Review Article

Benzoxazole: Synthetic Methodology and Biological Activities

Anuj Kumar [1*], Vivek Pal[2], Dr. Khushboo Mishra[2], Surbhi Singh[1]
[1]Research Scholar, [2]Associate Professor, Smt. Vidyawati College of Pharmacy, Jhansi, Uttar Pradesh, India.
***Corresponding author's E-mail:** anujkumar27129@gmail.com

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ABSTRACT

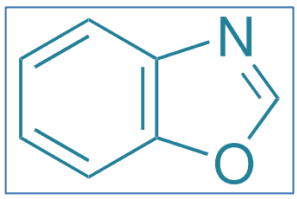
In medicinal chemistry, heterocycles have demonstrated significant significance in the creation of compounds with pharmacological activity. The therapeutic potential of most synthesised medicinal compounds is due to a heterocyclic scaffold. The small alterations in the heterocyclic moiety were linked to therapeutic modifications in the medication molecules. Numerous biological activity, including antibacterial, antifungal, anti-inflammatory, analgesic, and anticancer properties, have been described for benzoxazole nucleus. As a result, we attempted to compile the chemistry of several substituted benzoxazole derivatives, together with a variety of pharmacological activity and some of the key synthesis techniques, in the current review. Researchers seeking to create novel benzoxazole derivatives may find this review to be helpful in determining their efficacy and safety.

Keywords: Heterocyclic compounds, Benzoxazole, Synthetic methodology, Pharmacological action.

INTRODUCTION

As organic chemistry advanced in the middle of the 19th century, the history of heterocyclic compounds began. One important aspect of the chemical and biological sciences is heterocyclic molecules. Over 75% of the top 200 drugs in the pharmaceutical industry are from the heterocyclic family [1]. Many physiologically active chemicals are based on a series of simple and subordinate heterocyclic compounds with nitrogen, oxygen, and oxazole moieties. Heterocyclics make up the majority of naturally occurring agrochemicals and medicines [2, 3]. Because of their numerous biological activities, including antiviral, anticancer, antimicrobial, antitubercular, antimalarial, and antioxidant properties, the compounds derived from the heterocyclic moiety play a significant role in the advanced medication disclosure that is widely applied in the field of restorative science[4].

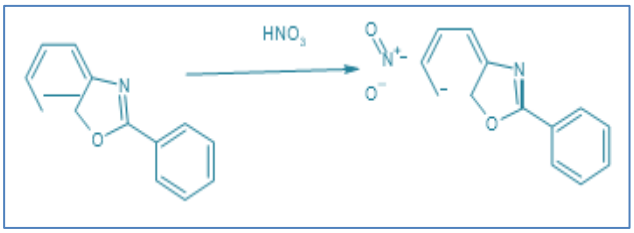
1.1 Benzoxazole: [5]



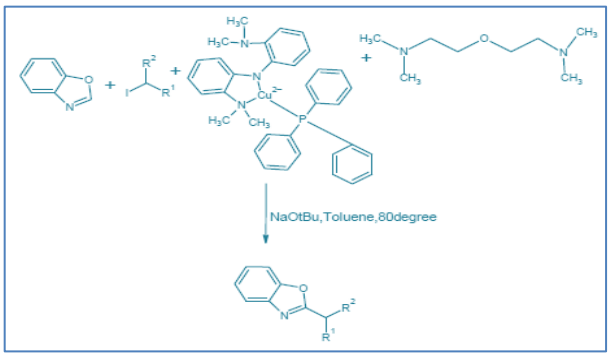
1. Benzoxazole, also known as 1-oxa-3-aza-1h-indene, is a member of the class of compounds known as benzoxazoles.
2. Benzoxazoles are organic compounds containing a benzene attached to an oxazole ring. Oxazole consists of a five-membered aromatic ring with a nitrogen and an oxygen atom at the 1- and 3- position, respectively.
3. Its molecular formula is C_7H_5NO and molar mass is 119.12 g/mol.
4. Benzoxazole is soluble (in water) and an extremely weak basic (essentially neutral) compound (based on its pKa).
5. Melting point is 27-30℃. Its odour is similar to pyridine.

