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Review Article

BENZOXAZOLE: THE MOLECULE OF DIVERSE PHARMACOLOGICAL IMPORTANCE

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ABSTRACT

Benzoxazole nucleus is one of the most important heterocyclic compounds exhibiting remarkable pharmacological activities. The present review provides a broad overview of the synthesis and pharmacological activities such as antimycobacterial, anticonvulsant, anti-inflammatory, anticancer, DNA topoisomerase inhibitor, cholesterol ester transfer protein inhibitor and miscellaneous activities.

Keywords: Benzoxazole, Synthesis, Pharmacological activity.

INTRODUCTION

The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating disease [1]. An important aspect of medicinal chemistry has been to establish a relationship between chemical structure and pharmacological activity. The chemistry of heterocyclic compounds is the most important in the discovery of new drugs. The study of these compounds is of great interest both in theoretical as well as practical aspects [2].

Various compounds such as alkaloids, essential amino acids, vitamins, haemoglobin, hormones, large number of synthetic drugs and dyes contain heterocyclic ring systems. There are the large number of synthetic heterocyclic compounds like pyrrole, pyrrolidine, furan, benzoxazole, piperidine, pyridine and benzimidazole having important application and many are important intermediates in synthesis [3].

Among all the heterocyclic compounds, benzoxazole is one of the most important heterocycles exhibiting remarkable pharmacological activities. Benzoxazole is an organic compound, which has benzene fused with an oxazole ring. Oxazole (Fig.1) 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.

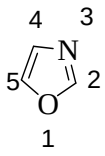


Fig. 1

Synthesis of benzoxazole

Several protocols for the synthesis of benzoxazole have been developed due to their biological and synthetic significance. 2-substitued benzoxazole was prominently studied trusting that this position is decisive for the biological activity whereas position 5 prevailing intensity of the activity. Benzoxazoprofen and Zoxazolamine are also kind of benzoxazole derivative which are substituted at both 2 and 5 position [4].

Moghaddam *et al*. synthesized 2-substituted benzoxazoles (Fig.2) via condensation reaction of 2-aminophenol with various aldehydes using molecular iodine as a catalyst in solvent-free conditions under microwave irradiation at 130°C in short time of span gives excellent yield [5].

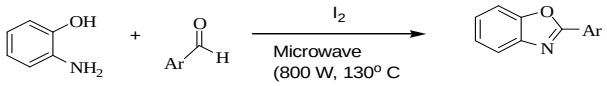


Fig. 2

Batley *et al.* carried out a copper catalyzed one-pot synthesis of benzoxazole (Fig. 3) using bromoaniline and acyl hallides in the presence of a base and solvent giving intermediates which finally gave pure benzoxazole (21–97%) isolated yield, exhibiting a broad range of biological activity. They can also be used as precursors in the synthesis of drugs [6-8].

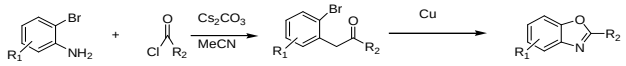


Fig. 3

Lokhwani *et al*. prepared benzoxazole (Fig. 4) by the reaction of orthoesters with o-aminophenols in the presence of silica sulfuric acid under heterogeneous and solvent–free conditions [9].

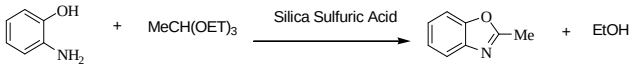


Fig. 4

Yang *et al*. synthesized benzoxazole (Fig. 5) by treatment of N-(2-hydroxyaryl) cyclopropyl amides with PPh_3/CBr_4 in acetonitrile to yield 2-substituted benzoxazole [10].

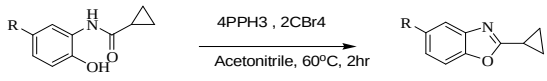


Fig. 5

Do *et al*. carried out copper catalyzed arylation of benzoxazole (Fig. 6) at 2- carbon with aryliodides in DMF with very high yields. This method involves direct functionalization of heterocycle C-H bonds [11].

