

**SYNTHESIS AND BENZOXAZOLE DERIVATIVES POTENTIAL ACTIVITY OF ANTI -
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ABSTRACT

This work is one of our efforts to discover potent anticancer agents. We modified the most promising derivative of our previous work concerned with the development of inhibitor candidates. Thirteen new compounds based on benzoxazole moiety were synthesized and evaluated against three human cancer cell lines. Benzoxazole and its derivatives of heterocyclic compounds possessing nitrogen, oxygen and oxazole moieties which are the important structures of several pharmacologically active compounds. Benzoxazole analogues show vigorous effects. According to the previous research, benzoxazole is produced by refluxing CS₂ and O-aminophenol. These derivatives of benzoxazole produce good anti-breast cancer activity. This review includes the synthesis and the anticancer activity of benzoxazole and its analogues. This study can help the future chemists focusing on the synthesis of drugs related to anticancer activity. Benzoxazole is having a key role in medicinal chemistry due to their wide spectrum of pharmacological activity. The biological activities shown by benzoxazole and its analogues are mainly antifungal, antihistaminic, anti-cancer, anti-inflammatory, anti-viral, anti-bacterial. Benzoxazoles gained importance because of use in intermediates for the preparation of new drugs.

KEYWORDS: Benzoxazole, heterocyclic compounds, vigorous effects, anti-cancer activity.**1. INTRODUCTION**

Synthetic organic chemistry is a very key part of highly integrated and multidisciplinary process of anticancer development. The five membered heterocyclic ring is present among the biologically active compounds. The number of deaths are constantly increasing in the world because of infectious diseases.^[1] It has been seen that there is rapid increase in multidrug resistant infections these days causing increase in various health problems. There are many kinds of diseases which are hard to treat with conventional antibiotics. Another most dangerous disease is Cancer despite of advanced treatments; cancer has become a reason for the second most leading cause of death. The exact biology of the cancer is mysterious and has a lot to experiment to produce new products. Understanding the drug action and pathogenesis of different types of neoplasm becomes clearer,^[2] it becomes easy to produce new drugs which helps in selective targeting of the tumor with less amounts of side

effects. Benzoxazole is having a key role in medicinal chemistry due to their wide spectrum of pharmacological activity. The biological activities shown by benzoxazole and its analogues are mainly antifungal, antihistaminic, anti-cancer, anti-inflammatory, anti-viral, anti-bacterial. Benzoxazoles gained importance because of use in intermediates for the preparation of new drugs. Benzoxazole can be considered as the structural isosteres of naturally produced nucleic acid bases like adenine and Guanine which helps in the interaction with polymers of living system.^[3] Different research groups have done much development in designing compounds with benzoxazole, synthesizing and collecting anti-cancer activity data of those against various human cancer cells. In the present study, we report the synthesis and anticancer activity of benzoxazole and its derivatives.^[4]

2. Chemistry of benzoxazole

- Benzoxazole, also known as 1-oxa-3-aza-1h-indene,

is a member of the class of compounds known as benzoxazoles.

- 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.
- Its molecular formula is C_7H_5NO and molar mass is
- 119.12 g/mol.
- Benzoxazole is soluble (in water) and an extremely weak basic (essentially neutral) compound (based on its pK_a).
- Melting point is 27-30°C. Its odour is similar to pyridine.^[5]

