Pharmacological Profile and Pharmaceutical Importance of Substituted Benzoxazoles: A Comprehensive Review

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Abstract: Enzoxazole constitute an important class of therapeutic compounds and efforts were made to synthesize varied derivatives in order to claim their potential biological profiles in previous decade. Variety of substituted benzoxazole has the ability to hinder the microbial growth, inflammatory reactions; various prostaglandins mediated reactions and also the DNA topoisomerase activities. Although benzoxazoles are very common heterocyclic compounds now a days, but still the results shown by previous studies emerge the fascination about the molecule. The present review focuses out various important synthetic derivatives of benzoxazole and their associated pharmacological profiles which may in turn helpful to the information seekers to develop some novel derivatives of medicinal interest.

Keywords: Benzoxazole, Antiinflammatory, Antimicrobial, Calcimycin.

1. INTRODUCTION

The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic, while countless additives and modifiers used in industrial application ranging for cosmetics, reprography, information storage and plastics are heterocyclic in nature\textsuperscript{1}.

The heterocyclic ring comprises of very core of the active moiety or the pharmacophore. Several Benz-fused hetero, bicyclic ring systems as indole, benzothiazole, benzimidazole, benzoxazole, have been studied and found to be possessing interesting pharmacological activities.

Biologically active benzoxazole derivatives have been known for long time, since they are the isosters of naturally occuring cyclic nucleotides and they may easily interact with the biopolymers of the organisms\textsuperscript{1}. Literature survey revealed that benzoxazoles possess most remarkable and a wide range of biological activities\textsuperscript{3}. The substituted benzoxazoles have been shown to exhibit antitumor\textsuperscript{4}, antihistaminic, antiparasitic, herbicidal, antiallergic, antihelmintic\textsuperscript{5}, COX-2inhibitory\textsuperscript{6}, antifungal, antibacterial, anticancer, antitubercular, anticonvulsant\textsuperscript{7}, diarrhea-predominant irritable bowel syndrome\textsuperscript{8}, hypoglycaemic\textsuperscript{9}, HIV-1 reverse transcriptase inhibitor\textsuperscript{10} & insecticidal\textsuperscript{3} activities. It has also been shown to have binding affinity to Aβ42 fibrils\textsuperscript{11}.

Recent observations suggest that substituted benzoxazoles and related heterocycles, possesses potential activity with lower toxicities in the chemotherapeutic approach in man\textsuperscript{12}.

A benzoxazole derivative, calcimycin, is a carboxylic polyether antibiotic from the strain of \textit{Streptomyces}
It was found to be very active against Gram-positive bacteria including some Bacillus and Micrococcus strains. Two calcimycin analogues, Routiennocin and Cezomycin which are 3-hydroxy-11, 15-desmethyl and 3-demetylamino derivatives of it, respectively, were found to be highly active against Bacillus cereus, Bacillus subtilis, Micrococcus luteus and Streptomyces rimosus. Additionally Frankamide, that is 11-demethyl cezomycin, showed some activity against Bacillus subtilis, Staphylococcus aureus, Enterococcus faecalis and against several plant pathogenic fungal strains.  

Although they have been known from long ago to be biologically active, their varied biological features are still of great scientific interest. Given below is a brief account of various alterations conducted on benzoxazole ring and their associated biological activities.

2. BIOLOGICAL ACTIVITIES-

2.1 ANTI INFLAMMATORY ACTIVITY

The benzoxazole moiety with some substitutions shows promising anti inflammatory activity. Its Methyl 2-[4-(dimethylamino) benzylideneamino], N-5-(2-arylidenehydrazinecarbonyl), Methyl-2-2-(4-nitrobenzylideneamino) derivatives act as potent anti-inflammatory agent.

A Srinivas et al., has been synthesized methyl-2-(arylideneamino) benzoxazole-5-carboxylate derivatives (Fig. 1) by reaction of methyl-2-(2-aminothiazol-5-ylamino)benzo[d]oxazole-5-carboxylate and 4-nitro benzaldehyde in absolute alcohol. It has been observed that the increased anti-inflammatory activity is attributed to the presence of pharmacologically active thiazole ring on the benzoxazole moiety at position-2.

