Review:

From Synthesis to Application: Advances in Macrocyclic Complexes

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Abstract: *Macrocyclic complexes, characterized by their large ring structure incorporating multiple donor atoms, have garnered significant attention due to their pivotal roles in both natural and synthetic systems. This review examines the synthetic methods of macrocyclic ligands and their metal complexes, highlighting their structural intricacies and coordination behaviors. The multifaceted applications of these complexes span various domains in pharmaceuticals as they enhance drug solubility and bioavailability; in catalysis, they facilitate oxidation reaction and water splitting processes; in sensing, calixarenes serve as selective ion and molecule detectors; and in biomedicine, certain macrocyclic compounds exhibit potential in targeting cancer stem cells. Despite these advancements, challenges persist, notably in achieving efficient macrocyclization and ensuring stability under diver's conditions. Future directions emphasize the incorporation of stimuli-responsive supramolecular assemblies to enhance drug delivery mechanisms and therapeutic interventions. This comprehensive overview emphasizes the importance of macrocyclic complexes in advancing chemical science and their potential in addressing contemporary scientific challenges.*

Keywords: *macrocyclic complexes; catalysis; drug delivery; biomedical applications; supramolecules*

■ INTRODUCTION

A macrocyclic compound has nine or more-membered rings incorporating all heteroatoms and three or more donor (ligating) atoms that can coordinate to a metal atom [1]. Macrocycles are "a macromolecular cyclic portion of a molecule or a cyclic macromolecule," as defined by IUPAC [2]. The design and synthesis of metal-containing macrocycles in chemistry is a compelling subject. The chemistry of macrocyclic complexes is currently garnering significant global interest due to its relevance in inorganic and biological chemistry. Consequently, macrocyclic ligands and their metal complexes hold considerable importance, as they are present in various critical biotic systems [3]. The following are a few biological macrocycles that are found in nature: heme is the active component of hemoglobin (Hb, a protein that transports oxygen). Hb has been termed the "honorary enzyme" is a porphyrin (Fig. 1(a)) containing iron (Fig. 1(b)). Heme is the prosthetic component of Hb [4]. The reversible attachment of oxygen to the heme groups requires that heme iron maintains its ferrous state and that oxygen binding is preferred over other possible heme ligands [5].

Vitamin B12 has a corrin ring (Fig. 2(a)) with a

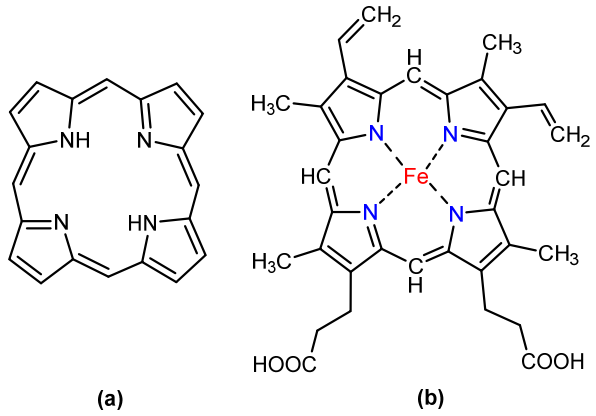


Fig 1. Structure of (a) porphyrin ring and (b) heme B

trivalent cobalt atom (Fig. 2(b)). It is essential for the normal development of erythrocytes and for normal growth and neurological functions [6]. Biosynthesis of DNA, the synthesis of methionine for protein synthesis and methylation, and prevention of homocysteine buildup are all essential functions of vitamin B12.

The researchers have observed that artificial macrocycles and associated metal complexes caused by their structural and functional similarities with natural macrocyclic complexes, besides their varied chemical action [7]. The opportunity of constructing coordination molecules with distinct shapes and stability is a reason for the study of macrocyclic ligand metal complexes is intriguing [3]. The utilization of synthetic macrocycles as models for biologically relevant systems has sparked various research initiatives, including the synthesis of novel ring systems and the investigation of properties and functionalities of macrocyclic complexes in addition to their possible applications in industry, medicine, and other fields [8]. Synthesized macrocyclic complexes will have a unique role in all branches of chemistry, thus providing advantageous outcomes in other fields of life for humanity.

■ HISTORICAL BACKGROUND

Macrocycles have been utilized as synthetic dyes for several decades. For instance, phthalocyanine (Fig. 2(c)), a dark blue porphyrin analogue, has been employed as a dye and pigment since its accidental discovery in 1928 during the industrial production of phthalimide at the Grangemouth works of Messrs. Scottish Dyes, Ltd. in 1934 [9] Linstead was fully characterized. However, no coordination between these species and metal ions has been reported.

The first of several innovative template reactions was published by Curtis in 1960 in the production of homoleptic *N*-donor macrocycles (cyclam derivatives) [10]. Pedersen's 1967 accidental discovery of the homoleptic *O*-donor macrocycle dibenzo[18]aneO6. Pedersen intended to develop bisphenol using mono-protected catechol and bis(2-chloroethyl) ether. The hexaether (dibenzo [18] aneO6) was acquired in trace

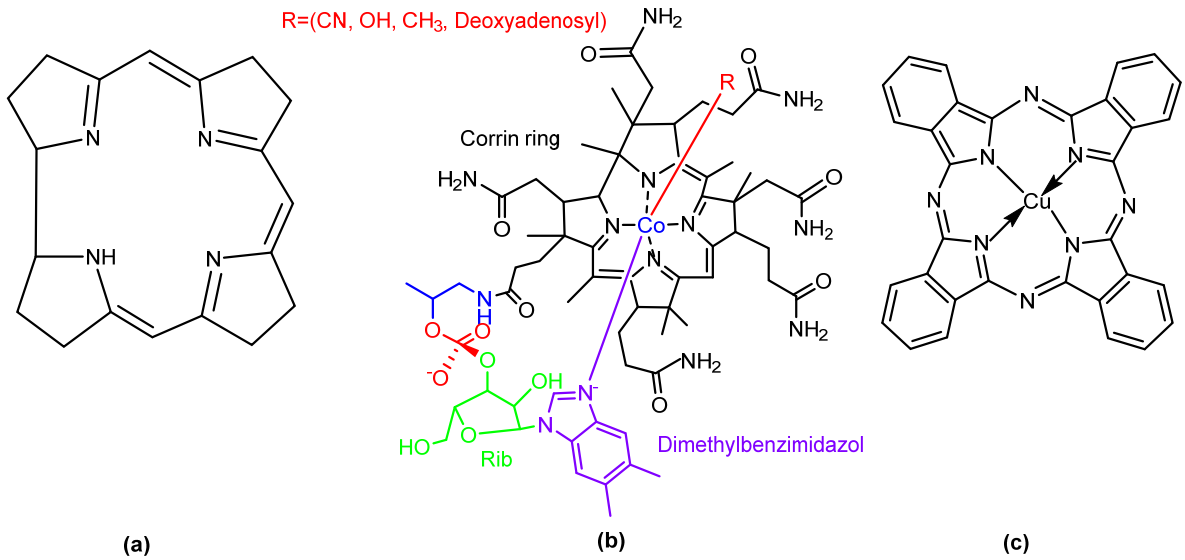
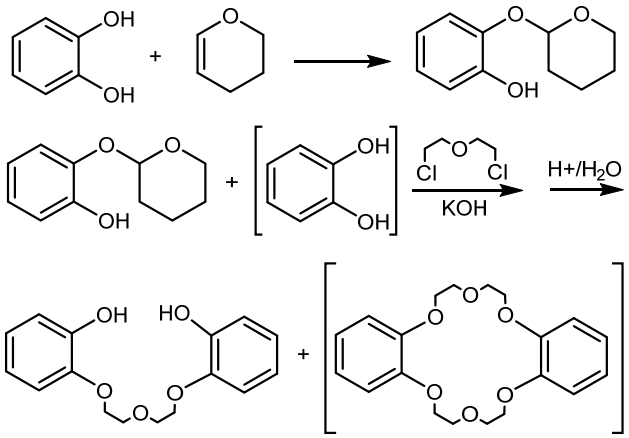


Fig 2. Structure of (a) corrin ring, (b) vitamin B12, and (c) phthalocyanine

quantities (0.4%) as a result of utilizing a marginally impure sample of the mono-protected catechol, which included some unprotected catechol as illustrated in Scheme 1 [11].

The synthetic method is not important in this discovery, but in the same way Pedersen observed peculiar properties of the new material. He mentioned exceptional crystallinity and remarkable solubility behavior. Hexa-ether was marginally soluble in methanol, but on adding sodium salts, it dissolved quite rapidly [11]. Pedersen fortuitously recognized that the resulting macrocyclic complex exhibits greater solubility than the macrocyclic ligand. Assuming the complex ion is a Lewis acid-base complex, the sodium ion functions as the Lewis acid and the hexa-ether as the Lewis base. Na^+ is a weakly cationic Lewis acid with a significant ionic radius, which reduces the electrostatic potential energy of the Na^+-solvent bond. Such that the inclusion of Na^+ salt enhances the solubility of the complex, this, together with the ability of potassium permanganate to dissolve in C_6H_6 or $CHCl_3$, drove him to make this at time bold assertion [11]: "*It seemed clear to me now that Na^+ had fallen into the hole in the center of the molecule and was held there by the electrostatic attraction between its positive charge and the negative dipolar charge on the six oxygen atoms symmetrically arranged around it in the polyether ring*".

