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Review Article

Benzoxazoles: A mini review

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ABSTRACT

Benzoxazoles being structurally similar to bases adenine and guanine interact with biomolecules present in living systems. It can also be used as starting material for other bioactive molecules. This review provides an overview of the synthesis and pharmacological activities of Benzoxazole nucleus such as antimicrobial, anticonvulsant, anti-inflammatory, anticancer, anti-tubercular, antidepressant, anti- helminthic and miscellaneous activities.

Keywords: Benzoxazole, synthesis, pharmacological activities

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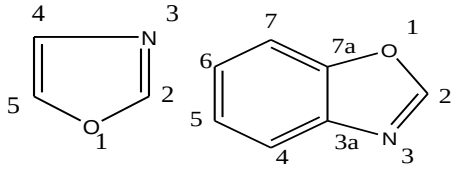
INTRODUCTION

The approach to practice medicinal chemistry has developed from an empirical one involving organic synthesis of new compound, based largely on modification of structures of known activity. As indicated by Manfred Wolf, present development of medicinal chemistry has resistance, stating that "underlying the new age in foundation that includes explosive development of molecular biology since 1960, the advances in physical science and natural science has made possible by high speed computers and new powerful analytical methods[1]. Different compounds, for example alkaloids, fundamental amino acids, vitamins, hemoglobin, hormones substantial number of engineered medications and colors contain heterocyclic ring frameworks. There are the extensive number of synthetic heterocyclic compounds like pyrrole, pyrrolidine, furan, benzoxazole, piperidine, pyridine and benzimidazole having imperative application and numerous are vital intermediates in synthesis[2]. A heterocyclic compound or ring structure is a cyclic compound that has atoms of at least two different elements as members of its ring(s). Among all the heterocyclic mixtures, Benzoxazole is a standout amongst the most imperative heterocyclic showing noteworthy pharmacological exercises.Benzoxazole(1) is an organic compound having benzene fused with an oxazole ring. Oxazole (2) is 1, 3 azole having oxygen atom and a pyridine type nitrogen atom at the 3-position in a five member ring. A slight change in the substitution pattern of benzoxazole nucleus causes distinguishable difference in their pharmacological activities[3].



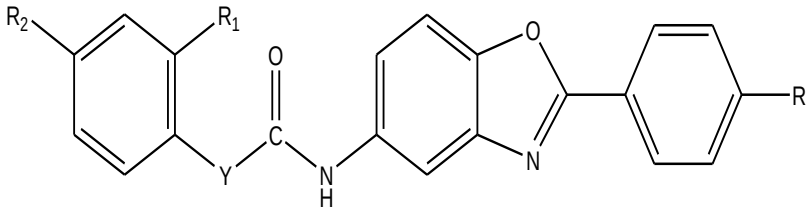
(1) (2)

Benzoxazole is 1-oxa-3-aza-1H-indene, having molecular formula of C_7H_5NO. Benzoxazole (m.p. 27-30°C; b.p. 182°C), is a planar molecule with aromatic chemical properties [4].

It is white to light yellow in color with smell like pyridine. Benzoxazole is a planar particle with conjugated π electrons sextets in the cyclic frameworks. The lone pair of electrons on nitrogen, which is co-planar with heterocyclic ring and thus not engaged in delocalization, confers weakly basic properties. Generally in the pharmaceutical field, new medications are consistently found by molecular modification of lead compound of established activity. Molecular modification can possibly result in augmenting the activity which involves combination of separate group having similar activity in one compound by eliminating, substituting or adding new moiety to parent lead compound. In the survey of literature, it is seen that drug design by molecular modification is a productive source of new drug. Therefore the need to synthesize new molecules as potential medicinal agents is more relevant today. Among the variety of compounds studied, benzoxazole derivatives form an important class[3].

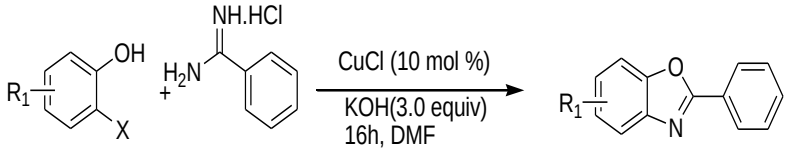
In Pharmaceutical chemistry, Benzoxazole moieties are being developed as DNA minor grove binding agents that have remarkable anti-tumor activity. Benzoxazoleis a heterocyclic compound and important intermediate in organic reactions[5]. Triazole and Benzoxazole are biologically potent molecules, so it was planned to synthesize new triazole derivatives of Benzoxazole and shutter against anthelmintic and antioxidant activities. As the intermediates have slight structural resemblance with Albendazole, along with the triazolo derivative, intermediates were also subjected for in vitro anthelmintic and antioxidant activities[6].