1.1.1 Chemical Properties: With the chemical formula C_7H_5NO, benzoxazole is an aromatic organic molecule made up of an oxazole ring fused to a benzene. Despite being a heterocycle with reactive sites that enable functionalisation, its aromaticity keeps it comparatively stable. It exhibits a range of electrophilic reactions, with substitution mostly taking place at positions 2, 3, and 6. Halogenation is favoured by the presence of an electron-withdrawing group [6, 7].

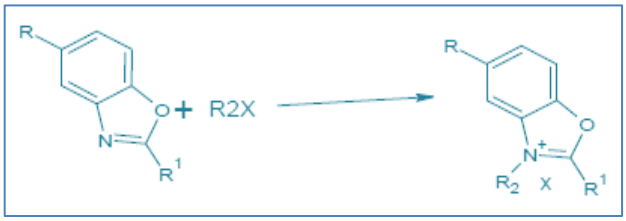
1. Nitration: Nitric acid and sulphuric acid are used in the nitration of benzoxazole. The C6-position is where nitration predominantly takes place. At normal temperature, 6-nitro-2-phenyl benzoxazole is produced by nitrating 2-phenyl benzixazole[8].



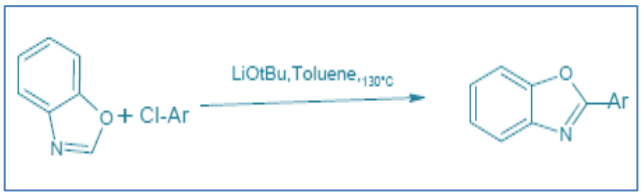
2. Alkylation: Benzoxazole undergoes alkylation at position two upon reaction with secondary alkyl halides in the presence of bis[2-(N,N- dimathylamino)ethyl]ether and copper(I) as a catalyst[9].



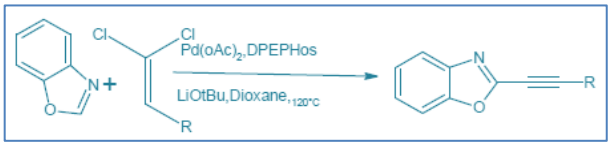
On the other hand, 2-substituted benzoxazoles can be treated with alkylating agents such as dialkyl sulphates and iodomethanes to produce N-alkylated compounds[9].



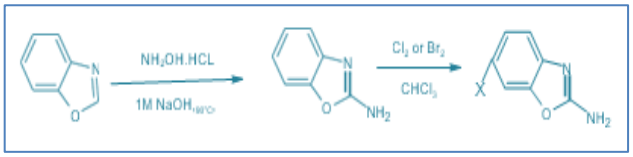
Aryaltion: When aryl chlorides are treated with a base, such as palladium catalyst and lithium tertiary butoxide, aryl benzoxazoles can be produced[9].



Alkynation: Benzoxazole is directly alkynated by Pd-catalyzed reactions with gem-dichloroalkenes at 120°C when DPEPHos and lithium tertiary butoxide are present in catalytic amounts[9].

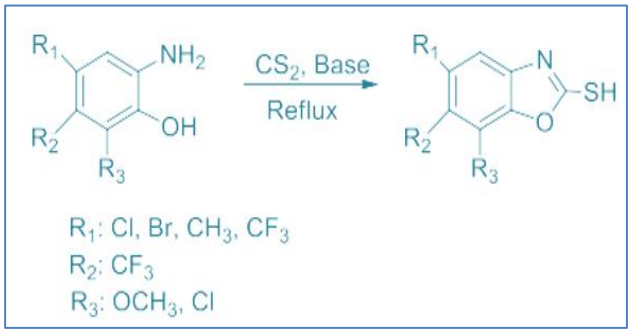


Amination: When benzoxazole is treated with hydroxylamine hydrochloride in 1M NaOH, an amino group enters at position three. The resultant amino benzoxazole subsequently produces matching chloro or bromo derivatives by reacting with Cl_2 or Br_2 in chloroform [8].