2-methylbenzo [d]oxazole-5-carboxylic acid (Fig. 4) had been synthesized by Sunila T.Patil et al., by the reaction of 2-methylbenzo [d]oxazole-5-carbohydrazide and pyridine with sulphonyl chloride. All the synthesized compounds showed moderate to potent anti-inflammatory activity with percent inhibition ranging from 26% - 55.8% when compared to standard drug Ibuprofen (50mg/kg).

2-substituted- [(N,N-disubstituted)-1,3-benzoxazole]-5-carboxamido (Fig. 5) had been synthesized by Sarangapani.M et al., by the reaction of 2-(substituted)-5-carboxamethoxy benzoxazole with different secondary amines under reflux conditions in the presence of alcohol. The anti-inflammatory activity of test compounds was evaluated against carrageenan induced paw edema in rats and all the synthesized benzoxazole derivatives exhibited significant anti inflammatory activity. The compounds with 2-substitutents were found to be relatively more potent than their unsubstituted analogs.
2.2 ANTIMICROBIAL ACTIVITY

The number of life threatening infections caused by multidrug-resistant Gram-positive pathogens has reached an alarming level in hospitals and the community. Infections caused by these organisms pose a serious challenge to the scientific community and the need for an effective therapy has led to a search for novel antimicrobial agents. Antimicrobial drugs are effective in the treatment of infection because of their selective toxicity that is they have the ability to injure or kill an invading microorganism without harming the host. It is evident from literature that benzoxazole derivatives are known to be associated with broad spectrum of biological activities like antibacterial, antifungal etc.

Ismail Yalcin et al., had been synthesized 5-substituted-2-cyclohexyl methylbenzoxazoles (Fig. 6) by the reaction of 2–hydroxy–5-substituted aniline and cyclohexylcarboxylic acid with sodium bicarbonate. The synthesized compounds showed moderate to good antibacterial and antifungal activity.

Zafer Asim Kaplancikli et al., had been synthesized ethyl {2-[(5-substituted-benzoxazol-2-yl)sulfanyl]acetylaminothiazol-4-yl} acetate by reaction of ethyl 2-[2-(2-chloroacetamido)thiazol-4-yl]acetate and 5-nitrobenzo [d]oxazole-2-thiol & potassium carbonate in acetone. Minimum inhibitory concentrations (MICs) were recorded as the minimum concentration of a compound that inhibits the growth of tested microorganisms. All of the compounds tested were illustrated significant antibacterial and antifungal activity when compared with reference drugs. The antibacterial evaluation revealed that the compounds possess significant activity. The MIC values are generally within the range of 3.9-250 μg/mL against all evaluated strains. In comparing their MIC values with Chloramphenicol, of all the compounds were effective against Bacillus subtilis, Escherichia coli and Klebsiella pneumoniae. Compounds 4-(benzoxazol-2-yl)-n-(4-fluorobenzylidene) exhibited good antifungal activity.

Dayakar Gadhe el al., synthesized methyl-2- [(arylidenearminoo) oxazol-4-ylamino] benzoxazole-5-carboxylate derivatives (Fig. 8) by the reaction of Methyl-2-(aminooxazol-4-ylamino) benzoxazole-5-carboxylate and appropriate aromatic aldehydes by dissolving in alcohol and finally washed with 1% sodium bicarbonate solution. The synthesized benzoxazole-5-carboxylate derivatives showed excellent antibacterial activity against Bacillus subtilis, E.Coli etc.

4-(benzoxazol-2-yl)-n-(4-fluorobenzylidene) (Fig. 9) had been synthesized by Shailendra K. Saraf et al., by the equimolar quantities of 4-benzoxazol-2-yl-phenylamine and 4-fluoro benzaldehydes in warm ethyl alcohol. All the compounds were subjected to antimicrobial evaluation which revealed that with the known standard antibiotics Ciprofloxacin (10μg/ml) and Fluconazole (10μg/ml) experimental compounds shows zone of inhibition of 20-23 mm and 18-20 mm against bacterial and fungal strains. Compounds displayed activity against Bacillus subtilis, Escherichia coli and Klebsiella pneumoniae. Compounds 4-(benzoxazol-2-yl)-n-(4-fluorobenzylidene) exhibited good antifungal activity.