This concept was not completely confined to separation. It was discovered that the alkali metal ions could be enclosed by certain natural products, such as valinomycin and nonactin in Fig. 3, also, they can transport them in biological systems, such as through membranes [12-15]. Pedersen suggested the term 'crown' as referring to these new macrocyclic compounds [16]. The contrast between naturally occurring ionophores and crown ethers is evident. Since 1960, several other artificial macrocycles have been prepared, resulting in significant growth in all phases of the chemistry of macrocyclic systems [17]. Since then, there has been a growing significance in the role of metal ions in biological systems, and many such bioinorganic experiments have involved complexes of both natural and artificial macrocycles. The 1987 Nobel Laureates, Charles J. Pederson, Donald J. Cram, and Jean-Marie Lehn formulated a collaborative



Scheme 1. Discovery of crown ethers

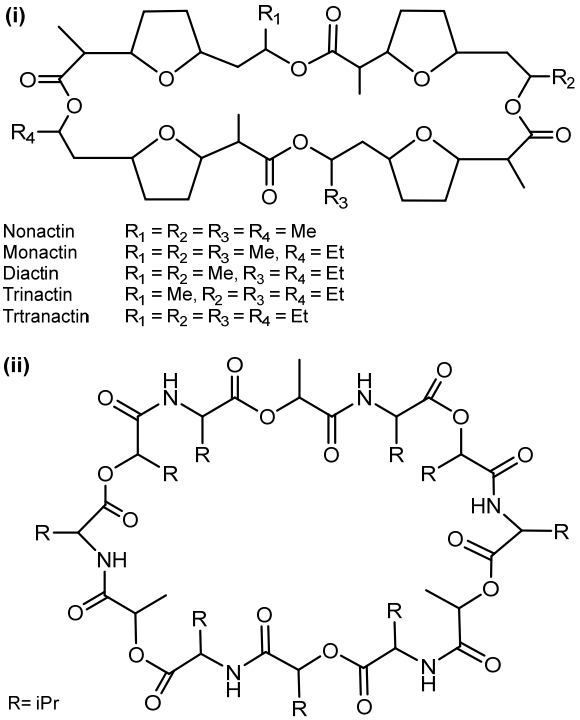


Fig 3. The natural product ionophores: (i) nonactin and (ii) valinomycin

framework for progressing supramolecular and macrocyclic compounds. This is a significant factor in bio and nanotechnology, catalysis, electronics, environmental protection, and medicine [18].

■ SYNTHESIS OF MACROCYCLIC COMPLEXES

Classical Methods

Template synthesis has been widely utilized as a powerful tool for creating functionalized macrocyclic

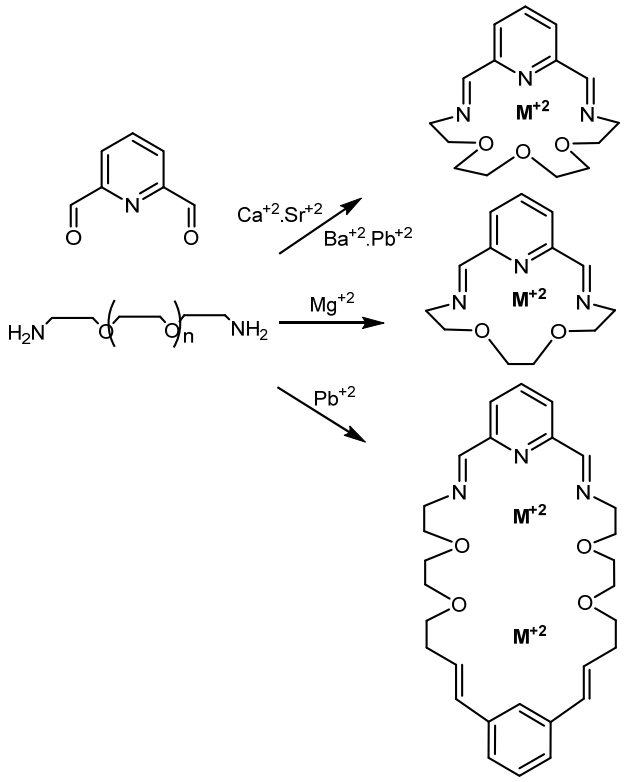
structures. "Template reaction" in chemistry is a type of ligand-based reaction occurring between two or more adjacent coordination sites on a metal center [19]. Transition metal ions are a templating agent. Metal ions are cyclic rather than oligomeric or polymeric materials. Due to their ability to accumulate and eliminate ligands in each uncertain geometry, transition metals can be achieved. The metal template can accelerate intramolecular or intermolecular reactions by binding to a linear molecule. Ideally, the macrocyclic complex is created by the addition of necessary metal ions to the ligand. Nevertheless, low production of desired products with cross-reaction, for example, polymerization and predominating causes due to the synthesis of the necessary macrocycle commonly decrease. To address this issue, the ring-closure phase in production may be conducted in "high dilution" conditions or "rigid groups" to limit rotation and internal entropy deficits in the open-chain precursor, thus promoting cyclization. The *in-situ* process is an efficient method for synthesizing macrocyclic complexes, where the inclusion of metal ions during the cyclization reaction significantly improves the yield of cyclic products. The metal ion is responsible for directing the steric trajectory of the reaction, which has been referred to as the metal-template effect [20]. In Scheme 2, the size of the cation used as a template has been crucial for guiding synthetic routes in Schiff base systems.

Template effects can be categorized into significantly more certain effects [21]. In illustrations where the thermodynamic template effect occurs, a metal ion disrupts a presented equilibrium in the organic system. The involved product is produced frequently with extreme yields as a metal complex. Compared to their open-chain counterparts, macrocyclic complexes are more selective and thermodynamically stable metal ion binders than they are. This resulted in a large amount of research in macrocyclic chemistry [22]. Secondly, the kinetic template effect, where, in the absence of the metal ion, which is explained in Scheme 3, the same organic reactants provide various products. Although the electronic properties of ligands (for example, acidity and electrophilicity) are altered by coordination, the coordination sphere's pre-organization is emphasized by the template effect. The dialkylation of a nickel dithiolate is an example of a reaction that is described as proceeding by a kinetic template effect [23].

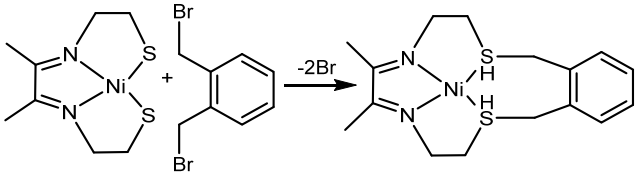
Despite the numerous benefits of this approach, not all metal ions function as templates. Furthermore, the stability of macrocyclic complex poses challenges in eliminating templating metal from macrocyclic ligand by demetallation (especially when the metal atom is not required in the result).

Modern Approaches

The efficient preparation of macrocycles is a major issue due to the elevated entropic penalty in the ring-closing process [24]. Ring-closing metathesis (RCM),



Scheme 2. Schiff base macrocyclic synthesis in the presence of non-transition metal templates



Scheme 3. The corresponding alkylation in the absence of a metal ion would afford polymers

cross-coupling, and copper-catalyzed azide-alkyne cycloaddition (CuAAC) have been highly utilized to create macrocycles [25]. Nevertheless, these toolkits are frequently predisposed to explicit procedures, including multiple-step synthesis of the bifunctional precursor [24], template-induced preorganization [24,26], and highly diluted conditions [27]. CuAAC reactions frequently exhibit requisite attributes for the implementation of effective, high-yielding, functional-group tolerant, orthogonal organic chemistry during the ring-closing phase, often known as the macrocyclization process. Scheme 4 illustrates 1,3-dipolar cycloadditions among azides and terminal alkynes that were examined by Huisgen and colleagues. This reaction is highly advantageous, but needs heating, and it does not exhibit regioselectivity (both 1,4-disubstituted- and 1,5-disubstituted-1,2,3-triazoles are formed) [28]. The catalyzed type of artificial method was established in the early 2000s. Sharpless and Meldal [29] presented foundational publications indicating that the reactivity of the reaction was markedly increased by catalysis using Cu(I) species, achieving rate improvements of up to 10^7 times. Additionally, the reaction can be conducted at room temperature. The catalyzed reaction showed a high selectivity towards the formation of 1,4-disubstituted triazole over the 1,5-disubstituted isomer.

The reaction is classified as "click chemistry". Sharpless characterized "click chemistry" as a modular reaction that is broad in applicability, delivers exceptionally high results and produces only benign byproducts that may be eliminated by non-chromatographic techniques [30]. Click processes are highly selective for a specific product and progress quickly to completion. Click chemistry has become widely regarded as a tool for constructing intricate molecular architectures due to its water-tolerant operational conditions and simplicity [31].