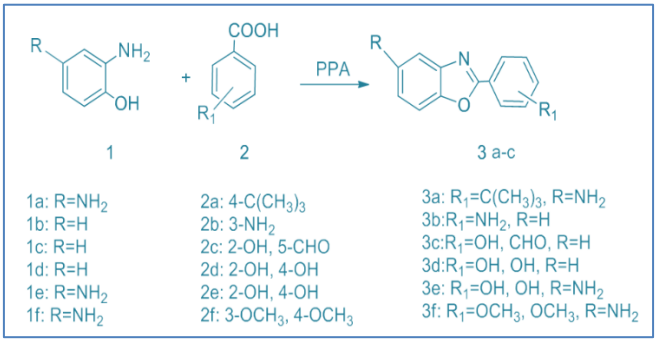


1.1.2 Synthetic Approach:

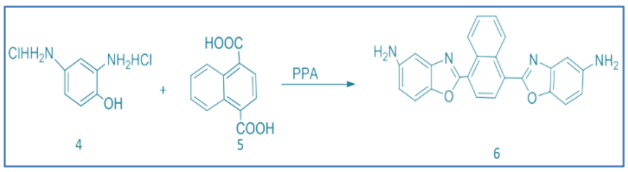
Scheme 1: There are various methods for synthesising the benzoxazole moiety. wherein PPA and the addition of CS_2/KOH are used in the majority of the synthetic process. Other synthetic techniques also exist, such as adding CNBr, using aldehydes, and using certain chemical agents like DDQ, IBD, etc. Aminophenol was one of the main reactants in the majority of synthetic techniques utilised to create the benzoxazole moiety. The necessary benzoxazole was produced in good yield when o-aminophenol was condensed using carbon disulphide in the presence of a base, such as potassium hydroxide or sodium hydroxide[10, 11].



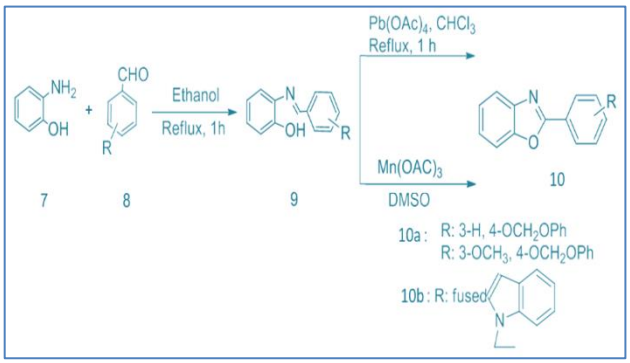
Scheme 2: 5-amino-2-(4-tert-butyl-phenyl)-benzoxazole (3a) synthesized by taking 2,4-diaminophenol (1a) with p-tert-butyl benzoic acid (2a) in polyphosphoric acid, o-aminophenol (1b) reacted with aminobenzoic acid (2b) in the presence of PPA gives 3-(benzo[d]oxazol-2-yl)aniline (3b), [12] synthesis of 2-(20-Hydroxyphenyl)benzoxazole (3c) by 5- Formylsalicylic acid (2c) and 2-aminophenol (1c) in polyphosphoric acid stirred at 180°C for 5 hour and 2,4-Dihydroxybenzoicacid (2d) with o-aminophenol (1d) in polyphosphoric acid forms dark brown precipitate which is (1H-benzo[d]oxazole-2-yl) benzene-1,3-diol (3d). 2-(3,4-Diimethoxy phenyl) benzoxazol-5-amine (3e) was prepared by heating 2,4-diaminophenol (1e) and 3,4-dimethoxybenzoic acid (2e) in presence of cyclizing agent PPA [13]. 5- amino-2-(20-hydroxy-40-methylphenyl) benzoxazole (3f) was synthesized by the reaction of 2,4-diaminophenol (1f) and 4-methylsalicylic acid (2f) in polyphosphoric acid (PPA) [14] at 150°C.