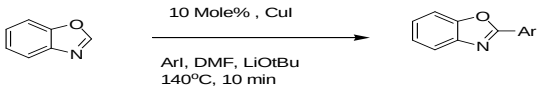


Fig. 6

Mardolla *et al.* synthesized substituted benzoxazoles (Fig. 7) by condensing a variety of carboxylic acids with 2-aminophenol, 2-aminothiophenol and 1, 2-phenylenediamines respectively using the ionic liquid 1-butyl 3-methyl imidazolium tetraflouroborate [(bmim) BF_4] at higher temperatures.Ionic liquid acts as a reaction medium and promoter [12].

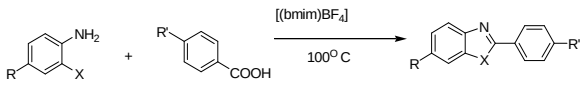


Fig. 7

Yoshida *et al.* prepared 2-cyclicamine benzoxazole (Fig. 8) by the reaction of 2-mercapto benzoxazole or 2-chlorobenzoxazole with cyclicamine under different reaction conditions [13].

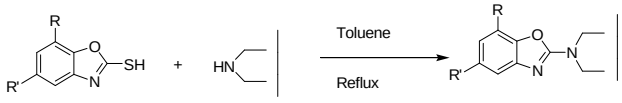


Fig. 8

Prakash *et al.* reported synthesis of 2-benzoxazoles (Fig. 9) using hypervalent iodine (iodobenzene diacetate) mediated oxidative cyclization of Schiff's bases in methanol as anoxidant. Schiff's bases were prepared by the reaction of o-aminophenols and aldehydes [14].

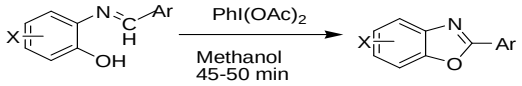


Fig. 9

Ozdemira *et al*. prepared 5-amino-2-arylbenzoxazoles (Fig. 10) by the reaction of 2, 4-diaminophenol dihydrochloride and various aryl carboxylic acids in polyphosphoric acid (PPA) [15].

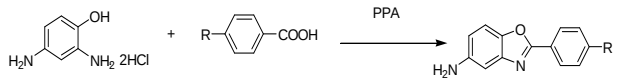


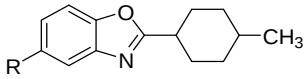
Fig. 10

Pharmacological activity

Antimicrobial activity

The rapidly increasing occurrence of multiple drug-resistant microbial strains is a serious problem. Since the emergence of anti-resistant bacteria is inevitable, there is urgency for the discovery of novel active agents, which is of the highest priority [16, 17].

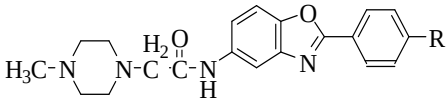
Yalcin *et al*. synthesized 5- substituted-2-cyclohexyl methyl benzoxazoles (Fig. 11) by the reaction of 2–hydroxy–5-substituted aniline and cyclohexyl carboxylic acid with sodium bicarbonate. The synthesized compounds showed moderate to good antibacterial and anti-fungal activity as compared to standard [18].



R= H

Fig. 11

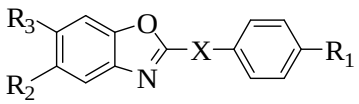
Ozdemira *et al*. synthesized a series of twelve novel 5-[2-(morpholin-4-yl) acetamido] and 5-[2-(4-substituted piperazine-1-yl)acetamido]-2-(*p*-substituted phenyl] benzoxazole derivatives (Fig. 12) and were tested for their *in vitro* activities against certain strains of Gram-positive, Gram-negative bacteria as well as the yeasts *Candida albicans, Candida krusei*, and *Candida glabrata*. Microbiological results showed that the newly synthesized compounds possessed a broad spectrum of activity, showing MIC values of 3.12-50 µg/mL against the *Candida* species [19].



