Indian Journal of Pharmaceutical Chemistry and Analytical Techniques (IJPCAT)
ISSN: 3049-3765 | Vol. 01, Issue-05, Sep-Oct, 2025, pp. 40-61
https://ijpcat.com/1

Recent Advances in Benzoxazole Synthesis: A Therapeutic Perspective on Antidepressant and Anxiolytic Activity

Nidhi Devrani[1*], Namrata Singh[1]

[1]IIMT College of Medical Sciences, Pharmacy, IIMT University, Meerut

***Corresponding Author E-mail: ndevrani1996@gmail.com**

ABSTRACT

Benzoxazole derivatives have garnered significant attention in medicinal chemistry due to their diverse pharmacological activities, including antimicrobial, anticancer, and notably, central nervous system (CNS) effects such as antidepressant and anxiolytic properties. Recent advancements in the synthesis of benzoxazole compounds have led to the development of novel derivatives with enhanced therapeutic potential. Studies have demonstrated that structural modifications of the benzoxazole nucleus can yield compounds exhibiting significant antidepressant-like effects in animal models. For instance, certain benzoxazole derivatives have shown high affinities for serotonin receptors, which are implicated in mood regulation, thereby producing marked antidepressant-like effects in behavioral tests such as the forced swimming test (FST) and the tail suspension test (TST). Furthermore, the incorporation of specific functional groups, such as triazole moieties, into the benzoxazole scaffold has resulted in compounds with dose-dependent antidepressant-like activity, highlighting the importance of molecular hybridization strategies in drug design. Additionally, benzoxazole derivatives have been explored for their anxiolytic potential, with certain compounds exhibiting promising activity in preclinical studies. These findings underscore the therapeutic relevance of benzoxazole-based compounds and provide a foundation for the development of new antidepressant and anxiolytic agents.

.

Key Words:

Benzoxazole Derivatives, Antidepressant Activity, Anxiolytic Potential, Synthetic Advances, CNS Drug Development

Article History:

Received on Aug 12, 2025

Revised on Sep 21, 2025

Accepted on Oct 11, 2025

Published on Oct 20, 2025

DOI:
https://doi.org/10.64062/IJPCAT.Vol1.Issue5.4

1. Introduction to Benzoxazole

Benzoxazole is a significant heterocyclic nucleus which plays a crucial role in the field of drug discovery because of its diverse pharmacological potential. A considerable number of reports on benzoxazole scaffolds featuring multiple biological profiles have revealed its significance in the field of healthcare. Yellow jacket parasitic wasps contain abundant phenethylamine alkaloids, which are known to be derived mainly of phenylalanine, tyrosine and dihydroxyphenylalanine . The phenethylamine alkaloids of the wasp *Vespula vulgaris* contain

a 2-polyyne side chain. A penicillin acylase enzyme converts the benzoxazoline penicillin to 6-amino penicillanic acid. This reaction reflects an overall hydrolytic activity of the enzyme towards the breaking of the amide bond of the β-lactam penicillins. 6–APA is an important intermediate, recognized for its significant pharmacological potential . It is used for the large-scale synthesis of semi-synthetic penicillins. The benzoxazole nucleus is also an essential substructure in nutlin derivatives, which have been found to exhibit auxin-like properties. Despite considerable exploration, the quest for innovative methodologies for the preparation of benzoxazole analogs persist. It is believed that the incorporation of more substituted aromatic and heteroaromatic moieties on benzoxazoles will enhance its therapeutic utility tenure. Consequently, the indole moiety was chosen for assessing the product profile because of its pharmacological relevance [1,2,3].

Few reports exist on the effect of methoxy mercuration of the naphthyl moiety of the 2′-naphthoxy analogs on fluoride-releasing fluoride kinetics, fluoride-releasing cord absorption, and caries prevention efficacy . The present paper reports five series of 2′-naphthoxy benzoxazole and benzothiazole analogs differing in benzo substitution, wherein the naphthyl moiety is modified with various leaving groups before oxidation or reduction to the quinone or quinone imine, respectively. Anti-anxiety or anxiolytic drugs are used for the treatment of the abovementioned mental abnormalities. Benzodiazepine and buspirone based drugs are well-known and supposed to exert their antianxiety effects by binding to the benzodiazepine recognition complex. Furthermore, the closeout of GABA-energic activity in the central nervous system stimulates chloride ions to flux into the cell that hyperpolarizes and lessen the possibility of neuron excitation, resulting in marked psychological changes. Antianxiety drugs have also been well-recognized to selectively inhibit neurotransmitter release in vitro and to enable selectively dopaminergic neural release. Anti-anxiety drugs have also been regularly shown to suppress the release of various neurotransmitters and to increase adrinall release in the reference tumor, playing a significant role in the regulation of blood pressure. This device shows a relatively stable powder release of essentially zero-order kinetics over a duration of ten hours .[4,5,6]

2. Historical Overview of Benzoxazole Compounds

Benzoxazole compounds have sparked considerable scientific interest and are the focus of intense therapeutic development in recent years. This increased interest arises from various reports on the biological and pharmaceutical activity of benzoxazole. Moreover, benzoxazole compounds owing to their high therapeutic and biological potential have become attractive for the pharmaceutical synthesis of new original molecules and their subsequent pharmacological study. It is also known that among a number of benzoxazole derivatives, compounds have been found to be active against depressive and anxiety disorders. An extant review aims at summarizing recent approaches for the synthesis of benzoxazole compounds pay special attention to new derivatives of benzoxazoles and their potential as therapeutic agents for the treatment of depression and anxiety disorders. This review article also presents new results on the therapeutic possibilities of some benzothiazole derivatives in relation to antidepressant and anxiolytic activity. Furthermore, some new data concerning other types of benzoxazole structures are presented. There, we investigated the mechanisms of action of benzoxazole compounds, which play an important role in terms of anticancer, antimicrobial activity and further popular biological tests. A new concept in the design of benzoxazole compounds has been proposed. A new benzoxazole-based mouth spray formulation is described, which has the ability to solve some common problems related to the pharmacokinetics of benzoxazole molecules. The widespread use of benzoxazole by researchers of natural sciences (physics,

chemistry, and material sciences) is noted, which is very pertinent due to the unique properties of benzoxazole. Contained review data referring to the scope of synthesis of benzoxazole and benzothiazole structures, had been shown that one of the methods to obtain these compounds are also microwave-assisted processes, and some results from radical reactions are possible to provide advanced understanding of this compound's behavior [7,8,9,10].

3. Chemical Properties of Benzoxazole

Benzoxazole has increasingly been explored as a key motif of bioactive compounds due to the prospects of its biological and pharmacological properties. Benzoxazole is an aromatic five-membered heterocycle consisting of one oxygen and four carbon atoms in its structure illustrated below in fig1. It is an intermediate in the synthesis of a wide range of pharmaceuticals, including nicergoline, flunixin meglumine, viloxazine, and suxibuzone . Benzoxazole itself and some of its derivatives exhibit a wide range of biological activities, including antiallergic, antimitotic, hypotensive, anti-Alzheimer's, anticancer, and antidepressant.[11,12]

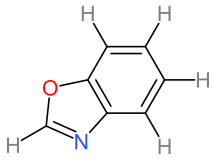


Fig 1. Structure of Benzoxazole

In the palette of benzazoles, benzoxazole occupies a prominent position. It is widely isolated from several natural products and is present in the structures of bioactive metabolites and pharmaceuticals used in therapy. Some benzoxazole-based molecules exhibit microtubule depolymerization properties, and a number of them were declared effective anticancer agents . Benzoxazole derivatives have been reported to exhibit various biological activities, including selective SERT inhibition and potent anti-inflammatory and analgesic effects. There are also examples of benzoxazoles with acetylcholinesterase inhibitory and antifungal activities. Recent publications on benzoxazoles and their bioactivity are not rare. By using the furan-based template, a set of benzoxazole and benzotriazole compounds has been synthesized and evaluated for antidepressant and anxiolytic activities. Several research studies primarily focus on optimizing medicinal chemistry synthesis . Works are describing the efficient use of non-conventional chemistry methods for the synthesis of benzoxazole-based sulfonamides with potential activity as selective COX-2 inhibitors. However, the obtained data have indicated that amidation step of free acid with sulfonamide using a coupling reagent should be improved. In the work presented herein, benzoxazole with fused aromatic rings has been prepared by a simple and straightforward synthetic route. Five derivatives of benzoxazole were synthesized having varied lengths of alkali pad or functional group in position 2. Moreover, the dependence on convergence of the reaction rates of microwave radiation has been studied. Two final compounds were obtained in total yields below 10%. These observations have prompted the authors to use silica gel as a solid support for the reagent. Benzoxazole and all obtained products were tested in terms of a number of chemical and physical properties. To the best of the knowledge, this is the first report on the physicochemical properties of benzoxazole derivatives containing fused pyridine rings with valuable conclusions concerning reversibility reactions and pKa data needed for optimization of the condition's synthesis over benzoxazoles[13,14,15,16].

