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General Overview of Benzoxazin-2-one Metal Ion Complexes: Synthetic Routes and Biomedical Applications

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Abstract

Benzoxazin-2-one derivatives are a unique class of organic heterocyclic compounds known for their remarkable chemical stability and bioactivity. These compounds exhibit diverse therapeutic properties, including anticancer, antioxidant, and antimicrobial activities. This review highlights the synthesis, interaction, and therapeutic applications of metal ion complexes derived from benzoxazin-2-one. Coordination with metal ions such as Zn^{2+}, Cu^{2+}, and Fe^{3+} enhances the chemical stability, solubility, and bioavailability of these compounds, significantly improving their pharmacological potential. Recent advancements in green chemistry have introduced sustainable and eco-friendly methods for synthesizing these complexes, contributing to reduced environmental impact. Additionally, nanoscale characteristics of metal ion complexes, such as increased surface area and improved reactivity, further enhance their therapeutic efficacy, enabling targeted delivery and reduced toxicity. The potential applications of these complexes span from combating infectious diseases to environmental monitoring and biosensing. This review provides a comprehensive overview of the synthetic strategies, molecular interactions, and promising biological applications of benzoxazin-2-one metal ion complexes, establishing them as vital candidates in drug design and development

Keywords: Benzoxazin-2-one derivatives; Biomedical applications; coordination chemistry; Green chemistry synthesis; Metal ion complexes; Nanoscale characteristics

Introduction

Background on Benzoxzazin-2-one Derivatives and Their Significance

A benzene ring is fused with an oxazinone moiety that contains both oxygen (O) and nitrogen (N) atoms within the heterocyclic ring to generate benzoxazin-2-one derivatives, a class of organic heterocyclic compounds defined by a distinctive structure [1]. Due to their structural framework, which also confers upon them a high degree of chemical reactivity, these compounds are highly adaptable in a variety of fields, including medical chemistry. The chemical structures of several benzoxazine

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isomers are shown in Fig.1 based on the positions of oxygen (O) and nitrogen (N) inside the ring [2]. The substances have gained a number of attentions seeing that they have numerous organic actions along with anticancer, antioxidant, antibacterial and anti-inflammatory properties[3]. Their capability to engage with important organic objectives, together with enzymes and receptors, makes them appealing options for drug improvement [4]. The new photo illustrates the chemical structures of certain biologically active benzoxazine derivatives and details their therapeutic applications, which include anticancer [5], antibacterial [6], and antioxidant activities [7]. These applications enhance the potential of these compounds to treat various diseases.

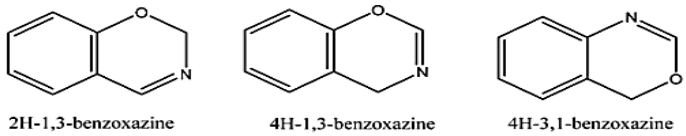

Figure 1. Chemical structures of various examples of benzoxazine isomers [8].

Overview of Metal Ion Complexes and Their Relevance

The scientific take a look at of iron ion complexes is critical to each biochemistry and inorganic chemistry because of their crucial position in both chemical and organic methods. Metal ions, such as zinc (Zn^{2+}) copper (Cu^{2+}), and iron (Fe^{2+}, Fe^{3+}), are vital in the formation of coordination complexes, while metal ions companion with organic or inorganic ligands [9]. The specific chemical properties of these complexes may also drastically exchange the characteristics of the ligand and metals. Metal ions act as cofactors for enzymes [10], stabilize protein structures [11], and facilitate electron delivery in metabolic pathways [12], playing a vital position in several biological procedures [13]. Metal-organic coordination has garnered full-size attention due to the creation of bioactive and strong complexes, which includes benzoxazin-2-one derivatives[14]. The chemical reactivity and pharmacological function of these complexes may be regulated via interactions between ligands and metals. Improved medicinal efficacy may be finished with the aid of coordinating metallic ions, consequently enhancing solubility, balance, and bioavailability[15]. Metal ions possess other mechanisms of action, including metal ion chelation and enzyme inhibition, which are useful in the treatment of diabetes, cancer, and microbial infections[16]. Fig.2 shows how metal ions can be used as a therapeutic therapy in complexes like cisplatin (a clinically authorized anticancer medication) and gold complexes that block enzymes.

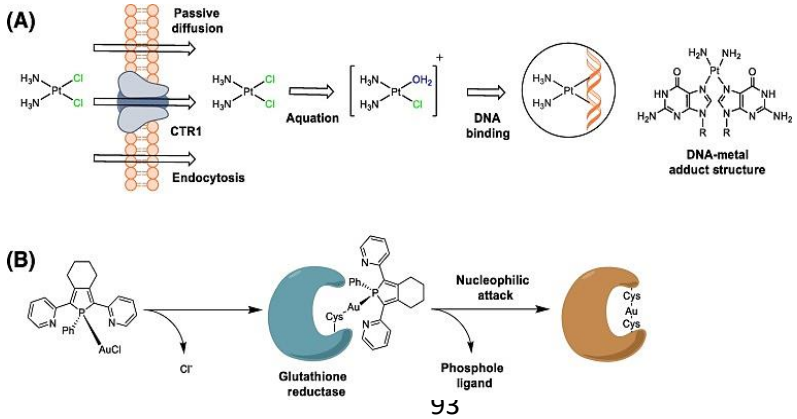

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Figure2. Ligand exchange activity of metal complexes. Mechanism of action of: (a) the clinically approved anticancer drug cisplatin; and (b) a coordinationally covalent bound Au(I) complex as an enzyme inhibitor [17]

Understanding important biological processes like oxygen transport and electron transfer requires an understanding of metal ion complexes that goes beyond pharmacology. For instance, iron is necessary for oxygen binding and transport in hemoglobin and myoglobin[18]. Effective oxygen transport in tissues is made possible by iron in deoxy myoglobin, which binds reversibly to oxygen at an empty spot in the heme group, as shown in Fig.3.

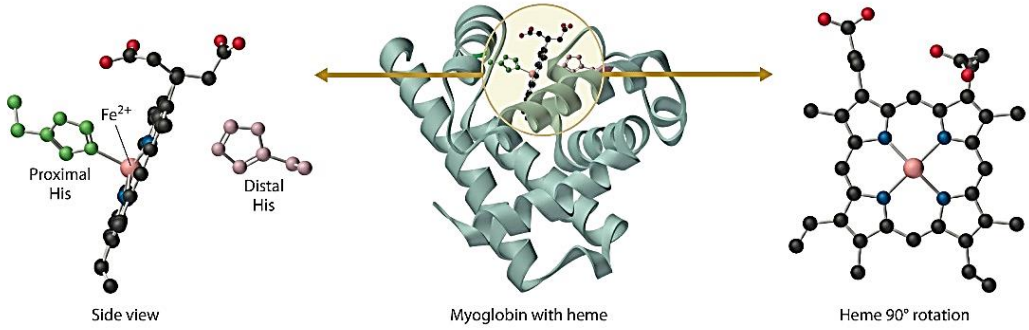


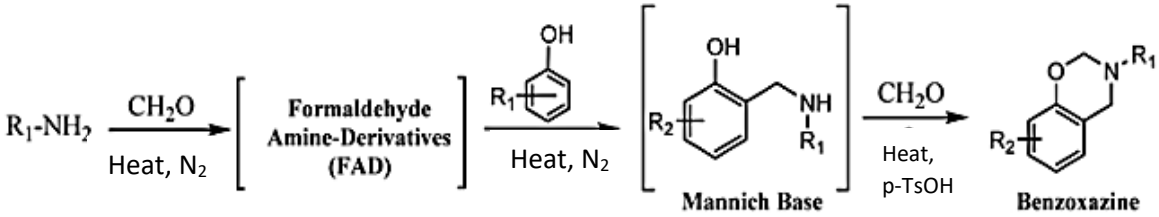
Figure3. The Structure of Deoxymyoglobin, Showing the Heme Group. The iron in deoxymyoglobin is five-coordinate, with one histidine imidazole ligand from the protein. Oxygen binds at the vacant site on iron.