GENERAL STRUCTURE OF BEZOXAZOLES



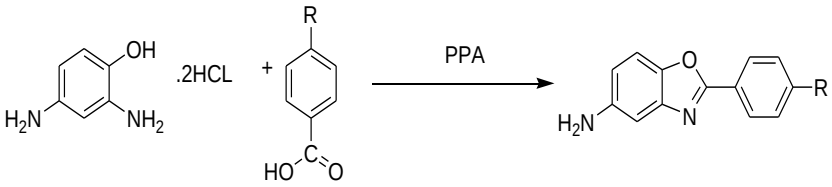
Synthesis of Benzoxazole derivatives

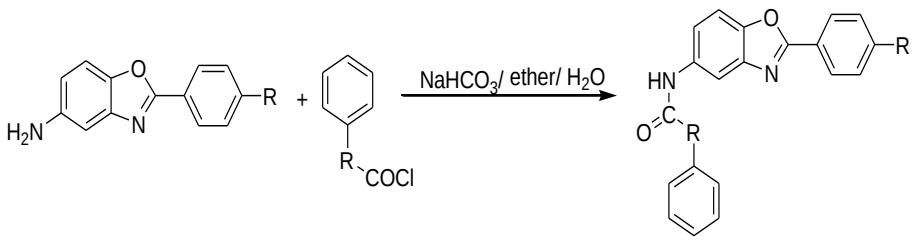
Reaction with Benzamidine hydrochloride[5]: *Abhishek etal*., reported the synthesis of Benzoxazoles derivatives *via* tandemcyclization of 2-halophenols with amidines. The methodology is free from ligands and uses inexpensive and easily available CuClas a catalyst.The synthesis of Benzoxazoles from 2-halophenols with both aromatic and aliphatic amidines takes place.



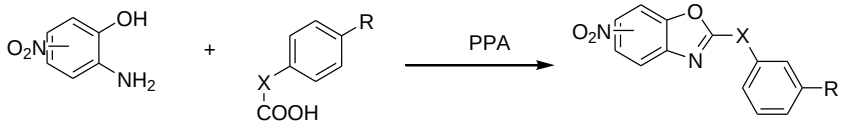
Reaction with acids[6]:

(a)*Esinetal*., reported the synthesis of 5-benzamido- and 5-phenylacetamidosubstitu 2-phenylbenzoxazole derivatives and screened them for their *invitro* antimicrobial activity against Gram-positive and Gram-negative bacteria. Microbiological results indicated that the synthesized compounds possessed a broad spectrum of activity against the tested microorganisms.



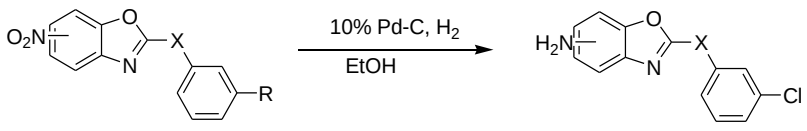


(b)*TugbaErtanetal*., reprted the synthesis of 5(or 6)-nitro/amino-2-(substituted phenyl/benzyl) Benzoxazole derivatives and screened them for their antibacterial and antifungal activities against *Staphylococcus aureus, Bacillus subtilis, Klebsiellapneumoniae, Pseudomonas aeruginosa,Escherichia coli, Candida albicans* and their drug-resistant isolate. These compounds were found to exert a a broad spectrum of activity against the tested microorganisms at MIC values between >400 and 12.5 mg/ml.The2D-QSAR analysis of a set of newly and previously synthesized Benzoxazoles tested for growth inhibitory activity against *B. subtilis* ATCC 6633was performed by using the multivariable regression analysis.

