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A review on Indole and Benzothiazole derivatives its importance

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ABSTRACT

In recent years heterocyclic compounds analogues and derivatives have attracted wide attention due to their useful biological and pharmacological properties. Indole, Benzothiazole and its analogs are versatile substrates, which can be used for the synthesis of numerous heterocyclic compounds. Indole, Benzothiazole and its derivatives are used in organic synthesis and they are used in evaluating new product that possesses different biological activities. Hence, their extensive structural modification has result in different analogues of Indole and Benzothiazole derivatives depicting wide range of biological and pharmacological activities such as antiviral, anticonvulsant, anti-inflammatory, analgesic, antimicrobial and anticancer. This review article literature survey summarizes the synthesis and pharmacological activities of Indole, Benzothiazole and its derivatives.

Keywords: Indole, Benzothiazole, antiviral, anticonvulsant, anti-inflammatory, analgesic, antimicrobial and anticancer

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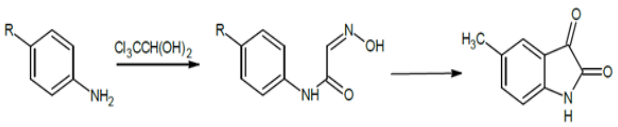
1. INTRODUCTION

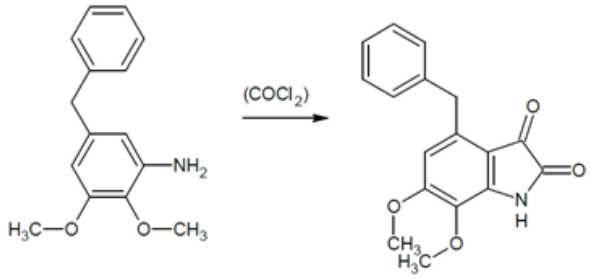
A number of heterocyclic derivatives containing nitrogen and sulphur atom serve as a unique and versatile scaffolds for experimental drug design. Isatin (1H-indolin-2,3-dione) [1-3], is an endogenous Indole molecule found in human (as a metabolite of adrenaline), which shows diverse pharmacological and biological activities. In 1840, Erdmann and Laurent discovered Isatin as product resulting from the oxidation of indigo dye by nitric acid and chromic acid.

Benzothiazole is one of the most important heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery [4]. Benzothiazole is a privileged bicyclic ring system. Benzothiazoles are fused member rings, which contain the heterocyclic bearing thiazole. Sulphur and nitrogen atoms constitute the core structure of thiazole and many pharmacologically and biologically active compounds. Thiazole is structurally related to thiophene and pyridine, but in most of its properties it resembles to the latter.

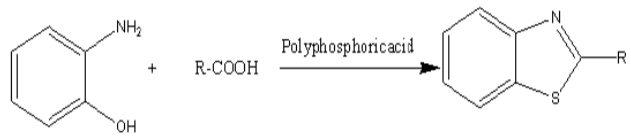
General methods for synthesis of Indole, Benzothiazole and its derivatives



Isonitrosoacetanilides have been synthesized from substituted anilines on reaction with chloral hydrate and hydroxyl amine hydrochloride. Substituted isonitroso acetanilides on subsequent reaction with sulphuric acid yielded corresponding indolin2, 3-diones [5-6]. The most important alternative to Sandmeyer synthesis is the method of Stolle. In this method anilines are reacted with oxalyl chloride to form an intermediate chlorooxalylanilide which can be cyclized in the presence of a lewis acid, usually aluminium chloride to give the corresponding Isatin [7].

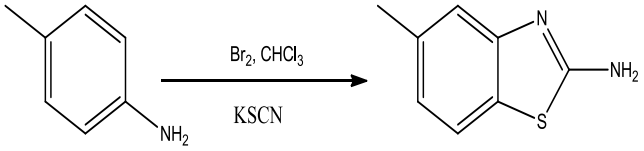


Condensation of o-aminophenol with acids: Treatment of 2-aminothiophenol and substituted aromatic acids in presence of Polyphosphoric acid provides a good method to synthesize 2- substituted benzothiazoles and gives a good yield [8].