Objectives of The Review and Scope of Coverage

In this review, we will mostly concentrate on benzoxazin-2-one derivatives and their interactions with metal ions, but we will also cover their chemistry, characteristics, and applications. In an effort to fill knowledge gaps, this study takes a methodical look at how metal ion coordination improves the therapeutic efficacy, bioactivity, and stability of benzoxazin-2-one-based drugs. The three primary goals of the review are as follows:

Exploring the Synthetic Routes and Chemical Properties of Benzoxazine-2- Derivatives

This section will examine the numerous synthetic methodologies employed to prepare benzoxazin-2-one derivatives. This encompasses a general technique that entails the reaction of phenol, primary amines, and formaldehyde to synthesize the benzoxazine ring [19]. Scheme 1 delineates the essential chemical processes and intermediates pertinent to the synthesis of benzoxazine derivatives, emphasizing the factors that affect their synthesis.



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scheme 1. standard method for the synthesis of benzoxazine from primary amine, phenol and formaldehyde[8]

Examining the Interaction of Benzoxazine-2-one Derivatives with Metal Ions and The Resultant Complexation Effects

This section will focus on the coordination chemistry of benzoxazin-2-one derivatives, specifically the effect of metal-ions on the biological and chemical characteristic of the generated complexes. The review will examine the influence of metal ions on the solubility, solubility, and interactions of these complexes with biomolecules, and how these factors improve their therapeutic efficacy.

Highlighting the Potential Therapeutic Applications of These Complexes in Drug Design and Development

In this section will analyze the therapeutic potential of benzoxazin-2-one metal ion complexes, concentrating on their application in the treatment of different health conditions. Numerous benzoxazine compounds exhibit diverse biological activity, encompassing antibacterial and anticancer properties [20], as depicted in Fig.4. These derivatives provide compelling prospects for the treatment of conditions such as cancer, infectious diseases, and neurological disorders, as they can improve their therapeutic efficacy when complexed with metal ions [4].

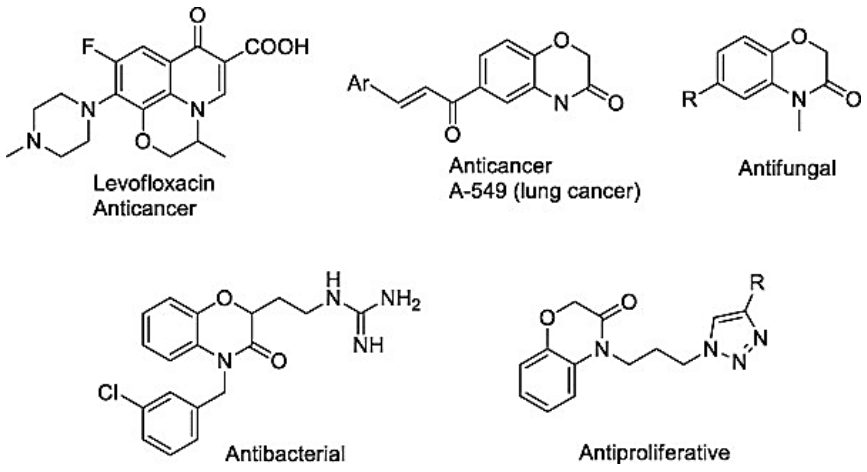

Figure 4. Certain biologically active compounds of Benzoxazin-2-one derivatives [18]

The review will present a current overview of the most promising findings in the coordination chemistry of benzoxazin-2-one derivatives, encompassing recent advancements and breakthroughs in the discipline. It examines strategies for optimizing their use in pharmaceutical development while emphasizing their molecular and biological impact. The review will serve as a comprehensive resource

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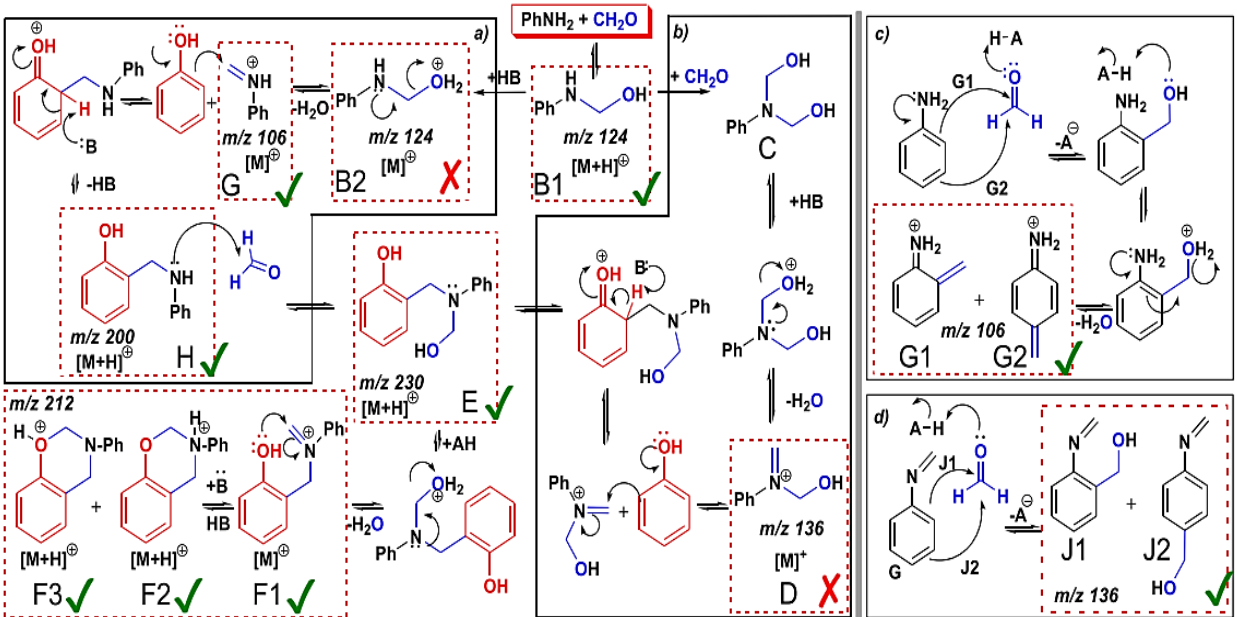
Synthesis of metal ion Complexes (General Synthetic Strategies for Benzoxazine-2-one-Based Complexes

Benzoxazine Formation Mechanism and Synthetic Routes

Various strategies have been developed for the synthesis of benzoxazin-2-one–based metal ion complexes to enhance coordination between ligands and metal centers. Typically, the benzoxazin-2-one ligand is first prepared through condensation and cyclization reactions that establish the heterocyclic ring essential for metal binding [21] . The prepared ligand is then reacted with suitable metal salts under controlled conditions to form the desired complexes. Reaction parameters such as solvent type, temperature, pressure, and metal choice play critical roles in determining the stability, solubility, and overall yield of the complexes. [22,23].

A notable mechanism proposed by Burke highlights the role of a key intermediate that facilitates coordination between the ligand and metal ion [24], as illustrated in (Scheme 2a). Other mechanisms have been suggested, including Ishida's sequential formaldehyde addition approach, where formaldehyde is used to generate benzoxazin-2-one complexes (Scheme 2b). However, unwanted side reactions can occur, resulting in by-products such as G1 and G2 formed by aniline attacking formaldehyde (Scheme 2c), and J1 and J2 produced by iminium species reacting with formaldehyde (Scheme 2d). These side reactions can adversely affect the yield and purity of the final complexes. By understanding these mechanisms and their reaction pathways [25], researchers can refine synthetic strategies to obtain complexes with improved pharmacological properties.