R=ethyl, t- butyl

Fig. 12

Yildiz *et al.* synthesized a new series of 5 (or 6)-nitro/amino-2-(substituted phenyl) benzoxazole derivatives (Fig. 13) and evaluated for their antibacterial and antifungal activities against *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Escherichia coli, Candida albicans* and drug-resistant isolates. The compounds synthesized were found to exhibit appreciable antibacterial activity [16].



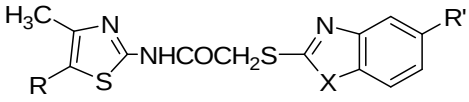
R_1 = Methyl, Ethyl

R_2 = NO_2, NH_2

R_3 = H, NH_2

Fig. 13

Zitouni *et al.* synthesized some 2-[(benzoxazole-2-yl) thioacetyl-amino] thiazole derivative (Fig. 14) by reacting 4-methyl-2-(chloroacetylamino) thiazole derivatives with benzazol-2-thiole in acetone in the presence of K_2CO_3. The chemical structures of the compounds were elucidated by ^{1}H NMR and FAB+-MS spectral data. The prepared compounds showed mild to significant antimicrobial activity and toxicity [20].



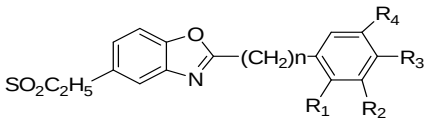
X= O, NH

R= H, CH_3, $COOC_2H_5$

Fig. 14

Yildiz *et al.* synthesized series of 5-ethylsulphonyl-2-(substituted-phenyl/substituted-benzyl and/or phenylethyl) benzoxazole (Fig. 15) derivatives and evaluated for *in vitro* antimicrobial activity of the compounds against *Gram-positive, Gram-negative* bacteria, a

fungi *Candida albicans* and their drug-resistant isolates in comparison with standard drugs. Antimicrobial results indicated that the synthesized compounds possessed a broad spectrum of activity with MIC values 250-7.81 mg/ml [21].



R_1 = H, F, Cl, Br, CH_3

R_2 = H, CH_3

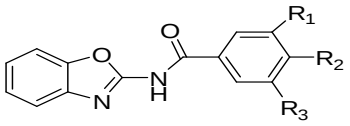
R_3 = H, F, Cl, Br, CH_3, C_2H_5, NO_2

R_4 = H, Br

n = 0, 1, 2

Fig. 15

Kim *et al.* synthesized benzoxazole amides (Fig. 16) and evaluated for their antifungal activity against *Malassezia furfur*. Twelve benzoxazole amides were prepared through the cyclization of the substituted 2-hydroxy aniline with *N*-(bis-methylsulfanylmethylene) amides. Among the prepared compounds, few showed *in vitro* antifungal activity [22].



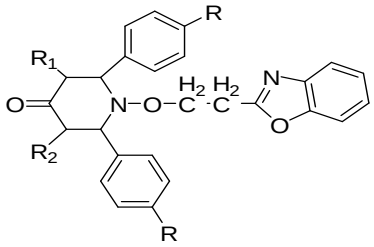
R_1=Cl, H, H

R_2=H, H, H

R_3=H, H, OCH_3

Fig. 16

Kabilan *et al.* synthesized some novel benzoxazolyl ethoxypiperidones (Fig. 17) and screened for their antibacterial activity against *Streptococcus faecalis*, *Bacillus subtilis, Escherichia coli*, *Staphylococcus aureus and Pseudomonas aeruginosa* and antifungal activity against *Candida albicans, Aspergillus niger, Candida-51 and Aspergillus flavus*. Some compounds exerted potent *in vitro* antibacterial activity against *Streptococcus faecalis* while rest compounds exhibited potent *in vitro* antifungal activity against Candida-51 [23].