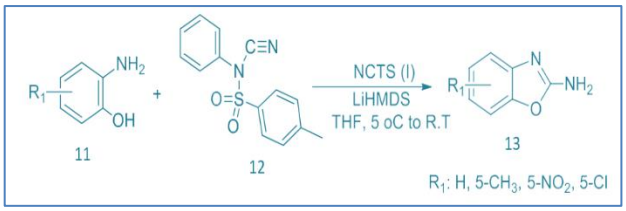
Scheme 3: A thick paste of 1,4-di (5-aminobenzoxazol-2-yl)naphthalene was created by dissolving 2,4 diaminophenol (4) and 1,4-naphthalene dicarboxylic acid (5) in poly (phosphoric acid) (PPA) under a nitrogen atmosphere, as per the literature, which states that cyclizing agents such as PPA are utilised for benzoxazole synthesis[15].



Scheme 4: Following ethanol reflux and oxidative cyclisation with lead tetra acetate, a mixture of 2-aminophenol (7) and 4-benzyloxy benzaldehyde (8) yielded the 2-[4-(Benzyloxy)phenyl]-1,3-benzoxazole molecule (10a). 3-Benzoxazole-N-Ethyl Carbazole (10b) was obtained by heating a mixture of schiff base compound (9) and manganese (III) acetate in DMSO to 140 °C for 24 hours[16].



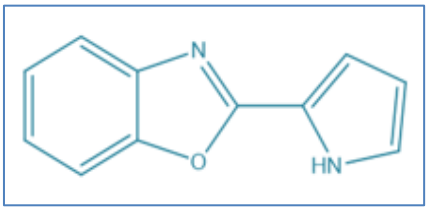
Scheme 5: N-cyano-N-phenyl-p-toluenesulfonamide (NCTS), a nontoxic electrophilic cyanating agent, can be used to easily synthesise 2-aminobenzoxazole (13) derivatives using various substituted 2-aminophenols (11) and benzene-1, 2-diamine derivatives in the presence of lithium hexmethyldisilazide (LiHMDS). [17]



1.1.3 Pharmacological Properties: Numerous biological activities, including anticancer, antihelmintic, cyclooxygenase inhibitory, anti-inflammatory, analgesic, cyclin-dependent kinase inhibitory, 5-lipoxygenase inhibitory, anticonvulsant, rho kinase inhibitory, and antihyperglycemic properties, are among the many promising biological activities of benoxazoles [18]. Benzoxazoles are known to be a significant scaffold in fluorescence probes such metal cation and anion sensors, in addition to its application in medicinal chemistry [19-21].

1. Antioxidant Activity: Using Cu^{+2} as an oxidising agent, Aichaoui et al. synthesised 2(3H)-benzoxazolone derivatives and evaluated their in vitro antioxidant activity at a dose of 10 µM to stop human LDL copper-induced oxidation. According to time- and dose-dependent measurements, Compound 1 exhibited more antioxidant potential and inhibited the start and spread of copper-mediated LDL oxidation[22].

2. Analgesic Activity: Praveen et al. used the tail immersion method to test their analgesic properties after developing a benzoxazole derivative by a cyclocondensation procedure. While compounds 4, 5, and 6 showed greater analgesic potency (73.5%, 76.4%, and 74%, respectively), compounds 2 and 3 showed intermediate analgesic potential (54.5% and 59.6%). In this experiment, pentazocine served as a positive control [23].



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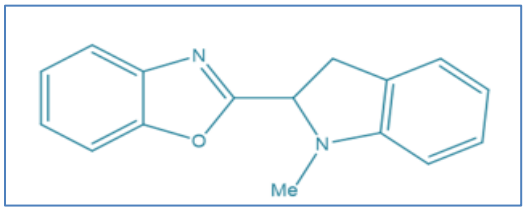

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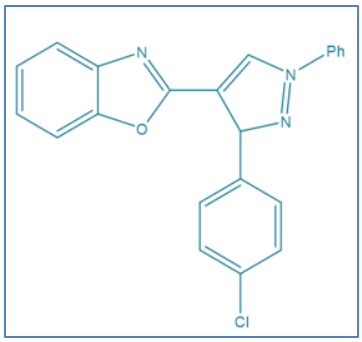

