Opuntia Vulgaris Mill in mice, Eur Bull Drug Res.2005,13,91-97.
36. Mazumder UK,Gupta M,Pal DK,Bhattacharya S,Induction of Carbonic anhydrase by cuscuta reflexaStem and Corchorus Olitorius Seed in mice,Indian J Pharm Sci,2003,65(4),401-403.