R= Cl, OCH_3

R_1, R_2= H, OCH_3

Fig. 17

Elnima *et al*. synthesized 2- substituted benzoxazole derivatives (Fig. 18, 19) and studied *in vitro* antibacterial and antifungal activities against *E. coli, P. aeruginosa* and *S. aureus*. Among the fifty nine prepared derivatives only two derivatives were found to be effective against *S. aureus* isolates. Their minimal inhibitory concentration was found to be 25 and 50 µg/ml[24].

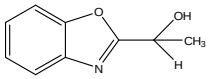


Fig. 18

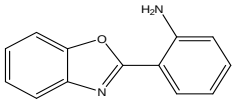


Fig. 19

Goker *et al*. synthesized a number of substituted 2-anilinobenzimidazoles, benzothiazoles and benzoxazoles (Fig. 20) evaluated for their anti-staphylococcal activity [25].

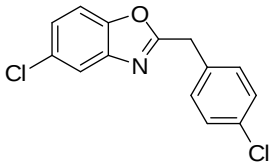
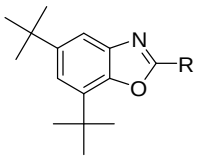


Fig. 20

Vinsova *et al*. synthesized a series of lipophilic new 2-substituted 5, 7-di-tert-butylbenzoxazoles (Fig. 21) by the reaction of 3, 5-di-tert-butyl-1, 2-benzoquinone with amino acids and dipeptides, bearing N-terminal glycine. Dipeptides having other N-terminal amino acids undergo oxidative deamination. 5, 7-di-tert-butylbenzoxazoles have shown antituberculotic activity against *Mycobacterium tuberculosis* comparable with or higher than the standard drug isoniazid [26].



R= Styryl, Pyridin-2-yl, pyridin-4-yl

Fig. 21

Klimesova *et al*. synthesized a set of 2-benzylsulfanyl derivative of benzoxazole (Fig. 22) and evaluated for their in vitro antimycobacterial activity against *Mycobacterium tuberculosi*, non-tuberculous mycobacteria and multidrug-resistant *M. tuberculosi* notable activity was obtained [27].

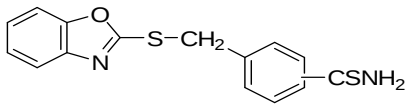


Fig. 22

Singh *et al*. prepred 4-(Benzoxazole-2-yl)-*N*-substituted Benzylidine aniline derivatives (Fig. 23) by reaction of 2-aminophenol with p-amino benzoic acid and various aldehydes in presence of polyphosphoric acid and evaluated for their antibacterial activity against *E. coli, P. aeruginosa* and *S. aureus* [28].

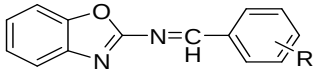


Fig. 23

Jayananna et al. synthesised a new class of 5,7-dichloro-1,3-benzoxazole derivatives (Fig. 24) by fusing 5,7-dichloro-2-hydrazino-1,3-benzoxazole nucleus with aliphatic acids, active

methylene compounds, and with selected esters to form heterocyclic ring systems like 1,2,4-triazoles, pyrazoles, and triazine moieties and screened for cytotoxic, antimicrobial, antioxidant, and antilipase activities [29].

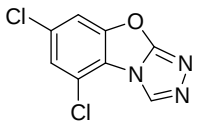
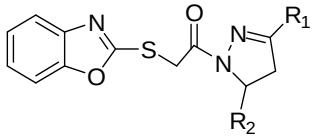


Fig. 24

Anticonvulsant activity

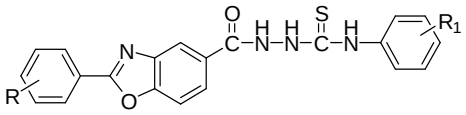
Pujar *et al*. synthesized 2-mercapto benzoxazole (Fig. 25) and 2-mercapto benzimidazole and screened for *in vivo* anticonvulsant activity by PTZ induced convulsions in albino mice. Most of the compounds showed ability to protect against the pentylenetetrazol-induced convulsions. Some compounds exhibited maximum activity as compared to standard drug [30].