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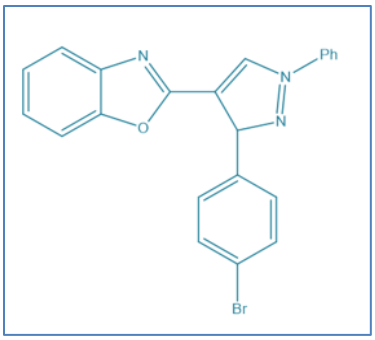

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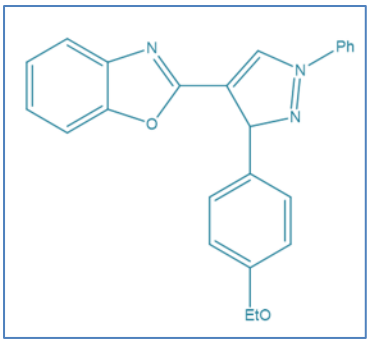

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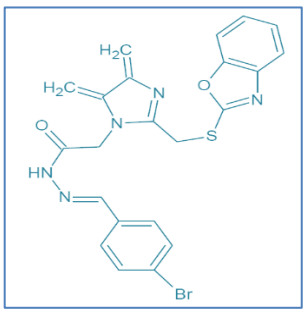
3. Anticancer Activity: 2-(2-((benzoxazol-2-ylthio) methyl)-1H-benzimidazol-1-yl) aceto hydrazide derivatives were synthesised, according to Balasubrahmanian N et al. The 2-(3-diethyl-amino-6-diethylazaniumylidene-xanthen 9-yl)-5-sulfobenzene-sulfonate (SRB) assay was utilised to determine the anticancer activity of the produced derivatives utilising the human colorectal carcinoma [HCT116 (ATCC (American Type Culture Collection) CCL247)] cancer cell line. Benzoxazole derivative synthesis was reported by Balasubrahmanian N et al. once more. Benzazole derivatives' antiproliferative properties were evaluated using the human colorectal cancer cell line HCT 116 (ATCC CCL-247). 5-fuorouracil is the usual medication (IC50=12.2 µM). [24]



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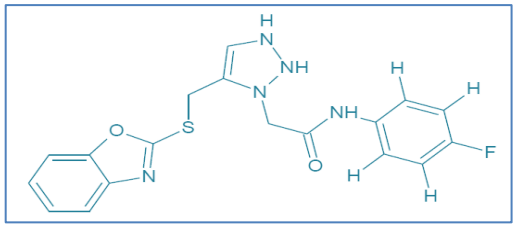

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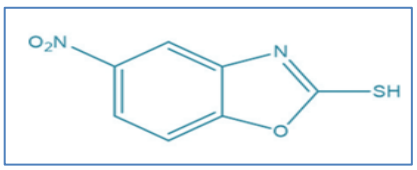
4. Anthelmintic activity: The anthelmintic activity of 5-nitro-1, 3-benzoxazole derivatives was synthesised and assessed by Satyendra et al. The study's findings showed that compounds 9 and 10 had strong anthelmintic effects. Additionally, the researcher conducted molecular docking experiments and came to the conclusion that the main mechanism underlying these synthetic drugs' anthelmintic properties is the suppression of the b-tubulin target protein linked to the parasites [25].



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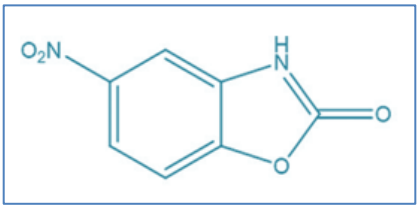