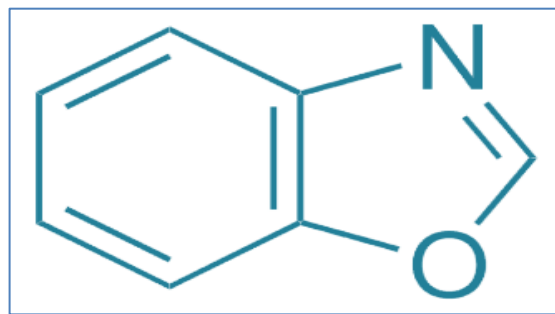
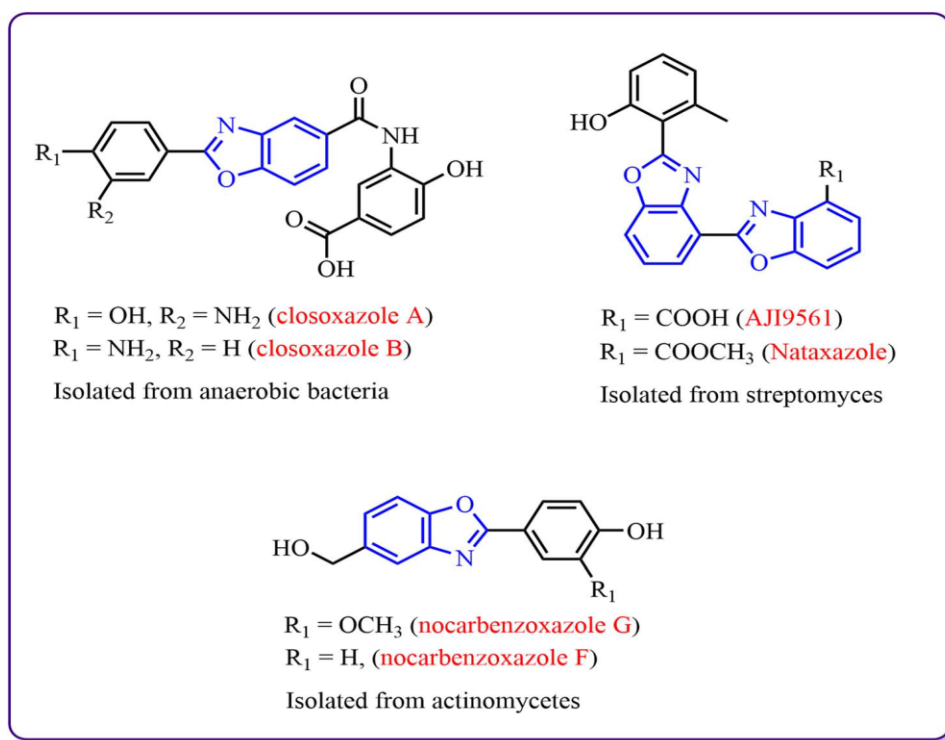


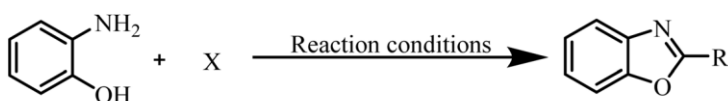
Figure 1: Structure of benzoxazole.

3. Synthesis of benzoxazole derivatives

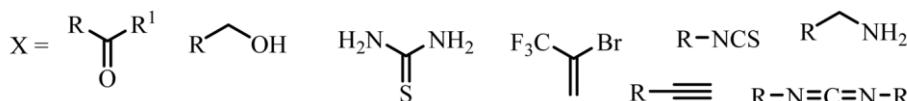
The traditional approach for benzoxazole synthesis is the condensation of 2-aminophenol with various carbonyl compounds under different reaction conditions (Scheme 1). In this review, several protocols are discussed using 2-aminophenol as a major precursor with different substrates like aldehydes, acids and their derivatives, benzyl alcohol, alkynes, isothiocyanates, ketones, ortho-esters, amongst others.^[6]



Diversity of benzoxazole moiety in natural sources.^[7]