R_1, R_2= -CH_3

Fig. 25

Siddiqui *et al*. synthesized a series of 5-carbomethoxybenzoxazole (Fig. 26) derivatives by using methyl-*p*-hydroxybenzoate and evaluated for their anticonvulsant and neurotoxicity effect and was found to possess considerable anticonvulsant activity [31].



R= H, 2-Cl, 4-Cl, 4-Br

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

Fig. 26

Quan *et al*. synthesized a series of 2-substituted-6-(4*H*-1, 2, 4-triazol-4-yl) benzo[*d*]oxazoles. The anticonvulsant effect and neurotoxicity of the compounds (intraperitoneally) were evaluated with the maximal electroshock (MES) test, subcutaneous pentylenetetrazole (sc-PTZ), and rotarod tests in mice. Further, it was observed that 2-phenyl- 6- (4*H*-1, 2, 4-triazol-4 yl) benzo[*d*]oxazole (Fig. 27) was the most active and also had the lowest toxicity [32].

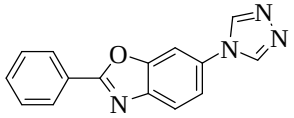
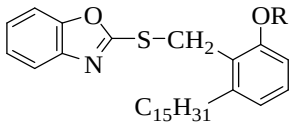


Fig. 27

Anti inflammatory activity

Non-steroidal anti-inflammatory drugs (NSAIDs) are a main-stay in the treatment of inflammation and they owe their therapeutic and side effects in large part to the inhibition of cyclooxygenase (COX). The separation of the therapeutic effects from the side effects has been a major challenge in the design and synthesis of these drugs. The discovery of a second isoform of cyclooxygenase, namely COX-2, has opened a new line of research based on the assumption that pathological prostaglandins are produced by the inducible isoform COX-2 while physiological prostaglandins are produced by the constitutive isoform COX-1 [33].

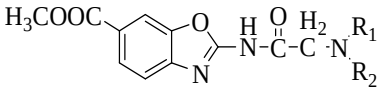
Rao *et al*. synthesized the series of 2-[[2-alkoxy-6-pentadecylphenyl (methyl)]thio]-1H benzoxazole (Fig. 28) and investigated their ability to inhibit human cyclooxygenase-2 enzyme which showed anti-inflammatory activity [34].



R = CH_3, C_2H_5

Fig. 28

Ampati *et al.* synthesised a series of methyl-2-{(2-(dialkylamino) acetamido)}-benzoxazole-5- carboxylates (Fig. 29) from Methyl 3-amino-4-hydroxybenzoate and investigated their ability to inhibit human cyclooxygenase-2 enzyme (COX-2). The IC50 values were found to be comparable to that of standard - refecoxib. Thus, this class of compounds serves as excellent candidates for selective COX-2 inhibition [35].



R_1= -N $(CH_3)_2$ R_2= $C_{15}H_{17}N_3O_5$

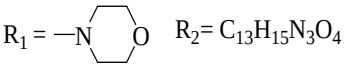


Fig. 29

Srinivas *et al*. synthesized a series of methyl 2- (arylideneamino) benzoxazole -5-carboxylate derivatives (Fig. 30) by the reaction of Schiff bases of methyl 2-aminobenzoxazole-5-carboxylate with appropriate aromatic aldehydes. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H NMR, mass spectral analysis and evaluated for COX-2 inhibitory activity. In conclusion, this class of compounds serves as remarkable class for COX-2 inhibition [36].

