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Review Paper

Macrocyclic Complexes: Auspicious Tool in the Medicinal World-A Review

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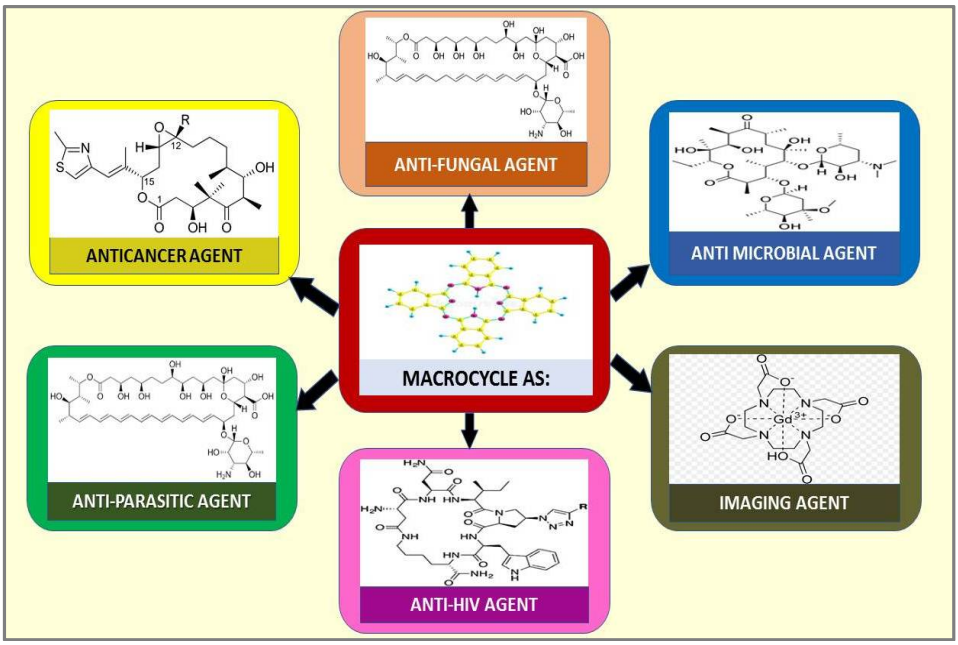
ABSTRACT

Macrocyclic natural products have evolved to fulfil numerous biochemical functions. The exclusive essential physicochemical properties of macrocyclic complexes have attracted researchers to conduct extensive research to discover novel molecules that could be useful for developing alternative medicines for the treatment of several diseases including cancer. The current advances in the field of macrocyclic chemistry, especially, having the ability to prepare metallomacrocycles, high affinity and selectivity have enabled human beings to invent new techniques for the preparation of antimicrobial and anti-tumor agents. This article throws light on application of macrocyclic complexes in the field of medicinal chemistry.

Graphical Abstract



Keywords: Macrocycle, Aantitumor activity, Antimicrobial activity, Imaging agents.

INTRODUCTION

Interest in discovering metal ion complexes with macrocyclic ligands has been continually increasing due to the recognition of their role played by these structures in remedies. Over the past several years, prevalence of biologically active macrocycles in medicinal chemistry literature has been increasing. Several recent review articles have discussed the role that macrocycles can play in medicinal chemistry, in particular looking beyond the established importance of natural product macrocycles in drug discovery [1-3]. Schiff base macrocycles have been of prodigious importance in macrocyclic chemistry. They were among the first artificial synthesized metal macrocyclic complexes. The metal complexes containing synthetic macrocyclic ligands have attracted a great deal of attention because they can be used as models for more intricate biological macrocyclic systems: metalloporphyrin's (myoglobin, haemoglobin, cytochromes, and chlorophylls), corrins (vitamin B_{12}) and antibiotics (valinomycin, nonactic). These discoveries created macrocyclic chemistry and its enormous diversity [4].

