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Biologically active Benzoxazole: A comprehensive review

Nupur Aggarwal, Avneet Kaur, Keshav Anand, * Hitesh Kumar, * SR Wakode

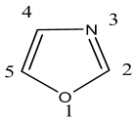
Department of Pharmaceutical Chemistry, Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR), Sector-3, Pushp Vihar, New Delhi, India

Abstract
This review constitutes a methods of preparation and biological activities of some substituted benzoxazoles. Benzoxazole moieties have attracted special attention in chemistry and biochemistry because of their structural similarity with nucleic bases, such as adenine and guanine, which allows their easy interaction with the biopolymers in living system. These compounds possess a wide range of biological activities such as antibacterial, antifungal, antiviral, anticancer activities and various other activities. This review may help medicinal chemists to develop newer compounds possessing benzoxazole moiety that could be better agents in term of efficacy and safety.

Keywords: benzoxazole, heterocyclic, synthesis, pharmacological activity

Introduction

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 compounds, benzoxazole is one of the most important heterocyclic exhibiting remarkable pharmacological activities. Benzoxazole (1) is an organic compound, which has benzene fused with an oxazole ring [2] Oxazole (2) is 1, 3 azole having oxygen atom and a pyridine type nitrogen atom at the 3-position in a five member ring [3] A slight change in the substitution pattern of benzoxazole nucleus causes distinguishable difference in their pharmacological activities.



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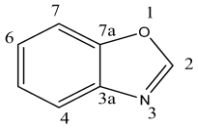


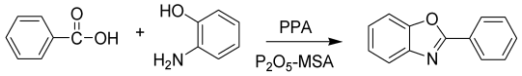
(2)

Benzoxazole is 1-oxa-3-aza-1H-indene, having molecular formula of C_7H_5NO, with melting point and boiling point of 29-30°C and 182°C. [14]. It is white to light yellow in colour with odour similar to pyridine. Benzoxazole is a planar molecule with conjugated π electrons sextets in the cyclic systems. The lone pair of electrons on nitrogen, which is co-planar with heterocyclic ring and therefore not involved in delocalization, confers weakly basic properties. Generally in the pharmaceutical field, new drugs are continuously discovered 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.

Synthesis of Benzoxazoles

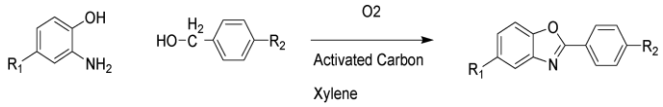
1. Reaction with Acids [3]

2-Aminophenols can cyclize to benzoxazoles in the presence of carboxylic acids upon heating to high temperatures in the presence of a dehydrating agent (polyphosphoric acid, phosphorus pentoxide-methanesulphonic acid, H_3BO_3) [11]. When equimolar amounts of 2-aminophenols and alkyl- or arylcarboxylic acids are heated to temperatures of 140-220°C are required for the formation of the corresponding 2-alkyl- or 2-arylbenzoxazoles.

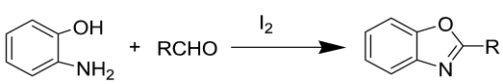


2. Reaction with Aldehydes

2-Arylbenzoxazoles were directly synthesized from substituted 2-aminophenols and aldehydes in the presence of activated carbon in xylene under an oxygen atmosphere.A simple and efficient protocol has been developed for the synthesis of 2-arylbenzoxazole derivatives of potential pharmaceutical interest. The method involves reaction between 2-aminophenol and substituted aromatic aldehydes in the presence of anhydrous bismuth trichloride as a catalyst in acetonitrile. The use of eco-friendly bismuth trichloride, overall mild reaction conditions, and moderate to good yield of products are some attractive features of this methodology [3].

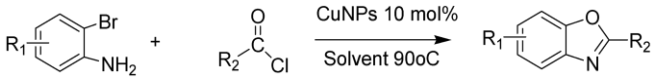


(iii) Rapid and efficient condensation of 2-amino phenol with various aldehyde were carried out using I_2 in solvent free condition with or without microwave irradiation to afford corresponding 2-substituted benzoxazole in good yield [16, 18].



3. Reaction with acid chloride

(i) A facile, highly efficient, and practical one-pot synthetic strategy 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 [3].