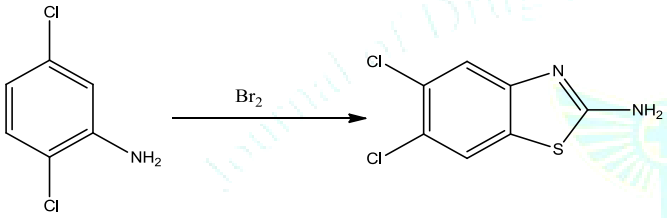


Synthesis of 2-substituted benzothiazole by using different type of catalysts: [9-10]

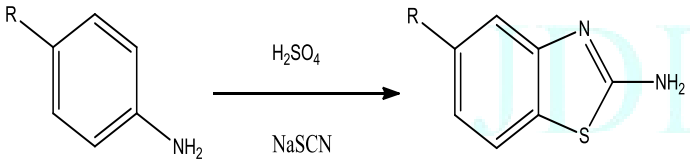
(i) Bromine as catalyst: Recently several methods reported which utilize bromine as catalyst. Basically cyclization with bromine achieved by oxidation of aniline, substituted aniline and arylthiourea in acid or chloroform with alkali thiocyanate. 2-aminobenzothiazole and found that an arylthiourea can be cyclized with liquid bromine in chloroform to form a 2- aminobenzothiaozles.



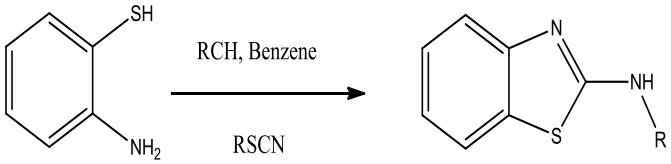
2-amino-5, 6-dichloro and 2- amino-6, 7-dichlorobenzothiazole by cyclization of suitable substituted aniline with help of thiocyanogen.



(ii) Sulphuric acid as a catalyst: Allen used sodium thiocyanate and cyclize p-substituted aniline into 2-amino-6-substituted benzothiazole in the presence of sulphuric acid which act as a catalyst.



(iii) Benzene as a catalyst: cyclizations of isothiocyanates to 2- aminobenzothiazole in presence of benzene.



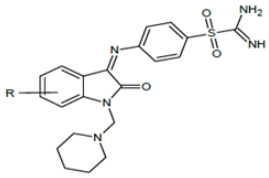
Pharmacological actives:

The main objective of present is to search for the potent compound for pharmacological activities with lesser adverse effects. Literature survey revealed that Indole and benzothiazole derivatives posses diverse biological activities. Various pharmacological activities are as follows:

Antimicrobial Activities:

U. K. Singh et al. [11] reported the synthesis of Schiff's and N-Mannich bases of isatin and its derivatives with 4-amino-N-carbamimidoyl benzene sulfonamide **(1)** and was tested for antibacterial activity by MIC method on strains: S. aureus, B. pumulis, B. subtilis, E. coli, S. abony, K. pneumoniae. All compounds exhibited very significant and better antibacterial activity.

Ramachandran *et al.* [12] reported the synthesis of schiff and mannich bases of Isatin derivatives **(2)** and were tested for antimicrobial activity by Cup-plate method on strains: like *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Klebsilla aerogenes, and Candida albicans*. Most of the compounds shown greater antibacterial and antifungal activities when compared with the standard drugs.



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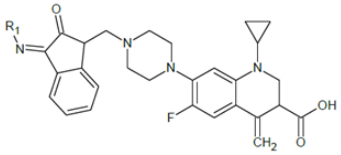


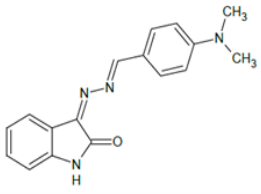
(2)

Antitubercular Activities

Sangamesh A. Patil *et al.* [13] reported the synthesis, biological evaluation Co (II), Ni (II),and Mn (II) metal complexes (1) of novel isatin schiff base ligand the complexes show activity against *Mycobacterium tuberculosis strain H37Rv.*

Sandeep K. Gupta *et al.*[14] reported the synthesis some thiobenzimidazolyl derivatives

(2). Most of them reported good antitubercular activity against *Mycobacterium tuberculosis.*



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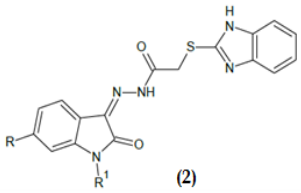
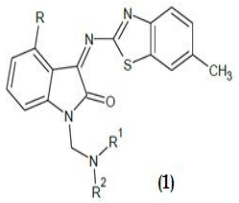


(2)

Anticancer activities

Hoyun Lee *et al.* [15] reported the hybrid pharmacophore design and synthesis of isatin benzothiazole analogs. All examined compounds (1) were quite effective on all the cancer cell lines examined. The compounds 4-bromo-1-diethylaminomethyl-1*H*-indole-2,3-dione and 4- chloro-1-dimethylaminomethyl-3-(6-methyl-benzothiazol-2-ylimino)-1,3-dihydroindol-2-one emerged as the most active compounds of this series.