The complexes with aza macrocyclic ligands have continued a focus of scientific attention for many decades [5]. Schiff base metal complexes have been widely studied because they have antibacterial, anticancer, antifungal, herbicidal and industrial applications [6]. A number of macrocyclic complexes with ligands, such as cyclen, cyclam and bicyclamhave been reported to exhibit antitumor activity [7]. The macrocyclic complexes of oxalyldihydrazide are a field of interest because of their applications as antiviral, anticancer, antifungal and antibacterial agents [8-10]. Widespread research work has been carried out on platinum-based chemotherapeutic compounds [11, 12]. Despite of their remarkable success with high efficiency against human testicular, ovarian, bladder, head and neck carcinomas, several side effect such as limited water solubility and the dose-dependent toxicities, mainly nephrotoxicity, cytotoxicity and emetogenesis are the major drawbacks associated with these drugs [12-14]. Moreover, the importance of aza-macro-cyclic transition metal complexes is due to the role they play as models for protein metal binding sites in biological systems, as synthetic ionophores [15], electrocatalyst in fuel cells [16], M.R.I contrastagents [17, 18], luminescent sensors [19], anticancer drugs [20] and radio immune- therapeutic agents [21]. These extensive applications have been worth investigating for the design of new macrocyclic ligands and their metal complexes for biological and industrial applications [22] (Figure 1).

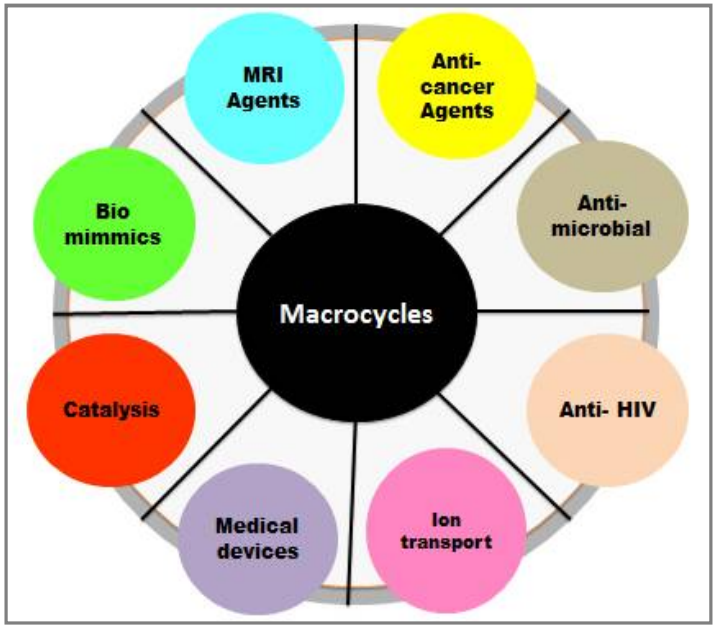


Figure 1. Graphical representation of Biological uses of Macrocycles.

Coordination compounds containing macrocyclic ligands have been reported to their wide applications in biological and sensor field. The first non-platinum complex tested in clinical trials was *cis*-[$(CH_3CH_2O)_2$ $(bzac)_2Ti(VI)$] used against a wide variety of ascites and solid tumors **[23, 24]**. One of the potential approaches in anticancer chemistry is focused on the design of new macrocyclic metal complexes with different substituent and labile sites which may increase their cytotoxicity, especially to cancer cells. In this context, a wide range of macrocyclic metal complexes have been synthesized and there *in vitro* anticancer activity has been tested against different cancerous cell lines along with normal cells. The Pd(II) complexes have been derived from a salen ligand and tested against a human hepatoma cancer cell line [**25**]. Tin based complexes exhibit a broad spectrum of biological activity which includes organotin derivatives having bactericidal, fungicidal, antitumor and acaricidal activity [**26**]. Recently, a number of metal complexes have been synthesized and some of these complexes were also tested for their cytotoxicity's on various cancer cell lines and their results showed moderate to good anticancer activity. In this present work we have reported the synthesis and characterization of octa azamacrocyclic complexes of Co (II), Ni (II), Cd (II) and Sn (II) derived from oxalyl dihydrazide and dibenzoyl methane are also studied for their *in vitro* anticancer activity. The evaluation of *in vitro* anticancer activity of these complexes was carried out against different human cancer cell lines (Hep3B, HeLa andMCF7) by using MTT assay [**27**].