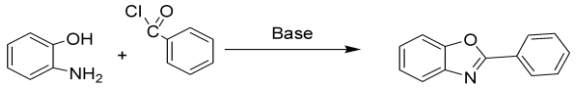


R1= H, CH3, CH3O, F

R2= alkyl, aryl, vinyl

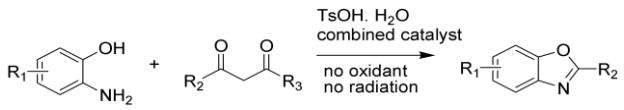
Furthermore, the solid catalyst could be recovered and reused conveniently several times with satisfactory yields.

(ii) Benzoxazole have been synthesized in non-polar high boiling solvent such as toluene and xylene in model reaction addition amino phenol react with acid chloride in presence of base.

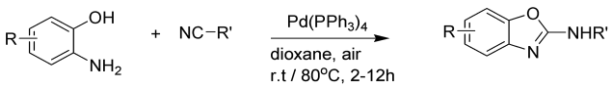


4. Synthesis of Benzoxazoles from 2-Aminophenols and β-Diketones

Cyclization reactions of 2-aminophenols with β-diketones catalyzed by a combination of Brønsted acid (p-Toluenesulfonic acid) and CuI are presented. Various 2-substituted benzoxazoles were obtained through these reactions. Different substituents such as methyl, chloro, bromo, nitro, and methoxy on 2-aminophenol are tolerated under the optimized reaction conditions [10].



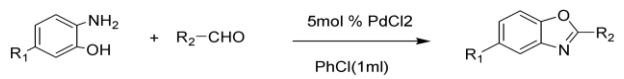
5. Reaction with isocyanide: A Pd-catalyzed aerobic oxidation of o-aminophenols and isocyanides gives 2-aminobenzoxazoles and 3-aminobenzoxazines in good yields and a broad substrate scope.[31]This methodology has the advantages of experimental simplicity, mild reaction conditions, and easily accessible starting materials. Furthermore, the synthesis of other types of useful nitrogen heterocyclic has been achieved.



R= alkyl, Bn, PMP

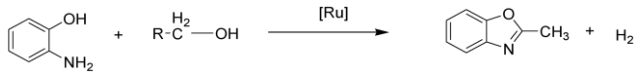
6. Reaction with palladium catalysed carbonylation

A novel and mild procedure for efficient synthesis of benzoxazoles by the cleavage reaction of carbon–carbon triple bonds with o-aminophenol in the presence of a catalytic amount of palladium chloride has been successfully developed, which provides rapid and efficient access to benzoxazoles.[49]



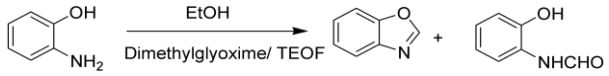
7. Reaction with alcohols

O-amino phenol reacts with alcohol in presence of a catalytic amount of a ruthenium complex to give 2-substuituted benzoxazole in good yield.



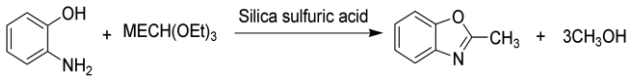
8. Reaction with oximes

Transformation of o-amino phenol with 0-alkylated oxime in to benzoxazole [41]



9. Reaction with ester

A mixture of trialkyl orthoester, o-aminophenol, O-phenylenediamine or 2-amino-3-hydroxypyridine and silica sulfuric acid was stirred at room temperature or at 85 oC for the appropriate time. The progress of the reaction was monitored by TLC (eluent: n-hexane: ethyl acetate, 2:1) [30]. After completion of the reaction, the mixture was diluted with CHCl3 (10 ml) and filtered. The solid material was washed with CHCl3 and dried at 60°C. The filtrate was evaporated and the residue was purified by recrystallization in n-hexane or by column chromatography on neutral alumina.



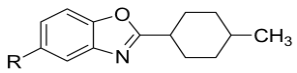
Pharmacological activity

Benzoxazole derivatives possess diverse variety of pharmacological activities [5]. 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 [15]. It is structurally similar with nucleic bases as well as the isosteres of natural occurring cyclic nucleotide such as adenine and guanine that is why it probably interacts with biopolymers in the living systems and show diverse biological activities like antimicrobial, anti-inflammatory, analgesic, antifungal, anticonvulsants, antitumor, anticancer, CNS activities, anti-hyperglycemic activity, anti-tubercular, anti-HIV agents [47], anthelmintic and other anticipated activities [22].