In vitro antimicrobial activities of the 2-(benzyl/p-chlorobenzyl)-5- [(substituted thiienyl/phenyl/phenyl thiomethyl/ benzy] carbamino] benzoxazole (Fig. 10) were investigated using two fold serial dilution technique against different two Gram-positive, two Gram-negative bacteria and three Candida spp. in
comparison with standard drugs. Microbiological results indicated that the newly synthesized derivatives possessed a broad spectrum of activity having MIC values of 6.25-100 µg/ml against the tested microorganisms.

![Fig. 10](image1)

**Fig. 10.** 2-(benzyl/p-chlorobenzyl)-5-[(substituted thiethyl/phenyl/phenylthiomethyl/benzyl) carbonyl amino] benzoxazole

Dayakr Gadhe et al.,\(^{19}\) had been synthesized Calcimycin (Fig.11) by treating methyl-2-(2-aminooxazole-4-ylamino)benzoxazole-5-carboxalate with appropriate aromatic aldehydes. The compounds were found to possess remarkable antimicrobial activity.

![Fig. 11](image2)

**Fig. 11.** Calcimycin

\[\text{Calcimycin} \quad [(5-Benzylidene)-2-aryl-4-oxo-1,3-thiazolidinhydrazinoacetyl]-mercaptobenzoxazole (Fig. 12) had been synthesized by P. Kohli et al.,\(^{20}\) by a equimolar solution of [(2-aryl-4-oxo-1,3-thiazolidin)hydrazinoacetyl mercaptobenzoxazole] and benzaldehyde in methanol. It posses promoting antimicrobial activity against bacterial strains.

![Fig. 12](image3)

**Fig. 12.** [(5-Benzylidene)-2-aryl-4-oxo-1,3-thiazolidinhydrazinoacetyl]-mercaptobenzoxazole

Some new antimicrobial active N-(2-hydroxy-4-nitrophenyl)-p-substituted benzamides (Fig. 13) and phenylacetamide analogues were prepared by 2-step procedures from the corresponding carboxylic acids as possible metabolites of benzoxazoles. Their antimicrobial activities were tested against various Gram-positive and Gram-negative bacteria & the fungus *Candida albicans*, and were also compared with several control drugs. Most of the compounds exhibited antifungal activity at a MIC value of 12.5 µg/mL against *C. albicans*. On the other hand, the antimicrobial activity of some amide derivatives was also compared with their cyclic analogues, benzoxazole derivatives. The compounds significantly possessed 2 or 3 dilutions better antimicrobial activity than its heterocyclic derivative, 2-(p-t-butylphenyl)-5-nitrobenzoxazole derivatives, against *Staphylococcus aureus*, *Streptococcus faecalis*, *Klebsiella pneumonia*, and *Escherichia coli*.\(^{17}\)

![Fig. 13](image4)

**Fig. 13.** N-(2-hydroxy-4-nitrophenyl)-p-substituted benzamides

QSAR analysis of some 5- or 6- methyl-2-substituted benzoxazoles/ benzimidazoles (Fig. 14) was studied for the antifungal activity against *C. albicans* using Hansch analysis. Prediction for the lead optimization in this QSAR analysis was attributed by the description of various hydrophobic, electronic, steric and structural parameters related to positions R\(_1\), R\(_2\), R\(_3\), R\(_4\), & Y. The cross validation method was also applied to the data set in order to prove the predictive power by using the BILIN statistical software. The resulting QSAR revealed that substitution at position Y with the CH\(_2\) group was significant for the improved antifungal activity. Moreover, hydrophobic properties of the substituents at position R\(_3\) are indicative for the antifungal activity against *C. Albicans*.\(^{21}\)