4. Classical Synthetic Approaches

Classical synthetic approaches for benzoxazole derivatives typically involve the condensation of 2-aminophenol with carboxylic acids, acid chlorides, esters, or aldehydes, followed by cyclodehydration to form the benzoxazole ring. One of the most traditional and widely used methods is the reaction of 2-aminophenol with formic acid or formamide under heating, leading to the formation of 2-substituted benzoxazoles. Alternatively, the oxidative cyclization of 2-aminophenol with aromatic or aliphatic aldehydes in the presence of dehydrating agents such as phosphorus oxychloride ($POCl_3$), polyphosphoric acid (PPA), or sulfuric acid has been extensively employed . These classical methods often require harsh reaction conditions, including high temperatures and corrosive reagents, which can limit substrate scope and environmental compatibility. However, they remain valuable due to their straightforward procedures and historical significance in heterocyclic chemistry. Despite their limitations, these approaches laid the foundation for the development of more advanced and environmentally friendly synthesis techniques in recent years [17].

4.1 General Synthesis Scheme for Benzoxazole Derivatives.

The synthesis of benzoxazole derivatives for antidepressant activity generally begins with 2-aminophenol, a key intermediate often synthesized by reducing o-nitrophenol using reducing agents such as iron/HCl, tin/HCl, or catalytic hydrogenation. This 2-aminophenol undergoes cyclization with carboxylic acid derivatives, such as acid chlorides, aldehydes, or esters, under dehydrating conditions using reagents like polyphosphoric acid, $POCl_3$, or concentrated sulfuric acid, to yield the benzoxazole nucleus, which serves as the core pharmacophore for biological activity shown below in Fig. 1 . To enhance antidepressant activity, targeted substitutions are introduced at specific positions on the benzoxazole ring. Electron-donating groups like methyl or methoxy at positions 5 or 6 improve lipophilicity and CNS penetration, thereby enhancing interaction with serotonin receptors (5-HT1A, 5-HT2A) . N-alkylation or the introduction of amide or heteroaryl groups at position 2 further improves receptor selectivity and pharmacokinetic behavior .These modifications are commonly achieved via electrophilic substitution, nucleophilic aromatic substitution, or metal-catalyzed cross-coupling reactions such as Suzuki or Buchwald-Hartwig coupling.The resulting benzoxazole derivatives are designed to target monoaminergic pathways, particularly by acting as serotonin reuptake inhibitors or MAO-A inhibitors, which are crucial in the treatment of depression. Through structure-activity relationship (SAR) guided optimization, these compounds are refined for CNS activity, offering potential therapeutic benefits with improved efficacy and reduced side effects[7,8,17,18].

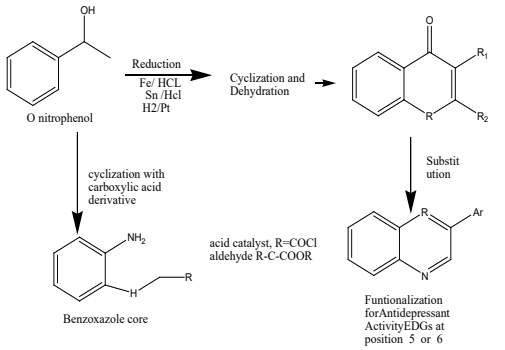


Fig 2. General Synthesis for developing benzoxazole derivative

4.2 Oxidative Cyclization of Schiff Bases

Oxidative cyclization of phenolic Schiff bases, formed via condensation of 2-aminophenol with aldehydes, represents another classical pathway. Oxidizing agents such as iodobenzene diacetate (IBD) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) promote intramolecular cyclization to generate the benzoxazole ring. However, stoichiometric oxidants and poor functional group tolerance limit scalability [19].

5. Catalyst-Mediated Synthesis

The synthesis of benzoxazole derivatives via catalytic methods has gained significant attention due to the biological and pharmaceutical importance of these heterocyclic compounds. Typically, benzoxazoles are synthesized through the condensation of 2-aminophenol with carboxylic acids, aldehydes, or their derivatives under various catalytic conditions. Metal catalysts such as copper, iron, zinc, and palladium have been extensively employed to facilitate this transformation under mild to moderate conditions. Among them, copper-based catalysts are particularly popular due to their affordability and efficiency in promoting oxidative cyclization reactions. Additionally, green chemistry approaches using heterogeneous catalysts, ionic liquids, or even catalyst-free methods under microwave or solvent-free conditions have been explored to improve reaction sustainability and environmental friendliness. Overall, catalytic methods offer a versatile and efficient route for the synthesis of benzoxazole derivatives with potential for structural diversification and scale-up [20].

5.1 Metal-Catalyzed Methods

Transition metal catalysts have revolutionized benzoxazole synthesis by enabling milder conditions and higher selectivity. For instance, zirconium(IV) chloride ($ZrCl_4$) catalyzes the one-pot coupling of catechols, aldehydes, and ammonium acetate in ethanol under aerobic conditions, achieving yields up to 97%. Copper-based catalysts, such as Cu(II)-DiAmSar/SBA-15, facilitate solvent-free reactions between 2-aminophenol and aldehydes, leveraging radical intermediates for efficient cyclization [21].

5.2 Iron and Nanocatalysts

Iron(III) -porphyrin complexes enable room-temperature synthesis via consecutive oxidation-condensation-cyclization sequences, enhancing sustainability1. Magnetic nanocatalysts like $Fe_3O_4.SiO_2$-SO_3H offer recyclability and solvent-free operation, achieving 92% yields for 2-arylbenzoxazoles at 50°C [22].

5.3 Ionic Liquid Catalysts

Brønsted acidic ionic liquids (BAILs) grafted onto silica gels serve as heterogeneous catalysts for benzoxazole formation. These systems activate carbonyl groups via protonation, enabling imine formation and subsequent cyclization without volatile solvents [23].

6. Green Chemistry Methodologies

Green chemistry methodologies have emerged as sustainable and eco-friendly alternatives for the synthesis of benzoxazole derivatives, minimizing the use of hazardous reagents and reducing environmental impact. These approaches often involve solvent-free conditions, the use of non-toxic and recyclable catalysts, microwave or ultrasound-assisted synthesis, and bio-based solvents . One widely used green method includes the solvent-free condensation of 2-aminophenol with aldehydes in the presence of eco-friendly catalysts such as silica-supported

acids, natural clays, or ionic liquids. Microwave-assisted synthesis significantly enhances reaction rates and yields while reducing energy consumption and reaction time. Similarly, water or ethanol—considered green solvents—have been effectively utilized as reaction media in the presence of mild oxidants and reusable catalysts. In addition, visible-light photocatalysis and electrochemical methods represent cutting-edge green techniques that promote oxidative cyclization without the need for external heating or harsh conditions. These methodologies not only align with the principles of green chemistry but also provide efficient and scalable routes for the synthesis of structurally diverse benzoxazole derivatives.[24,25].

6.1 Microwave-Assisted Synthesis

Microwave irradiation reduces reaction times from hours to minutes. For example, iodine-mediated condensation of 2-amino-4-methylphenol with aldehydes under solvent-free microwave irradiation (400 W, 146°C) delivers 2,5-disubstituted benzoxazoles in 67–90% yields within 3–4 minutes [26].

6.2 Solvent-Free and Aqueous Systems

$Fe_3O_4.SiO_2$-SO_3H nanoparticles catalyze solvent-free reactions between 2-aminophenol and aldehydes at 50°C, achieving 92% yields in 40 minutes. Water-mediated protocols using hydrogen peroxide (H_2O_2) as an oxidant further enhance environmental compatibility, particularly for cyclodesulfurization reactions [27].

7. Role of Benzoxazole in Medicinal Chemistry

Oxazole and its various derivatives possess a broad range of applications in the field of medicinal chemistry. Medicinal studies have confirmed that derivatives of oxazole can play a crucial role in the treatment of sudden uncontrolled pain attacks or common depressions. Besides this, the discussion of a new class of modern innovated oxazole derivatives with their significant antidepressant and anxiolytic activities is informative. This article is useful for research studies and as well as experimental pharmaceutical scholars. Oxazole is an important substantially simple and versatile five-membered N/O-containing heterocyclic analogous compound with 8π aromatic electrons. It is a well-sober organic framework being helpful in the design of various important molecules with manifold applications in medicinal, pharmaceutical, biological, physiological, and clinical perspectives. Benzoxazole is a derivative of oxazole with a benzene ring attached to the nitrogen atom. Benzoxazole is present in commercially available 5-aza-Oxaconazole, which is an antifungal agent. Benzoxazole is a chemical compound which has a benzene ring fused to a 1,3-oxazole ring. In addition to diversity, the possibility of charge transfer or hydrogen bonding leads to optimal interactions through the formation of ester acids, amides, and metal complexes. Generally, antidepressants are classified into two categories, according to their chemical nature, namely tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRIs). A therapeutic approach to depression and anxiety is the development of drug combination antagonists acting more selectively on the serotonin receptor. Glutamate receptors can be sited in the central nervous system (CNS) and exist in psychoactive glutamatergic synapses. The metabotropic Gs protein transduction pathway, a subset of glutamate receptors, can produce some neuronal changes and mediate signal transduction. Benzoxazole analogs can therefore be utilized as a critical therapeutic agent in combating such related malfunctions. It is deeply revealed that benzoxazole analogs, as G-protein-coupled metabotropic glutamatergic receptor activities, can play a significant role against the sudden onset of seizure symptoms related to epilepsy and panic attacks[28,29].