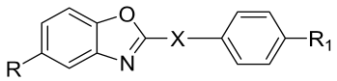
1. Antimicrobial activity [6]

The number of life threatening infections caused by multidrug-resistant gram-positive pathogens has reached an alarming level in hospitals and the community [13] 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.[44] 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 [17] It is evident from literature that benzoxazole derivatives are known to be associated with broad spectrum of biological activities like antibacterial, antifungal etc. [19].

5- substituted-2-cyclohexyl methyl benzoxazole were prepared and tested for their antibacterial activity against *Pseudomonas aurigenosa* [7].

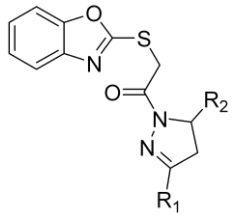


A new series of 5 (or 6)-nitro/amino-2- (substituted phenyl) benzoxazole derivatives were synthesized and evaluated for their antibacterial and antifungal activities against *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Escherichia coli, Candida albicans* and drug-resistant isolates [33]. The compounds synthesized were found to exhibit appreciable antibacterial activity [34].



2. Anticonvulsant Activity

2-mercapto benzoxazole and 2-mercapto benzimidazole were 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.

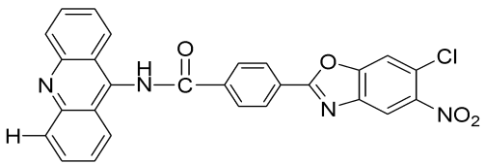


R_1, R_2= -CH3

3. Anti-inflammatory Activity

Non-steroidal antiinflammatory 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) [4]. The separation of the therapeutic effects from the side effects has been a major challenge in the design and synthesis of these drugs [25]. The discovery of a second isoform of COX, namely COX-2, has opened a new 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 [8].

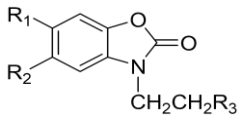
A series of N-(acridin-9-yl)-4-(benzo[d]imidazol/oxazol-2-yl) benzamides were synthesized by the condensation of 9- amino acridine derivatives with benzoxazole derivatives and characterized by FT-IR, 1H NMR, MS and elemental analysis. These compounds were found to possess appreciable anti-inflammatory activity [42].



4. Analgesic Activity

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, and $COCH_3$) 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 [25].

A series of 3-(2-pyridylethyl) benzoxazolinones derivatives were synthesized which exhibited antiinflammatory and analgesic activity [42].



R_1= H, Cl

R_2=CH_3CO, C_6H_5CHO

R_3= 2-pyridyl, 4-pyridyl

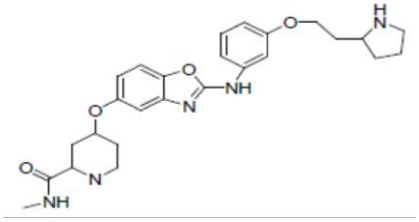
5. Anticancer Activity

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 [7]. 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) [29].

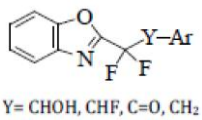
From the different groups of heterocycles, many synthetic small molecules with cytotoxic activity have been reported and several of them under gone for the clinical trials. The 2-substituted-1, 3-benzoxazoles with the influence of the presence of cyclic amine moiety in the benzoxazole scaffold and evaluated 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 [48].

6. Miscellaneous [27, 36].

A series of 2-aminobenzoxazoles are evaluated for their selective vascular endothelial growth factor-2 receptor kinase inhibitor activity displaying good pharmacokinetic profile [24].



They are also being evaluated in vitro and in vivo imaging agents for Alzheimer's disease (AD)-related amyloid plaque.[26] Some fluorine containing benzoxazole derivatives are tested for activity against HIV-I for used in AIDS treatment.[45]



Y= CHOH, CHF, C=O, CH_2

Ar = Aryl, hetrocycle

Conclusion

Synthesis and biological activity of benzoxazole derivatives have gained interest in the field of medicinal chemistry. This

moiety is expanding its pharmaceutical importance and is found to have several biological activities. The article has outlined the biological activities of the Benzoxazole scaffold such as antiviral, antibiotic, antibacterial, antifungal, antitumor, anti-inflammatory, antiulcer, antitubercular, analgesic activities. The broad spectrum antibacterial and antifungal activity of the mentioned compounds could lead to a new series of antimicrobials activity. Further investigation of this scaffold may lead to development of new derivatives of benzoxazole producing higher yield and screen them for their various other biological activities.

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