■ STRUCTURAL CHARACTERIZATION

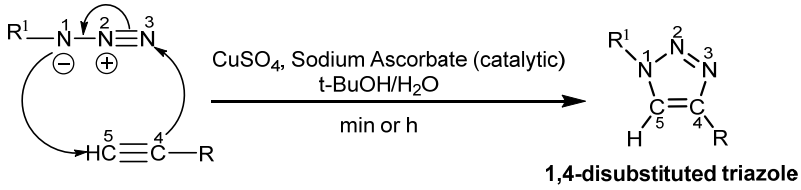
Techniques

Instrumental techniques, such as elemental analysis, thermal methods, Raman spectroscopy, Fourier transform infrared spectroscopy (FTIR), electron paramagnetic resonance, UV-vis spectrophotometry, mass spectrometry (MS), surface enhanced Raman spectroscopy (SERS), X-ray crystallography (XRC), and scanning electron microscopy (SEM) are employed to characterize the complex composition [32].

Spectroscopic Methods

X-ray crystallography (XRC)

The field of crystallography, which involves the investigation of the atomic and molecular arrangement within a crystal, has significantly improved our understanding of chemical bonding and non-covalent interactions [33]. Preliminary investigations established the standard sizes of atoms and validated numerous theoretical frameworks of chemical bonding. These include tetrahedral bonding of carbon in diamond structure [34], the octahedral bonding of metals observed in ammonium hexachloroplatinate(IV) [35], and the resonance observed in the planar carbonate group [36] and in aromatic molecules [37]. The separation between two chemically bonded atoms is a highly responsive indicator of the strength of the bond and its bond order. Consequently, investigations using XRC have revealed the existence of even more extraordinary forms of bonding in inorganic chemistry, including metal-metal double bonds, metal-metal quadruple bonds, and three-center, two-electron bonds [38]. The XRC technique, specifically an experiment involving inflexible Compton scattering, has offered supporting suggestions for the moderately covalent nature of hydrogen bonds and also



Scheme 4. Prototypical conditions for the CuAAC reaction, a 1,3-dipolar cycloaddition

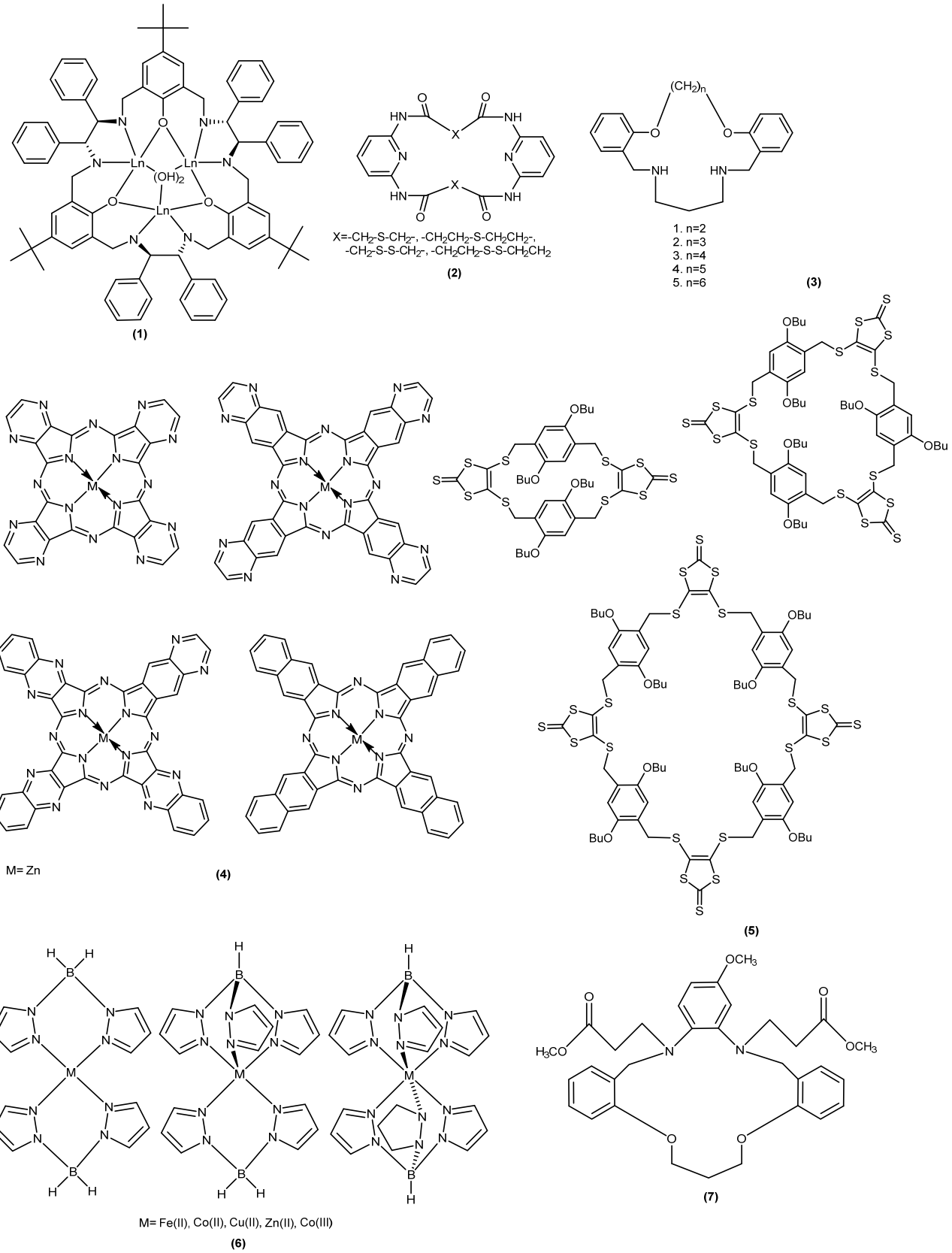


Fig 4. Macrocyclic complexes detected by different techniques

helps to confirm coordination modes of metal ions in macrocyclic ligands [39]. Complex (1) in Fig. 4 is an example compound that can be characterized with XRC [40].

UV-vis spectroscopy

UV-vis spectroscopy is an analytical technique that measures the quantity of UV and visible light that is absorbed by a sample [41]. It is widely employed in chemistry to detect and quantify compounds in a variety of samples [42]. UV-vis spectroscopy is generally employed in analytical chemistry to determine a wide range of analytes or samples containing transition metal ions, greatly conjugated organic compounds, and biological macromolecules. Organic molecules, particularly those exhibiting significant conjugation, similarly exhibit light absorption in the UV or visible parts of the electromagnetic spectrum [43]. Complexes (4) in Fig. 4 are an example compound that can be characterized with UV-vis Spectroscopy [44].

Fourier transform infrared (FTIR) spectroscopy

A chemical analysis method that utilizes the interaction between infrared light and matter, utilizes the infrared spectrometer to measure light energy and to originate molecular vibrations in a sample. Every functional group in the molecule has unique vibrations that appear at distinct frequencies in the FTIR spectrum. Furthermore, individual bands in FTIR spectrum may be utilized to determine functional groups in a sample. Bands of all these different functional groups together create a FTIR spectrum that can be categorized as a fingerprint of the sample [45]. Complex (2) in Fig. 4 is an example compound that can be characterized with FTIR Spectroscopy [46].

Mass spectrometry (MS)

MS serves both qualitative and quantitative purposes. These tasks encompass the identification of unfamiliar compounds, the isotopic composition of elements inside molecules, and the determination of the compound's structure through observation of its fragmentation. Additional uses encompass quantification; these measures can commonly be utilized to ascertain the precise molecular weight of the sample constituents, as well as, quantify identified compounds, and to determine the structure and chemical properties of the molecules. Complex (5) in Fig. 4 is an example compound that can be characterized with MS [47].

NMR spectroscopy

NMR is an essential analytical tool for organic chemists, based on the phenomenon of nuclear magnetic resonance. It refers to the study of molecules by detailing radiofrequency electromagnetic radiation interactions with nuclei of molecules located within a strong magnetic field. NMR spectroscopy has been the most effective method for determining the structural properties of chemical species. It can also provide a report on the structure, reaction state, and chemical surroundings of molecules, but it can also determine the content and purity of the sample [48]. Complex (2) in Fig. 4 is an example compound that can be characterized with NMR spectroscopy [49].

Thermogravimetric analysis (TGA)

TGA technique is used to analyze thermal properties by measuring the change in mass of a sample over time, such as when the temperature varies. TGA is a common method for identifying mass loss or gain due to decomposition, oxidation, and combustion. It provides a quantitative assessment of the mass change in materials associated with transition and thermal degradation. This measurement yields data on various physical events, such as phase transitions, absorption, and desorption. It also offers insights into chemical procedures, containing chemisorption, thermal breakdown, and solid-gas reactions, such as oxidation or reduction, different weight loss stages corresponding to the loss of solvent molecules, coordinated ligands, or metal residues. Furthermore, it establishes the level of purity in a mineral, inorganic chemical, or organic molecule. Complex (3) in Fig. 4 is an example compound that can be characterized with TGA [50].