$R = H, \text{ alkyl, aryl, } R^1 = H, \text{ alkyl, OH, OR}$



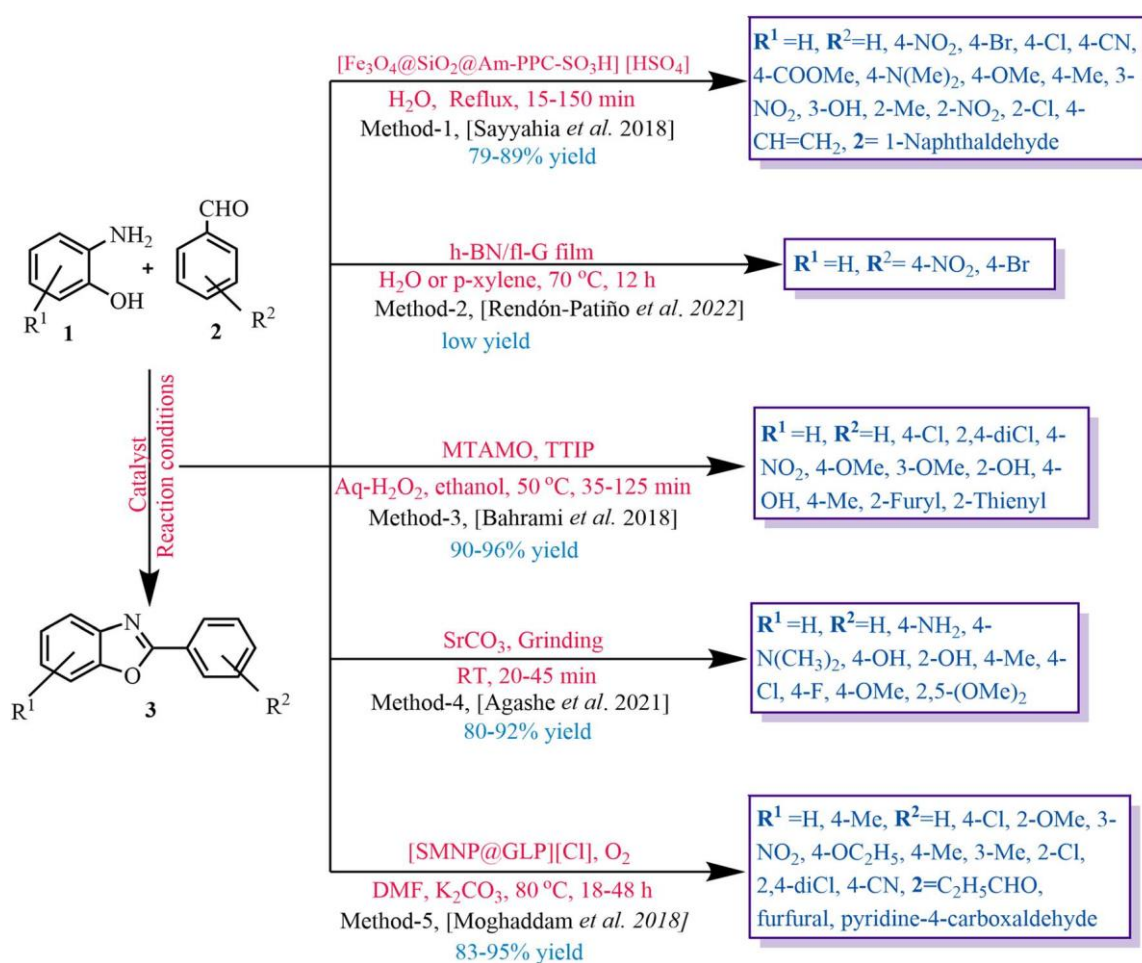
Scheme 1 A general mechanism for benzoxazole synthesis.

3.1 Reaction of 2-aminophenol with aldehydes^[8]

In this part of the review, benzoxazole synthesis using 2-aminophenol with different aldehydes under various circumstances and with catalysts like nanocatalysts, metal catalysts, ionic liquid catalysts, and a few other catalysts are demonstrated.^[9]

Nanocatalyzed synthesis. Nanocatalysts are metalsupported nanoparticles which play a major role in the catalysis process. They are used in several organic transformations due to their special properties like high reactivity, high surface area, selectivity, stability at high temperature, and reusability, and they also give optimal yields as they show escalated mixing with reactants and are furthermore readily separated. Several methods for benzoxazole synthesis using nanocatalysts are

summarized here.^[10] introduced a new magnetic solid acid nanocatalyst ([Fe₃O₄SiO₂@Am-PPC-SO₃H] [HSO₄]) for benzoxazole synthesis using 2-aminophenol (1) and aldehyde (2) in water under conditions for about 45 min and found 79–89% yield. The catalyst can be easily separated and used for 4 consecutive runs with significant catalytic activity. High yield, shorter reaction time, and ambient reaction conditions are additional of the present protocol. Thin-layered nano h-BN/ were prepared and applied as an active catalyst to the synthesis of benzoxazole derivatives by Rendón-Patiño and co-authors.⁴⁶ The coupling of 2-aminophenol (1) and p-substituted benzaldehyde (2) in water/p-xylene at 70 °C showed a low yield of the desired product. The authors further devised an experiment for the reusability of the catalyst for 5 sequential cycles.^[11]