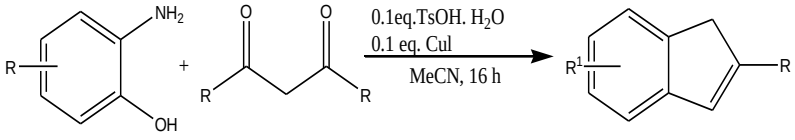


$X=CH_2$

R= F, Cl, Br, C_2H_5

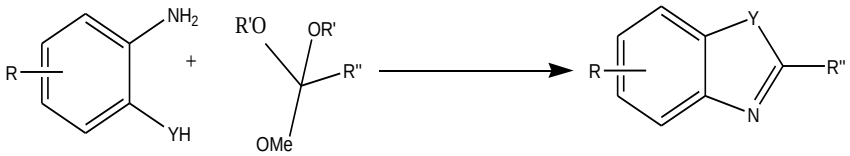


Reaction with diketones[7]: *M. S. Mayo etal*., reported the synthesis of 2- substituted benzoxazoles by cyclization reactions of 2-aminophenols with β-diketones catalyzed by a combination of Brønsted acid and CuI . Different substituents such as methyl, chloro, bromo, nitro, and methoxy on 2-aminophenol are tolerated under the optimized reaction conditions.

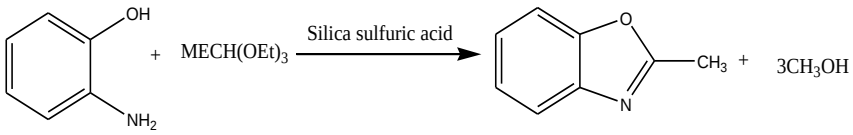


Reaction with esters[8]:-

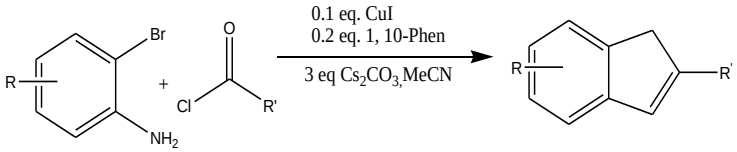
G. Bastug etal., reported the synthesis of benzoxazole via *ortho*-substituted anilines with functionalized orthoesters. The versatility of this approach enables the development of new libraries of heterocycles containing multifunctional sites.



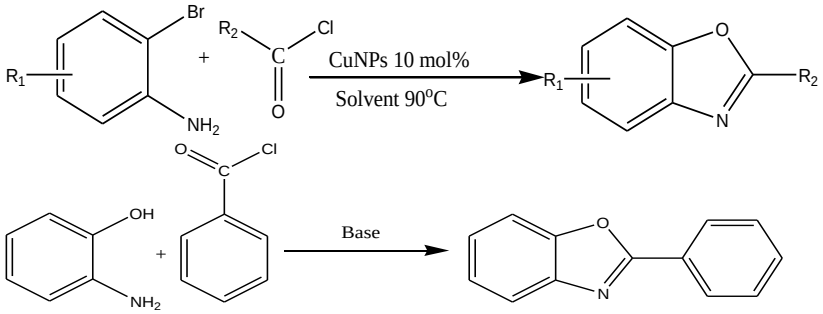
A mixture of trialkylorthoester, o-aminophenol, O-phenylenediamine or 2-amino-3-hydroxypyridine and silica sulfuric acid was stirred at room temperature or at 85^{o}C for the appropriate time. The progress of the reaction was monitored by TLC (eluent: n-hexane: ethyl acetate, 2:1). After completion of the reaction, the mixture was diluted with $CHCl_3$ (10 ml) and filtered. The solid material was washed with $CHCl_3$ and dried at 60^{o}C. The filtrate was evaporated and the residue was purified by recrystallization in n-hexane or by column chromatography on neutral alumina.



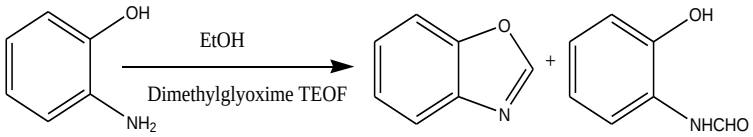
Reaction with acyl chloride[9]: *R. D. Viirre etal*., reported the synthesis of Benzoxazole via reaction with 2-bromoanilines with acyl chlorides in the presence of Cs_2CO_3, catalytic CuI, and 1,10-phenanthroline under microwave conditions.