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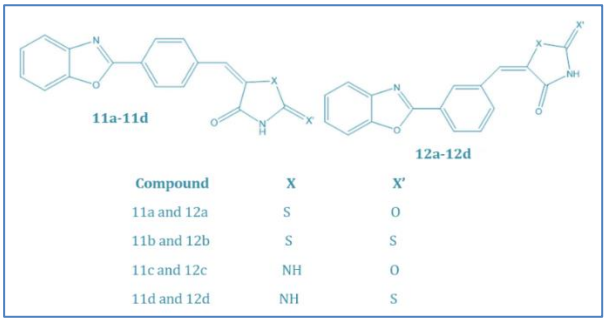
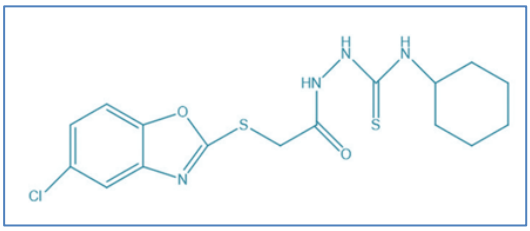
5. Antihyperglycemic Activity: Benzazole compounds 11a-11d and 12a-12d were synthesised by Singh et al., who also investigated their α-amyloglucosidase inhibitory action. Compounds 11a and 11c showed the least inhibitory action against α-amyloglucosidase, with IC50 values of 22.00 ± 1.21 and 29.03 ± 1.11 µM, whereas compounds 11b and 12b showed strong IC50 values in the range of 0.24 ± 0.01–0.94 ± 0.01 µM. Other compounds showed moderate potential. In this experiment, acarbose served as a positive control [26].



Compound	X	X'
11a and 12a	S	O
11b and 12b	S	S
11c and 12c	NH	O
11d and 12d	NH	S

6. Anticonvulsant Activity: Ibrahim et al. produced 5-chloro-2-substituted sulfanyl-benzoxazole and tested its anticonvulsant properties on mice that had seizures caused by pentylenetetrazole. In order to evaluate synthetic drugs' binding affinities to the KCNQ2 receptor, researchers also looked at their molecular docking studies. The study's findings showed that compounds 13, 14, 15, and 16 had the most anticonvulsant potential and the highest binding affinities towards the KCNQ2 receptor. [27]



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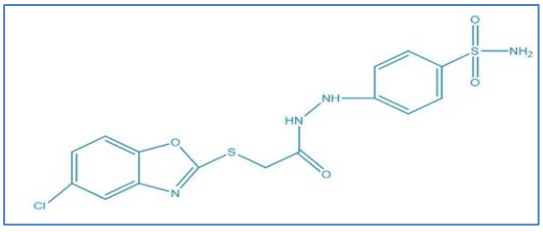

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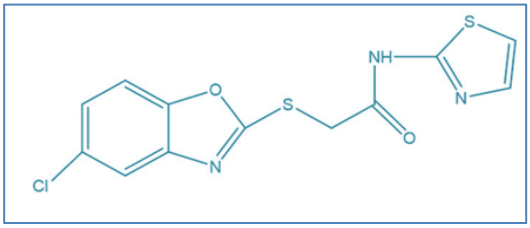

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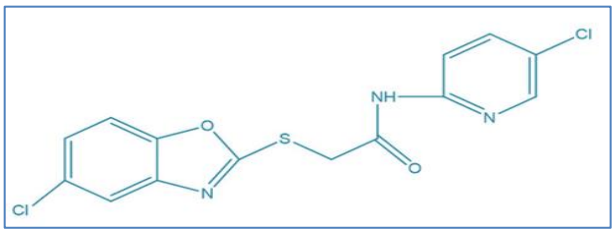

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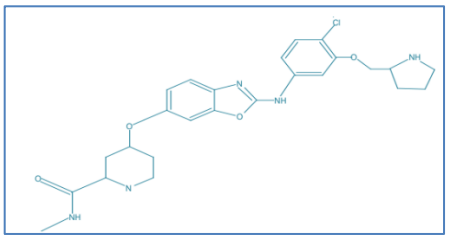
7. Benzoxazoles as vascular endothelial growth factor-2 receptor tyrosine kinase inhibitors: After synthesising a number of 2-aminobenzimidazoles and benzoxazoles, Michele H. Potashman et al. discovered that benzoxazole was a strong and specific VEGFR-2 inhibitor with a favourable pharmacokinetic profile. Compound 17 showed effectiveness in the rat corneal angiogenesis paradigm (ED_{50} = 16.3 mg/kg) in the murine matrigel model for vascular permeability (79% decrease seen at 100 mg/kg). [28]