Electron paramagnetic resonance (EPR)/electron spin resonance (ESR)

EPR/ESR spectroscopy is employed to detect and identify unpaired electrons, known as free radicals, in various states of matter, including solids, liquids, and

gases [51]. It is particularly suitable for studying metal complexes and organic radicals [52]. Electrochemical systems and materials exposed to UV light can be utilized to detect both organic and inorganic radicals [53]. In many cases, the reactions that generate radicals and their subsequent reactions are of significance, whilst in other cases, EPR is employed to elucidate a radical's geometry and the orbital of the unpaired electron [54]. Complexes (6) in Fig. 4 are an example compound characterized by EPR/ESR [55].

EC

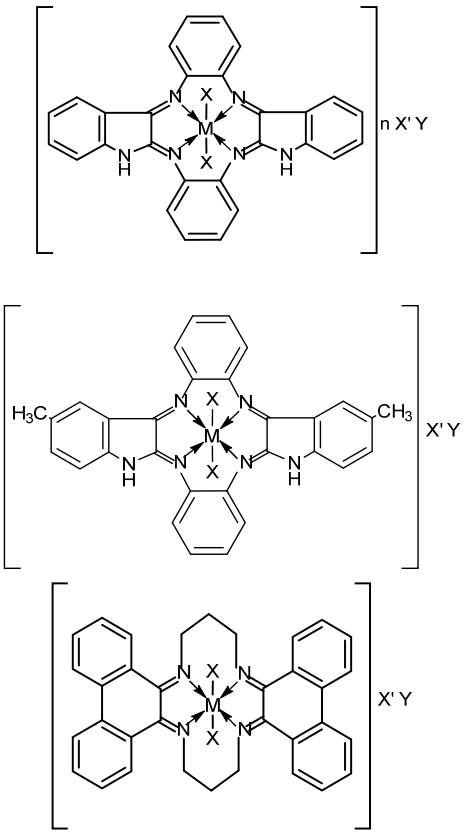
EC device is employed to quantify the electrical conductivity of a solution. Conductivity measurement yields data on the precise electrical conductivity of a metal, enabling inferences to be constructed on its composition, microstructure, and mechanical properties. Conductivity meters are utilized in various scientific applications. In chemistry, they can be utilized to determine the concentration of ions in the solvent. The EC profile of a solution is a quantitative evaluation of its ability to facilitate the flow of electricity. The more ions are present in a solution, the more conductive it is. Complex (7) in Fig. 4 is an example compound characterized by EC [56].

■ PHYSICAL PROPERTIES

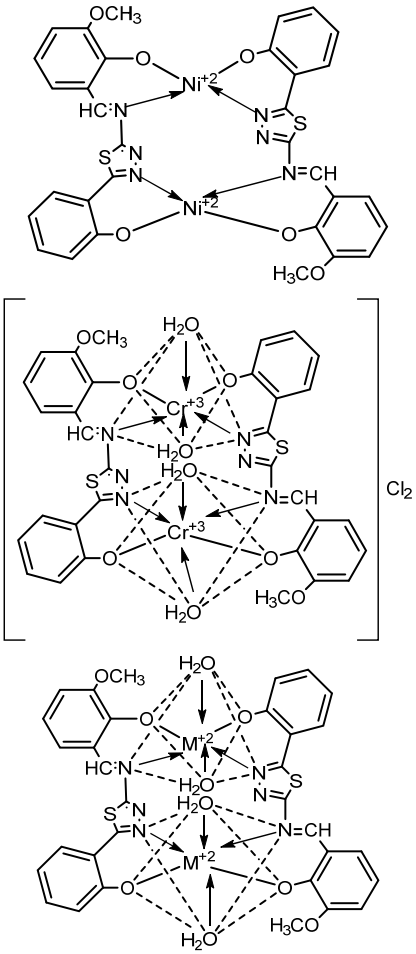
Optical and Electronic Properties

Porphyrins are planar macrocyclic compounds composed of four pyrrole units interconnected in a ring structure via four methine carbons at their α-positions. These prevalent molecules are universally found in all living species in various forms, with chlorophyll shown in Fig. 5 and heme being the best recognized [65]. The aromatic character of the porphyrin macrocycle, which comprises 18-p electrons, is distinct by its strong diatropic ring current. The bright coloration of these compounds, together with their distinctive electrical and redox characteristics, results from the heavily conjugated π-system [66]. By two primary interactions, the association between central metal ion and porphyrin

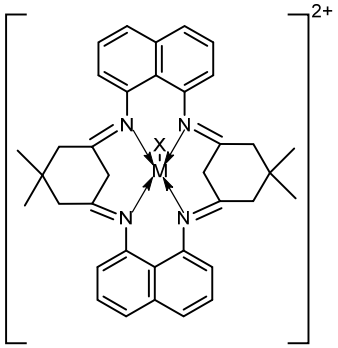
Table 1. Literature survey of the application of the macrocylic compounds

Three tetradentate Schiff base macrocyclic ligands and their complexes with Cr(III), Mn(II), Co(II), Ni(II), Cu(II) and Cd(II) was produced where ligands are (L1 = benzo[1",2"-2,1]benzo[1"',2"'-8,7]indolo[3',2'-4,5]cyclododeca[10,11-b]indole, L2 = 4,13–dimethylbenzo[1",2"-2,1]benzo[1"',2"'-8,7]indolo[3',2'-4,5]cyclododeca[10,11-b]indole, and L3 = 10,11,12,23,24,25-hexahydrophenanthro[9,10-a]phenanthro[9,10-h][14]annulene. Chloride and nitrate complexes of Cr(III), Mn(II), Co(II), Ni(II), Cd(II), and Cu(II) have octahedral geometries, while Cu(II) acetato complex has a tetragonal geometry. Ligands and complexes have been sorted *in vitro* versus some bacteria (*Staphylococcus aureus* and *Escherichia coli*) and fungi (*Candida albicans* and *Aspergillus flavus*) to study their ability to inhibit their growth [57].	

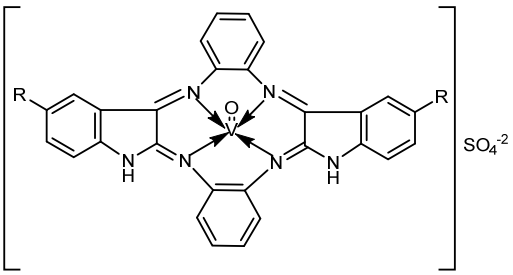
New Schiff base complexes of Cr(III), Co(II), Ni(II), Cu(II) and Zn(II) as binuclear formula $[M_2(H_2L)_2(H_2O)_4]$ with M(II)= Co, Cu and Zn of octahedral shape, $[Ni_2(H_2L)_2]$ of square planner shape and $[Cr_2(H_2L)_2(H_2O)_4]Cl_2$ of octahedral shape that only Cr complex is in salt stat. The Schiff base ligand was synthesized from vanillin with 2-amino-5-(2-hydroxy-phenyl)-1,3,4-thiadiazole. All prepared compounds evaluated four bacteria *S. aureus*, *E. coli*, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* showed significant activity results [58].



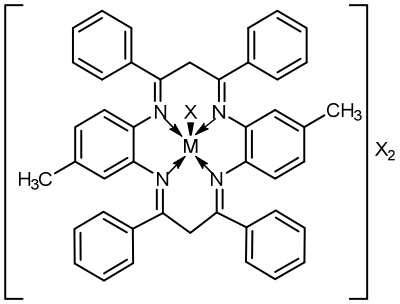
Six macrocyclic complexes of type $[M(C_{36}H_{36}N_4)X]X_2$, where M(III) = Cr, Fe and X = Cl^-, NO_3^-, CH_3COO^- were produced using 1,8-diaminonaphthalene and 5,5-dimethylcyclohexane-1,3-dione. All complexes were screened against some bacteria (*S. aureus*, *B. subtilis, and E. coli*) and antioxidant (by free-radical scavenging using DPPH) was variable and they have square pyramidal geometry [59].



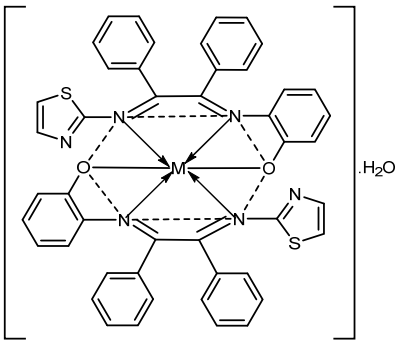
Three various sequences of oxovanadium(IV) tetraazamacrocyclic complexes of the type $[VO(mac)]SO_4$ were prepared from a reaction of 1,2-diaminobenzene and isatin/5-chloroisatin/5-bromoisatin in the presence of oxovanadium(IV) sulphate. All complexes have square pyramidal geometry. The produced oxovanadium(IV) complexes were found to be constant in the air at room temperature, moreover, verified in-vitro against Gram-positive bacteria (*B. subtilis*, *S. aureus*), and Gram-negative (*E. coli*), in addition to fungal strains for example *A. niger* and *C. albicans* [7].