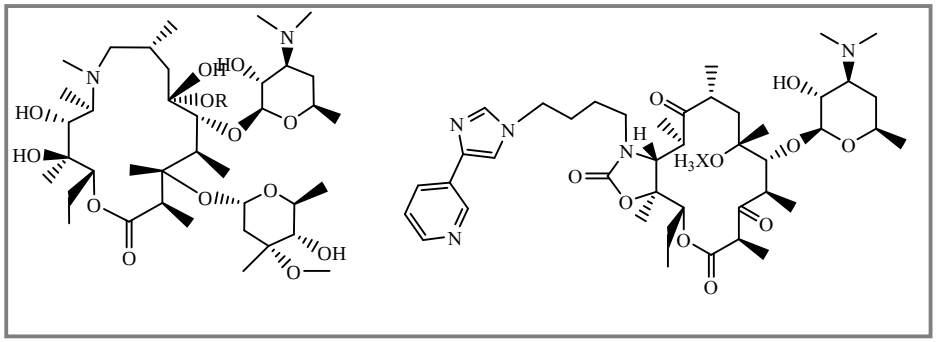
From a historic and clinical point of view, macrocyclic molecules have had a massive impact on the fields of chemistry, biology, and medicine. Many naturally occurring macrocycles have been successfully introduced to the clinic; as such, macrocyclic natural products continue to serve as invaluable starting points and to drive and inspire organic and medicinal chemists to determine new and better drugs. The structural and conformational flexibility of the macrocyclic ring offer's subsequent functional advantages, e.g., it has the potential of being highly potent as well as being selective when key functional groups interact with biological targets [**1**]. In addition, from a chemistry point of view, macrocyclic compounds can offer various functionality and stereochemical complexity in a conformationally restricted manner. Moreover, macrocycles are favorable drugs due to their properties, including good solubility, increased lipophilicity, enhanced membrane penetration, improved metabolic stability, and good oral bioavailability with desirable pharmacokinetic and pharmacodynamic properties [**1, 2**]. Medicinal inorganic chemistry offers additional occasions for the design of therapeutic agents not accessible to organic compounds. The wide range of coordination numbers and geometries, available redox states, thermodynamic and kinetic characteristics, and intrinsic properties of the cationic metal ion and ligands offer the medicinal chemist a large variety of reactivity's to be exploited.

One structural feature which is common in the larger natural products is the macrocycle: Ring architecture of 12 or more atoms. The macrocycle ring allows a molecule to achieve a degree of structural pre-organization, such that key functional groups can interact across extended binding sites in proteins without a major entropic loss on binding. Thus, Macrocycles are highly potent as well as selective. However, macrocycles are not rigid compounds. Instead, they provide cooperation between structural pre-organization and sufficient flexibility to mould to a target surface and maximize binding interactions. Furthermore, macrocycles are not just bigger versions of small molecules, but can be measured as the smallest examples of biomolecules that exhibit functional sub-domains [**28**].

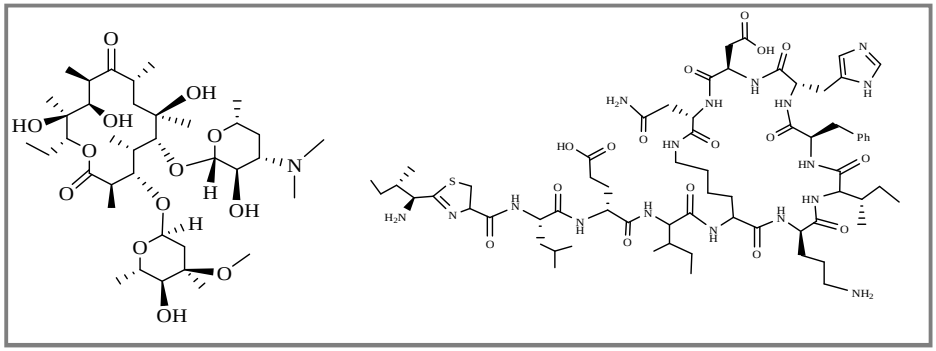
Macrocycles as Antibiotics Agents: Historically, macrocyclic molecules represent an effectively documented medicinal class in the clinic. In this section we analyse clinically used macrocyclic drugs. Notably, the macrocyclic antibiotics constitute one of the most successful classes of macrocyclic drugs in clinical training. Among them vancomycin is a macrocyclic glycopeptide antibiotics which is used for the treatment of Gram-positive bacterial infection, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumonia* [**29, 30**]. Chemically, vancomycin is a hydrophilic glycopeptide which contains a