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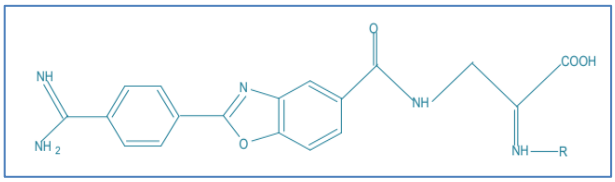
8. Benzoxazole as glycoprotein IIb/IIIa inhibitors: A powerful class of benzoxazole GPIIb/IIIa inhibitors was created by Chu-Biao Xue et al. A benzamidine as the basic moiety and an α-carbamate or sulphonamide substituted β-alanine as the acidic moiety are necessary for the great effectiveness of these group of compounds in inhibiting platelet aggregation. [29-32]



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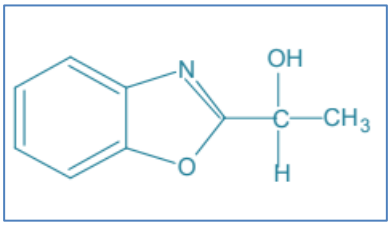
9. Benzoxazole with Antimicrobial Activity: The antifungal and antibacterial properties of six benzimidazole and benzoxazole derivatives were investigated in vitro by Elnima EI et al. They were examined in comparison to 59 clinical isolates and reference strains. Only two of the six compounds—both benzoxazoles—were active, whereas the others showed no activity at all. All of the typical strains, including fungi and gram-positive and gram-negative bacteria, showed significant growth suppression upon treatment with these drugs. The susceptibility of fifty-nine clinical isolates of Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli to the two substances was examined. The isolates of S. aureus were the most vulnerable. Compound (20) exhibited somewhat higher activity than compound (19), but both compounds had similar efficacy against all isolates. Their respective minimal inhibitory concentrations for 90% inhibition of S. aureus were 25 and 50 µg/ml. The gram negative bacteria were resistant to the two compounds and required minimal inhibitory concentrations of 200 µg/ml for a similar degree of inhibition. [33]



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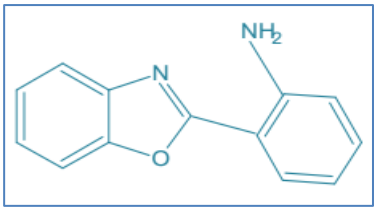

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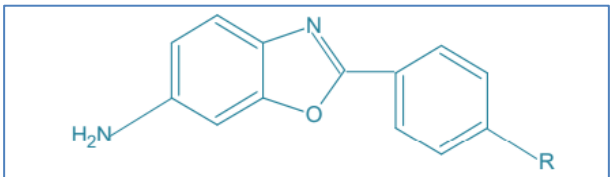
5-amino-2-(p-substituted-phenyl) benzoxazole derivatives were synthesised by Sener E. et al. In the presence of polyphosphoric acid, 2, 4-diaminophenol was heated with the proper carboxylic acids to create them. Since position 5 predominates in terms of activity intensity, 2-substituted benzoxazoles were extensively researched in the belief that this position determines biological activity. Benzoxazole compounds that are replaced at positions two and five include benzoxazoprofen and zoxazolamin. [34]



5-Amino-2-(p-Substituted-Phenyl) Benzoxazole Derivatives

R	Acid used as starting compound
H	Benzoic acid
C_2H_5	p-Ethyl benzoic acid
Br	p-Bromo benzoic acid
F	p-Fluorobenzoic acid
$N(CH_3)_3$	p-Dimethylaminobenzoic acid
NO_2	p-Nitrobenzoic acid

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CONCLUSION

Benzoxazole nucleus modifications have produced a wide range of molecules with various pharmacological properties. Because of their prospective uses, the synthesis, structures, and biological activities of benzoxazole derivatives have long been the subject of medical study attention. Compared to previous compounds, the biological characteristics of these new generations of benzoxazoles show significant advancements. For medicinal chemistry researchers focussing on the creation of new molecules

with benzoxazole scaffolds, this review might offer a fresh perspective. Although many derivatives with strong biological activity were created by researchers, further clinical research on these molecules is still necessary.

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