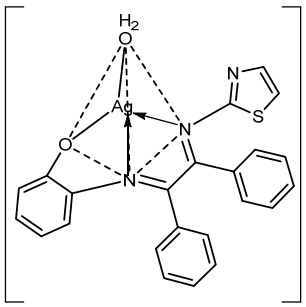


In addition to research, diaminotoluene-based tetra-azamacrocyclic-14 membered [N_4] macrocyclic complexes of nitrate, chloride, and acetate trivalent transition metal salts of Cr and Fe were produced. These six prepared complexes of formula [MLX]X_2 in which L is a macrocyclic ligand and square pyramidal geometry, were tested for their antimicrobial effectiveness against a few strains of bacteria and fungi. The bacterial activity of complex $[Fe(C_{44}H_{36}N_4)(OAc)](OAc)_2$ is good versus *B. cereus* and complex $[Fe(C_{44}H_{36}N_4Cl)]Cl_2$, $[Fe(C_{44}H_{36}N_4)(OAc)](OAc)_2$, $[Cr(C_{44}H_{36}N_4Cl)]Cl_2$ having strong activities against *E. coli*. Fungicidal activities were found in complex $[Cr(C_{44}H_{36}N_4)(OAc)](OAc)_2$, $[Cr(C_{44}H_{36}N_4)(NO_3^-)_2$, $[Fe(C_{44}H_{36}N_4)(NO_3)](NO_3^-)_2$ [3].

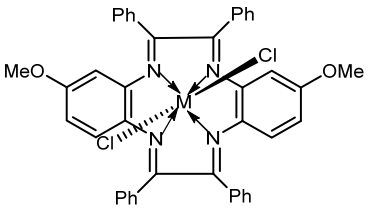


A new sequence of complexes of 2-((1*E*,2*E*)-1,2-diphenyl-2-(thiazol-2-ylimino)ethylidene)amino)phenol (DPTYEAP) has been produced by reaction of the ligand with metal chlorides of Ni(II), Cu(II), Pt(IV), and $AgNO_3$ in ethanol solvent. The geometric structure of all complexes is octahedral, except for the Ag(I) complex, which is tetrahedral. It was established that ligand and Pt(IV) complexes have high antioxidant activity against free radicals after conducting applications and biological activity examinations on the ligand and prepared complexes. Also, it was found that the platinum complex is more efficient against breast cancer cells (MCF-7); thus, it can be utilized as a potential drug after studying it well [60].

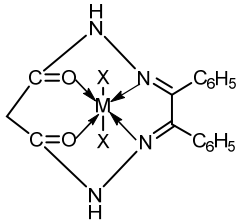


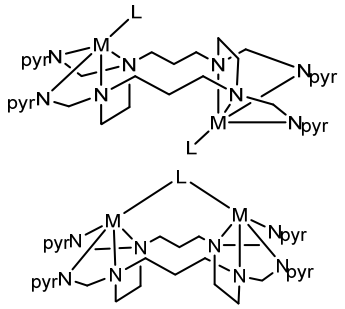
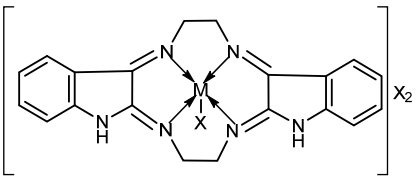


Synthesized two tetraaza [N_4] macrocyclic complexes of Fe(III) and Co(II) metal ions from the reaction of 3,4-diaminomethoxybenzene and benzyl is another model for the synthesis of macrocyclic complexes. Spectral analysis in this work showed an octahedral geometry for both macrocyclic complexes. Antimicrobial activities of two complexes were tested against *E. coli*, *P. aeruginosa*, *B. cereus*, *S. aureus*, whereas antifungal activities against *C. albicans* were compared with the standard drug "Gentamycin" [61].



Novel sequences of macrocyclic complexes of type $[M(C_{17}H_{14}N_4O_2)X_2]$ have been produced by condensation reaction of malonyldihydrazide with benzyl in the presence of divalent metal ions where M(II) = Co, Ni, Cu, Zn or Cd and X = Cl^-, NO_3^- or CH_3COO^-. These complexes (of six-coordinate distorted octahedral geometry) were experimented for their *in vitro* antibacterial (*B. subtilis*, *B. stearothermophilus*, *E. coli*, *P. putida*) and antifungal activities (*A. flavus*, *A. niger*). The minimum inhibitory concentration observed by these complexes was compared to standard drugs. However, as a result, none of these produced macrocyclic metal complexes exhibited a good antibacterial activity versus the tested bacterial strains, but some Co, Ni and Cu complexes were described to show some antibacterial activities versus several bacterial strains [62].



The additional study involved the synthesis and characteristics of 2 new nitrato complexes of Zn and Ni with 1,4,8,11-tetrakis(2-pyridylmethyl)-1,4,8,11 tetraazacyclotetradecane (tpmc). The biological activity of these complexes was studied by screening 8 different bacterial strains and 2 cancer cell lines. This free ligand and its complexes were examined on 6 Gram-positive and 2 Gram-negative bacterial strains. Compared to their activities on Gram-positive strains, all compounds established weak antibacterial action against Gram-negative strains *E. coli* and *Klebsiella*, while the free ligand was almost inactive against selected bacterial strains and showed only low activity against isolated strains of *S. pseudintermedius*. In normal human HS-5 cells and MCF-7 and MDA-MB 231 breast cancer cells, the cytotoxicity of the investigated compounds was established. Experimental results have shown that after 3 d increase, both complexes exhibited lower cytotoxic activities on cancer cell lines and normal human cells. Only Zn complex showed better antimicrobial action versus bacteria, while complexes did not demonstrate significant antiproliferative activity towards MCF-7 and MDA-MB-231 cancer cells [63].	
Synthesized condensation products of isatin and ethylenediamine in the presence of metal salt of macrocyclic complexes of the type $[M(TML)X]X_2$, where M(III) = Cr, Fe is an additional study, where TML is a tetradentate macrocyclic ligand, and X = Cl^-, NO_3^-, CH_3COO^-. The study suggests five-coordinate square pyramidal geometry for these complexes. These complexes were assessed for their *in vitro* antibacterial efficacy versus four bacterial strains: *B. cereus*, *Salmonella typhi*, *E. coli*, and *S. aureus*. Certain complexes displayed poor or no antibacterial activity [64].	

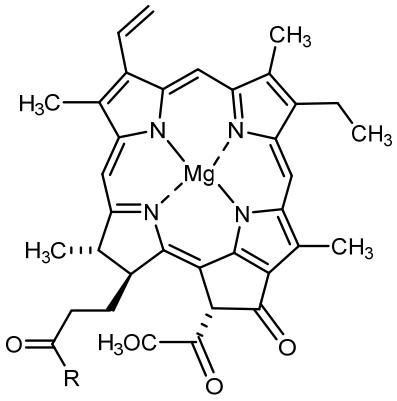


Fig 5. The chemical structure of chlorophyll

is facilitated, which includes: σ-coordination of nitrogen lone pairs oriented towards the center metal atom and π-interaction between metal p–π and d–π orbitals and nitrogen p–π orbitals [67]. This electron system exhibits visible light absorption of metalloporphyrin in the range of 400–600 nm, characterized by Soret and Q-bands [68]. Porphyrins and their derivatives can self-assemble into one-dimensional (1D) to three-dimensional (3D) nanostructured materials via noncovalent molecular interactions, employing various mechanisms dependent on their electrostatic characteristics and aqueous solubility (Table 1). Their optical characteristics influence the formation of nanostructures and, thus functional applications. Porphyrin nanomaterials possess significant potential due to their robust absorption in the visible light spectrum and effective electron transport via well-ordered crystal structure harvesting, as they possess considerable potential. To convert solar energy into chemical energy, researchers have exerted considerable effort to employ artificial chlorophylls generated from porphyrins and their derivatives. This technique entails the generation of hydrogen via water separation, which serves as a clean and sustainable substitute for fossil fuels and their related environmental issues. Metalloporphyrins, adept at stabilizing high-valent metal centers, can supply the extensively dispersed metal ions that operate at catalytically active positions. These characteristics are essential for the synthesis of oxygen reduction reaction (ORR), hydrogen evolution reaction (HER), and oxygen evolution reaction (OER) [69].

Photodynamic therapy (PDT) was identified over a century ago. It is already a successful and therapeutically

effective treatment for cancer and non-malignant disorders, including infections [70]. PDT includes three fundamental elements: photosensitizer (PS), light, and oxygen. To generate an excited singlet state, subsequently transitioning to the long-lived excited triplet state, photosensitizers are activated by visible light. In the presence of oxygen, this triplet state can conduct photochemical reactions to produce reactive oxygen species (singlet oxygen, $^1O_2$). $^1O_2$ has the potential to rapidly induce significant toxicity, resulting in cell death through necrosis or apoptosis. Most PS utilized in cancer treatment are comprised of porphyrin, including hematoporphyrin derivative (HPD). The primary PS employed in clinical PDT is photofrin, which is produced by the partial purification of HPD to remove highly reactive porphyrin monomers [71]. Hydrophobicity, aggregation state and specific ionic state all influence the transport of a sensitive agent in the body and its subsequent localization. Lipoproteins and serum albumin are the main transporters in the circulatory system. The study has exhibited that hydrophobic porphyrin-based sensitizers are mostly transported in the bloodstream by lipoproteins (such as lipid-dense lipoproteins (LDLs) with low affinity for water) [72]. LDLs are important due to their recognition by a specialized receptor known as the apo B/E receptor [73]. The fast internalization and transportation of LDL particles to the lysosomal compartment is due to this recognition [74]. Tumor cells typically host a greater quantity of LDLs than their normal counterparts. The superabundance of cholesterol and phospholipids in hyperproliferating cells is facilitated by the development of receptors that regulate extracellular LDL metabolism [75]. The accumulation of hydrophobic sensitizers by a tumor is believed to occur due to their transport to cells through the effective LDL receptor pathway. Nevertheless, certain porphyrins are coupled to high-density lipoproteins (HDLs) yet exhibit a sluggish rate of turnover in the bloodstream.