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Scheme 2. Reaction Mechanism Proposals for the Benzoxazines Synthesis Based on (a) Burke's Mechanism via Intermediate H; and (b) Ishida's Sequential Formaldehyde Proposal, a (c) Side Products G1/G2 Formation by Aniline Attack to Formaldehyde; and (d) Side Products J1/J2 Formation Promoted by the Iminium G Attack to Formaldehyde [25]

Synthetic Strategies for Benzoxazin-2-one Ligands

Benzoxazin-2-one frameworks are typically prepared through the formation of a heterocyclic ring starting from ortho-aminophenol or anthranilic acid derivatives. These compounds serve as essential building blocks that determine the final properties of the ligand, such as chemical stability, solubility, and coordination ability with metal ions. The most commonly employed synthetic approaches include:

Intramolecular Acylation Cyclization:

In this route, ortho-aminophenols or anthranilic acid derivatives are first acylated using suitable carboxylic acid derivatives to form an acyl intermediate [26]. Ring closure is then promoted intramolecularly to yield the benzoxazine ring. Safe phosgene alternatives, such as triphosgene or carbonyl diimidazole (CDI), are often used to provide a safer reaction environment and reduce the formation of toxic by-products. This method is effective for producing mono- or multifunctional ligands and allows the introduction of diverse functional groups on the benzoxazine ring to enhance metal coordination [27].

Condensation and Cyclization:

This approach involves reacting aminophenols or anilines with carbonyl sources such as aldehydes or carboxylic acids, initially forming an imine intermediate [28]. Ring closure is then promoted by mild oxidation or dehydration using gentle chemical reagents. This method is relatively flexible and can be adjusted to yield ligands with additional functionalities that increase metal-binding capability, while minimizing unwanted side reactions [29].

Sequential Formaldehyde Pathway (Ishida Method):

This method utilizes formaldehyde to generate an iminium intermediate capable of intramolecular attack by the aminophenol group, forming the benzoxazin-2-one ring [30]. Although effective for synthesizing structurally diverse rings, this pathway may lead to side reactions that require careful control of temperature and pH to ensure reaction selectivity. It is often employed for producing multifunctional ligands but typically requires additional purification steps to obtain a pure product [31].

The choice of the appropriate synthetic pathway depends on the desired functional groups, practical considerations, and chemical safety requirements. Factors such as solvent selection, temperature, and type of oxidizing or acidic agent significantly influence reaction efficiency and ligand

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purity. Strategically employing these approaches enables the design of benzoxazin-2-one ligands tailored for highly effective metal ion coordination, with applications in analytical chemistry, pharmaceutical research, and nanomaterials [32,31].

General Strategies for the Formation of Metal Complexes Using Benzoxazine Derivatives

After the preparation and characterization of the ligand , which is a benzoxazine derivative, several common strategies are employed to form coordination complexes with metal ions. These approaches focus on controlling the coordination environment, stoichiometry, and geometry to obtain stable and well-defined complexes.

Direct Complexation in Protic or Aprotic Solvents:

The benzoxazine ligand is dissolved in a suitable solvent such as ethanol, methanol, or polar aprotic solvents like DMF or DMSO[33]. A solution of the metal salt (e.g., chloride, nitrate, or acetate) is then added gradually under stirring. The metal ion coordinates directly with the donor atoms in the ligand, usually oxygen or nitrogen, forming the desired complex. This method is applicable to a wide range of transition and main group metals, providing moderate to high yields depending on the solubility and reactivity of the ligand and metal salt [34].

Deprotonation to Facilitate Coordination:

Protonated donor groups in the benzoxazine ligand, such as –OH or –NH, can limit coordination. Deprotonation using mild bases like sodium acetate or triethylamine enhances the nucleophilicity of these groups, promoting stronger binding with the metal ions. This approach is particularly useful for metals that favor anionic ligands or for controlling the formation of mono- versus polynuclear complexes [35].

Metal-Templated Synthesis (One-Pot Complexation):

In this strategy, the benzoxazine ligand is synthesized in the presence of the metal ion. The metal acts as a template, guiding the cyclization or condensation reaction to form the ligand in situ while simultaneously forming the complex. This method improves reaction efficiency and selectivity, especially for transition metals that prefer specific coordination geometries. It is highly effective for constructing macrocyclic or multidentate complexes where the metal dictates the final structure [36].

Isolation and Purification:

After complexation, the product is typically isolated by precipitation or solvent evaporation. The solid complex is filtered, washed with cold alcohol or ether to remove unreacted ligand or metal salts, and dried under vacuum [37]. Recrystallization from suitable solvent mixtures can yield high-quality crystals suitable for X-ray diffraction or further spectroscopic characterization (IR, UV-Vis, NMR, elemental analysis). Proper purification ensures complexes with defined composition and reproducible properties [38].

By applying these strategies, researchers can design metal complexes using benzoxazine derivatives with controlled geometry, stability, and activity, with broad applications in catalysis, materials science, biological modeling, and medicinal chemistry.

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Geometry and Resulting Complexes:

The geometry of the resulting complex depends strongly on the type of metal ion. For instance, zinc (Zn^{2+}) typically forms tetrahedral or octahedral complexes [39]. Copper (Cu^{2+}) generally adopts square planar or distorted octahedral geometries depending on the ligand's denticity [40]. Iron (Fe^{3+}) usually prefers octahedral coordination [41]. Similarly, other transition metals such as cobalt, nickel, manganese, chromium, and some main group metals can form diverse geometries and stoichiometries, with the final structure influenced by the ligand's size, electronic properties, and the nature of the solvent [42].

Synthesis Challenges for Benzoxazine Complexes

The synthesis of benzoxazin-2-one metal complexes is associated with several challenges that can reduce product yield or quality. One of the most frequent issues is hydrolysis, particularly with iron(III), as Fe^{3+} tends to form hydroxide or oxide species even in the presence of trace amounts of water [43]. This can lead to polynuclear or μ-oxo-bridged species instead of the desired mononuclear complexes. To prevent this, it is recommended to use anhydrous solvents or work under controlled acidity, while adding iron gradually at low temperatures [44].

Another common problem arises when the goal is to obtain a mononuclear complex, but polynuclear or heterogeneous complexes form instead. This typically occurs when the ligand-to-metal ratio is not precisely controlled, or when excess water or elevated temperatures are present. Careful control of stoichiometry, the use of a slight excess of ligand, and maintaining moderate reaction temperatures can minimize this issue [45].

Side reactions associated with formaldehyde, as in the Ishida method, represent an additional challenge. The iminium or aniline intermediates can react with formaldehyde to produce undesired compounds that reduce the purity of the final product. To address this, it is advisable to use limited amounts of formaldehyde, conduct the reaction at low temperatures, and monitor it in real time using spectroscopic techniques [46].

Finally, attention must be paid to the stability of the complexes in relevant biological media, as well as their solubility and redox behavior before evaluating biological activity. Neglecting acute or chronic toxicity studies may lead to misleading results in biomedical applications. By addressing these challenges with awareness and systematic planning, researchers can improve the yield and quality of benzoxazine metal complexes, ensuring reproducible and reliable results that support advances in drug design and biomedical applications.

Optimal Conditions for Coordination Reactions

Experimental conditions play a crucial role in the successful formation and quality of benzoxazin-2-one metal complexes. Factors such as solvent type, temperature, pH, and reaction time are interconnected and directly influence the yield, stability, and reproducibility of the final product [47,43]. For instance, polar solvents such as ethanol or water–alcohol mixtures are commonly used because they provide a suitable medium for dissolving both the ligand and the metal salts, enhancing effective molecular collisions and facilitating coordination [48].

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Temperature is also a key factor. Increasing temperature can accelerate the reaction rate and improve the solubility of solid reactants; however, excessive heating may lead to ligand decomposition or undesired side products[49].

The pH of the reaction medium affects the ionization state of functional groups in the ligand, such as hydroxyl or amine groups. Strongly acidic conditions can protonate coordination sites, preventing metal binding, while highly basic conditions may decompose certain metal salts or cause their precipitation. For this reason, most reactions are performed under neutral or near-neutral pH conditions [50].