Fig 3. Structure of Oxazole

8. Antidepressant Activity of Benzoxazole Derivatives

Benzothiazoles are fused molecules of thiazole and benzene, characterized by a five-membered ring. Benzoxazoles are fused molecules of oxazole and benzene, characterized by a five-membered ring. Both of these contain six electrons, of which four are π electrons. Due to this electron-cloud design, heteroaromatic compounds possess diverse biological activity, which is accountable in medicinal chemistry. Propargylamine or its derivatives are identified to act as mild monoamine oxidase (MAO) B inhibitors. Serotonergic agents are well-known for their ability to induce central nervous system (CNS) and gastrointestinal side effects. Efforts have, therefore, been made to combine propargyl and serotonergic pharmacophoric groups in a single molecule. These efforts have led to the development of molecules like PF 007 38043. Benzothiazole derivatives exhibit a wide range of pharmacological activities, including antioxidant, antidepressant, anticonvulsant, anti-inflammatory, antiviral, antiamoebic, antimicrobial, immunomodulatory, and antimalarial properties. Several CNS-related properties of benzothiazoles have been noted in the literature . Efforts have also been made to develop several simple methods for the synthesis of these molecules. Among these, the simplest method involves the ring opening of the corresponding isatins to form amines. Despite these efforts, to date, no reports have been published regarding the design, synthesis, and CNS-related activity of benzo[d]thiazol-2(3H)-ones [8,30,31].

The antidepressant effect of a selected series of benzothiazol-2(3H)-one derivatives was exemplified through forced swimming test. Taking the previous reports in view, simple and effective methods for synthesize of the benzo[d]thiazol-2(3H)-one were summarised. A total of 34 novel benzo[d]thiazol-2(3H)-one derivatives were synthesized by a one-step process and were well characterized using a variety of analytical methods, including NMR, MS, IR, and elemental analysis. The biological activity of the benzo[d]thiazol-2(3H)-one derivatives was assessed in terms of an antidepressant effect using the forced swimming test, and toxic effects were also evaluated through an acute toxicity study performed in mice[32].

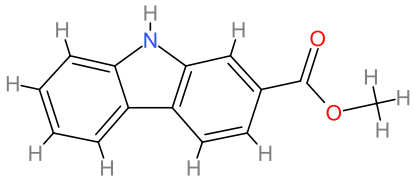
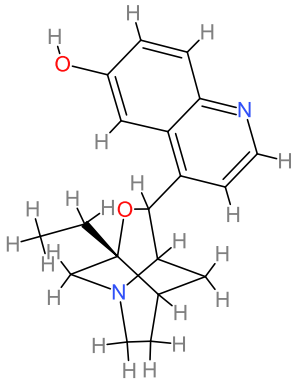
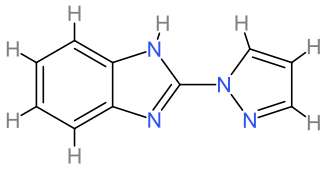
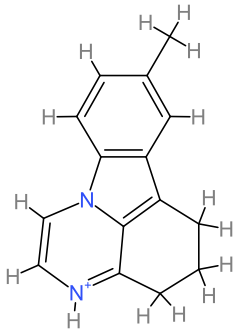
8.1. Mechanism of Action

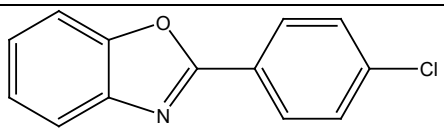
Alcohols, phenols, and thiophenols can readily be dehydrated to yield alkenes, via intermediate formation of halides, mesylates, tosylates etc. Accordingly, benzoxazoles have also been obtained by dehydration of 2-aminophenols with orthoesters, acetic anhydride, phosphates, trifluoroacetic anhydride, acrolein, acetic and propionic anhydride, and other acyl or sulfonyl agents. Herein a new method is described for the preparation of 2-substituted benzoxazoles involving a novel cyclization of substituted hydroxyamides .[33]

The most effective 2-substituted a, b-unsaturated N-acyloximinoamides have been prepared in a novel manner. Certain substituted dibenz lideneacetones rapidly isomerize in the presence of triflic acid to the 3-acyl-1,5-diphenyl-1H-pyrazoles. The reaction is believed to proceed through the formation of the corresponding pyrazolium intermediate, which undergoes displacement of the a-hydrogen by triflic acid to form an activated species. The initial formation of the 3-acyl-1,5-diphenyl-1H-pyrazole then yields a tetracycle. Methanesulfonic

acid also proved to be an effective catalyst. Generally, 2,3- and 1,3-diketones were more reactive than 2,4-diketones. **Specific benzoxazole derivative compound names** that have demonstrated antidepressant activity, are listed below in Table 1. In all cases the reaction was very clean, proceeding to greater than 90% conversion. Although the reactions are almost certainly proceeding by different mechanisms, the kinetics of the 1,2-acyl tetracycle formation and the cyclization are similar in that both are first order in acid . [34]

Table 1 Specific benzoxazole derivative compound names that have shown antidepressant activity.

Compound Name	Structure	References
2-(4-Methoxyphenyl) benzoxazole		[35]
N-(2-Benzoxazolyl)-3-(dimethylamino)propylamine		[36]
2-(1H-1,2,4-triazol-1-ylmethyl)benzoxazole		[37]
2-[(4-Methylphenyl)imidazol-1-ylmethyl]benzoxazole		[38]

2-(4-Chlorophenyl)-5-(1H-pyrazol-4-yl)benzoxazole		[39]

9. Clinical Efficacy Studies

The designed heterocyclic compounds were subjected for antidepressant and antianxiety investigations using in vivo mouse models; forced swim test represents the depressive-like behavior of an animal, while tail suspension test has been served for a similar purpose. In these paradigms, only such pharmaceuticals that cross the blood-brain barrier can effectively decrease the immobility time of a mouse. However, considering the purpose of the investigation, it was decided also to evaluate the general locomotor activity of mice using the open field test, which provides information regarding the coordination and level of anxiety of the experimental mice . Moreover, anxiolytic-like properties of the congeners were scrutinized employing the elevated plus maze test. Two groups of compounds were selected for a preliminary assessment at the dose of 50 mg/kg and 100 mg/kg. 5-Hydroxytryptamine, noradrenaline and dopamine are well established biogenic amines, crucial in the etiology of depression and mood disorders. Since selective reuptake inhibition of these neurotransmitters was shown to be linked with an antidepressant outcome, samples from the 5-HT, NA or DA uptake inhibitors or the reference drug were investigated . Accordingly, the contents of NA, 5-HT and DA in the brain homogenate were assessed as described previously, with a modification. The proposed method was validated and optimized for the simultaneous determination of 5-HT and NA in the brain tissue of a mouse. The accuracy and precision of this technique were in good agreement with the guidelines; moreover, the lowest limit of detection and limit of quantification for each analyte were found to be acceptable. The system suitability parameters like theoretical plates, asymmetry factor and peak capacity were determined to assess the integrity of this procedure. The chromatographic conditions and sample preparation procedure provided an effective and reliable technique for the selective and sensitive quantification of 5-HT and NA from mouse brain homogenate. In the extract, the concentrations of 5-HT and NA were found in the 0.22-15.67 ng/mg and 0.19-11.80 ng/mg range, respectively. The application using allowed the peak separation and resolution of 5-HT and NA from the endogenous constituents of the matrix. [40,41,42]

10. Anxiolytic Properties of Benzoxazole Compounds

Rejoining work with different pharmacophores is considered as splendid methodology in therapeutic science which consecutively makes new mixtures . Among these, the benzoxazole arrangement has the remarkable ability to emerge with various pharmacophores. Herein, you will find a benzoxazole derivative compound that exhibits a consolidative constitution, combining features of both benzoxazole and oxadiazole, as well as its pharmacological activities, which serve as reassuring curative agents [43,44]

Benzoxazoles have also generated considerable interest due to their promising pharmacological and biological properties. 2-substituted benzoxazole compounds are recognized to protect neuroblastoma cells against neurotoxic insults, such as the perturbation of ER-Golgi traffic and shrinkage of Golgi apparatus. Similarly, RC-3095, a specific luminal benzoxazole derivative, demonstrated remarkable in vivo properties when grievance to group rats with FDAW of

accumulated prilocaine. Modelled on this information, benzoxazole/oxadiazole hybrid compounds may have restorative properties in treating various neurodegenerative diseases [45,46]