![Fig. 14](image5)

**Fig. 14.** 5- or 6- methyl-2-substituted benzoxazoles/ benzimidazoles

Novel benzoxazole substituted thiazolidinone derivatives (Fig. 15) were synthesized through cyclisation of unsymmetrical imine with mercapto acid in the presence of st anus chloride dehydrated. All the synthesized compounds were tested each at 50 µL, 100 µL and 150 µL concentration to find out their efficacy in inhibiting the growth of the four human pathogenic bacteria. The synthetic compounds efficiently inhibited the growth of *Proteus mirabilis*, *Staphylococcus aureus* and *Salmonella typhi* followed by *Klebsiella pneumonia*. A positive correlation existed between the concentration of the compound and the inhibitory action against the pathogens tested.\(^{22}\)
The quantitative structure activity relationship of 5-substituted-phenyl-benzoxazole derivatives (Fig. 16) were studied including quantum-chemical parameters, based on extrathermodynamic method. It was found, that the antifungal activity of these compounds against *candida albicans* highly correlated with the decreasing order of $\varepsilon_{\text{LUMO}}$, molecular weight, resonance effect and $\varepsilon_{\text{HOMO}}$. Overall charge transfer interaction between benzoxazole compounds and receptor site indicate, that $\varepsilon_{\text{LUMO}}$ (energy of the lowest unoccupied molecular orbital) value of the derivatives are playing an additive role for the antifungal activity against *Candida albicans*. This situation reveals, that benzoxazole ring moiety is the most important part in the molecule for the interaction with the receptor site.

Ilkay Yaldiz et al.\textsuperscript{23} had been synthesized 2-(substitutedphenyl/benzyl)-5-[(2-benzofuryl)carboxamido]benzoxazole derivatives (Fig. 17) by 5-amino-2-[p-substitutedphenyl/benzyl]benzoxazoles and 5-amino-2-[o-bromophenyl] benzoxazole with benzofuran-2-carboxylic acid chloride. Antimicrobial activity of the compounds was determined against some Gram-positive, Gram-negative bacteria and fungi 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 500-15.625 µg/ml.

Esin Sener et al.\textsuperscript{26} had been synthesized 5-substituted-2-(3-pyridyl)benzoxazoles (Fig. 20) by the reaction of 2-hydroxy-5-substituted anilines and nicotinic acid, heated in polyphosphoric acid. Antimicrobial activities of derivatives for some Gram-positive bacteria and Gram-negative bacteria and the yeast *Candida albicans* was performed and the compounds exhibited significant activity against the screened microorganisms, having MIC value between 25 and 12.5µg/ml.
Synthesis of 5(or 6)-nitro/amino-2-(substituted phenyl/benzyl)benzoxazole derivatives (Fig. 21) had been carried out by Ilkay Yildiz et al., by 2-(p-substituted phenyl/benzyl)-5(or 6)-nitrobenzoxazoles and nickel(II) chloride hexahydrate in methanol. Derivatives evaluated for antibacterial and antifungal activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans* and their drug-resistant isolate. Microbiological results indicated that the synthesized compounds possessed a broad spectrum of activity against the tested microorganisms at MIC values between >400 and 12.5 µg/ml. The results against *B. subtilis*, *P. aeruginosa*, drug-resistant *B. subtilis*, drug-resistant *E. coli*, and *C. albicans* isolate for these kinds of structures are quite encouraging. The 2D-QSAR analysis of a set of newly and previously synthesized benzoxazoles tested for growth inhibitory activity against *B. subtilis* ATCC 6633 was performed by using the multivariable regression analysis. The activity contributions for substituent effects of these compounds were determined from the correlation equation for predictions of the lead optimization.