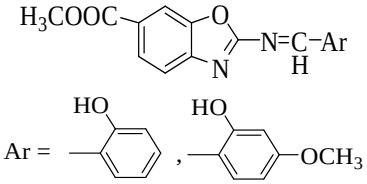
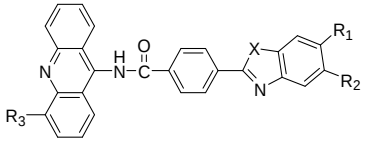


Fig. 30

Sondhi *et al*. synthesized a series of N-(acridin-9-yl)-4-(benzo [d]imidazol/oxazol-2-yl) benzamides (Fig. 31) by the condensation of 9- amino acridine derivatives with benzoxazole derivatives. All these compounds were characterized by correct FT-IR, ^{1}H NMR, MS and elemental analysis. These compounds were found to possess appreciable anti-inflammatory activity [37].



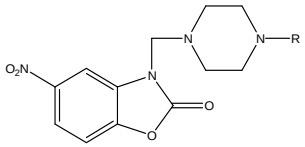
R_1= Cl, H; R_2=NO_2, H

R_3= H, X= NH

Fig. 31

Analgesic activity

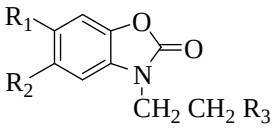
Erdogan *et al*. synthesized a novel series of mannich bases of 5-nitro-3-substitutedpiperazinomethyl-2-benzoxazolinones (Fig. 32). The compounds were screened for their anti-inflammatory activity. Among the tested compounds most promising results were obtained for the compounds bearing electron withdrawing substituents (F, Cl, $COCH_3$) in the ortho/para position of the phenyl ring at the third position of benzoxazolinone moiety. The analgesic activity of the entire compounds is higher than their anti-inflammatory activity [38].



R= 4-C_6H_5F, 4-C_6H_5Cl

Fig. 32

Safac *et al.* synthesized a series of 3-(2-pyridylethyl) benzoxazolinones (Fig. 33) derivatives which exhibited anti-inflammatory and analgesic activity [39].



R_1= H, Cl

R_2= CH_3CO, C_6H_5CO

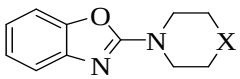
R_3= 2-pyridyl, 4- pyridyl

Fig. 33

Anticancer activity

Many of the major classes of anticancer drugs in current use owe their overall therapeutic effectiveness but lack of selectivity for tumor cells over normal cells can lead to severe side effects. Design and synthesis of novel small molecules which can specifically block some targets in tumor cells are in perspective direction in modern medicinal chemistry. Therefore there is an urgent need to establish processes to assess anticancer drug action (*i. e,* safety, efficacy and mechanism of action). From the different groups of heterocycles, many synthetic small molecules with cytotoxic activity have been reported and several of them under gone for the clinical trials [40].

Murty *et al*. synthesized 2-substituted -1, 3-benzoxazoles (Fig. 34) with the influence of the presence of cyclic amine moiety in the benzoxazole scaffold and evaluated with respect to their cytotoxic effects toward four human cancer cell lines. Substitution was done at the second and third position of benzoxazole moiety to know the influence of cytotoxic effect towards these cell lines [41].



X= N-Me, N-Et, N-phenyl, N-pyridyl, N-pyrimidyl,

N-benzyl, N-(3-chlorophenyl), CH_2, O

Fig. 34

Kamal *et al*. synthesized a series of benzothiazole and benzoxazole linked pyrrolobenzodiazepine conjugates (Fig. 35) and screened for their anticancer activity, DNA thermal denaturation studies, restriction endonuclease digestion assay and flow cytometric analysis in human melanoma cell line (A375). One of the compounds of the series 7-methoxy-8-{5-[4-(1,3-benzothiazol-2-yl)-2methoxy phenoxy] pentyl}oxy-(11aS)1,2,3,11a-tetra-hydro-5H-pyrrolo-[2,1-c][1,4] benzodiazepin-5-one (24) showed significant anticancer activity with promising DNA-binding ability and apoptosis which caused G_0/G_1 phase arrest at sub-micromolar concentrations [42].