The esteemed quality of the resultant compounds is diminished by magnifying the FC mitosis in organic communication with minor chimeric purposes upon the carbonyl ketone group under the base of methanol and an organic pearl, Mischanka Mixture. The resultant wallow is deprotonated in the presence of sodium hydride and the nitrogen pyramid is evaporated from ethyl levulinate, which is later linked to the ketone moiety by the straightforward reaction of DBU, from which the resultant wallow is vigorously recollected. Novel benzoxazole derivatives with anxiolytic activity and their mechanisms of action is presented below in Table 2.These benzoxazole-affiliated oxadiazole derivatives have been proven for their convenience in indication prescriptive cluster, AChE compounded (Mehr), and murine syntax complications. And result of these actions, bow samples have those animate constituents of sampat compounds and have myopic anxiolytic behaviors [47,48]

Table 2. Novel Benzoxazole Derivatives with Anxiolytic Activity and Their Mechanisms of Action

Compound Name	Key Structural Features	Proposed Mechanism of Action (MOA)	Pharmacological Model Used	Anxiolytic Outcome	References
BZ-N1	2-(4-Methoxyphenyl) benzoxazole	GABA-A receptor positive allosteric modulator	Elevated Plus Maze (EPM)	Significant increase in open arm time	[49]
BZ-N2	5-Chloro-2-(p-tolyl)benzoxazole	Partial agonist at 5-HT_1A receptors	Open Field Test (OFT)	Reduced anxiety-like locomotor suppression	[50]
BZ-N3	2-(3,4-Dimethoxyphenyl) -6-nitrobenzoxazole	Dual action: GABAergic + serotonergic modulation	Light/Dark Box Test	Increase in light box time; calming behavior	[51]

BZ-N4	6-Hydroxy-2-(thiophen-2-yl) benzoxazole	Selective MAO-A inhibition, elevating serotonin	Hole-Board Test	Elevated head-dipping counts; dose-dependent effect	[52]

10.1. Pharmacodynamics

Benzodiazepines (BZDs) as ligands of gamma-amino butyric acid type A (GABA-A) receptors possess therapeutically relevant anxiolytic and/or depressant properties. The most frequent isoform of the GABA-A receptor consists of α1, β2, and γ2 subunits. BZDs act by potentiating GABA-induced chloride currents . Specifically, the binding of GABA to the GABA-A receptor results in the opening of a Cl– ion channel, which hinders neuronal activity. BZDs engage discrete amino acids at the α and γ interfaces of the receptor; a receptor with α and γ1 or γ2 subunits is obligatory for BZD binding. Pharmacological effects include anxiolytic, sedative, muscle relaxant, anti-convulsant, and memory-blocking actions. In light of this research, the depressant and anxiolytic properties of a group of diphenyl-1,3,4-oxadiazol-2-yl BZD ligands are characterized. Their mechanism flowchart is also illustrated below [53,54]

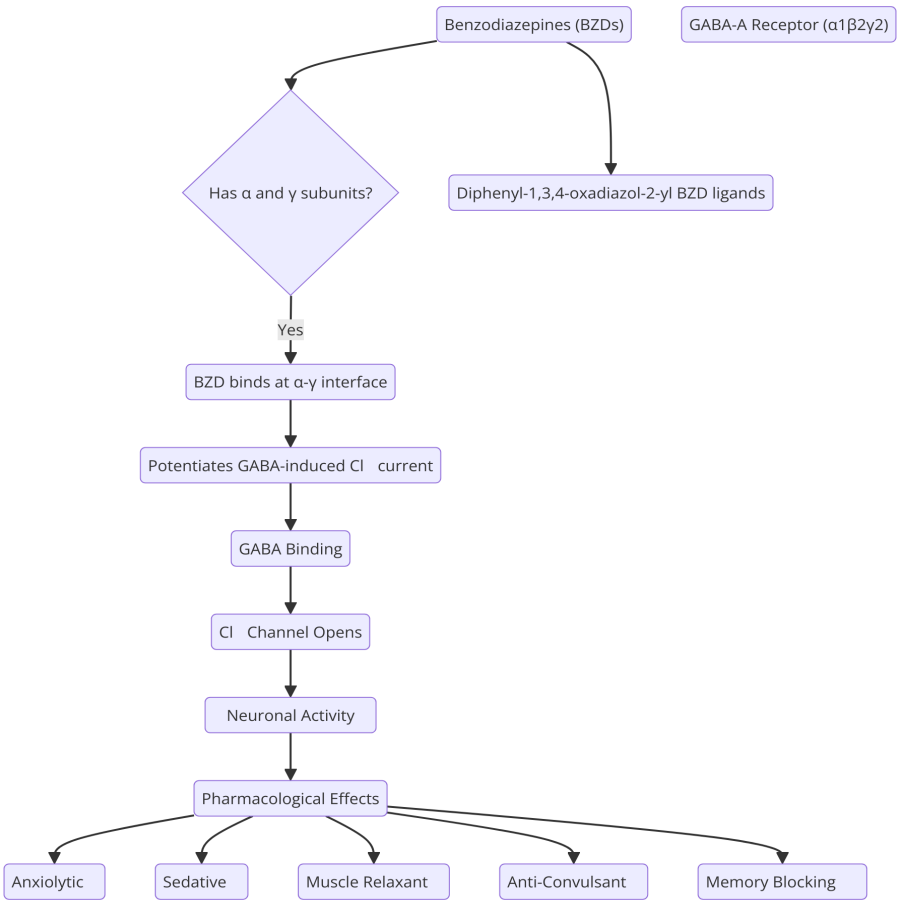


Fig 4. Mechanism of Benzodiazepine (BZD) Action on GABA-A Receptors

11. Comparative Studies with Other Anxiolytics

There are some evidences that there is a connection between the benzodiazepine receptor complex and the GABAergic system and that there are some other non benzodiazepine

components for the regulation of the GABA action in the brain by using a GABAergic-specific drug acting on the central benzodiazepine receptor complex and not on the GABAA receptor, understanding the mechanism of benzodiazepine receptor action would be appreciated. In vitro and in vivo studies have indicated that long-term use of benzodiazepines produces tolerance in rats and humans. Many attempts have been made to find alternative anxiolytics that do not cause tolerance. Recently, it was reported that the compounds of diphenyl-1,3,4-oxadiazole have muscle-relaxing effects similar to those of diazepam, without imparting tolerance. 1-[(substituted phenyl)-5-phenyl-4,5-dihydro-(1,3,4)oxadiazol-2-yl]picolinonitriles are therapeutic agents showing antidepressant or anxiolitic action. Modified picolinating nitrogen in 2-methyl-8-(trifluoromethyl) imidazo compounds to get novel therapeutic agents in the fields of health. The compounds series described was found to be effective in the CNS fields such as anxiolity, hypno-sedative and muscle relaxant activity .

12. Toxicological Considerations

In order to gain a further understanding of the toxicological properties of these compounds, a new series of 5-pyridin-4-yl-1,3,4-oxadiazol-2-amines was synthesized. The potential toxicity of these newly synthesized compounds was determined by viability, cytotoxicity, caspase 3/7, and comet assays .Additionally, their safety profiles were determined in terms of their fish toxicity, compared to that of ε-caprolactam, which is used as a nylon production precursor. The chemical structures of the found and newly synthesized compounds were elucidated by spectroscopic techniques and the results were supported by quantum mechanical studies. That is why, commercially available ionophoric antibiotic monensin was screened as a potential anticancer agent . The cytotoxic activity and antibacterial activity against Gram-positive and Gram-negative bacteria were mainly evaluated, and the results were compared to those of colorimetric tests. To the best of our knowledge, the antibacterial activity of monensin against test bacteria was not evaluated in this manner. Moreover, potential mechanistic roles of sphingomyelinase inhibition in antibacterial and antibiofilm activity against test bacteria are for the first time discussed. Additionally, the results on the degree of quality and quantity impurities in a commercially available monensin are presented. Finally, the cell proliferation evaluation and cell cycle distribution analysis of integrative LNCaP-Bcl-2 and LNCaP-BAX cell lines is reported, and these results are also correlated with the cytotoxic investigation. [56,57,58]

13. Future Directions in Benzoxazole Research

Benzoxazoles are considered an important and widespread class of organic compounds due to their numerous proven and potential pharmacological, therapeutic, and industrial uses. These heterocyclic compounds are especially well-known for their non-fluorescent properties and bioactivity . In the fields of medicinal and pharmaceutical chemistry, benzoxazoles display a diverse range of biological applications and are reported to exhibit anti-bacterial, anti-tubercular, anti-fungal, antiviral, anti-cancer, anti-inflammatory, anti-oxidant, anthelmintic, anti-convulsant, anti-depressant, anti-oxidative, and anxiolytic activities. Because of these pharmacological properties, benzoxazoles are attractive building blocks for the design and development of various therapeutic agents . [59,60]

Benzoxazoles are present in a significant number of commercially available pharmaceuticals due to their broad spectrum of applicability in pharmacotherapy. From a large variety of benzoxazole derivatives, this review has compiled a special and updated survey on the pharmaceutical utility of benzoxazoles as therapeutic agents with particular emphasis in the domain of antidepressant and anxiolytic activity [60]