Ilkay Oren et al., had been synthesized 5(or 6-methyl-2-substituted) benzoxazoles (Fig. 22) by p-substituted phenylacetic acid/ p-substituted phenoxyacetic acid/ thiophenoxyacetic acid/ 3-phenylpropionic acid and 2-hydroxy-4-methylaniline/2-hydroxy-5-methylaniline. They were added to a solution of PPSE in 1, 2-Dichlorobenzene mixture. The chemical, physical and spectral data of the synthesized compounds reported antimicrobial activity of the compounds in comparison to some control drugs is indicates that the compounds are able to inhibit growth of a number of microorganisms exhibiting MIC values between >200 and 6.25 µg/ml. The synthesized compounds provided a wide range of antibacterial activity against the tested microorganisms.

Biologically active benzoxazole derivatives (Fig. 23) have been known since long time and 2-substituted ones were prominently studied. It was seen that position 2 is decisive for the biological activity, whereas position-5 determines the intensity of the activity.

The previous QSAR study of benzoxazole derivatives was found that overall charge transfer interactions between the compounds and site of action, as the energy of the lowest unoccupied molecular orbital values (E_{LUMO}) of the benzoxazoles, showed additive contributions for the antifungal activity against *C. albicans*.

Ilkay Yildiz Oren et al., had been studied 3D-QDAR using comparative molecular field analysis (CoMFA) approach on set of 2(p-substituted phenyl)-5-(substituted carbonylamino) benzoxazole (Fig. 25) as antibacterial agent against *Staphylococcus aureus*. The CoMFA analysis gave cross-validated r² value of 0.480 and non cross –validated r² = 0.950 with an optimized component. The model deduced from this investigation provides underlying structural requirements and good predictive ability, which could, aid the new antibacterial agents for *Staphylococcus aureus* prior to their synthesis.
Fig. 25. 2(p-substituted benzyl)-5-(substituted carbonylamino) benzoxazole

2.3 CYCLOOXYGENASE-2 INHIBITORS
Srinivas . A et al., had been synthesized methyl-2-[2-(disubstituted amino) acetamido] benzoxazole-5-carboxylates (Fig. 27) by the reaction of a solution of Methyl 2-(2-chloroacetamido) benzoxazole-5-carboxylate in dry Acetone & N, N-dialkylamine. All the synthesized benzoxazole derivatives were shown good to moderate activity. Some compounds shown the IC\(_{50}\) values of 12.69, 20.13, 23.85 and 21.09 respectively.

Fig. 26. methyl-2-[2-(disubstituted amino) acetamido] benzoxazole-5-carboxylates

Recently some benzoxazole-5-carboxylates (Fig. 28) has been developed as selective COX-2 inhibitor using TMPD assay method by Srinivas . A et al.,\(^3\) The title compounds were synthesized by treating the methyl-2-aminobenzoxazole-5-carboxylate with appropriate aromatic aldehyde to get a novel series of methyl-2-(arylideneamino) benzoxazole -5-carboxylate derivatives. In conclusion, these classes of compounds may serve as excellent agents for selective COX-2 inhibition.

2.4 DNA TOPOISOMERASE INHIBITOR
5-phenylacetamidosubstituted-2-phenylbenzoxazole derivatives (Fig. 29) had been synthesized by Aysegul Akbay et al.,\(^3\) 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\(\times\)10\(^5\) µmol/1-0.34 µmol/l and their activities were compared to some standard drug such as 3’-azido-2’,3’-dideoxythymidine triphosphate and dideoxythymidine triphosphate.

Fig. 28. methyl-2-(arylideneamino) benzoxazole -5-carboxylate derivatives.

Emine Oksuzoglu et al.,\(^3\) investigated the inhibitory effects of some novel fused heterocyclic compounds (Fig. 30) on eukaryotic DNA topoisomerase II in a cell free system and 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. The structure-activity relationships for these tested compounds indicated that the benzoxazole ring was more important than the benzimidazole ring for DNA topoisomerase II inhibitory activity. 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.

Fig. 29. 5-phenylacetamidosubstituted-2-phenylbenzoxazole derivatives

Fig. 30. 5(or 6-methyl-2-substituted) benzoxazoles

The versatile and synthetically accessible 2-arylbenzoxazole scaffold has provided the inspiration for the discovery of a number of new antitumor agents with unusual mechanisms of action in recent years. The 2-(4-aminophenyl)benzoxazoles provide a case in
point and illustrate the wider benefits of a “chemistry-led” approach to drug discovery.