Reaction time and stirring or heating duration also influence the completion and regularity of the complexation. Studies have shown that carefully extended reaction times allow for the formation of more ordered and stable complexes. In some cases, slow evaporation or gradual crystallization is employed to improve crystal purity and obtain structures suitable for X-ray crystallographic analysis [51].

Additional factors, such as oxygen-free conditions or the use of inert gases like argon or nitrogen, can prevent unwanted oxidation of sensitive metals such as Fe^{2+}. Modern techniques, including ultrasonic irradiation or microwave-assisted synthesis, have also been applied to accelerate reactions and reduce energy consumption [52].

Careful control of these parameters not only improves reaction efficiency and complex yield but also produces materials with high thermal and chemical stability, as well as superior biological properties. Therefore, studying the optimal conditions for coordination reactions is essential for developing advanced benzoxazin-2-one metal complexes with promising pharmaceutical, industrial, and biomedical applications.

Green and Nanoscopic Synthetic Approaches

Modern synthetic chemistry increasingly focuses on environmentally friendly and sustainable methods for the preparation of metal ion complexes derived from benzoxazin-2-one. These approaches not only minimize hazardous waste but also enhance reaction efficiency and product quality [53]. Mechanochemical synthesis (solvent-free) has gained significant attention due to its ability to facilitate complex formation under mild conditions while eliminating harmful organic solvents. Microwave-assisted synthesis, providing a more energy-efficient approach, significantly reduces reaction times and improves yields by delivering rapid and uniform heating, thereby obviating the need for elevated temperatures and prolonged reaction times [54]. Fig. 5, Ultrasonic irradiation also enhances mass transfer, promoting effective mixing and accelerating complexation.

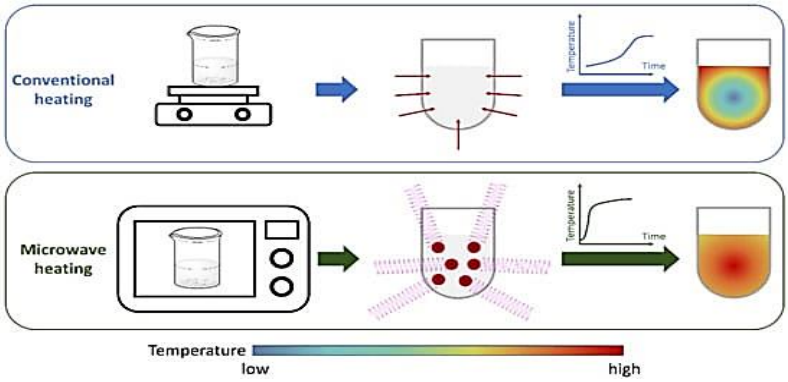

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Figure 5. Schematic difference between conventional and microwave heating [54]

Replacing traditional toxic solvents such as DMF and DMSO with ethanol or water aligns with green chemistry principles. Similarly, employing safer reagents such as CDI (carbonyl diimidazole) or triphosgene instead of phosgene reduces environmental and health risks [55]. These strategies are applicable across a wide range of metals—including transition, post-transition, and rare earth elements—allowing researchers to design tailored complexes for specific catalytic or biomedical applications. The classification of green solvents into water-based, bio-based, deep eutectic, and supercritic

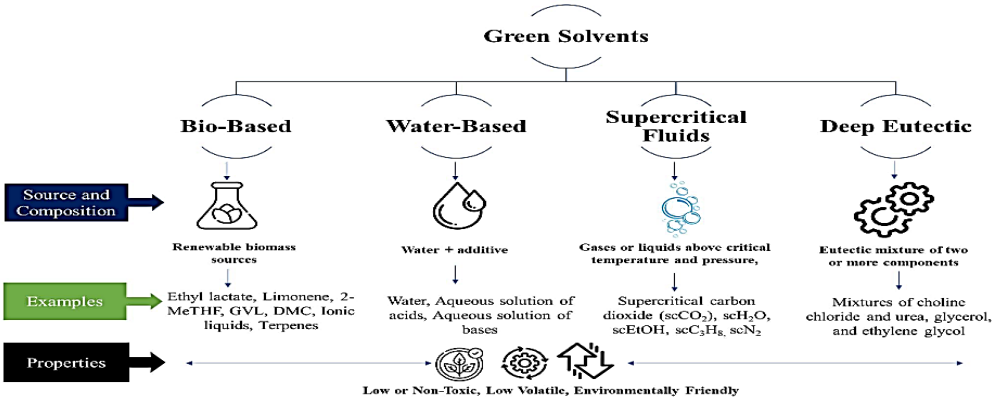

Figure 6. Classifications of green solvents [56]

At the nanoscale, the preparation of metal ion complexes offers additional advantages, including enhanced cellular uptake, improved solubility, targeted delivery, and reduced systemic toxicity [57]. For example, nano-sized complexes derived from benzoxazin-2-one ligands with Cu^{2+}, Fe^{3+}, and Zn^{2+} ions exhibit superior bioavailability and pharmacological performance compared to their larger counterparts, making them promising candidates for drug delivery, bioimaging, and biosensing applications [58,59].

Additionally, enzyme-mediated processes or biocatalysis have gained attention as a means of reducing the environmental impact of metal ion complex synthesis. Under mild conditions, enzymes can facilitate highly selective reactions, often leading to higher yields and fewer byproducts [60]. The use of biocatalysts represents a particularly eco-friendly approach to metal-ligand complex formation [61]. Furthermore, the development of closed-loop systems that minimize waste and enable recycling of solvents and reagents has been explored. For instance, recyclable metal catalysts are employed to reduce waste generation and lower production costs. Optimized reaction pathways also reduce byproducts and enhance overall sustainability, resulting in improved yields and reaction efficiency. Fig.7 illustrates the advantages of green solvents, demonstrating their enhancement of environmental sustainability, reaction efficie

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Figure 7. Advantages of green solvents [54]

By integrating these modern strategies—mechanochemistry, microwave and ultrasonic irradiation, green solvents, safer reagents, nanoscale design, and biocatalysis—researchers can achieve metal ion complexes that are not only highly efficient and stable but also eco-friendly and suitable for advanced biomedical and industrial applications.

Impact of Reaction Parameters (Temperature, PH, Ligand Type) on Obtaining Targeted Nano-Sized Complexes

The efficiency and stability of the final nanoparticles are influenced by several critical factors affecting the synthesis of nano-sized complexes. The dimensions, distribution, and physicochemical properties of nanoparticles are highly sensitive to reaction parameters such as temperature, pH, and ligand type [62]. This segment analyzes how these elements affect the formation of nanoscale complexes with the preferred traits in benzoxazin-2-one derivatives, ensuring optimal size, stability, and bioactivity for biomedical or catalytic applications.

Effect of Temperature on The Synthesis of Nano-Sized Complexes

Temperature plays an vital position inside the manufacturing of nanoscale complexes [34]. The interaction between metallic ions and ligands can be notably inspired by way of temperature fluctuations. In positive reactions, accelerated temperatures are vital to decorate the response charge, selling the advent of stable complexes [63]. Studies suggest that temperature influences the structural and morphological characteristics of zinc oxide (ZnO) nanoparticles synthesized via the zinc-air cellular system technique, with high temperatures main to an increase in particle length [64]. Fig.8 illustrates that high temperatures purpose particle boom and alterations of their traits, potentially resulting in the advent of larger complexes than intended, consequently rendering them inappropriate for packages necessitating tight control over particle length [65]. Conversely, reduced temperatures can slow the reaction rate at the same time as facilitating enhanced manipulate over particle size, perhaps resulting in the production of nanosized complexes with a greater precise shape [66]. Consequently, sustaining the appropriate temperature range is crucial to acquiring the favored nanoscale and balance of the compounds.