Sarangapani Manda *et al.* [16] reported the synthesis of certain 3-{4-(5-mercapto-1, 3, 4-oxadiazole- 2- *yl*) phenylimino} indolin-2-one derivatives (2). All derivatives 15 were screened for anticancer activity against HeLa cancer cell lines using MTT assay.



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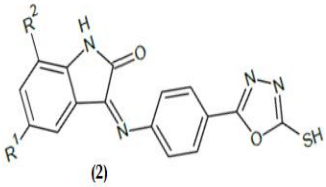


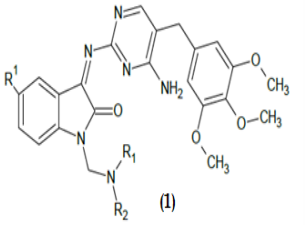
(2)

Anti HIV Activity

Dharmarajan Sriram *et al.* [17] reported the synthesis of aminopyrimidinimino isatin analogues Compound 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7[[*N*-4-[3'- (4'-amino 5'tri methoxy benzyl pyrimidin-2'-yl) imino- 1'-isatinyl] methyl]*N*-1-piperazinyl]-3-quinoline carboxylic acid (1) emerged as the most potent broad-spectrum chemotherapeutic agent active against HIV, HCV.

S. N. Pandey *et al.* [18] reported the synthesis of 1-[*N*, *N*-dimethylaminomethyl] isatin-3-[1'(6''- chlorobenzothiazol-2''-yl)] by reacting 3-[-1-(-6- chlorobenzothiazol-2-yl) thiosemicarbazone] and formalin with dimethylamine (2). The synthesized compounds were screened for anti-HIV activity at HIV-1(III B) in MT-4 cells.

Y. Teiltz *et al.* [19] reported synthesis of *N*-methyl isatin- β-4',4'-diethylthiosemicarbazone (3) and shown inhibition of HIV by their action on reverse transcriptase, viral structural proteins.



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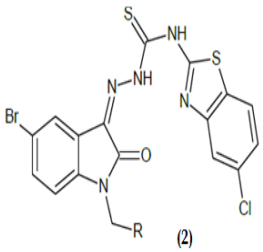

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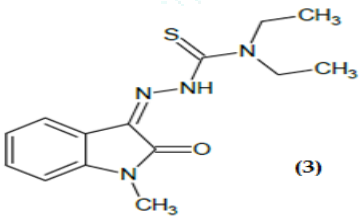
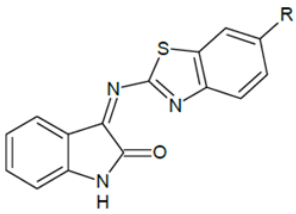


(3)

CNS depressant activity

Prince P Sharma *et al.* [20] reported the synthesis of some novel isatin schiff's bases (1). These compounds were screened for anticonvulsant activity.

Krishan Nand Singh *et al.* [21] had been synthesized (3*Z*)-5-bromo-1-methyl-3-[(4- nitrophenyl)imino]-1,3- dihydro-2*H*-indol-2-one by reacting 5-substituted *N*-methyl/*N*-acetyl isatin and aromatic amine (2) with glacial acetic acid and has shown to possess good anticonvulsant activity.



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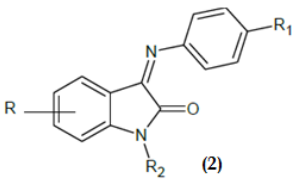
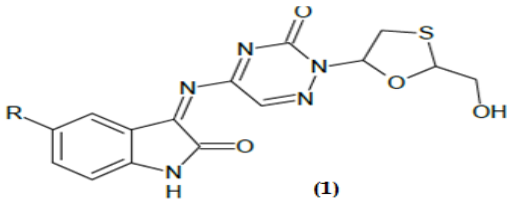


(2)

Antiviral activity

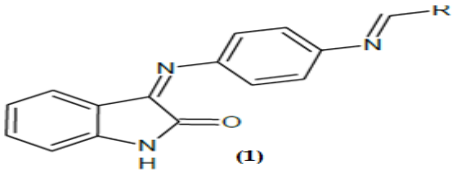
Sriram *et al.* [22] reported the synthesis of a novel series of lamivudine prodrugs involving N4- substitution with Isatin derivatives (1). The synthesized compounds showed *in-vitro* antiretroviral activities and one compound were found to be equipotent to lamivudine with EC50 OF 0.0742 ± 0.04 µM.