The major exportable 6-hydroxylated metabolite from drug-CYP1A1 interaction was found to be inactive and antagonistic to the antitumor activation process, leading to the development of fluorinated benzoxazoles to thwart the deactivation process. Among the fluorinated analogues, 2-(4-amino-3-methylphenyl)-5-fluorobenzoxazole (Fig. 31) emerged as the lead compound and, based on a favorable comparison with doxorubicin against a panel of breast cancer xenografts is now in phase 1 clinical trial in the U.K.

The synthesis of a range of 2-phenyl-benzoxazoles, related to the potent antitumor lead compound 2-(3,4-dimethoxyphenyl)-5-fluorobenzoxazole has been accomplished. Evaluation against the MCF-7 and MDA 468 breast cancer cell lines revealed compounds within the new series with potent (submicromolar GI50) activity in both cell lines. Although none of the new series was able to recapitulate the potent antitumor properties. The new compounds were significantly more active than the structurally related benzimidazoles. Surprisingly, SAR studies indicated that minor modifications of the dimethoxyphenyl group, removal of the fluoro group, or its replacement with other halogens had a profoundly dyschemotherapeutic effect with respect to in vitro growth-inhibitory activity.

The Aβ fibrils binding agents may potentially be useful for early detection and monitoring the progression of Alzheimer’s disease. Currently, development of specific imaging agents available for direct mapping of Aβ aggregates in the living brain has been recently investigated. Recently the synthesis and evaluation of a of benzoxazole derivatives with high affinities for Aβ42 fibrils using [125I]TZDM have been identified by Young Shine Chun et al. The synthesis has been carried out by refluxing the benzoxazolylmalononitriles with carbonyl compounds in pyridine, malononitrile and triphenylphosphine. Functionalized benzoxazole derivatives (Fig. 32) based on the structural features of PIB and FDDNP showed excellent binding affinities to aggregated Aβ 42 fibrils. These compounds could be considered as ligands for molecular imaging agents to monitor Aβ 42 fibrils in AD brain due to their high binding affinity.

The final compounds were evaluated for the ability to activate PPARα and PPARγ in a transactivation assay in CV-1 cells, respectively. All compounds revealed significant PPARγ activities, although known BRL 48482 showed the most potent agonism to PPARγ. It was found that methyl substituent on the exocyclic nitrogen was the most suitable for PPARγ activities. Further SAR study of the thiazolidinedione (TZD) analog with various steric and electrostatic functional groups at the exocyclic nitrogen is currently under investigation.

**2.5 MISCELLANEOUS-**

**2.5.1 Aβ42 FIBRILS BINDING AFFINITY**

The Aβ fibrils binding agents may potentially be useful for early detection and monitoring the progression of Alzheimer’s disease. Currently, development of specific imaging agents available for direct mapping of Aβ aggregates in the living brain has been recently investigated. Recently the synthesis and evaluation of a of benzoxazole derivatives with high affinities for Aβ42 fibrils using [125I]TZDM have been identified by Young Shine Chun et al. The synthesis has been carried out by refluxing the benzoxazolylmalononitriles with carbonyl compounds in pyridine, malononitrile and triphenylphosphine. Functionalized benzoxazole derivatives (Fig. 32)
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.

CONCLUSION

Benzoxazole moiety is expanding their pharmaceutical importance and have been studied frequently for the exploration of their pharmacological assistance in varied pharmacological circumstances. The benzoxazole derivative have beneficial effects on inflammatory disorders, microbacterial infection, COX-2 mediatary responses and on DNA topoisomerases. The contributing physical chemical properties for their therapeutic efficacy need to established by QSAR studies, which may also provide imminent to the essential structural modifications to this class of compounds. The scrutiny have been guiding for development of benzoxazole nucleus , which results in a lead compound for future development of new drug to be used against varity of ailments.

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