glycosylated hexapeptide chain and aromatic rings cross linked by aryl ether bonds into a rigid molecular framework. It is not orally bioavailable because its absorption is poor in the gastrointestinal tract; however, it can be used as an oral antibiotic for the treatment of *C difficile*-associated diarrhea and enterocolitis caused by *Staphylococcus aureus* [29, 30]. In 2009, its synthetic lipoglycopeptide derivative telavancin was approved by the U.S. FDA for the treatment of skin structure infections and complicated skin (cSSSIs) caused by MSSA, MRSA, and vancomycin-susceptible *Enterococcus faecalis*, and *Streptococcus pyogenes*, *Streptococcus agalactiae*, or *Streptococcus anginosus* group [30-32]. Automatically, this glycopeptide class inhibits the peptidoglycan biosynthesis of bacterial cell wall by binding tightly to D-alanyl-D-alanine portion of cell wall precursor, as well as disrupts cell membrane integrity [30, 33, 34].

In addition, daptomycin is a new cyclic lipopeptide antibiotic [35]. It was approved by the U.S. FDA in 2003 used for the treatment of cSSSIs caused by susceptible aerobic Gram-positive organisms and *S. aureus* bacteraemia caused by MSSA or MRSA [30, 36]. Daptomycin rapidly depolarizes bacterial membrane by binding to components of the cell membrane of susceptible organisms and inhibits macromolecular biosynthesis of DNA, RNA, and protein [30, 37]. Fidaxomicin, obtained from the fermentation broth of *Dactylosporangium aurantiacum* subspecies hamdenesis, represents the first in a new macrocyclic class of narrow spectrum antibiotics [38-40]. It was approved by the U.S. FDA for the treatment of *C. difficile*-associated diarrhea in 2011 [30]. Bacitracin A, generated from the licheni form is group of *Bacillus subtilis*, is a branched cyclic polypeptide broad spectrum antibiotic targeting both Gram-positive and -negative organisms [41, 42]. It works by inhibiting the late stage peptidoglycan biosynthesis and disrupting plasma membrane function [43]. The prototype macrolide antibiotic erythromycin, bearing a 14-membered macrocyclic lactone motif, was isolated from the fermentation broth of the fungus *Saccharopolyspora erythraea* and used for the treatment of susceptible bacterial infections [47, 48]. Clarithromycin, a semisynthetic derivative of erythromycin with a 6-methoxyl ether functionality and improved acidic stability, is an effective macrolide antibiotic for the treatment of chronic bronchitis and erysipelas [49, 50]. Azithromycin, the derivative of erythromycin, is another advanced and effective antibacterial agent in this macrolide class [49, 50].



(a).Azithromycin, (b). Telithromycin

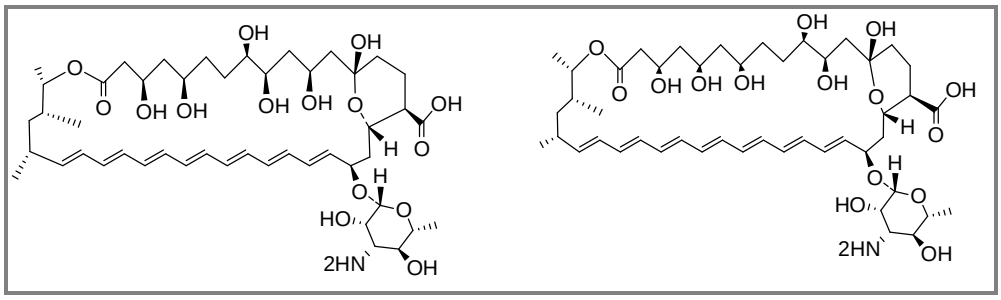


(c). Erithromycin, (d). Bacitracin A

Figure 2. Clinically used macrocyclic antobiotics.

Polymyxins A-E belong to an old class of cationic cyclic polypeptide antibiotics that consist of a cyclic positively charged decapeptide with an either 6-methyl-octanic acid or 6-methyleptanoic acid fatty acid side chain. Only polymyxins B and E in this class are used in the clinic, which are primarily used for the treatment of Gram-negative bacterial infections such as *Acinetobacter* species, *Pseudomonas aeruginosa*, *Klebsiella* species, and *Enterobacter* species [**30, 44–46**]. Polymyxin B disrupts bacterial membrane integrity by binding to phospholipids in cytoplasmic membranes [**30, 45**].