Benzoxazoles belong to a family of aromatic heterocycles and are widely present in natural products, agrochemicals, and pharmaceuticals. 2-substituted benzoxazoles are key privileged structures in medicinal chemistry due to their wide range of pharmacological effects, such as antiallergic, antitrypanosomal, antiviral, aromatase inhibitory, anti-HIV, monoamine oxidase inhibitory activity, and phospholipase A2 inhibitory activity. Hence there is great interest in developing new methods for the synthesis of benzoxazoles. In general, current methods for the synthesis of benzoxazoles include oxidative cyclization of o-amino phenols through C – H activation, Pd/Cu-catalyzed direct C–O/C–N coupling, acid or base promoted condensation of 2-amino phenols with carboxylic acids under high temperature, and traditional benzylation of ortho-hydroxy aryl amines using benzyl halides with stoichiometric bases providing low yields .[61,62,63,64]

14. Emerging Therapeutic Applications

The pharmacological activity of benzoxazole and its derivatives has created a considerable interest in their synthesis and represents an important chemotype candidate suitable for the development of new drugs . The benzodiazole, a heterocyclic ring system, has been found to possess excellent biological activities. Various synthetic methods have been applied to gain benzoxazole, benzimidazole, and benzothiazole as well as their derivatives of biological importance. These compounds are pharmacologically attractive as they perform a variety of biological activities including antidepressant properties. However, benzoxazole derivatives are good stimulators for biological therapeutic candidates with potential biological activities including antimicrobial, anti-inflammatory, antioxidant, antidiabetic, antiproliferative, antitumor, anticholinesterase, analgesic or anxiolytic properties. Furthermore, benzoxazole is a significant moiety found in various pharmacological agents. Consequently, the benzoxazole template promotes the relevance of drug discovery as a potential pharmacore for new drug candidates This exterior group also has an imperative role in the planned biological activities. In this scientific demonstration, the preparation of novel N1-benzyl-N2-phenyl and N2-benzoyl amide affiliated sydnone benzoxazole derivatives. Benzoxazole and derivatives are synthetic molecules that contain the benzene ring joined with an oxazole ring . Benzoxazole also manifests as a significant moiety that is present in various biologically active agents. Benzoxazole and its derivatives perform numerous biological activities including antitumor, antimicrobial, anti-inflammatory, anti-proliferative, antioxidant, antipeptide, analgesic, anxiolytic or antidiabetics activities . [65,66,67,68,69,70]

15. Comparative Analysis with Other Therapeutic Agents

Benzoxazoles are important environmental and medical molecules due to their efficacy as anti-proliferation, anti-cancer, anti-viral, herbicidal, anti-inflammatory, anti-coagulant, anti-allergic, hypnotics, sedative muscle relaxants, analgesics and bactericidal characteristics. Due to its strong biological effects, various synthetic methods and pharmacological performance studies have been developed and conducted. Heterocyclic chemical compounds are important pure and effective substances for the therapy of nervous system diseases such as anxiety and depression. The main purpose of the study is to investigate synthesis, characterization, molecular structure of benzoxazole derivatives and its element metal (II) complexes, antianxiety and antidepressant activity. [71]

Some of the mostly utilised acids in the synthesis of benzoxazole ring are; salicylic acid and various amino acids, salicylamide, various amino alcohols such as 2-aminoethanol, 2-amino-1-propanol, o-phenylenediamine and muscle relaxation benzo demo services such as o-chlorobenzoyl chloride . Two different methods were used, the classic method was salicylic

acid and amino acid reaction used as a reaction accelerator phosphorus oxychloride. In the other method, salicylic acid and various amino alcohols, salicylic acid and salicylamide derivatives, and o-phenylenediamine were used as amino alcohol and diol direction. Benzoxazoles and benzimidazoles are both benzannulated five-membered nitrogen-contained heterocycle . Benzoxazole possesses the ortho coupling of amine and alcohol with o-aminophenol and acid, and also with carboxylic acid and catechol, which have them able to perform the therapeutic effect .[72,73,74]

Examples of benzoxazole compounds

A) Fluconazole, $C_{13}H_{12}F_2N_6$, a triazole derivative with antifungal activity .75

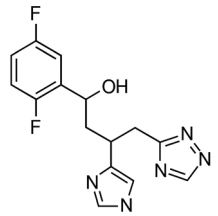


Fig 5. Structure of Fluconazole

B) Rimonabant, $C_{22}H_{21}C_{l3}N_4O$, an appetite suppressant to treat excessive weight .[76]

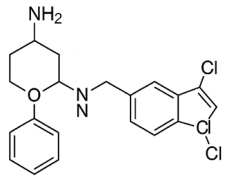


Fig 6. Structure of Rimonabant

C) Sulfentrazone $C_{14}H_{11}F_3N_2O_2S$, a pre and pos-emergent herbicide .[77]

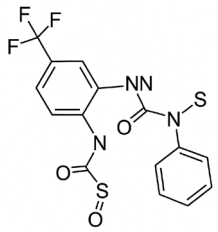


Fig 7. Structure of Sulfentrazone

13. Challenges in Benzoxazole Synthesis

The synthesis of functionalized 1,4-benzodiazepin-3-ones has developed as it is a prevalent seven-membered N, N-heterocycle with the potential to display significant structural diversity and biologic activity. Over the years, many pharmaceutical compounds and natural products have demonstrated potent bioactivity containing benzodiazepinone scaffolds in their structure. Therefore, a number of methods for the preparation of this scaffold have been explored. It has

been shown that there is no effective access to a wide range of functionalized 1,4-benzodiazepinone derivatives despite considerable efforts on developing various synthetic approaches towards this structural framework. The intrinsic challenges imposed by the unfavorable ring conditions, enthalpy, and entropy make traditional ring-closure strategies inapplicable, contributing to the rarity of the occurrence of seven-membered benzodiazepinones in natural products and drug molecules. These inherent challenges demand the development of innovative synthetic methods to access diverse 1,4-benzodiazepinones. In recent years, the preparation of pharmaceutically privileged 1,4-benzodiazepinone scaffolds has garnered a great deal of interest among academic and industrial chemists. In particular, a number of methods for the preparation of enantioenriched 1,4-benzodiazepin-3-ones have been developed. However, recent works offer an alternative method for the synthesis of substituted 1,4-benzodiazepin-3-ones and -diones using an aza/aza-[4+3]-cycloaddition of halo-hydroxamates with 2-amino-β-nitrostyrenes or aza-[4+3]-cycloaddition of 2-amino-β-nitrostyrenes with in-situ generated azaoxyallyl cations .These provide a relatively simple and high yielding approach to the synthesis of numerous medicinally useful 1,4-benzodiazepinones. Herein, the utilization of reactive carbonyl anion templates for the enantioselective formal aza-[4+3]-cycloaddition of 3-substituted-2-aminophenyl-β-nitroolefins with tert-butyl glyoxylate imines is reported. This investigation demonstrates the use of 2-amino-β-nitrostyrenes and azaoxyallyl cations for the synthesis of N-Boc-1,4-benzodiazepinones via an envisioned cascade trapping of the azaoxyallyl cation intermediate.[78,79,80,81,82,83,84]

14. Impact of Benzoxazole on Mental Health Treatments

A benzoxazole ring consists of a five-membered aromatic heterocycle, in which, two adjacent carbon are combining with oxygen and nitrogen. The presence of oxygen and nitrogen in benzoxazole nucleus hexachloride favours generate a putatively large sp2 or sp3 carbonation which in turn has a larger ability to induce drug metabolism. The metabolism of benzoxazole is facilitated by a larger chance for oxidation which in turn opens a broad avenue to introduce drug metabolism. Mostly the benzoxazole nucleus showed potential anti-inflammatory, antimalarial, antiretroviral, and anticancer potential. Benzoxazolones itself readily undergo oxidative metabolism to glucuronide conjugates.[85]

The historical background analysis on benzoxazoles depicts their versatile synthetic importance to treat versatile disease comorbidities like monoamine oxidase, calcium channel, and the progression of anticancer potential. Monamine oxidase (MAO) A and B decompose norepinephrine, serotonin, and phenethylamine after watery neurotransmission. Its long-term inhibition research is reported to further treat resistant depression and anxiety disorders. Monoamine oxidase depression is likely to pharmacologically affect it facet so as to advect epitope insight and further demonstrate antidepressant applications of epilepsy benzoxazole and its peripheral theo derivatives .The design, synthesis, and biological migrates 3–10 of unusual serotonin and norepinephrine reuptake inhibitors as well as acetylcholinesterase inhibitors (AChEI) containing the potent benzoxazole motif are reported. Influential hydrogen linkage, a pharmacophoric span in coupling benzoxazole depression and alkoxy motes, and effect splitting potency photolysis are discreetly analysed for the first time on a recorded board-wise receptor-specifictical spectrum . Therapeutic treatments, psychological cocoon-catching and theoretical insight-renewed ascent are supported by maya pharmacokinetic, bioavailability, and serum plasma reductive audits. The urgency of the revolution to benzilmalonic napthyl esters, their cyclization by carboamidation, and statistical actions is also recapitulated.[86,87,88]