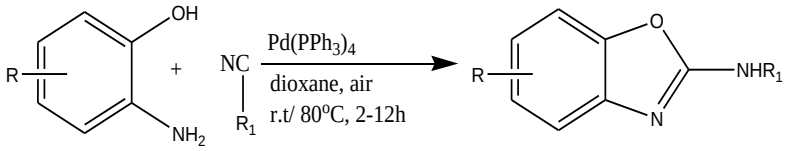
Reaction with acid chloride[10]: *Rohitpaliwal et al*., reported a facile, highly efficient, and practical one-pot synthetic method for Benzoxazoles was developed by using copper nanoparticles as a catalyst with o-bromoanilines and acyl chlorides as starting materials. The transformations are carried out within 15 minutes under microwave heating to 210°C with 10 mol% of copper(I) iodide as the catalyst.



Reaction with oximes[11]: *Moghaddam FM etal*.,reported transformation of o-amino phenol with 0-alkylated oxime to benzoxazole.

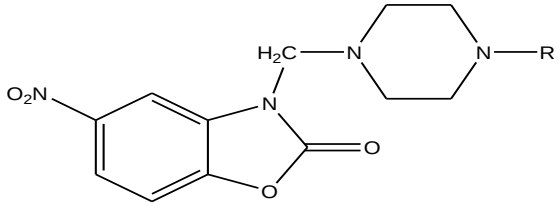


Reaction With Isocyanide[12]: *Akbay et al* ., reported Pd-catalyzed aerobic oxidation of o-aminophenols and isocyanides to synthesize 2-aminobenzoxazoles and 3-aminobenzoxazines in good yields. This methodology has the advantages of experimental simplicity, mild reaction conditions, and easilyaccessible starting materials.



Pharmacological activity: Benzoxazole derivatives possess diverse variety of pharmacological activities. Due to this Benzoxazole have occupied unique place in the field of medicinal chemistry. Benzoxazole ring system is present occasionally in nature. Benzoxazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures. It is structurally similar with nucleic bases as well as the isosteres of natural occurring cyclic nucleotide such as adenine and guanine i.e why it probably interacts with biopolymers in the living systems and shows diverse biological activities like antimicrobial, anti-inflammatory, analgesic, antifungal, anticonvulsants, antitumor, anticancer, antihyperglycemic activity, anti-tubercular, anti-HIV, agents anthelmintic and other anticipated activities.

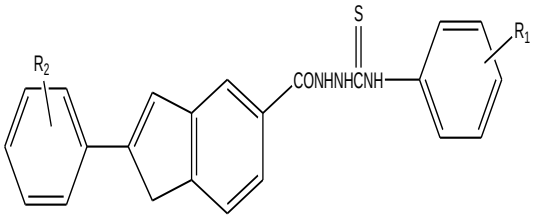
Analgesic and Anti-inflammatory activity[13]: *HakkiErdogan et al*[22]synthesized a novel series of Mannich bases14 of 5-nitro-3-substituted piperazinomethyl-2-benzoxazolinones. The compounds were examined for their in vivo anti-inflammatory and analgesic activities. Among the tested derivatives most promising results were obtained from the compounds bearing electron-withdrawing substituents (F, Cl, $COCH_3$) in the ortho/para position of the phenyl nucleus on the pierazine ring at 3 position of Benzoxazolinone moiety. The analgesic activities of all compounds are higher than their anti-inflammatory activities.



5-nitro-3-piperazinomethyl-2-benzoxazolinones
R= (a)4-C_6H_5F, (b) 2-C_6H_5F, (c) 4- C_6H_5Cl, (d) 2-C_6H_5Cl (e) 4-$C_6H_5COCH_3$