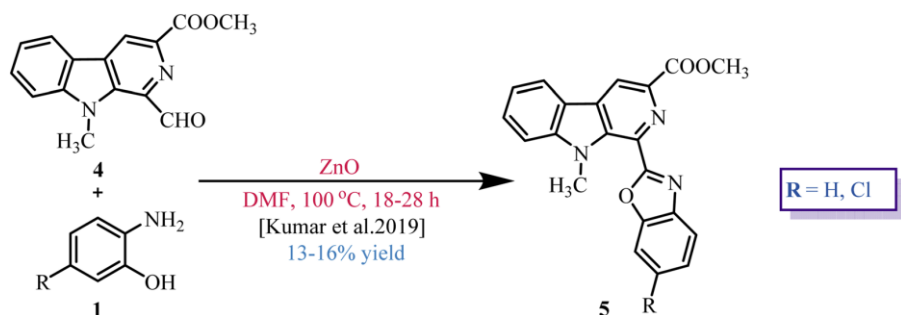
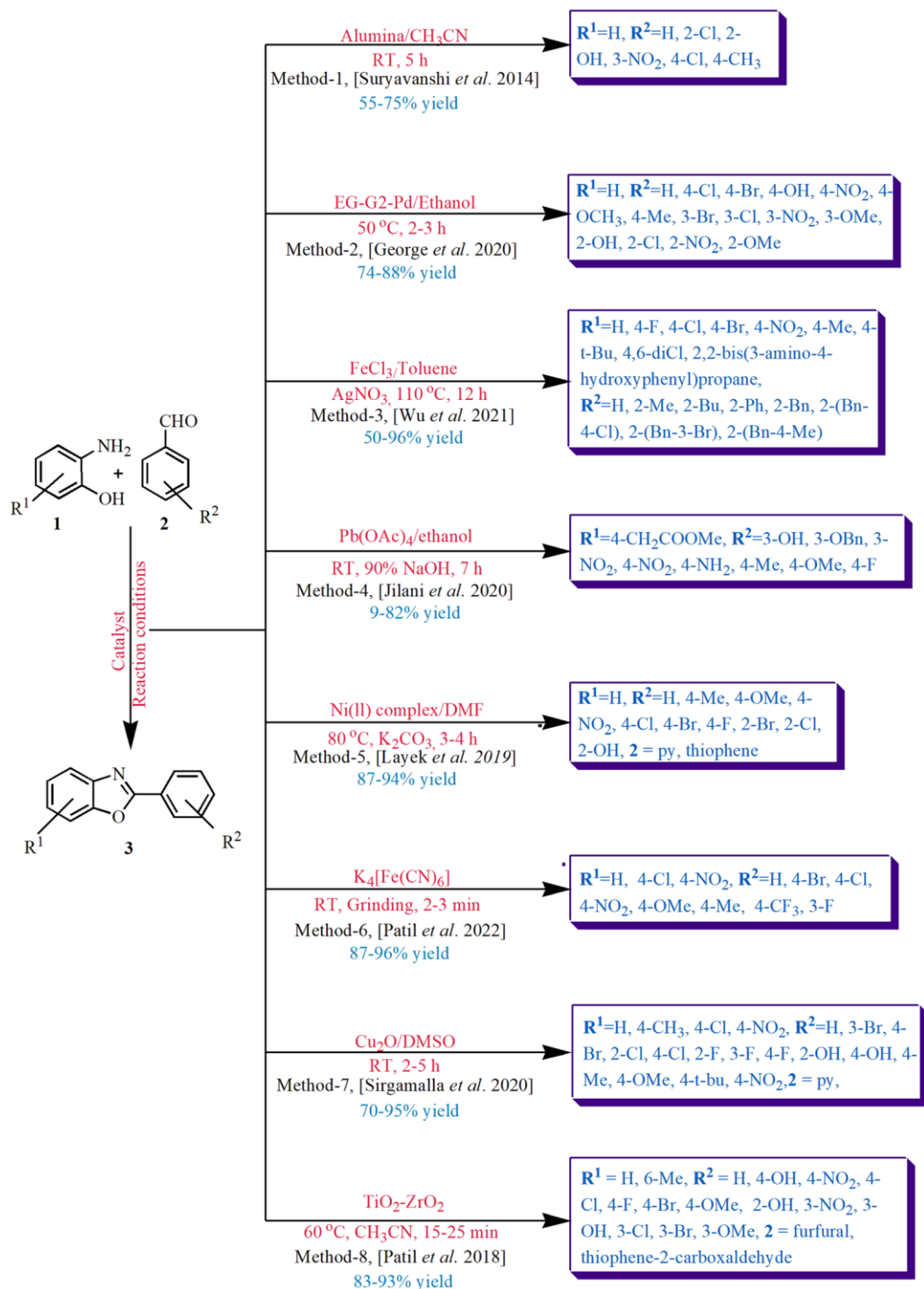