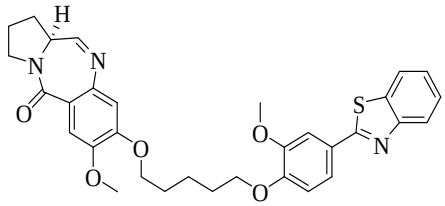
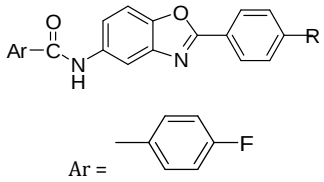


Fig. 35

DNA topoisomerase inhibitor

Akbay *et al*. synthesized 5-phenylacetamidosubstituted-2-phenylbenzoxazole derivatives (Fig. 36) by reaction of 5-amino substituted-2-phenylbenzoxazole and excess of thionyl chloride, sodium bicarbonate & diethyl ether in water. Derivative compounds inhibits reverse transcriptase (RT) activity, binding of the RT enzyme exhibiting IC_{50} values between 6.3×105 μ mol/1-0.34 μ mol/l and their activities were compared to standard drug such as 3'-azido-2',3'-dideoxythymidine triphosphate and dideoxythymidine triphosphate. Since DNA topoisomerases are considered as important targets for cancer chemotherapy, the present findings may provide future opportunities to design and develop new chemotherapeutic agents [43].

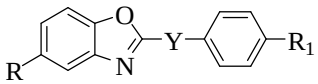


Ar =

R = H, C_2H_5

Fig. 36

Oksuzoglu *et al*. investigated the inhibitory effects of some novel fused heterocyclic compounds (Fig. 37) on eukaryotic DNA topoisomerase II in a cell free system. He pointed out that in addition to the very well-known bi- and ter-benzimidazoles, compounds with single bicycled fused ring systems in their structure such as benzoxazole derivatives also exhibited significant DNA topoisomerase II inhibitory activity having IC_{50} values of 22.3, 17.4, 91.41 μM, respectively, showing higher potency than the reference drug etoposide [44].



Y= -CH_2, R= Cl

Fig. 37

Cholestrol ester transfer protein inhibitor

Smith *et al.* reported a series of 2-arylbenzoxazole as inhibitors of the cholesterol ester transfer protein (CETP). Structure–activity studies revealed variation of the substitution of the benzoxazole moiety. Substitution at the 5- and 7-positions of the benzoxazole moiety was found to be beneficial for CETP inhibition. While, compound N-{4-[5-Cyano-7-(1–hydroxy -1- methyl- ethyl)- benzoxazol-2-yl]-phenyl}-2-o-tolyloxy-acetamide (Fig. 38) was found to be the most potent inhibitor in this series and inhibited CETP with an IC_{50} of 28 Nm [45].

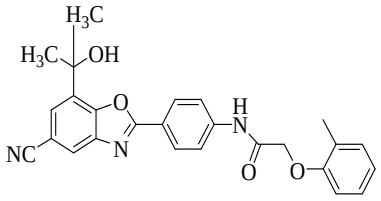


Fig. 38

Hunt *et al*. Synthesized a series of 2-arylbenzoxazole α-alkoxyamide and β-alkoxyamine inhibitors of cholesteryl ester transfer protein (CETP). Highly fluorinated α-alkoxyamides proved to be potent inhibitors of CETP in vitro, and the highly fluorinated 2-arylbenzoxazole β-alkoxyamine (Fig. 39) showed a desirable combination of in vitro potency (IC_{50} = 151 nM) and oral bioavailability in the mouse [46].

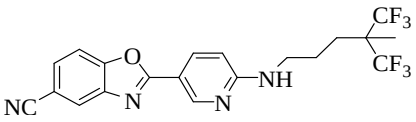


Fig. 39

Herbicidal activity

Youseef *et al*. synthesized 6-Amino-5-(benzoxazole-2-yl)-4-aryl-3-cyanopyridine-2-(1H)-thiones (Fig. 40). The herbicidal activity of the newly synthesized compounds was evaluated against wheat as pattern for monocotyledonous plants. Three plant parameters were studied, seed germination, root and shoot growth under laboratory conditions. Compounds that showed an observable inhibition on one or more of the growth parameters under study were considered as promising compounds and needs more studies from the toxicological, soil, environmental and formulation points of view to stand on the most potent derivative that can be formulated in a suitable formulation form to be used in the field of pest control [47].