(1)

Antioxidant activity:

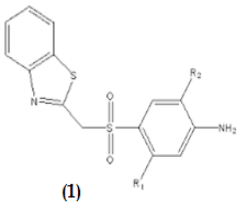
C.R. Prakash *et al.* [23] reported the synthesis of some novel isatin derivatives and analogs (1). These compounds were screened for antioxidant activity. In this method, the compound 3-(4-(4- dimethylaminobenzylideneamino) phenylimino) indoline-2-one showed highest antioxidant activity.



(1)

Anti tubercular and Anti diabetic activity

Bhusari KP *et al.* [24] reported Some 4-Amino-N-(1,3-benzothiazol-2-yl) benzenesulphonamide derivatives(1) were prepared and found to have good *in-vitro* Antimycobacterial activity (A) against *H37Rv* strain of *mycobacterium tuberculosis* and other derivatives (B) and (C) were also found active as antibacterial and antifungal agents. Pattan S *et al.* [25] reported Synthesized 2-amino [5 (4-sulphonylbenzylidine)-2,4- thiazolidnedione] - 7 – chloro – 6 - flurobenzothiazole series (2) and screened for their antidiabetic activity on albino rat by alloxan induced tail tipping method.



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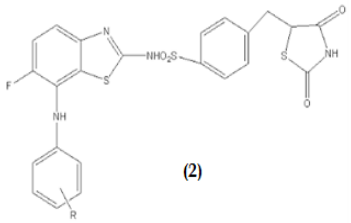
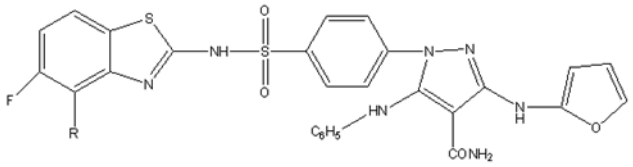


(2)

Anthelmentic activity

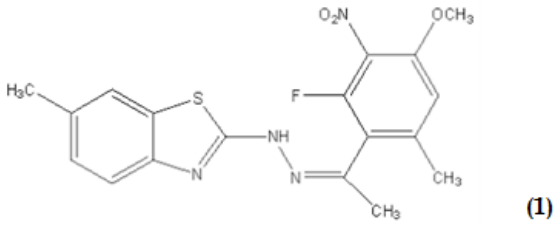
Sreenivasa M *et al.* [26] reported Flurobenzothiazole comprising sulfonamide pyrazole derivatives (1). They screened synthesized for anthelmentic activity by using earthworms (Peritumaposthum). Albendazole was used as standard drug. The compounds were evaluated by time taken for complete paralysis and death of worms.



(1)

Antibacterial and antifungal activity

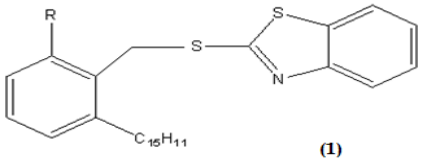
Alang G *et al.* [25] reported Some 2- substituted benzothiazoles (1) is examined against E. coli and S. aureus for antibacterial activity and Candida albicins and Aspergillus Niger for antifungal activity. Most of the compounds showed promising results for both activitity.



(1)

Cyclooxygenase inhibitor activity

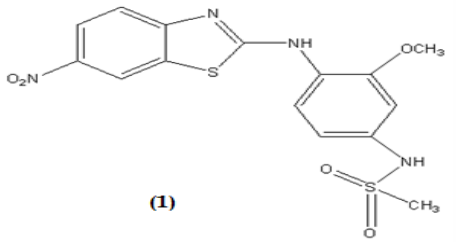
Paramashivappa R et al. [28] reported A series of 2-[(2- alkoxy-6-pentadecylphenyl) methyl] thio-1-Hbenzimidazoles/ benzothiazole from anacardic acid (pentadecyl salicylic acid) (1) and investigated their ability to inhibit human cyclooxygenase enzyme-2.