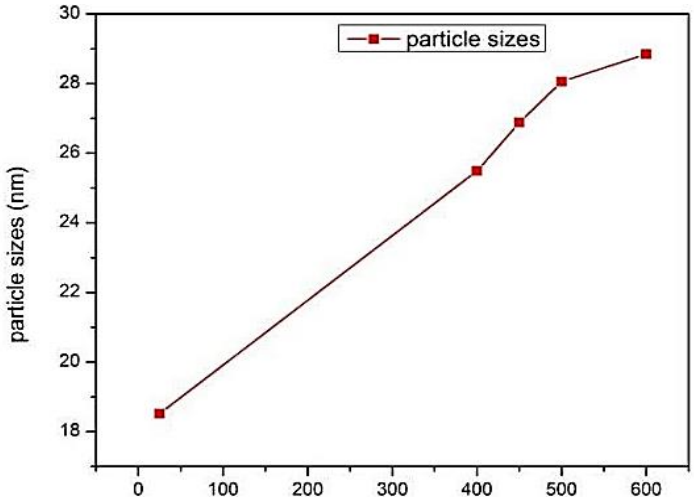

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Figure 8. Effect of Annealing Temperature on Structural, Morphology and Optical Properties of ZnO Nano-Needles Prepared by Zinc-Air Cell System Method [67]

Effect of PH on The Synthesis of Nano Complexes

The pH of the reaction medium is crucial in regulating the manufacturing of nano complexes, as it at once impacts the ionization of metal ions and ligands [67]. This subsequently affects the coordination and stability of the formed complexes . For example, in acidic situations, sure ligands can also show off enhanced stability, however in fundamental settings, steel ions may enjoy alterations in oxidation country, for that reason impacting the traits of the complicated [68,41], Furthermore, pH influences the scale and geometry of the complexes, because the protonation of either the ligand or the steel ion should modify the general shape [69]. By meticulously regulating the pH, one may manipulate the dimensions and morphology of the nanoscale complexes [70,41]. Fig.9 shows the pH-dependent coordination mechanism between metals and polyphenols, revealing the influence of pH on the stability and characteristics of these complexes.

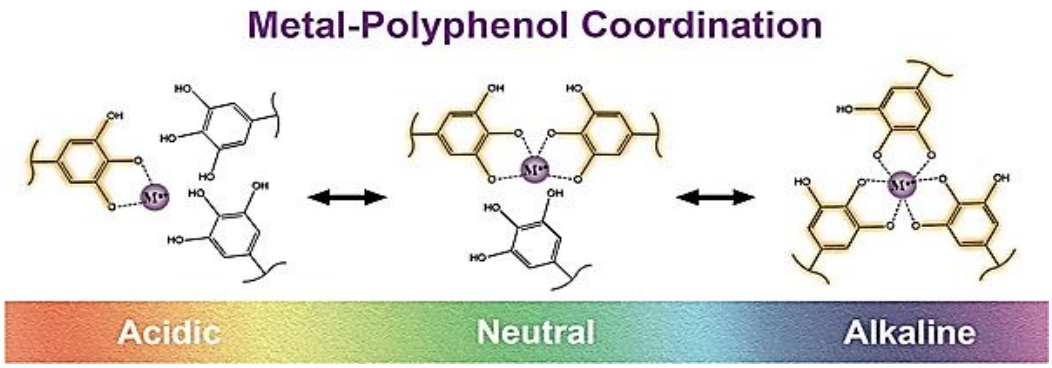

Figure 9. pH-Dependent metal-polyphenol coordination process.

Effect of Ligand Type on Nano-Sized Complexes

The ligand employed in the synthesis process greatly impact the characteristics of the resultant nano complexes [71]. Ligands differ in their capacity to coordinate with metal ions, and their structure is pivotal in influencing the size, stability, and shape of the complexes. Certain ligands with multiple binding sites allow the creation of more stable, smaller nano complexes. The geometry of the complex may be affected by the ligand structure, resulting in various coordination environments, including

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trigonal, hexagonal, or octahedral, prismatic configurations [72,73]. Fig.10 illustrates six kinds of ligands and their respective coordination geometries, highlighting how differences in ligand type can result in unique structural forms of the resultant complexes. A monodentate ligand coordinates with the metal distinctively compared to a bidentate ligand, as illustrated in Fig.11, influencing the dimensions and stability of the complexes [74]. Moreover, ligands with functional groups like carboxyl, amines, or phosphines groups can affect the electrical environment of the metal core, resulting in more regulated particle development and size [75]. By choosing a suitable ligand, researchers can enhance the regulation of the stability, size, and geometry of nano complexes.

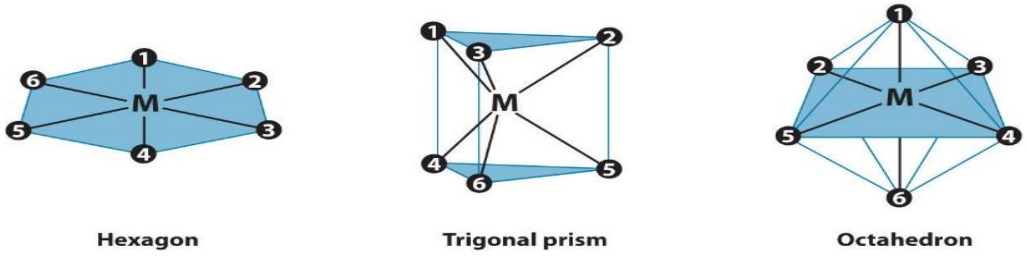

Figure 10. Different ligands and their coordination geometries.

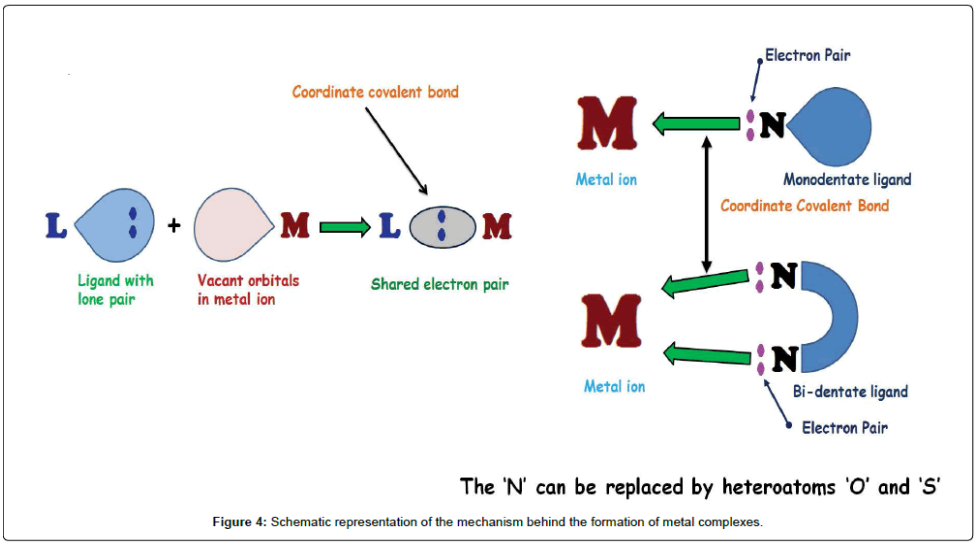

Figure 11. The coordination of Monodentate and bidentate ligands with metal-ions.

Interaction Between Parameters and its Impact on Nano Complexes Formation

By carefully controlling reaction parameters such as temperature, pH, and ligand type, it is possible to obtain nano-sized complexes in benzoxazin-2-one derivatives with defined size, homogeneous distribution, excellent chemical and thermal stability, and enhanced biological properties [76]. It should be noted that the interaction between these parameters can be intricate, as

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altering one variable may affect the others. For instance, high temperatures in a neutral medium may promote the formation of specific nano complexes, whereas an acidic medium could lead to larger complexes. Similarly, the choice of ligand can influence how temperature and pH affect the outcome, including the size and morphology of the final complex [77].