Scheme 2: Nanocatalyzed synthesis of benzoxazole derivatives.^[12]

Metal-catalyzed synthesis. Transition-metalsupported catalysts are widely used in organic transformations as they enhance the reaction rate by lowering the energy barrier between the reactants and the products. They are used in reactions like reduction, oxidation, and coupling, amongst others. Metal catalysts are recyclable, provide a high yield, and are easy to handle. However, transition-metalcatalyzed reactions have a heavy environmental impact due to the extraction and depletion of rare metal resources, byproducts, and the generation of large

amounts of waste. Here, several metal-catalyzed benzoxazole synthesis methodologies.^[13]

Are demonstrated. Suryavanshi and co-authors⁵¹ utilized a metal oxide alumina catalyst for benzoxazole synthesis. 2-Aminophenol (1) and aldehyde (2) were stirred in acetonitrile solvent at room temperature for 5 h to attain a moderate yield (55–75%). The use of green solvents, recyclable catalysts,^[14]



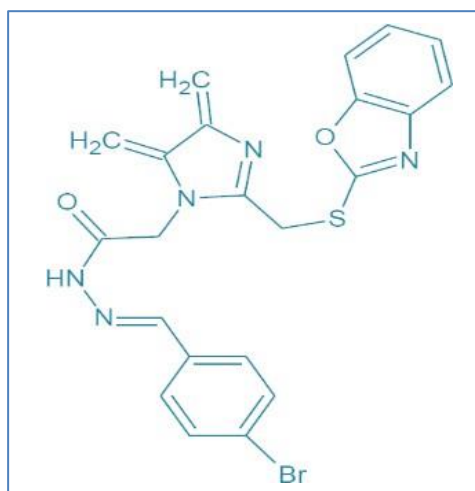
4. Pharmacological Properties

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 benzoxazoles. Benzoxazoles are known to be a significant scaffold in fluorescence probes such as metal cation and anion sensors, in addition to its application in medicinal chemistry.^[17]

4.1 Anti-cancer activity

Benzoxazole and its analogues have potent activity against cancer. They give moderate to good anti-breast cancer activity and are also effective against human colorectal carcinoma. Human colorectal carcinoma cancer cell line was used for evaluating the anticancer activity of the prepared benzoxazole compounds using sulforhodamine B assay. C27H25N5O5S exhibited the best anti-cancer activity.^[18]

Anticancer Activity: 2-((benzoxazol-2-ylthio)methyl)-1H-benzimidazol-1-yl) aceto hydrazide derivatives were synthesised, according to