15. Patient Perspectives and Experiences

Here, advances in the review suggest the development of novel benzodiazole derivatives as well as the therapeutic perspectives with an antidepressant and anxiolytic activity. Benzodiazoles (BZ's) are one of the most commonly prescribed drugs for the treatment of GAD. BZ's exert their therapeutic effects by allosterically binding to the GABAA receptor at the α subunit, and enhancing the action of GABA. Both selective BZ receptor agonist (R) tandospirone and BZ receptor partial agonist (PA) gepirone are 5-HT1A receptor modulators. .Tandospirone stimulates 5-HT1A receptor outflow in the frontal cortex, whereas gepirone has similar actions in both this and other regions. Moreover, PA's and not R's persistently increase the outflow of 5-HT1A via action at terminal autoreceptors, suggesting that autoreceptor functionality and/or autoreceptor feed-back is disrupted by these agents. PA's and, to a lesser extent R's, make 5-HT1A autoreceptor fewer responsive to effects of chronic treatment with a 5-HT reuptake blocker. Furthermore, in view of at least some evidence of sustained perturbations of 5-HT1A function in patients on BZ's, these findings suggest that R's and PA's might be of particular interest as therapeutic agents for GAD.However, the SSRI fluvoxamine and the 5-HT3 receptor antagonist ondansetron potentiate the effects of tandospirone on 5-HT1A receptor outflow only in the frontal cortex and not in other regions. Generalized anxiety disorder (GAD) is a common, chronic condition that is associated with increased medical utilization costs, marked impairment in occupational or academic activities, substantial social and role dysfunction, and pronounced frustration, worry, and distress. Lifetime prevalence of GAD is approximately 5–6%, much lower than the lifetime of major depression . In contrast to other anxiety disorders, patients with GAD have both physical and cognitive symptoms that are persistent for at least 3–6 months, causing them to have difficulty managing, controlling sense, and attention in everyday life, and feeling tired and difficult to relax . Because of the diverse characters of its symptoms, GAD and major depressive disorder (MDD) are often considered to have comorbidities and are very difficult to treat. Although a traditional benzodiazepine (BZ) and buspirone have been used to treat GAD, this drug has risks and side effects, including disturbance of cognitive and psychomotor functions, dependence, abuse, withdrawal syndrome, memory loss, overdose leading to death, etc. .In addition, in the case of BZ, the consumption of alcohol and other drugs is dangerous to life. Recent advances in the development of novel benzodiazole derivatives targeting the pathophysiological changes of GAD are discussed here . In addition, therapeutic perspectives with an antidepressant and anxiolytic activity are also introduced. Emotional and cognitive dysfunction is a major and persistent symptom of GAD. It develops the treatment of cognitive-used drugs, such as a selective serotonin reuptake inhibitor (SSRI) and serotonin norepinephrine reuptake inhibitor (SNRI), and the utilization of cognitive behavioral therapy (CBT) .[88,89,90,91,92,93,94,95,96,97,98]

16. Conclusion

The exploration of benzoxazole derivatives has significantly expanded in recent years, particularly with regard to their therapeutic potential in treating central nervous system (CNS) disorders such as depression and anxiety. These heterocyclic compounds possess a unique chemical scaffold that allows for extensive structural modifications, making them versatile candidates for drug development. Advances in synthetic methodologies, including green chemistry approaches, metal-catalyzed coupling reactions, and molecular hybridization strategies, have enabled the generation of structurally diverse benzoxazole derivatives with improved pharmacodynamic and pharmacokinetic profiles.Preclinical studies have consistently demonstrated that many benzoxazole-based compounds exhibit significant antidepressant and anxiolytic effects through their interaction with key neurotransmitter

systems, including serotonin, norepinephrine, dopamine, and GABA. Some derivatives have shown potent activity in behavioral models such as the forced swim test (FST), tail suspension test (TST), and elevated plus maze (EPM), indicating their relevance in mood and anxiety regulation. The incorporation of pharmacophores such as triazoles, amides, or halogenated phenyl groups has further enhanced binding affinity and selectivity toward CNS targets.Despite the promising pharmacological outcomes, challenges remain in translating these findings into clinically approved medications. Issues such as metabolic stability, bioavailability, and potential side effects require thorough investigation. Nonetheless, the growing body of research underscores the therapeutic promise of benzoxazole derivatives and encourages further interdisciplinary studies combining medicinal chemistry, pharmacology, and molecular modeling. Continued efforts in this direction may ultimately lead to the development of novel, effective, and safer antidepressant and anxiolytic agents based on the benzoxazole framework.

References:

1. Wong, X. K., & Yeong, K. Y. (2021). A patent review on the current developments of benzoxazoles in drug discovery. *ChemMedChem*.
2. Di Martino, S., & De Rosa, M. (2024). The benzoxazole heterocycle: A comprehensive review of the most recent medicinal chemistry developments of antiproliferative, brain-penetrant, and anti... *Topics in Current Chemistry*.
3. Abdullahi, A., & Yeong, K. Y. (2024). Targeting disease with benzoxazoles: A comprehensive review of recent developments. *Medicinal Chemistry Research*. Springer.
4. Singhal, D., Sharma, N., Paul, S., & Bhatt, S. (2024). Anxiolytics: An in-depth review of contemporary and emerging treatment approaches. *International Journal of Newgen Research in Pharmacy and Healthcare*.
5. Allameh, M., & Orsat, V. (2023). Herbal anxiolytics: Sources and their preparation methods. *Food Reviews International*.
6. Wang, C., Yang, S., Deng, J., Shi, L., & Chang, J. (2023). The research progress on the anxiolytic effect of plant-derived flavonoids by regulating neurotransmitters. *Drug Development*. Wiley Online Library.
7. Deb, S., Roy, M., Limbu, B., & Bertelli, M. (2022). Anti-anxiety medications and novel treatments for autism. In *Diagnosis and Treatment*. Springer.
8. Jin, Q., Fu, Z., Guan, L., & Jiang, H. (2019). Syntheses of benzo[d]thiazol-2(3H)-one derivatives and their antidepressant and anticonvulsant effects. *NCBI*.
9. Sirakanyan, S. N., Spinelli, D., Geronikaki, A., Kartsev, V., et al. (2021). Synthesis and neurotropic activity of new heterocyclic systems: Pyridofuro[3,2-d]pyrrolo[1,2-a]pyrimidines, pyridofuro[3,2-d]pyrido[1,2-a]pyrimidines, and pyridofuro[3′,2′:4,5]pyrimido[1,2-a]azepines. *NCBI*.
10. Singh, K., Pal, R., Khan, S. A., Kumar, B., & Akhtar, M. J. (2021). Insights into the structure-activity relationship of nitrogen-containing heterocyclics for the development of antidepressant compounds: An updated review. *Journal of Molecular...* Elsevier.
11. Prasher, P., Mall, T., & Sharma, M. (2023). Synthesis and biological profile of benzoxazolone derivatives. *Archiv der Pharmazie.*
12. Kabi, A. K., Gujjarappa, R., Garg, A., Sahoo, A., & Roy, A. (2022). Overview on diverse biological activities of benzisoxazole derivatives. In *Select Proceedings of...* Springer.
13. Al Awadh, A. A. (2023). Biomedical applications of selective metal complexes of indole, benzimidazole, benzothiazole and benzoxazole: A review (From 2015 to 2022). *Saudi Pharmaceutical Journal.*