(1)

Antimalarial activity

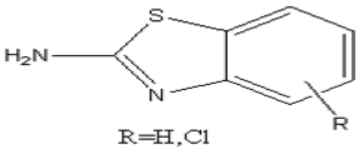
Hout S et al. [29] reported Antimalarial activity of 2-substituted-6- nitro and 6-amino benzothiazoles (1) and their anthranilic acids were carried out on W2 and 3D7 strains of P. falciparum. The results revealed the potency of compounds as the antimalarial agents of clinical and biological research.



(1)

Anti Inflamatory activity

Venkatesh P et al. [30] reported in the recent years, a large number of benzothiazole based anti-inflammatory agents have been synthesized (1). Some novel 2-amino benzothiazole derivatives and evaluated them for anti-inflammatory activity. Test compounds showed significant anti-inflammatory activity and it was noted that when the 2-amino benzothiazole is substituted at 4 or 5 positions with electron withdrawing groups like Cl, NO_2, OCH_3 increase in anti-inflammatory activity was found.



R=H,Cl

(1)

CONCLUSION

The Indole, Benzothiazole and its analogs research elucidated in this review furnishes the various pharmacological activities. A further modification in its main nucleus provides more efficient derivatives with more potent therapeutic efficacy. This review illustrates many efficient protocols for the synthesis and evaluation of various pharmacological activity of Indole, Benzothiazole nucleus substituted with different aromatic, heterocyclic and other groups.

ACKNOWLEDGEMENT

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REFERENCES

1. Pakravan P. Biochemical and pharmacological characterization of Isatin and its derivatives: from structure to activity. Pharmacological Reports. 2013; 65(2):313-335.
2. Erugu. Design, an efficient ecofriendly synthesis of spirooxindole derivatives and their anticancer activity supported by molecular docking studies. World J. Pharmacy Pharm. Sci. 2014; 3:1895-1914.
3. Lesyk R, Havrylyuk D, Lelyukh M. Synthesis and anticancer activity of Isatin, oxadiazole and 4-thiazolidinone based conjugates. Chemistry & Chemical Technology. 2015; 9:29-36.
4. Achson A. An introduction to the chemistry of heterocyclic compounds. 3rd ed., Willy-Intersciences, India, 2009.
5. Wang Z. Comprehensive organic name reactions and reagents. 3rdedition. Wiley-interscience; 2009.
6. Sumpter WC. The chemistry of Isatin. Chemical reviews, 1944; 34(3):393-434.
7. Ajmer singh grewal. Isatin derivatives with several biological activities. Interntional journal of pharmaceutical research, 2014; 6(1):1-7.
8. Bhusari KP, Amnerkar Nd, Khedekar PB, Kale MK and Bhole RP: Synthesis and in vitro antimicrobial activity of some new 4-amino-N-(1,3-Benzothiazol-2-yl) benzenesulphonamide derivatives. Asian J. Research Chem. 2008, 1(2):53-58.
9. Umesh RP, Jyotirling RM, Dhanaji VJ, Ramrao AM. J. Tetrahedron Letters 2009; 50:1352-1354.
10. Mu Xue-Jun, Zou Jian-Ping, Zeng Run-Sheng, Wu Jun-Chen. Tetrahedron Letters 2005; 46:4345–4347.
11. Singh U.K., Pandeya S.N., Singh A., Srivastava B.K., Pandey M. Synthesis and antimicrobial activity of schiff's and N-mannich bases of Isatin and its derivatives with 4-amino-carbamimidoyl benzene sulfonamide. Int. J. Pharm. Sci. Drug. Res. 2010; 2:151-154.
12. Ramachandran S. Synthesis and antimicrobial evaluation of some novel Schiff and Mannich bases of Isatin derivatives. Int. J. Res. Pharm. Chem. 2011; 1:289-294.
13. Sangamesh A.P., Manjunatha M., Udaykumar V.K., Prema S.B. Synthesis, spectral characterization and biological evaluation Co(II), Ni(II), Cu(II) and Mn(II) metal complexes of novel Isatin schiff base ligand. Der. Pharm. Chem. 2011; 3:97-108.
14. Sandeep K.G., Shyam S.P. Synthesis and evaluation of antitubercular activity of some thiobenzimidazolyl derivatives. Der. Pharm. Chem. 2011; 3:274-279.
15. Hoyun L., Solomon V.R., Changkun H. Hybrid pharmacophore design and synthesis of Isatin– Chemistry. Bioorg. Med. Chem. 2009; 17:7585-7592.
16. Sarangapani M., Rajyalakshmi G., Rama N.R. Synthesis, characterization and anticancer activity of certain 3-{4-(5-mercapto-1, 3, 4-oxadiazole-2- yl) phenylimino} indolin-2-one derivatives. Sau. Pharm. J. 2011; 19:153–158.
17. Dharmarajan S., Tanushree R.B., Perumal Y. Aminopyrimidinimino Isatin analogues: Design of novel nonnucleosideMHIV-1 reverse transcriptase inhibitors with broadspectrum chemotherapeutic properties. J. Pharm. Pharmaceut. Sci. 2005; 8:565-577.
18. Pandeya S.N., Sriram D., Nath G., Clercq E.D. Synthesis, antibacterial, antifungal and anti HIV activity of Schiff and Mannich bases of Isatin with N-6-chlorobenzthiazol-2-ylthiosemicarbazide. Indian. J. Pharm. Sci. 1999; 61:358-361.
19. Teitz Y., Ladizensky E., Barko N., Burstein E. Selective repression of V-alb encoded protein by N-methylisatin-beta-4',4'-diethyl thiosemicarbazone and N-allylisatin-beta- 4',4'-diallylthiosemicarbazone. Antimicrob. Agents. Chem Ther 1993; 37:2483–2486.
20. Prince P.S., Pandeya S.N., Roy R.K., Anurag Verma K., Gupta S. Synthesis and anticonvulsant activity of some novel Isatin Schiff's bases. Int. J. Chem. Tech. Res. 2009; 1:758-763.
21. Singh K.N., Verma M., Pandaye S.N. Synthesis of 3Z)-5-bromo-1-methyl-3-[(4- nitro phenyl) I Mino]-1, 3-dihydro-2H-indol-2-