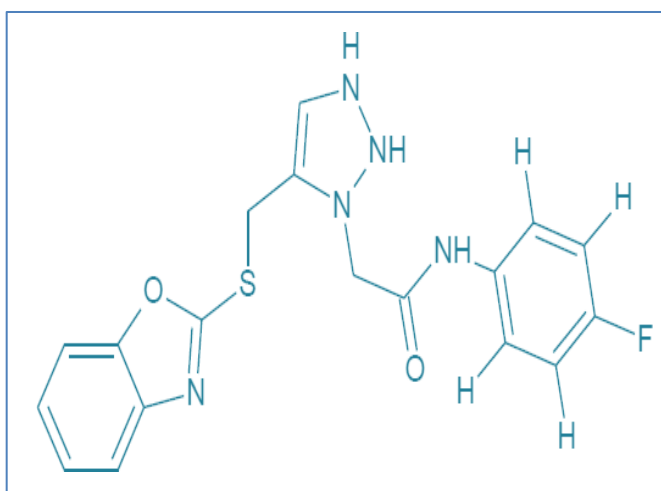
Benzoxazole-1, 3,4-oxadiazole moiety: 1,3,4-oxadiazole is very effective and shows a variety of biological activity. Benzoxazole-1, 3,4-oxadiazole was prepared and anti-cancer activity was screened against human cancer cells i.e. lung cancer, breast cancer, melanoma cancer, colon cancer and its anticancer activity against HT 29 cancer cell line and the results were better than the standard drug.^[23]

Benzoxazole-pyrazolinone derivative: New derivatives of benzoxazole, benzothiazole, benzothiazole and benzimidazole are prepared. By the observation, we got to know that absence of substitution at N-2 shows very poor anti-proliferative activity as compared to substitution at N-2 of pyrazolinone. N-2 substituted pyrazolinone derivatives are active towards the cancer cell lines.^[24]

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.^[19] Benzoxazole derivative synthesis was reported by Balasubrahmanian N et al. once more. Benzoxazole derivatives' antiproliferative properties were evaluated using the human colorectal cancer cell line HCT 116 (ATCC CCL-247). 5-fluorouracil is the usual medication (IC₅₀=12.2 μM).^[20]

4.2 Anticancer activity of benzoxazole attached with different moieties^[21]

Benzoxazole-piperazine moiety: Benzoxazole attached to piperazine is tested over A-549 lung carcinoma cell. At first the results were not satisfactory because of low solubility of aryl piperazine and these piperazine compounds are precipitated in cell culture. The solubility can be increased by using N-methylpiperazine at position 6 of benzoxazole and methyl group at position-2. Long chain piperazines attached to benzoxazole couple with oxadiazoles have shown anti-cancer effect.^[22]

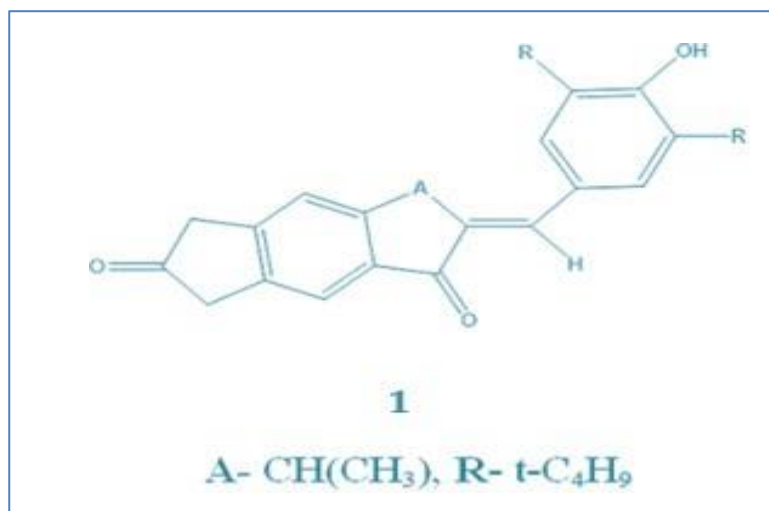


Benzoxazole-1,2,4-oxadiazole moiety: 1,2,4-oxadiazole shows potent anti-proliferative activity. Benzoxazole fused with benzofuran and 1,2,4-oxadiazole was synthesised in minimum steps and it is active against human breast cancer, lung cancer, melanoma cancer and colon cell lines.^[25]