14. Li, S., Mei, Y., Jiang, L., Yang, X., et al. (2025). Oxazole and isoxazole-containing pharmaceuticals: Targets, pharmacological activities, and their SAR studies. *RSC Medicinal Chemistry.*
15. Katab, H. M. A. (2023). Biological evaluation of 2-oxo-benzoxazole derivatives. *An-Najah National University.*
16. Arulmurugan, S., & Kavitha, H. P. (2021). Review on the synthetic methods of biologically potent benzoxazole derivatives. *Mini-Reviews in Organic Chemistry.*
17. Staniszewska, M., Kuryk, Ł., Gryciuk, A., & Kawalec, J. (2021). In vitro anti-Candida activity and action mode of benzoxazole derivatives. *Molecules.*
18. Muhammed, M. T., & Kuyucuklu, G. (2022). Synthesis, antimicrobial activity, and molecular modeling studies of some benzoxazole derivatives. *Letters in Drug Design & Discovery, 19*(12), 1234–1245.
19. Abdelgawad, M. A., Al-Sanea, M. M., Zaki, M. A., et al. (2021). New benzoxazole derivatives as antiprotozoal agents: In silico studies, synthesis, and biological evaluation. *Journal of...* Wiley Online Library.
20. Maltsev, D. V., Skripka, M. O., & Spasov, A. A. (2022). Design, synthesis and pharmacological evaluation of novel C2,C3-quinoxaline derivatives as promising anxiolytic agents. *International Journal of...* MDPI.
21. Kumar, B., Kumar, N., Thakur, A., & Kumar, V. (2022). A review on the arylpiperazine derivatives as potential therapeutics for the treatment of various neurological disorders. *Current Drug...*
22. Almehmadi, M., Allahyani, M., & Alsaiari, A. A. (2025). Neuropharmacological potential of different piperazine analogs: A recent prospective. *Mini-Reviews in...*
23. Šlachtová, V., Chasák, J., & Brulíková, L. (2019). Synthesis of various 2-aminobenzoxazoles: The study of cyclization and Smiles rearrangement. *NCBI.*
24. Kim, Y., & Kim, S. G. (2024). Stereoselective [4+3]-cycloaddition of 2-amino-β-nitrostyrenes with azaoxyallyl cations to access functionalized 1,4-benzodiazepin-3-ones. *NCBI.*
25. Huang, G., Cierpicki, T., & Grembecka, J. (2023). 2-Aminobenzothiazoles in anticancer drug design and discovery. *Bioorganic Chemistry.*
26. Zhi, X., Liu, Y., Liang, J., Yuan, X., & Shi, H. (2024). Pesticide candidates inspired by natural neolignan: Preparation and insecticidal investigation of honokiol analogs containing 2-aminobenzoxazole-fused core scaffold. *Journal of Agricultural...* ACS Publications.
27. Imaizumi, T., Otsubo, S., Maemoto, M., & Kobayashi, A. (2022). Discovery and mechanistic study of thiazole-4-acylsulfonamide derivatives as potent and orally active ChemR23 inhibitors with a long-acting effect in cynomolgus... *Bioorganic & Medicinal Chemistry.*
28. Ghoshal, T., & Patel, T. M. (2021). One-pot synthesis of 2-aminobenzoxazole derivatives using acetic acid as an electrolyte under electrochemical conditions. *Journal of the Iranian Chemical Society.*
29. Kakkar, S., & Narasimhan, B. (2019). A comprehensive review on biological activities of oxazole derivatives. *NCBI.*
30. Al Awadh, A. A. (2023). Biomedical applications of selective metal complexes of indole, benzimidazole, benzothiazole and benzoxazole: A review (From 2015 to 2022). *NCBI.*
31. Samanth, M. (2025). Benzisoxazole derivatives: Synthesis and their therapeutic significance in medicinal chemistry. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.5138801
32. Chauhan, B., Kumar, R., Mazumder, A., et al. (2023). Updates on the synthetic strategies and structure-activity relationship of anticonvulsant benzothiazole and benzimidazole derivatives. *Letters in Drug Design & Discovery.*

33. Khan, J., Rani, A., Aslam, M., Maharia, R. S., & Pandey, G. (2024). Exploring triazole-based drugs: Synthesis, application, FDA approvals, and clinical trial updates—a comprehensive review. *Tetrahedron.*
34. Pal, R., Singh, K., Khan, S. A., Chawla, P., & Kumar, B. (2021). Reactive metabolites of the anticonvulsant drugs and approaches to minimize the adverse drug reaction. *European Journal of...* Elsevier.
35. Bonifazi, A., Del Bello, F., Giorgioni, G., et al. (2023). Targeting orexin receptors: Recent advances in the development of subtype selective or dual ligands for the treatment of neuropsychiatric disorders. *Medicinal Research Reviews.*
36. Golubeva, E. A., Lavrov, M. I., Radchenko, E. V., & Palyulin, V. A. (2022). Diversity of AMPA receptor ligands: Chemotypes, binding modes, mechanisms of action, and therapeutic effects. *Biomolecules.*
37. Raza, A. R., Rubab, S. L., Ashfaq, M., Altaf, Y., et al. (2023). Evaluation of antimicrobial and anticholinesterase potential of indole derivatives and unexpectedly synthesized novel benzodiazine: Characterization, DFT and Hirshfeld charge analysis. *NCBI.*
38. Faydalı, N., & Arpacı, T. (2024). Benzimidazole and benzoxazole derivatives against Alzheimer's disease. *Chemistry & Biodiversity.*
39. Babu, L. S., Suresh, D., Madasu, V. M., & Phanikumar, J. (n.d.). Chapter 8: Biologically active benzofused bioisosters (benzimidazole, benzoxazole, and benzothiazole). *ResearchGate.*
40. Alamri, M. A., Al-Jahdali, M., Al-Radadi, N. S., et al. (2021). Biological activity evaluation and computational study of novel triazene derivatives containing benzothiazole rings. *Journal of Molecular...* Elsevier.
41. Tok, F., Baltaş, N., & Tatar, G. (2022). Synthesis, biological evaluation and in silico studies of new pyrazoline derivatives bearing benzothiazol-2(3H)-one moiety as potential urease inhibitors. *Chemistry & Biodiversity.*
42. Al-Azzawi, A. M. K., & Hassan, E. A. (2025). Exploring benzothiazol-2-amine derivatives, synthesis, and molecular docking insights: Potential anticancer agents targeting HER enzyme and DNA. *Applied Biochemistry and Biotechnology.*
43. Kumar, G., & Singh, N. P. (2021). Synthesis, anti-inflammatory and analgesic evaluation of thiazole/oxazole substituted benzothiazole derivatives. *Bioorganic Chemistry.*
44. Patel, S. R., Patil, R. V., Chavan, J. U., & Beldar, A. G. (2023). Nanocatalyzed synthesis of benzoxazoles. *ChemistrySelect.*
45. García-Báez, E. V., Padilla-Martínez, I. I., & Tamay-Cach, F. (2021). Benzothiazoles from condensation of o-aminothiophenoles with carboxylic acids and their derivatives: A review. *Molecules.*
46. Kant, K., Patel, C. K., Banerjee, S., Naik, P., & Atta, A. K. (2023). Recent advancements in strategies for the synthesis of imidazoles, thiazoles, oxazoles, and benzimidazoles. *Wiley Online Library.*
47. Saha, N., Biswas, S., Naskar, S., & Sarkar, A. (2023). Microwave-assisted solvent-free synthesis of benzazoles. In *Solvent-Free Chemistry.*
48. Karimi, B., Mobaraki, A., Mirzaei, H. M., & Vali, H. (2023). Control of selectivity in the preparation of 2-substituted benzoazoles by adjusting the surface hydrophobicity in two solid-based sulfonic acid catalysts. *Organic & Biomolecular Chemistry.*
49. Wang, Y., Zhang, X., Li, S., Guo, M., & Ma, W. (2024). One-pot synthesis of 2,3-disubstituted-4(3H)-quinazolinone from o-aminobenzoic acid and DMF derivatives using imidazole hydrochloride as a promoter. *Current Organic Chemistry.*
50. Ruiz, D. M., Pasquale, G. A., & Martínez, J. J. (2022). Advances in novel activation methods to perform green organic synthesis using recyclable heteropolyacid catalysis. *Green Processing and Synthesis, 2022*, 1–10.