A deep understanding of these interacting factors enables researchers to precisely control the formation of nano-sized complexes, ensuring optimal performance in biomedical applications, drug delivery, biosensing, and bioimaging, thereby enhancing the significance of these complexes in modern drug design and biomedical applications.

Biological Applications

The biological packages of metallic-ion complexes, drastically the ones generated from benzoxazin-2-one, have attracted substantial interest in current years due to their huge capability usage in various sectors, especially in medication and environmental monitoring. These complexes show different organic characteristics, making them exciting candidates for therapeutic and diagnostic applications. The next sections will elucidate many good-sized biological programs of these complexes.

Antimicrobial and Antifungal Activity

The antibacterial and antifungal residences of steel-ion complexes represent some of their most important organic features. Benzoxazin-2-one derivatives, whilst complexed with metal ions inclusive of zinc, copper and silver, have advanced organic interest against several microbial pathogens, consisting of microorganism and fungi [78,79]. The metallic ions in these complexes engage with microbial cellular walls, compromising their structural integrity, which can lead to cell death [80]. Moreover, the benzoxazin-2-one ligand regularly contains functional businesses that facilitate effective binding to microbial cellular membranes, thereby enhancing usual antibacterial hobby. By enhancing the metal ion and ligand structure, researchers can optimize those complexes for particular antibacterial and antifungal treatments, hence augmenting their efficacy as healing alternatives for infections [50].

Antioxidant Properties

The antioxidant pastime of metallic-ion complexes represents a full-size organic function. These complexes display a brilliant ability to neutralize loose radicals, an important method in decreasing oxidative damage within cells [81]. Oxidative pressure is linked to numerous diseases, which encompass most cancers, cardiovascular conditions, and neurological problems. The steel ions in these complexes sell redox reactions by undertaking electron transfer sports that put off loose radicals. Furthermore, the ligand in benzoxazin-2-one derivatives is vital for keeping the steel ion in its energetic kingdom, as a result augmenting antioxidant action [82]. Recent investigations imply that metal-based totally benzoxazin-2-one complexes own big antioxidant homes, making them promising candidates for the prevention and treatment of ailments related to oxidative pressure.

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Anticancer and Cytotoxic Studies

The anticancer ability of steel-ion complexes has been thoroughly investigated, and complexes based on benzoxazin-2-one is blanketed in this research. These complexes have exhibited encouraging results in cytotoxicity experiments, demonstrating their ability to suppress the proliferation of many most cancers cell sorts [83]. The steel ions in these complexes can cause DNA harm or disrupt essential cell procedures critical for cancer cellular survival, which includes cell department and apoptosis [84]. Furthermore, the benzoxazin-2-one ligand could affect the complex's interaction with cancer cellular membranes, growing mobile absorption and improving its healing efficacy. The amalgamation of the metal ion with the benzoxazin-2-one derivative engenders a twofold mechanism of movement, improving the efficacy of these complexes in concentrated on neoplastic cells [85]. Current study investigates how changes in metallic ions or ligand systems can also enhance selectivity and diminish toxicity to healthful cells, hence improving the therapeutic index for cancer treatments.

Environmental and Biosensing Applications

In addition to their therapeutic significance, metallic-ion complexes provide good sized packages in environmental tracking and biosensing. Benzoxazin-2-one derivatives, while complexed with metal ions, can be utilized to detect environmental pollution, consisting of toxic heavy metals together with mercury (Hg^{2+}) and lead (Pb^{2+}), which present sizeable threats to human fitness and the environment. These complexes can exhibit colorimetric or fluorescence alterations following interaction with target steel ions, rendering them appropriate for utility in sensors and diagnostic instruments for environmental monitoring [86]. Besides environmental programs, those complexes also are vast in biosensing, allowing the identification of particular biomolecules or sicknesses in biological samples[87]. This skill can enable early ailment analysis, improving the potentialities for spark off intervention. The adaptability of those complexes, at the side of their extended sensitivity and specificity, renders them powerful units for environmental and clinical detection [88].

A detailed table summarizing benzoxazine derivatives, their applications, and additional information is provided to highlight the breadth of prior research in this field Table 1. This table is supported by over 25 references, offering a comprehensive overview of the current knowledge base.

Table 1. Benzoxazine Derivatives and Their Applications

Benzoxazine Derivative Name	Application	information	Ref.
Ethyl 3,4-dihydro-3-oxo-4,6,7-trisubstituted-2H-1,4-benzoxazine-2-acetate	Anti Additional microbial activity	The compounds had been evaluated in opposition to a couple of Gram-high-quality and Gram-bad microorganism, in addition to some Candida species. They verified a wide range of pastime, with MIC values spanning from 6.25 to a hundred mg/ml. QSAR evaluation turned into conducted to observe the impacts of substituents and to forecast lead optimization for boom inhibitory movement towards Candida krusei.	[89]
Benzoxazine-6-sulfonamide derivatives	Antibacterial and antifungal activity	The synthesized compounds showed low inhibitory concentration (MIC of 31.25 and 62.5 µg/mL) against Gram-positive and Gram-negative bacteria as well as fungi. The	[6]

		results were comparable to the inhibitory effects of standard drugs.	
Hydroxyl-containing imine-linked COF modified to benzoxazine	Antibacterial activity, drug delivery	A new two-dimensional covalent organic framework (COF) was synthesized and modified to introduce benzoxazine groups via cyclization. The modified COF exhibited good antibacterial activity against E. coli and S. aureus, with over 90% efficiency. The structure of the COF was preserved, ensuring that its drug delivery and release properties remained unaffected.	[90]
TF-BOZ monomers and PBOZ resins	Antibacterial activity, antifouling materials	A series of biobased benzoxazine monomers (TF-BOZs) were synthesized and showed significant broad-spectrum antibacterial activity against S. aureus, E. coli, and P. aeruginosa. The monomers could be polymerized to form polybenzoxazine resins (PBOZs) with excellent thermal stability. PBOZs exhibited resistance to bacterial adhesion, highlighting their potential as antifouling materials.	[91]
6,6'-cyclohexane-1,1-diyl bis (3-substituted-3,4-dihydro-2H-1,3-benzoxazine)	Antimicrobial activity	The compounds were synthesized via a two-step process involving phenol, cyclohexanone, and several primary amines. Antimicrobial testing showed that some of the compounds exhibited better antibacterial activity than standard drugs like streptomycin and nystatin.	[92]
1,3-benzoxazine derivatives synthesized via ternary Mannich condensation	Antimicrobial activity	The compounds were synthesized using 2-propenylphenol, formaldehyde, and primary amines. Antimicrobial activity was evaluated against several pathogens, and the benzoxazine containing a benzyl fragment showed the best antimicrobial properties. The minimal suppressing concentration (MIC) was determined as 0.035 mg/L. Electron microscopy confirmed the effect on E. coli cell ultrastructure.	[93]
Benzoxazine-grafted-chitosan copolymer films	Antimicrobial activity, wound healing, packaging materials	Benzoxazine monomers were grafted onto chitosan to form copolymer films using a low-temperature, greener method. The films exhibited excellent bactericidal properties against E. coli and S. aureus, and demonstrated hydrophobicity, good thermal, and solution stability.	[94]
6-aryl, 8-aryl, and 8-aryl-6-chloro-2-morpholino-1,3-benzoxazines	PI3K and DNA-PK inhibition, antiproliferative activity	A series of benzoxazine analogues were synthesized, with compound 20k (LTURM34) identified as a potent DNA-PK inhibitor, 170-fold more selective for DNA-PK compared to PI3K. Compound 20i was a selective PI3Kδ inhibitor and showed strong antiproliferative activity against A498 renal cancer cells, warranting further investigation.	[95]
6 and/or 8-substituted derivatives of 1,3-benzoxazines with flavone moiety at 3-position	Cytotoxic activity against MCF-7 (human breast cancer) cell lines	A series of benzoxazine derivatives with a flavone moiety at the 3-position were synthesized. Methyl, methoxy, and chloro derivatives showed potent cytotoxicity, with IC50 values ranging from 8.03 to 17.1 μM. Molecular docking studies suggested binding to the ATP-binding site of EGFR.	[96]
BXN-01 and BXN-02	Antitumor activity against HL-60 leukemia cell line	Benzoxazine derivatives BXN-01 and BXN-02 were evaluated for antitumor activity, showing IC50 values of 5 nM and 25 nM, respectively, which were more effective than the standard drug etoposide (IC50: 10 μM). Molecular docking studies predicted possible interactions with hTopo IIα, HDAC2, and RXRA. In silico ADME/Tox studies suggested favorable drug-likeness and pharmacokinetic properties.	[97]
13d and 13d−f (tyrosine-derived benzoxazine)	Anti-breast cancer agent	The benzoxazine derivative 13d showed strong anticancer activity with IC50 values of 0.20 to 0.65 μM, inducing	[98]