Benzoxazole-combrestatin derivative: Series of ten benzoxazole derivatives of combrestatin A-4 were synthesised and evaluated against various cancer cell lines like Coco-205 (colon), A-549 (lung), MCF-7 (breast) cell line and it was observed that compound 8d was more potent than the standard compound against MCF-7 and A-549 cell lines. Combrestatin A-4 is a natural product isolated from South African willow tree *Combretum caffrum* in 1989 and it shows anti-cancer activity against various cell lines.^[26]

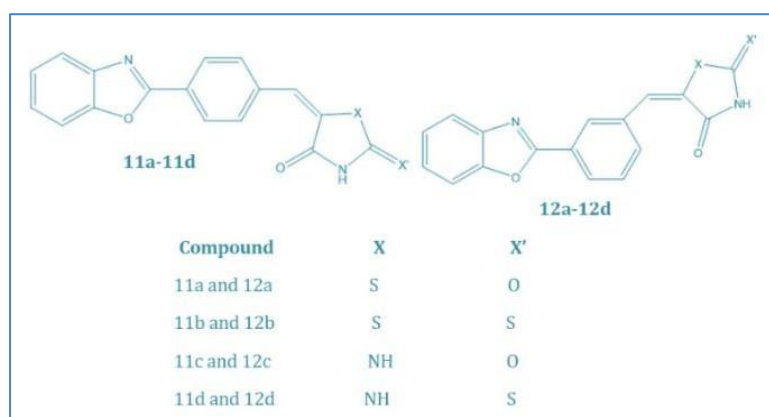
4.3 Antioxidant Activity: Using Cu^{+2} as an oxidising agent, Aichaoui et al. synthesised 2(3H)-benzoxazolone derivatives and evaluated their in vitro antioxidant activity at a dose of 10 μM to stop human LDL copper-

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.^[27]



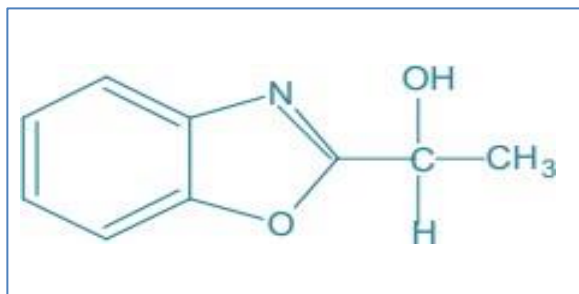
4.4 Antihyperglycemic Activity: Benzazole compounds 11a-11d and 12a-12d were synthesised by Singh et al., who also investigated their α -amyloglucosidase inhibitory action. Compounds 11a and 11c showed the least inhibitory action against α -amyloglucosidase, with IC_{50} values of 22.00 ± 1.21 and 29.03 ± 1.11 μM , whereas compounds 11b and 12b showed strong IC_{50} 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.^[28]

4.5 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.^[29]



4.6 Benzoxazole with Antimicrobial Activity: The antifungal and antibacterial properties of six benzimidazole and benzoxazole derivatives were investigated in vitro by Elnima El 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^[30] exhibited somewhat higher activity than compound^[31], but both compounds had similar efficacy against all isolates. Their respective minimal inhibitory concentrations for 90% inhibition of *S. aureus* were 25 and 50 $\mu\text{g/ml}$. The gram negative bacteria were resistant to the two compounds and required minimal inhibitory concentrations of 200 $\mu\text{g/ml}$ for a similar degree of inhibition.^[32]



5. 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. Benzoxazole derivatives have evolved as an essential motif in organic chemistry with applications in medicinal, pharmaceutical, and industrial areas. This review article outlined recent synthetic methodologies of benzoxazole derivatives using 2-aminophenol with various other substrates like aldehydes, ketones, acids and acid derivatives

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