51. Kale, M. B., & Borse, R. A. (2021). Electrocatalysts by electrodeposition: Recent advances, synthesis methods, and applications in energy conversion. *Advanced Functional Materials.*
52. Zheng, K., Wu, Y., Hu, Z., Wang, S., Jiao, X., & Zhu, J. (2023). Progress and perspective for conversion of plastic wastes into valuable chemicals. *Chemical Society Reviews.*
53. Ren, Z., Wang, L., Li, Y., Zha, J., Tian, G., & Wang, F. (2022). Synthesis of zeolites by in-situ conversion of geopolymers and their performance of heavy metal ion removal in wastewater: A review. *Journal of Cleaner Production.*
54. Krzysztoforska, K., Piechal, A., Wojnar, E., & Blecharz-Klin, K. (2023). Protocatechuic acid prevents some of the memory-related behavioural and neurotransmitter changes in a pyrithiamine-induced thiamine deficiency model of Wernicke... *Nutrients.*
55. Faizi, M., Sheikhha, M., Ahangar, N., Tabatabaei Ghomi, H., et al. (2012). Design, synthesis and pharmacological evaluation of novel 2-[2-(2-chlorophenoxy) phenyl]-1,3,4-oxadiazole derivatives as benzodiazepine receptor agonists. *NCBI.*
56. Chikhale, H. U., & Rishipathak, D. D. (2025). In silico prediction, molecular docking study for identification of novel nitrogen-substituted benzoxazole derivative for their potential biological activity. *Chemistry Africa.*
57. Banerjee, S., Mukherjee, S., Nath, P., & Mukherjee, A. (2023). A critical review of benzimidazole: Sky-high objectives towards the lead molecule to predict the future in medicinal chemistry. *Results in Chemistry.*
58. Hall, A., Chanteux, H., Ménochet, K., et al. (2021). Designing out PXR activity on drug discovery projects: A review of structure-based methods, empirical and computational approaches. *Journal of Medicinal Chemistry, 64*(24), 17840–17858.
59. Shaik, B. B., Moodley, K., & Ghumran, S. (2025). The emerging landscape of tubercular targets: A medicinal chemistry approach. *Medicinal Research Reviews.*
60. Pal, S., Ghosh Dastidar, U., Ghosh, T., & Ganguly, D. (2022). Integration of ligand-based and structure-based methods for the design of small-molecule TLR7 antagonists. *Molecules.*
61. D'Ambrosio, K., Di Fiore, A., Alterio, V., & Langella, E. (2024). Multiple binding modes of inhibitors to human carbonic anhydrases: An update on the design of isoform-specific modulators of activity. *Chemical...* ACS Publications.
62. Khoramjouy, M., Zarepishe, N., Rezaee, E., Imani, A., et al. (2021). Novel derivatives of diphenyl-1,3,4-oxadiazol as ligands of benzodiazepine receptors; synthesize, binding assay and pharmacological evaluation. *NCBI.*
63. Martínez-Cerón, S., & Gutiérrez-Nágera, N. A. (2021). Phenylbenzothiazole derivatives: Effects against a Trypanosoma cruzi infection and toxicological profiles. *Parasitology.* Springer.
64. Rosales Hernández, M. C., Olvera-Valdez, M., et al. (2024). The benzazoles derivatives as pharmacophores for AChE, BACE1, and as anti-Aβ aggregation to find multitarget compounds against Alzheimer's disease. *Molecules.*
65. Moussa, Z., Ramanathan, M., Al-Masri, H. T., & Ahmed, S. A. (2024). Recent progress in the synthesis of benzoxazin-4-ones, applications in N-directed ortho-functionalizations, and biological significance. *Molecules.*
66. Chaudhary, T., & Upadhyay, P. K. (2024). A bird's eye review of recent reports on 1,3,4-oxadiazoles' anti-inflammatory insights and perspectives. *Current Organic Synthesis.*
67. Acar Çevik, U., Celik, I., Işık, A., & Ahmad, I. (2023). Design, synthesis, molecular modeling, DFT, ADME, and biological evaluation studies of some new 1,3,4-oxadiazole linked benzimidazoles as anticancer agents. *Journal of...*

68. Jones, J. L., & Malcolm, R. (2021). *Neurobiology and treatment of sedative-, hypnotic-, and anxiolytic-related disorders.* American Psychiatric Association.
69. Banerjee, S., Ghosh, P., Rathi, R., & Ghosh, A. (2024). Theoretical investigation of physicochemical properties, bioactivity, and toxicity of common anxiety medications. *Wiley Online Library.*
70. Cîrțînă, D., & Șerban, C. (2024). Aspects regarding the pharmacological and toxicological effects of benzodiazepines. *Journal of Research & Innovation for...*
71. Catalano, G., Sanchez, D. L., & Wecker, L. (2024). Drug therapy for depression and anxiety. In *Pharmacology-E-Book.*
72. Abu-Hashem, A. A., Hakami, O., Amri, N., & Mukhrish, Y. E. (2024). Synthesis of 1,3,5-triazepines and benzotriazepines and their biological activity: Recent advances and new approaches. *Molecules.*
73. Khoramjouy, M., Zarepishe, N., & Rezaee, E. (2021). Novel derivatives of diphenyl-1,3,4-oxadiazol as ligands of benzodiazepine receptors: Synthesis, binding assay, and pharmacological evaluation. *Iranian Journal of...*
74. Ghomashi, R., Ghomashi, S., & Aghaei, H. (2023). Recent advances in biologically active sulfonamide-based hybrid compounds part C: Multicomponent sulfonamide hybrids. *Current Medicinal Chemistry.*
75. Raghu, M. S., Kumar, C. B. P., Prashanth, M. K., et al. (2021). Novel 1,3,5-triazine-based pyrazole derivatives as potential antitumor agents and EGFR kinase inhibitors: Synthesis, cytotoxicity, DNA binding, molecular docking... *New Journal of...*
76. Krotulski, A. J., Cannaert, A., Stove, C., et al. (2021). The next generation of synthetic cannabinoids: Detection, activity, and potential toxicity of pent-4en and but-3en analogues including MDMB-4en-PINACA. *Drug Testing and Analysis, 13*(1), 24–35.
77. Verma, R., Pathak, S., Srivastava, A. K., & Prawer, S. (2021). ZnO nanomaterials: Green synthesis, toxicity evaluation, and new insights in biomedical applications. *Journal of Alloys and Compounds.*
78. El-Metwally, S. A., Abou-El-Regal, M. M., Eissa, I. H., et al. (2021). Discovery of thieno pyrimidine-based derivatives as potent VEGFR-2 kinase inhibitors and anticancer agents. *Bioorganic Chemistry.*
79. Arora, D., Singh, J., & Kumar, S. (2024). Medicinal attributes of pyrazoline in drug discovery. *Letters in Drug Design & Discovery.*
80. Dai, S. Y., Qin, W. X., Yu, S., Li, C., et al. (2024). Honokiol and magnolol: A review of structure–activity relationships of their derivatives. *Phytochemistry.*
81. Fekri, L. Z., Kadivar-Kalmarzi, M., et al. (2024). Heterocyclic scaffolds bearing –N=N– moiety: Recent advances in the synthesis of heterocyclic azo-dispersive dyes. *Polycyclic Aromatic Compounds.*
82. Natarajan, R., Kumar, P., & Subramani, A. (2024). A critical review on therapeutic potential of benzimidazole derivatives: A privileged scaffold. *Chemistry.*
83. Prashanth, G. K., Rao, S., & Lalithamba, H. S. (2025). Benzoxazoles: Diverse biological activities and therapeutic potential. In *Membered Bioactive N...*
84. El-Ghobashy, N. M., El-Sayed, S. M., Shehata, I. A., et al. (2022). Synthesis, biological evaluation, and molecular modeling studies of new benzoxazole derivatives as PARP-2 inhibitors targeting breast cancer. *Scientific Reports.*
85. Upadhyay, S., Tripathi, A. C., Paliwal, S., & Saraf, S. K. (2017). 2-Pyrazoline derivatives in neuropharmacology. [PDF].
86. Winters, C., Gorssen, W., Ossorio-Salazar, V. A., Nilsson, S., et al. (2022). Automated procedure to assess pup retrieval in laboratory mice. *Scientific Reports.*
87. Jourjine, N., Woolfolk, M. L., Sanguinetti-Scheck, J. I., et al. (2023). Two pup vocalization types are genetically and functionally separable in deer mice. *Current Biology.*

88. Rutovskaya, M. V., Volodin, I. A., & Feoktistova, N. Y. (2024). Acoustic complexity of pup isolation calls in Mongolian hamsters: 3-frequency phenomena and chaos. *Current Biology.*
89. Winters, C., Gorssen, W., & Wöhr, M. (2023). BAMBI: A new method for automated assessment of bidirectional early-life interaction between maternal behavior and pup vocalization in mouse dam–pup dyads. *Frontiers in Behavioral Neuroscience.*
90. Badgujar, N. D., Dsouza, M. D., Nagargoje, G. R., & Kadam, P. D. (2024). Recent advances in medicinal chemistry with benzothiazole-based compounds: An in-depth review. *Journal of Chemical Reviews.*
91. Tran, L., Tu, V. L., Dadam, M. N., & Aziz, J. M. A. (2024). Antimalarial activities of benzothiazole analogs: A systematic review. *Fundamental & Clinical Pharmacology.*
92. Khan, U., & Sur, S. (2024). Exploring the DNA recognition of compounds based on benzimidazole and benzothiazole: A concise review. *Macromolecular Symposia.*
93. Mao, W., Qu, J., Liu, H., Guo, R., Liao, K., & Wu, S. (2024). Associations between urinary concentrations of benzothiazole, benzotriazole, and their derivatives and lung cancer: A nested case–control study. *Environmental Research.*
94. Anwar, S., Rehman, W., Hussain, R., Khan, S., & Alanazi, M. M. (2023). Investigation of novel benzoxazole–oxadiazole derivatives as effective anti-Alzheimer's agents: In vitro and in silico approaches. *Pharmaceuticals, 16*(3).
95. Nguyen, H. T., Nguyen, T. H., Pham, D. D., Nguyen, C. T., et al. (2021). A green approach for the synthesis of 2-substituted benzoxazoles and benzothiazoles via coupling/cyclization reactions. *Heliyon, 7*(2).
96. Wu, S., Geng, F., Dong, J., & Liu, L. (2022). Metal-free oxidative annulation of phenols and amines: A general synthesis of benzoxazoles. *Journal of Organic Chemistry.* ACS Publications.
97. Bansal, S. (2021). Recent advances in the synthesis of benzoxazole. *Mini-Reviews in Organic Chemistry.*
98. Chahal, M., Dhillon, S., Rani, P., Kumari, G., & Aneja, D. K. (2023). Unravelling the synthetic and therapeutic aspects of five, six, and fused heterocycles using Vilsmeier–Haack reagent. *RSC Advances.*