In contrast, albumin and other proteins found in the bloodstream mostly transport hydrophilic PS like water-soluble porphyrins and phthalocyanines. Covalent binding of porphyrins and other electric PS to serum albumin can significantly enhance their retention in tumor cells. The oxygen supply in tumor tissue to vigorously proliferating tumor cells is often inadequate, although not to the degree where PDT is significantly hindered. Therefore, substantial amounts of lactic acid are produced because glucose is primarily used by anaerobic pathways [76]. The excess of acid in cells is absorbed into the external environment. Contrary to normal tissues, the pH of interstitial fluid in different types of tumors was repeatedly seen to be lower. Therefore, there is a possibility that acid-base balances are involved in the increased incorporation and retention of PS having ionizable groups by tumors [77]. It was reported that active species are formed upon irradiation of localized PS to cause a variety of negative reactions in target tissue components. The primary targets for cell death by photosensitization are caused by biological membranes, particularly mitochondrial membranes. Photodynamic processes were reported through photosensitized damage of DNA, even if PDT is essentially caused by membrane damage. Many observations demonstrate that the efficiency of PDT may not be linked directly to damaging tumor cells [78]. The latest research suggests that an indirect mechanism leading to tumor necrosis may be due to initial vascular damage and following tumor cell anoxia [79].

Magnetic Properties

Early in the past, macrocyclic metal complexes have been facilitated by diagnostic and therapeutic medicinal applications of macrocyclic ligands. In industrial, analytical, and medical applications, many nitrogen/oxygen donor macrocyclic derivatives have been employed [80]. Macrocyclic metal complexes of lanthanides, such as Gd(III), are employed as magnetic resonance imaging (MRI) contrast agents [81]. MRI is the medical procedure employed to provide 2D and 3D images of tissues and organs in the body. This powerful tool detects, diagnoses, and monitors illnesses such as cancer, Alzheimer's, and Parkinson's. Since the initial contrast agent developed for MRI was accepted for medical use in 1988, MRI has been widely recognized as a valuable diagnostic imaging instrument. Currently, tens of millions of MRI tests are performed on patients.

Among them, Gd(III) complex-based contrast agents are most prevalent and utilized in around 40% of examinations. Gd(III) complexes' benefits are contingent upon their robust nuclear relaxation, magnetic susceptibility, prompt imaging post-injection, extensive biodistribution and rapid pharmacokinetic clearance. The most frequently employed MR contrast agents are Gd complexes. Due to its unique electronic structure, Gd is highly paramagnetic, which refers to the presence of unpaired electrons, resulting in a non-zero magnetic moment [82]. Paramagnetism is an intrinsic property of specific materials to be permanently magnetized when placed in an external magnetic field [83]. The fact is that Gd is one of only four elements that can be observed at room temperature. The other three are Fe, Ni, and Co [84]. The powerful paramagnetic properties of Gd make it extremely beneficial as an MR contrast agent. Gd-based contrast agents (GBCAs) can detect abnormal tissues in MRI scans with more detail [85]. They benefit physicians in diagnosing inflammation, tumors, and blood clots by providing them with clearer, brighter images from the inside of the body.

■ REACTIVITY AND COORDINATION CHEMISTRY

Reactivity Patterns

In recent years, the field of drug discovery has witnessed a rise in the field of macrocycles. Approval of numerous drug candidates and an empirical suggestion that macrocyclization has the potential to make significant changes in both biological and physiochemical properties when compared to their acyclic counterparts are the reasons for increasing focus on macrocyclic complexes, as confirmed by numerous sources. The high affinity of metal cations for macrocyclic ligands in comparison to their acyclic referents is referred to as "macrocyclic effect" [86]. Macrocyclic ligands frequently exhibit this attribute. The grouping of entropic effect observed in the chelate effect and additional energetic influence that is derived from the preorganized nature of ligating groups (i.e., no additional strains are introduced to the ligand during coordination), all these reasons cause high affinity of macrocyclic ligands [87]. In contrast to the stability of the complex with corresponding open-chain amine, the stability of Cu(II) complex with macrocyclic ligand cyclam (1,4,8,11-tetraazacyclotetradecane, Fig. 6(a)), was significantly higher than anticipated. This phenomenon was labeled as "macrocyclic effect" and it was also referred to as the "entropy effect" [88]. According to the cavity size in which metal ion is added when the complex is formed, the variance between macrocyclic ligands and open-chain (chelating) ligands is that they possess selectivity for metal ions [89]. For example, in comparison to a smaller Na^+, crown ether 18-crown-6 (Fig. 6(b)) forms significantly more potent complexes with K^+ [90].

Due to the favorable chelate bite angle within the five-membered chelate ring, K^+ is most strongly solvated in solution of all ethylenedioxy-based crown ethers [91]. However, in the gas phase, Na^+ is selected on charge density grounds [92]. In solid-state binding equilibria, as a result, inter-ion selectivity is of only indirect importance and structural features such as size and shape complementarity become more significant. Furthermore, in the solid phase, molecular geometry and stoichiometry in labile crown ether-based systems are subject to the operation of equally directional and non-directional crystal packing forces [91]. As early as 1971, it was proposed that for the insertion of metal ions within the macrocycle, the cation radius to crown ether internal van der Waals diameter ratio of 0.75–0.90 was appropriate [93]. The size fit argument as the basis for solution selectivity patterns has been significantly revised and enhanced as crown ether chemistry has been developed. Solvation, preorganization, chelate ring size, and complementarity are the most significant factors in the solution selection of crown ethers [91]. It is intuitively logical that the optimal binding will occur when the

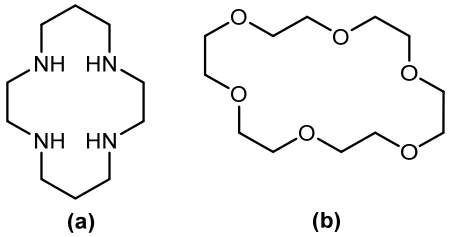


Fig 6. (a) Cyclam and (b) crown ether 18-crown-6

interior cavity ("hole") of the crown ether is approximately equivalent to that of a specific cation. This intuition gave rise to the "hole size relationship".

■ APPLICATIONS

Drugs

All drugs must hold certain levels of aqueous solubility and be lipophilic to enter biological membranes versus passive diffusion to be pharmacologically active [94]. It is widely recognized that the lipid membrane enveloping the cell selectively allows only lipid-soluble substances to pass through [95]. Because of the limited conjugation of its positive charge with the donor group throughout the chelate ring structure, chelation decreases the polarity of metal ions [96]. This phenomenon, by promoting its penetration through the lipid layer of the membranes, will enhance the lipophilic properties of the core metal atom. Consequently, the metal complex will experience a more efficient crossing of the bacterial membrane, thus augmenting the activity of the complexes. The capacity and type of formulation of any drug will determine its water solubility [97]. Dissolved drug molecules will not divide from an aqueous exterior into a lipophilic biomembrane and then permeate the membrane if the drug is hydrophilic [98]. High-throughput screening approaches to drug development have resulted in an increase in the number of lipophilic water-insoluble drugs whose clinical effectiveness is hindered by their insolubility in water. Recently, there has been a significant rise in interest in cyclodextrins (CDs). They have been inspected for their potential applications in the pharmaceutical, food and biomedical applications, for example, drug delivery, theragnostic, tissue engineering, fabrication/coating of medical devices and biosensors/bio-imaging applications. CDs in Fig. 7 are cyclic oligosaccharides that are formed by the enzymatic degradation of starch.

A torus-like macro ring is formed by an assembly of D-(+) glucopyranose groups that are connected by α-(1,4)-glycosidic bonds [99]. Due to their availability, cost, and biocompatibility, CDs have become wildly popular. It has a hydrophobic core to transport several hydrophobic drug molecules by making complexes, and it has been an attractive material for different pharmaceutical applications [100]. Indeed, the potential of CDs to enhance solubility, bioavailability, dissolution rate, permeability, physicochemical stability, intensity or duration of therapeutic activity, and reduction of tissue irritation/toxicity of existing and emerging drug candidates has been demonstrated. Furthermore, CDs are highly versatile oligosaccharides that can be easily controlled to alter their physicochemical properties and could be linked with other excipients, such as polymers, to achieve a synergetic effect. In the pharmaceutical industry, CDs are employed as complexing agents to enhance the aqueous solubility of poorly soluble drugs and their bioavailability and stability.