		apoptosis and cell cycle arrest in breast cancer cells. Formulation 13d−f, using cyclodextrin, improved solubility and demonstrated better tumor growth regression in a rat syngenic mammary tumor model compared to tamoxifen. 13d could be a promising lead for breast cancer treatment.	
Triazolyl benzoxazine derivatives	Antiproliferative activity against cancer and antibacterial	The triazolyl benzoxazine derivatives were synthesized via Cu(I)-catalyzed 'Click' cycloaddition. The compounds showed antiproliferative activity against cervical cancer (HeLa), colorectal adenocarcinoma (HT-29), and ovarian adenocarcinoma (SKOV-3). Some compounds also exhibited antibacterial activity against Pseudomonas aeruginosa and Bacillus subtilis.	[99]
1,4-Benzoxazine Derivatives	Antifungal agents against different fungal species	The derivatives were designed and synthesized as part of a program aimed at developing new antifungal agents. Docking studies predicted good interactions with CYP51 enzyme.	[100]
4H-benzoxazin-3-one derivative	Antifungal & Anticancer	Evaluated for antifungal activity against different fungi species and cytotoxicity against Hep-G2 and SW cell lines.	[101]
Spiro[benzoxazine-piperidin]-one derivatives	Chitin synthase inhibition, Antifungal activity	The compounds showed strong chitin synthase inhibition and broad-spectrum antifungal activity, including against drug-resistant strains. Their combination with fluconazole enhanced antifungal effects.	[102]
2-ethyl-2H-1,4-benzoxazin-3(4H)-one (4a)	Antifungal activity	Inhibits mycelial growth of seven agricultural fungi (Botrytis cinerea, Phythophtora cactorum, Rhizoctonia solani, Phoma betae, Fusarium culmorum, Fusarium oxysporum, Alternaria alternata) at 200 mg L−1.	[103]
2-ethyl-7-fluoro-2H-1,4-benzoxazin-3(4H)-one (4g)	Antifungal activity	Inhibits mycelial growth of seven agricultural fungi at 200 mg L−1.	[16]
4-acetyl-2-ethyl-2H-1,4-benzoxazin-3(4H)-one (6)	Antifungal activity	Completely inhibits fungal growth at 200 mg L−1 for seven fungi; Inhibits at 100 mg L−1 against F. culmorum, P. cactorum, and R. solani. Active against P. cactorum at 20 mg L−1.	
Ethyl 3,4-dihydro-3-oxo-4,6,7-trisubstituted-2H-1,4-benzoxazine-2-acetate derivatives	Antimicrobial activity	Showed broad-spectrum activity with MIC values of 6.25–100 mg/mL against various Gram-positive, Gram-negative bacteria, and Candida species. QSAR analysis performed for growth inhibitory activity against Candida krusei.	[62]
1,4-benzoxazin-3-one derivatives containing acylhydrazone moiety	Antifungal activity	Compounds 5L and 5o showed notable inhibition against Gibberella zeae (EC50 values: 20.06, 23.17 μg/ml), compound 5q was effective against Pellicularia sasakii (EC50: 26.66 μg/ml), compound 5r exhibited inhibition against Phytophthora infestans (EC50: 15.37 μg/ml), and compound 5p showed good activity against Capsicum wilt (EC50: 26.76 μg/ml).	[104]
6,8-diisopropylspiro[1,3-benzoxazine-2,1'-cyclohexan]-4(3H)-one	Antibacterial activity	Showed moderate activity against Acinetobacter baumannii (27% inhibition at 32 μg/ml).	[105]
6,8-diisopropyl-2-methyl-2-(4-nitrophenyl)-2,3-dihydro-4H-1,3-benzoxazine-4-one	Antifungal activity	Exhibited fungicidal activity against Candida albicans strain.	[19]

8-benzylamino-substituted-3-alkyl-1,4-benzoxazines (5a–o)	Neuroprotective activity	Most promising derivatives, exhibiting potent neuroprotective activity without intrinsic cytotoxicity. Substituents at the 3- and 8-positions are key for effectiveness.	[106]
5,7,8-trimethyl-1,4-benzoxazine/catechol or resorcinol hybrids	Antioxidant, anti-ageing, cosmetic	Two catechol derivatives were found to be more potent in scavenging radicals, inhibiting ROS, and inducing gene expression (ho-1). One catechol derivative enhanced skin fibroblast viability, suggesting potential for skin aging-related products.	[54]
Morpholine and benzoxa(thia)zine derivatives	Antioxidant, anti-inflammatory, atherosclerosis treatment	These compounds exhibit antioxidant activity, inhibit LDL oxidation, and reduce lipidemic parameters in hyperlipidemic mice. They also show significant COX-1 and COX-2 inhibition, making them promising agents for atherosclerosis treatment.	[107]
1,4- and 1,5-disubstituted 1,2,3-triazoles linked benzoxazine conjugates	Antimicrobial, antioxidant, anti-inflammatory	These compounds exhibited superior activity against bacterial strains (S. aureus, M. luteus, P. aeruginosa), moderate activity against E. coli, potent antifungal activity against C. albicans and C. krusei, and strong antioxidant properties. The most promising compounds (4a, 4b, 4d) also showed significant anti-inflammatory activity and were further validated through docking studies.	[108]
1H-benzoxazine-2,4-diones	Antimicrobial, antioxidant, toxicity	The compounds were synthesized with yields between 57-98%. Compound 4c exhibited the highest antioxidant capacity (DPPH 35.4%, FRAP 0.063 µmol TEs/µmol). The antimicrobial activity was tested against nine human bacterial pathogens, and toxicity was assessed using a brine shrimp assay.	[109]
Benzoxazine Derivatives (BD)	Protein binding (BSA and HSA), Antioxidant (AOA), Potential cancer treatment	BDs interact with proteins (BSA and HSA) via hydrogen bonding and hydrophobic interactions. Fluoro-substituted BDs showed strong binding due to hydrogen bonding at para positions. Fluorescence quenching confirmed complex formation. Scatchard analysis revealed four binding sites for BSA and six for HSA, with higher binding strength for HSA. Docking studies showed interactions with fluoro and alkyl groups. BDs also demonstrated more than 70% radical scavenging activity in antioxidant tests, indicating medicinal potential in cancer treatment.	[110]
(3-tert-butyl-8-phenylethylamino-3,4-dihydro-2H-1,4-benzoxazin-5-yl) (phenyl) methanone	Antioxidant, neuroprotective agent.	Prevents ATP depletion caused by 24 hours of hypoxia in astrocytes. Effective in a mouse model of brain damage resembling cerebral palsy.	[111]
Poly(benzoxazine) derivative	developing amperometric microbiosensors for glucose and ATP detection	Enhanced sensitivity for glucose and ATP, and improved mechanical stability.	[60]
Liquid bio-benzoxazine precursor	Conversion into porous graphene (LIG) for lubricant additives	3D porous LIG was used in PAO4 lubricants, resulting in a significant decrease in friction and wear rate.	[112]