one by reacting 5-substituted N-methyl/Nacetyl Isatin and aromatic amine with glacial acetic acid. Acta. Pharm. 2004; 54:49-56.
22. Sriram D., Yogeeswari P., Gopal G. Synthesis, anti HIV and antitubercular activity of lamivudine prodrugs. Eur. J. Med. Chem. 2005; 40:1373-137.
23. Prakash C.R., Raja S., Saravanan G., Dinesh K.P., Panneer S. Synthesis and evaluation of antioxidant activities of some novel Isatin derivatives and analogs. Asian. J. Res. Pharm. Sci. 2011; 1:140-143.
24. Bhusari KP, Amnerkar Nd, Khedekar PB, Kale MK and Bhole RP: Synthesis and in vitro antimicrobial activity of some new 4-amino-N-(1,3-Benzothiazol-2-yl) benzene sulphon amide derivatives. Asian J. Research Chem. 2008; 1(2):53-58.
25. Pattan S, Suresh C, Pujar V, Reddy V, Rasal V, Koti B. Synthesis and antidiabetic activity of 2-amino[5"(4-sulphonylbenzylidine)-2, 4-thiazolidinenone]-7-chloro-6-flurobenzothiazole. Ind J Chem. 2005; 44B:2404-2408.
26. Sreenivasa M, jaychand E, Shivakumar B, Jayrajkumar K, Vijaykumar J. Synthesis of bioactive molecule flurobenzothiazole comprising potent heterocylic moieties for anthelmintic activity. Arch Pharm Sci and Res. 2009; 1(2):150-157
27. Alang G, Kaur R, Singh A, Budhlakoti P, Singh A and Sanwal R: Synthesis, Characterization and antifungal activity of certain (E)-1-(1-(substituted phenyl) ethylidene)-2-(6-methylbenzo[d]thiazol-2-yl) hydrazine analogues. International Journal of Pharmaceutical & Biological Archives 2010; 1(1):56-61.
28. Paramashivappa R, Phanikumar P, Subbarao P, Srinivasarao A. Design synthesis and biological evaluation of benzimidazole/benzothiazole and benzoxazole derivatives as cyclooxygenase inhibitors. Bio org med chem., Lett, 2003; 13:657-60.
29. Hout S, Azas N, Darque A, Robin M, Giorgio C, Gasquet M, Galy J and David P: Activity of benzothiazoles and chemical derivatives on Plasmodium falciparum. Parasitology 2004; 129:525-542.
30. Venkatesh P and Pandeya SN: Synthesis, characterization and anti-inflammatory activity of some 2-amino benzothiazole derivatives. International Journal of Chem Tech research 2009; 1(4):1354-1358.