CD is a truncated conical shape featuring an interior

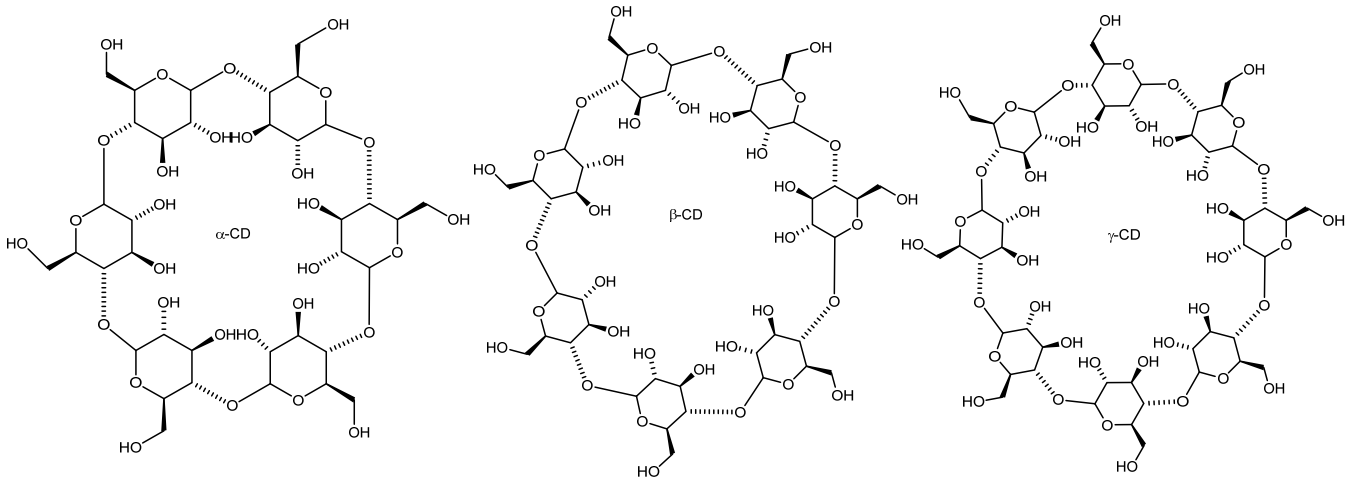


Fig 7. Chemical structure of the three main types of cyclodextrins

hydrophobic environment that typically encapsulates tiny hydrophobic molecules and, to a lesser extent, portions of polymeric structures through noncovalent interactions. In aqueous solutions and by absorbing drug molecules or lipophilic fractions of molecules into the central cavity, CDs can form inclusion complexes with a variety of pharmaceuticals. During complex formation, no covalent bonds are formed or broken, and drug molecules in complex are in rapid equilibrium with free molecules in solution. CD is not readily absorbed by biological membranes owing to its molecular weight, chemical composition, and extremely minimal octanol/water division coefficient [101]. Only the free form of the drug (which is in equilibrium with D/CD complexes) can be absorbed into lipophilic membranes. CDs do not develop the permeability of hydrophilic water-soluble drugs by lipophilic biological membranes. The physicochemical properties of the drug (its solubility in water), composition of the drug formulation (aqueous or non-aqueous), and physiological composition of membrane barrier (the presence of an aqueous diffusion layer) will determine the CDs' ability to facilitate or impede drug delivery through a biological membrane. CDs enhance drug delivery through aqueous diffusion-controlled barriers, yet they could delay drug delivery over lipophilic membrane-controlled barriers. Oxidation of organic substrates, especially alcohols, constitutes a significant category of industrially pertinent reactions, leading to substantial interest in the development of heterogeneous catalysts for this application. Heterogeneous catalysts afford numerous benefits in synthetic environments, such as ease of separation, waste reduction, and reusability. Subsequently, they remove the requirement for distillation or extraction to isolate products from the catalyst; the development of such catalysts is the focus of green chemistry [102].

Synthetic metalloporphyrins possess a particular location in the area of oxidation catalyzed by transition-metal complexes. Oxidation of organic substrates in nature is one of the most prominent roles in the classification of metalloproteins identified as "hemoproteins" [103]. As a cofactor, these proteins possess iron protoporphyrin IX (hem or FePPIX). They are essential for a diverse array of metabolic functions in organisms, including gas binding (for example, Hb and myoglobin), electron transference (example, cytochromes a, b, and c), ligand sensing (for example, guanylyl cyclase), and redox catalysis (example; cytochrome P450s and peroxidases such as horseradish peroxidase, HRP). Hemoproteins were shown to catalyze the reactions with high stereo-, chemo- and regio-selectivity by utilizing the FePPIX cofactor. Scheme 5 illustrates the mentioned biomedical and catalysis applications depending on macrocyclic complexes.

Catalysis

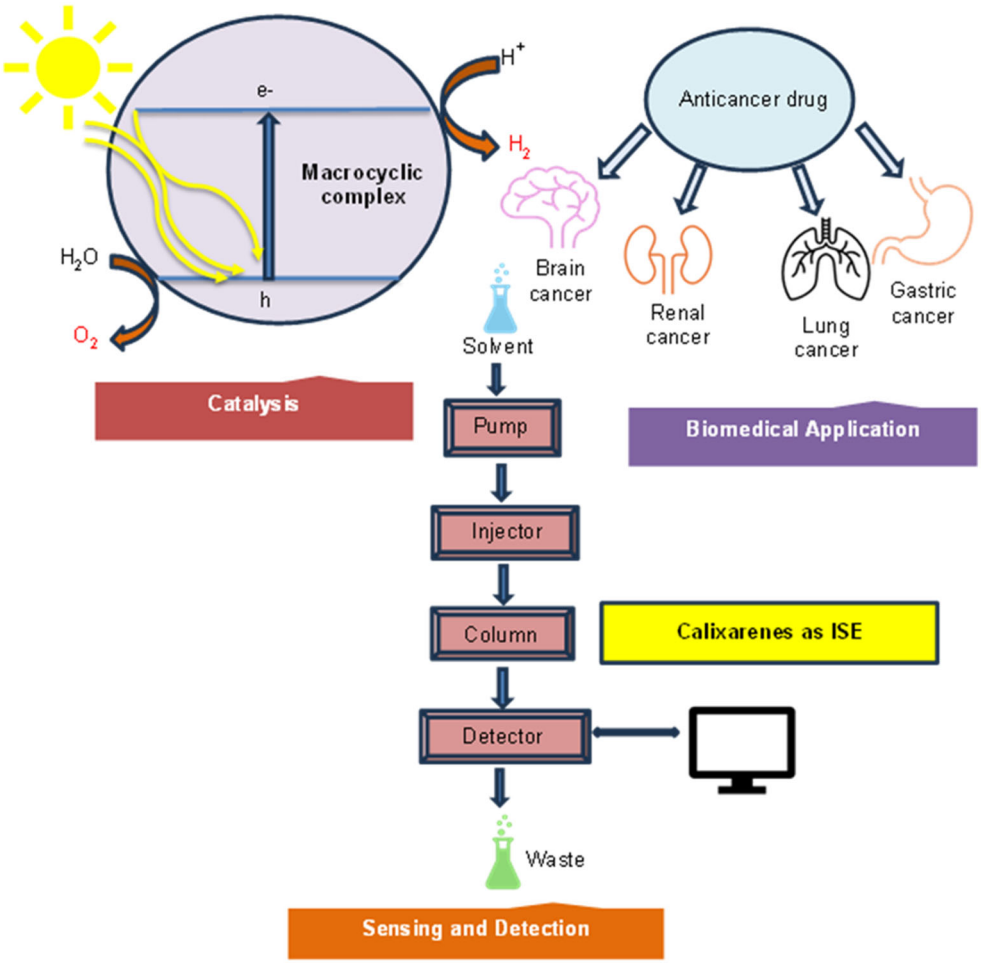
Water reduction catalysts (WRCs) are typically complexes that contain Co and Ni as central atoms [104], in which catalysts and PS separate water into its constituent elements to generate H_2 as a renewable energy source and O_2. The exchange of solar energy into chemical energy is an efficient method for storing captured sunlight [105], which is seen as an eco-friendly approach to attaining an inexhaustible fuel source [106]. Solar energy is saved in chemical bonds of H_2 and O_2. Using H_2 as fuel releases H_2O as the only component of combustion, the renewable cycle is closed [107]. In Scheme 6, aqueous photocatalytic generation of H_2, Co(II) complexes with tetra and pentapyridyl ligands exhibit excellent catalytic activity [108].