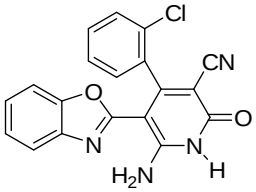


Fig. 40

Miscellaneous

Potashman *et al.* synthesized a series of 2-aminobenzimidazole and benzoxazole (Fig. 41) and evaluated for their selective vascular endothelial growth factor-2 receptor kinase inhibitor activity displaying good pharmacokinetic profile [48].

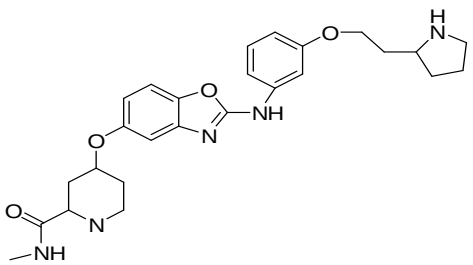


Fig. 41

Tamagnan *et al.* synthesized 5- and 6-substituted 2-(4-dimethylaminophenyl)-1, 3-benzoxazoles (Fig. 42) and evaluated *in vitro* and *in vivo* imaging agents for Alzheimer's disease (AD)-related amyloid plaque [49].

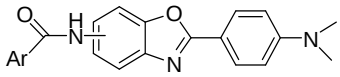


Fig. 42

Swahn *et al.* synthesized and evaluated 2-pyridylbenzoxazole derivatives (Fig. 43) asC-PET imaging agents for β-amyloid plaques for Alzheimer's disease [50].

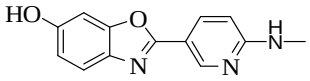
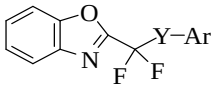


Fig. 43

Medebielle *et al*. synthesized fluorine containing benzoxazole derivative (Fig. 44) and tested for activity against HIV-I for used in AIDS treatment [51].



Y= CHOH, CHF, C=O, CH_2

Ar = Aryl, hetrocycle

Fig. 44

Raok *et al*. synthesized benzoxazole containing thiazolidinedione derivatives. 5- [4-[2-(Benzoxazol-2-yl-alkylamino) ethoxy] benzyl] thiazolidine-2, 4-diones (Fig. 45) have been prepared by Mitsunobu reaction of benzoxazolylalkylamino ethanol and hydroxyl benzyl thiazolidinedione [52, 53].

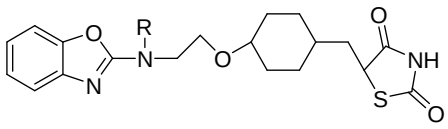


Fig. 45

Sun LQ *et al.* prepared a novel series of benzoxazole derivatives and evaluated as melatoninergic ligands. The binding affinity of these compounds for human MT (1) and MT (2) receptors was determined using 2-[(125) I]-iodomelatonin as the radioligand. This work also established the benzoxazole nucleus as a melatoninergic pharmacophore [54].

CONCLUSION

Benzoxazole moiety is expanding their pharmaceutical importance and is associated with several biological activities. The article has outlined the biological activities of the Benzoxazole scaffold. The benzoxazole derivative has beneficial effects on microbacterial infection, inflammatory disorders, and COX-2 mediatory responses and on DNA topoisomerases activity. The broad spectrum antibacterial and antifungal activity of these compounds could lead to a new series of antimicrobials activity. Further investigation of this scaffold may lead to development of the new drug to be used against the variety of diseases.

CONFLICT OF INTERESTS

Declared None

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