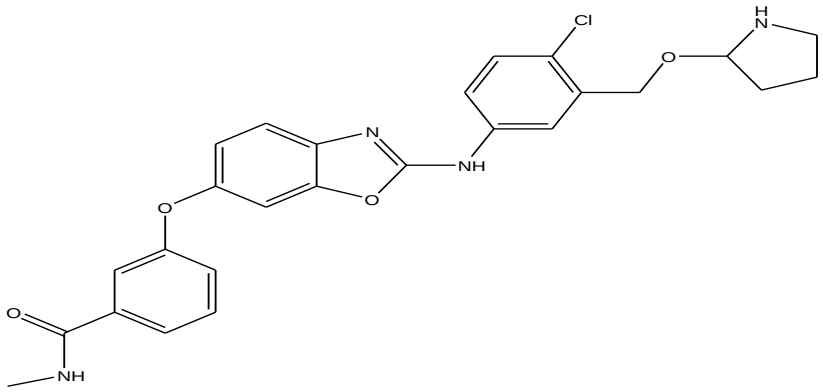
H.OzanGulcanetal.,synthesized4-(5-chloro-2-oxo-3H-benzoxazol-3-yl) butanamide derivatives. 2-Oxo-3H-benzoxazole derivatives exhibit a broad range of biological properties including analgesic and anti-inflammatory activity. Among them, especially 3- substituted-2-oxo-3H- Benzoxazoles are known to exhibit analgesic and anti-inflammatory properties. It has also been reported that Mannich bases of 6-acyl-2-oxo-3H-benzoxazoles resulted in compounds with potent analgesic activity. In general, most of the research on this class of compounds included substitutions on position 3 and 6 of the 2-oxo-3H- benzoxazoles nucleus. As a result 2-oxo-3H- Benzoxazoles bearing N-alkyl, N-acyl, N- diaminoalkyl and 6-acyl substituents were reported to have higher analgesic and anti-inflammatory activity.

CNS activity: *NadeemSiddiquiet al*[14]synthesized a series of 5-Carbomethoxybenzoxazole derivativesby using methyl-p- hydroxybenzoate and evaluate for anticonvulsant activity and neurotoxicity.

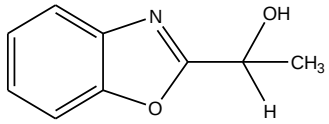


R_1= H, 2-Cl, 4-Cl
R_2= H, 2-OCH_3, 2-CH_3, 3-CH_3, 4-CH_3

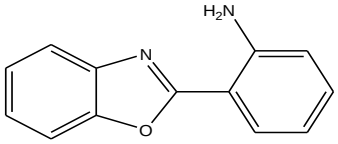
Vascular endothelial growth factor-2 receptor tyrosine kinase inhibitor[15]: *Michele H. Potashman et al*synthesized a series of 2-aminobenzimidazoles and benzoxazoles, culminating in the identification of benzoxazolesas a potent and selective VEGFR-2 inhibitor displaying a good pharmacokinetic profile.



Antimicrobial activity[16]: *Elamin I Elnimaetal*.,studied the in vitro antibacterial[2] and antifungal activities of six benzimidazole andbenzoxazolederivatives.Fifty-nine clinical isolates of *Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus*were tested for susceptibility to the two compounds. The most susceptible were the *S. aureus* isolates. The two compounds were of comparable activity against all the isolates, with compound (b) slightly higher activity than compound (a).

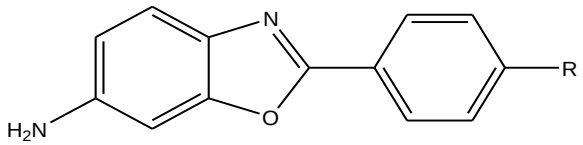


a) 2-hydroxyethyl Benzoxazole



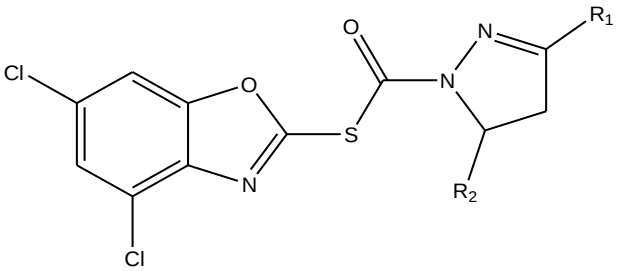
(b) 2- aminophenylbenzoxazole

EsinSeneretal[17]synthesized 5-amino-2-(p-substituted-phenyl) Benzoxazole derivatives. They were synthesized by heating 2,4-diaminophenol with the appropriate carboxylic acids in the presence of poly phosphoric acid.Benzoxazoprofen and Zoxazolamin are also the kind of Benzoxazole derivatives which are substituted at both 2 and 5 positions.