Sensing and Detection

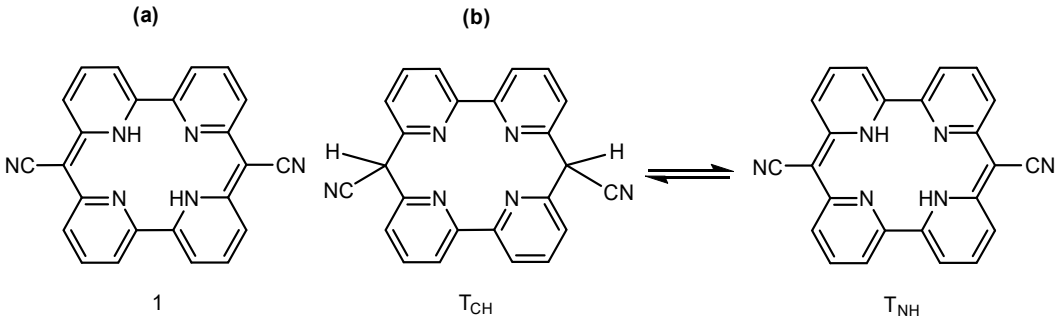
Calixarenes in Fig. 8(a) are synthesized through the oligomerization of phenol and formaldehyde [109]. In 1990, they were presented in a brief overview focusing on the application of these compounds for chemical separations [110]. Calixarenes are utilized in chromatography, refining, catalysis, phase transfer, enzyme mimetics, ion-selective electrodes (ISE), membrane transport, ion channels, and self-assembling monolayers. Calixarene chromoionophores have been identified as specific molecules and ion indicators in the past three decades [111]. Calixarenes serve as the optimal "molecular platforms" for the systematic incorporation of specified ligating arms in prearranged on the nature of ligating groups and the size of the macrocyclic scaffold. Complex groups (situated at the upper rim of

calixarenes) can selectively attract certain molecules [112]. The physical features of calixarenes are caused by the bottom rim functional groups of calixarenes [113].

Calixarenes, which contain ester, ether, carboxylic acid, and carbamate, were identified as ISEs for alkali metal ions. Calixarenes are commonly utilized as mobile phase additions in HPLC and as chemically bonded stationary phases in GC and HPLC. HPLC is favored by calixarene-bonded stationary phases due to the high absorbance of calixarenes, which hinders the UV detection of analytes [114]. Furthermore, the reduced solubility of the majority of calixarenes hinders their utilization as additives in



Scheme 5. Applications of macrocyclic complexes in biomedical and catalysis fields



Scheme 6. (a) Basic ligand framework of a tetradentate macrocyclic bisbipyridyl18 (porphyrin) and (b) tautomeric forms of porphyrins

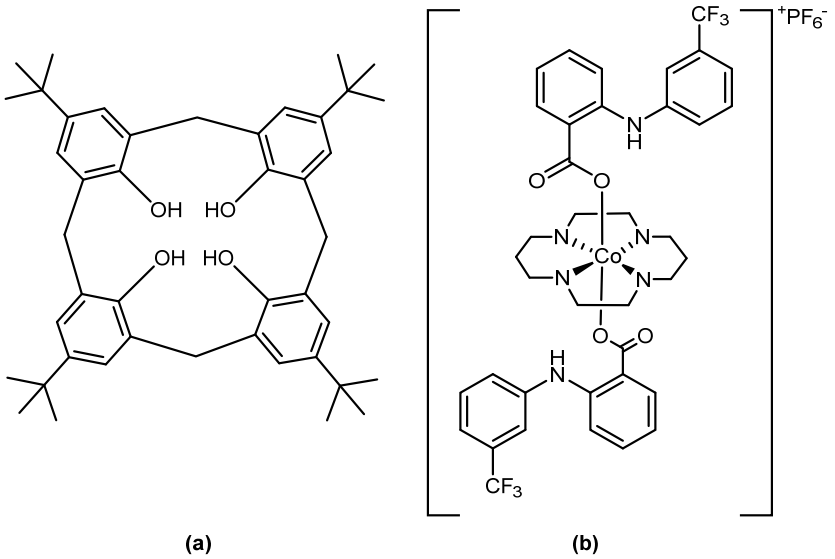


Fig 8. (a) Calix[4]arene with *p-tert*-butyl substituents and (b) cobalt(III)-cyclam

aqueous eluents [111]. The ionophoric characteristics of calixarenes were evaluated through their application in the development of ion-selective potentiometric sensors [115]. Moreover, the ligands employed in the hydrometallurgical processes for radioactive waste treatment must function under severe chemical and radiolytic conditions [111].

Biomedical Applications

Cancer stem cells (CSCs) are specific groups of cells within the tumor that possess characteristics like stem cells. These characteristics involve the ability to regenerate themselves and develop into multiple cell types. CSCs avoid traditional cancer medicines (such as chemotherapy and radiation) because they possess cell cycle profiles slower than bulk cancer cells, which require selectively killing fast-growing cells. Also, CSCs can escape surgical interventions because they exist in difficult-to-reach areas in the tumor microenvironment. Given the biological importance and medical ramifications of CSCs, several ongoing research initiatives focus on producing anticancer medicines that can eliminate both the main population of cancer cells and CSCs [116]. Among chemically synthesized pharmaceutical drugs, macrocyclic compounds with a ring of 12 or more atoms are preferred for synthesizing potential anticancer derivatives in chemical, biological, and medical fields [117]. Prodrugs that can accumulate in the CSC microenvironment and undergo activation have the potential to efficiently eliminate CSCs. Given that oxidized Co(III), d6 formula is inactive and reduced Co(II), d7 formula is labile and can release coordinated bioactive ligands, six-coordinate Co(III) complexes with bioactive ligands in Fig. 8(b) can be utilized for this purpose [116].

Investigations have demonstrated that macrocyclic compounds have the potential to be potent chemotherapeutic agents for patients with SCLC, the deadliest form of lung cancer [118]. The inflexible structures of macrocyclic molecules enable robust interactions with their binding sites to impede DNA transcription, hence suppressing the function of RNA-polymerase II [119]. By binding to the DNA minor groove, it effectively suppresses the transcription of rapidly proliferating cancer cells and strongly triggers immunogenic cell death.

■ CHALLENGES

There are two major problems in the synthesis of macrocycles. First and foremost, the ring-closing reaction typically includes two functional groups that should interact intramolecular rather than intermolecular, as the latter would result in dimerization, oligomerization, or polymerization. Ring-closing reactions do not facilitate the formation of massive rings, which is the

primary obstacle to macrocyclization. In contrast, microscopic rings or polymers are more likely to form. Second, as numerous studies have shown that conformational preorganization is essential for macrocyclization reaction, the ring-closing reaction itself can be challenging. The macrocyclic structure began to decompose after the macrocyclic ligand was heated [120]. Although these complexes contain salts with elevated organization constants, many bind O_2 or are oxidized by it. Additionally, the elevated [H^+], such as 0.01–1.00 M, causes many macrocycles to quickly decay. These properties restrict their function in specific applications, particularly in reactions that must be performed in acidic media. Macrocycles have not yet occupied a significant position in conventional drug design. This is likely due to the challenges associated with regulating conformation, which in turn affects the proper and robust binding to receptors and the complexity of syntheses [121]. Formation of macrocyclic metal complexes usually needs ligands to be present in a folded conformation.

■ FUTURE DIRECTIONS

Supramolecular chemistry has attracted considerable interest in chemistry and materials science since its formal introduction, demonstrating its importance in molecular recognition and assembly via weak and reversible noncovalent interactions. The accumulated progress in the field of supramolecular nanotechnology has been thoroughly examined for biomedical applications, and numerous previous studies have provided an excellent review [122]. Stimuli-responsive supramolecular assemblies have garnered important interest owing to their ability to undergo structural modifications upon stimulus application and, in certain instances, to revert to their original configurations upon application of an additional stimulus [123]. Macrocyclic and even macro-acyclic hosts are suitable for designing stimuli-responsive supramolecular assemblies due to their cavity size-dependent host capabilities [124]. By utilizing stimuli-responsive triggers (a commonly explored path to getting more advanced drug delivery) to manipulate drug biodistribution with spatiotemporal control, such that the drug acts equally when it is needed and at the site where it is needed. In this design, prior knowledge of the position of need for the therapeutic method could be coupled to the regionally regulated application of a stimulus such as light, pulsed ultrasound, or magnetic field [125]. By utilizing microenvironments, such as low pH and hypoxia, states of self-assembly and molecular recognition can be modulated, thus resulting in controlled drug release. Also, the receptor should match the substrate in size and shape to maximize the attractive non-covalent interactions between the two entities.

■ CONCLUSION

Macrocyclic complexes are cyclic macromolecules present in nature and have considerable importance in biotic systems. Also, macrocyclic complexes have increased attention, particularly those that can be used as models for naturally occurring biological systems and have various catalysis, sensing, detection, and biomedical applications. Template synthesis is a classical technique for preparing macrocyclic complexes and click chemistry has become a modern method due to its simplicity, and the characterization of the produced macrocyclic metal complexes may be easily accomplished with the help of numerous physiochemical techniques. Additionally, macrocyclic complexes have a significant role in PDT for cancer and nonmalignant diseases. The powerful paramagnetic properties of these complexes make it suitable for MRI to diagnose cancer, Alzheimer's, and Parkinson's disease. The advancements in supramolecular nanotechnology, such as stimuli-responsive triggers for drug delivery, have been a great source of interest since their structures can be altered by applying a stimulus.

■ CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

■ AUTHOR CONTRIBUTIONS

All authors contributed to the development of the manuscript. Nabaa Abbas was primarily responsible for drafting the manuscript and conducting the literature review. Ammar Jihad Alabdali and Mohammed Hussein Al-Mashhadani contributed to the organization of the content and providing critical feedback. Zamzam

Alhuwaymil, Mohammed Saeed Alyami, and Sohad Abdulkhaleq Alshareef reviewed the final version and approved it for submission.

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