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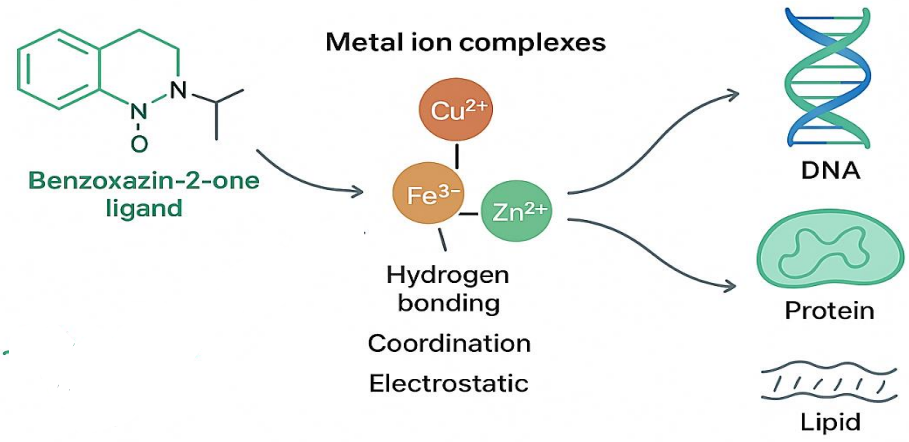
Vanillin/furfurylamine-based biomass benzoxazine (Va-Bz)	Biosensing for Pb2+ and NO2– detection	PBIF-Va-modified electrodes showed stronger electrochemical responses and improved detection limits for both Pb2+ and NO2–.	[113]
1,4-Benzoxazines (functionalized via multicomponent chemistry)	Biosensing and enzyme immobilization	The multienzyme cascade system was immobilized on electroactive lignin nanoparticles, improving sustainability and recyclability.	[114]

Mechanisms

The essential mechanisms via which metal-ion complexes have interaction with biomolecules decide how efficient they may be in lots of biological applications, mainly those based totally on derivatives of benzoxazin-2-one. Both the unique qualities of nanomaterials and the molecular shape of the complexes have an impact on those interactions. This phase examines the methods wherein those complexes show organic activity, emphasizing how they interact with biomolecules and how their nanoscale characteristics contribute to their effectiveness.

Interaction of Complexes with Biomolecules

The fundamental manner that propels the biological activity of metal-ion complexes is their interplay with biomolecules. Proteins, DNA, lipids, and carbohydrates are examples of biomolecules which can be important for keeping the composition and functionality of cells. These biomolecules can engage with metal-ion complexes via a number of special mechanisms, which include as hydrogen bonding, coordination, and electrostatic attraction [115] as shown in scheme 3. The complexes' iron ions play a crucial position in those interactions because they've the capability to change the structure or hobby of the biomolecules through forming coordination bonds with unique purposeful businesses on them [116]. For instance, those complexes can intervene with the movement of enzymes after they attach to proteins, probably resulting in antimicrobial or anticancer consequences. Similar to this, DNA harm can get up through the interplay of steel-ion complexes with DNA; this mechanism is regularly utilized in anticancer treatment options [117]. By promoting the complex's binding to biomolecules and adjusting its hobby, the ligand thing (benzoxazin-2-one) also performs a function inside the interplay. Because it reduces the effect on healthful cells and tissues, these complexes' capacity to target unique biomolecules selectively is vital for their therapeutic makes use of [118].



Metal ion complexes, such as those derived from benzoxazin-2-one, can interact with biomolecules through hydrogen bonding, coordination, and electrostatic attractions, potentially affecting enzyme activity and cell targeting.

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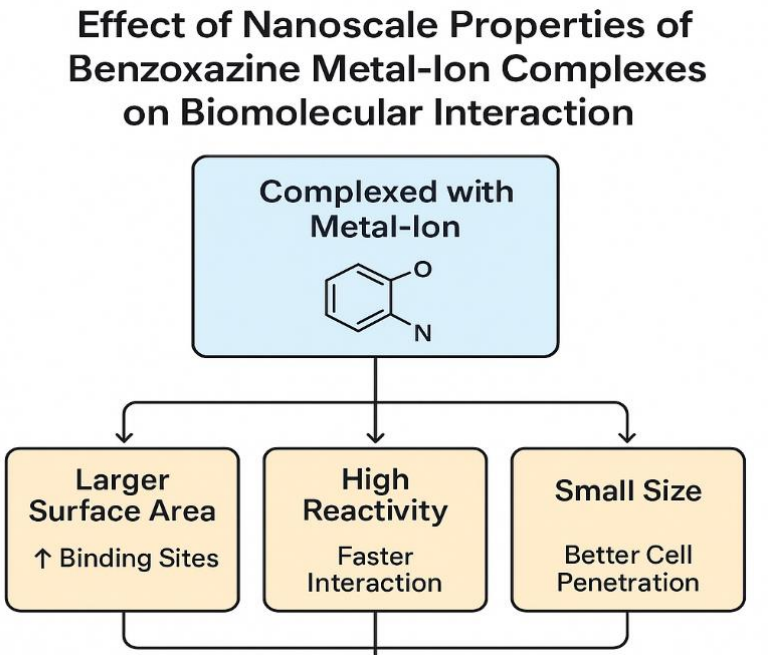
Scheme 3. Benzoxazine interaction with biomolecules

Role of Nanoscale Properties in Enhancing Activity

Metal-ion complexes' organic hobby is greatly expanded by way of their nanoscale traits. Compared to bulk substances, nanomaterials have unique homes such a larger surface region, higher reactivity, and less complicated penetration of organic membranes [119,120]. These characteristics are more advantageous whilst steel-ion complexes are shrunk to the nanoscale, which improves the complexes' potential to have interaction with biomolecules.

Enhancing mobile absorption is one of the essential benefits of nanoscale metal-ion complexes. These complexes can greater effortlessly pass cell membranes because of their high surface place and tiny length, which permits greater powerful distribution to target areas [121] as illustrated in scheme 4. This is mainly essential for applications like most cancers' treatment, wherein unique transport of the complicated to tumor cells is vital to optimize healing effects and reduce harm to close by healthy tissues [122]. Furthermore, the compound may end up greater solid in biological settings because of the nanoscale length. Better interplay with biomolecules is made possible by means of the larger surface vicinity, which may enhance the complicated's binding affinity and, as an end result, its efficacy in biological packages [123]. Additionally, due to the fact the complex may be engineered to pay attention selectively at the target place, minimizing systemic facet effects, nanoscale traits may make contributions to lowering the complicated's toxicity to non-target cells [124].



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Scheme 4. Effect of nano scale to the Benzoxazine -metal-ion complexes

Conclusion

In conclusion, benzoxazin-2-one derivatives and their metal ion complexes represent a promising avenue in medicinal chemistry and related fields. Their unique structural features, combined with their ability to coordinate with metal ions, enhance their stability, bioavailability, and therapeutic efficacy. Recent advancements in green and eco-friendly synthesis methods have further improved the accessibility and sustainability of these compounds, aligning with global efforts toward environmentally conscious research. Additionally, the nanoscale properties of these complexes amplify their bioactivity, making them effective candidates for applications ranging from anticancer and antimicrobial therapies to environmental monitoring and biosensing. By leveraging their chemical versatility and biological relevance, future studies can unlock the full potential of benzoxazin-2-one derivatives, paving the way for innovative drug development and diagnostic tools.

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Author's Declaration

-We hereby confirm that all the Tables in the manuscript are original and have been created by us. Furthermore, any Figures and images, have been included with the necessary permission for re-publication

-We have obtained ethical clearance for our study from the local ethical committee at [Al-Nahrain University/College of Sciences]. This approval underscores our commitment to ethical research practices and the well-being of our participants.

-Ethical Clearance: The project was approved by the local ethical committee at [Al-Nahrain University/College of Sciences], ensuring adherence to ethical standards and the protection of participants' rights and welfare.

Author's Contribution Statement

All Author: Contributed to the conception and design of the study, data rearrangement and drafted the initial manuscript, collection all part of literature review and conducted some characteristics of the products

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