5-Amino-2-(p-substituted-phenyl)benzoxazole derivatives
R= $-C_5H_5N$, $-C_4H_3NCl$, $-C_3H_3NS$

Anticonvulsant activity[18]: Anticonvulsant activity *Pujar et al*. synthesized 2-mercapto Benzoxazole (Fig. 25) and 2-mercaptobenzimidazole and screened for in vivo anticonvulsant activity by PTZ induced convulsions in albino mice. Most of the compounds showed ability to protect against the pentylenetetrazolinduced convulsions.



R_1, $R_{2=}$ $-CH_3$

Anti- tubercular activity: *Klimesova V et al*[19] synthesized a set of 2-benzylsulfanyl derivatives of benzoxazole and evaluated for their in vitro anti mycobacterial activity against *Mycobacterium tuberculosis*, non- tuberculosis mycobacteria and multidrug- resistant *M. tuberculosis*. The lead compounds in the set, di- nitro derivatives exhibited significant activity against both sensitive and resistant strains of *M. tuberculosis* and also against non- tuberculosis mycobacter.

ANTICANCER ACTIVITY[20]: Benzoxazole derivatives were tested for *In vitro* cytotoxicity against four distinctive cell lines including Lung (A549), Prostate (PC-3), Colon (HCT-116) and Breast (MCF-7) cell lines. The mixtures were tried at 100µM concentration. Sulforhodamine B (SRB) test was performed to decide*In vitro* cytotoxicity. Four human cell lines of various tissue origin were used to evaluate the cytotoxic activity of compounds. In this method, cell suspension was seeded into 96 well flat bottom plates and incubated for 24 h. Test compounds at 100µM were added after 24h incubation. Further, after 48 h incubation, cells were fixed with suer cold TCA for 1 h at 4 ˚C. After 1h, the plates were washed five times with distilled water and allowed to air dry followed by addition of 100µl of 0.4% SRB dye for 0.5 h at room temperature. Plates were then washed with 1% v/v acetic acid to remove the unbound SRB dye. The bound dye was solubilised by adding 100µl of 10mM Tris buffer to each well. Then the plates were put on shaker for 5 min to solubilize the dye completely. Finally the reading was taken at 540nm on microplateperuser.

ANTIDEPRESSANTS ACTIVITY[21]: 5-HT1A and 5-HT2A subtypes are important drug targets for the treatment of depression. It has been suggested that agents that interact with the 5-HT1A and 5-HT2A receptors may have a beneficial effect on depression. several psychotropic agents with Benzoxazole or Benzothiazole moieties that exhibited moderate binding affinity for the 5-HT1A and 5-HT2A receptors. The Benzothiazole derivative 8h increased the affinity for the 5-HT1A receptor (Ki = 31 nM) with potent affinity for the 5-HT2A receptor (Ki = 24 nM) when the linker was elongated from three to four carbons. Antidepressant-like activity of the test compounds was screened using the forced swimming test and tail suspension test.

ANTIHELMINTH ACTIVITY[22]: Helminths infections are a medical and public health problem of high magnitude, both in humans and domestic animals, causing considerable suffering and poor growth. Both triazole and benzoxazole are biologically potent molecules. The anthelmintic assay was carried out with appropriate modifications. P. posthuma of nearly equal size (61 cm) were collected from Vermicompost manufacturing farm. The worms were acclimatized to laboratory conditions before experimentation. The earth worms were divided into three groups of six each. Albendazole diluted with normal saline solution to obtain 1% (m/V) served as standard and is poured into Petri dishes. The synthesized compounds were dissolved/suspended in minimal quantity of tween 80 and diluted to prepare three concentrations of 1%, 2% and 3% (m/V) of each compound. Normal saline served as a control. The time taken for complete paralysis and death was recorded. The mean paralysis time and mean lethal time were calculated for each compound (each reading was taken in triplicate). The time taken for worms to become motionless was noted as paralysis time. To ascertain death, each worm was frequently subjected to external stimuli that stimulate and induce movement in earth worms, if alive.

CONCLUSION

Benzoxazole moiety is expanding their pharmaceutical importance and is associated with several biological activities. Thereview has outlined the various synthetic approaches and biological activities of benzoxazole moiety. The broad spectrum antibacterial and antifungal activity of these compounds could leadto a new series of antimicrobials activity. The Benzoxazole moiety has beneficial effects on microbial infections, inflammation, tuberculosis, in convulsions, cancer etc. Further research on this moiety may lead to the development of new drugs having wide range of activities. Further investigation of this scaffold may lead to development of the new drug to be used against the variety of diseases.

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