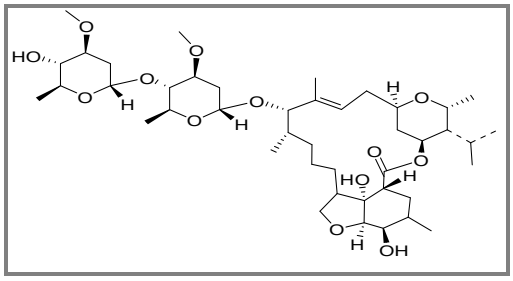
Macrocycles as Antifungal Agents: Macrocyclic antifungal agents are illustrated in figure 3. Nystatin, amphotericin B, and natamycin both belongs to a chemical class of polyene antifungal drugs, which structurally consists of a macrocyclic lactone scaffold; a hydrophilic region containing multiple OH groups, a COOH functionality, and an amino sugar moiety; and a hydrophobic region containing a chromophore of the 4–7 conjugated double bond system. This class of naturally occurring antifungal drugs works by binding to ergosterol in fungal cell membrane and thus disrupting fungal membrane function [54, 55]. Nystatin, the first clinically used agent in this polyene class, displays potent activity for invasive *Candida* infection; however, it can only be used topically due to its Spartan toxicity for systemic use [**30**]. Amphotericin B is used parenterally for the treatment of severe systemic and CNS fungal infections caused by susceptible fungi [**54**]. Only Natamycin is the topical ophthalmic antifungal agent approved by the U.S. FDA for the treatment of conjunctivitis, blepharitis, and keratitis caused by susceptible fungi (*Aspergillus*, *Candida*, *Cephalosporium*, *Fusarium*, and *Penicillium*) [**54**] (Figure 3).



(a) Amphotericin B (b) Nystatin

Figure 3. Clinically used macrocyclic antifungal and antiparasitic agents.

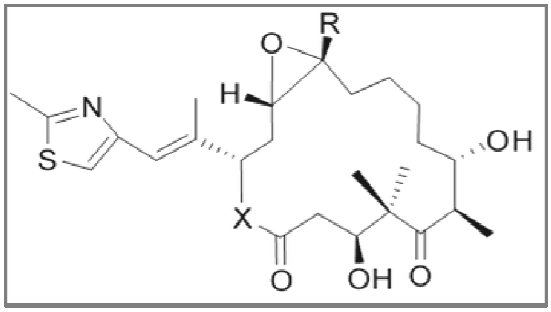
On the other hand, macrocycles have also been used as antiparasitic agents. One such example, ivermectin, bearing a 16-membered macrocyclic ring, is an effective antiparasitic and anthelmintic agent for treatment of strongyloidiasis of the intestinal tract and onchocerciasis, as well as the topical treatment of head lice [**54, 59, 60**]. Ivermectin binds to glutamate-gated chloride ion channels with high selectivity and strong affinity in invertebrate nerve and muscle cells, which ultimately leads to the death of the parasite due to increased permeability of cell membranes to chloride ions and subsequent hyperpolarization of the nerve or muscle cell [**30, 59**] (Figure 4).



Ivermectin

Figure 4. Macrocycle used as antiparasitic agents.

Macrocycles as Cancer Chemotherapeutic and Immunosupprssant agents: Macrocyclic anticancer chemotherapeutic agents are shown in Figure 4. As one of the older chemotherapy drugs, dactinomycin, isolated from soil bacteria of the genus *Streptomyces*, is a cyclic polypeptide intravenous antibiotic with anticancer activity [**61**]. It binds to DNA and causes subsequent inhibition of RNA synthesis and is used in the treatment of Wilm's tumour, gestational trophoblastic neoplasia and rhabdomyosarcoma [**30**]. Epothilone B, a 16-membered polyketide macro-lactone with a methylthiazole side chain, exerts its cytotoxic effects through promoting microtubule assembly, interfering with the late G2 mitotic phase, and inhibiting cell replication [**30**]. It has similar mechanistic profile as Texans but improved solubility and milder side effect and become a new class of anticancer drugs for the treatment of metastatic or locally-advanced breast cancer (refractory or resistant) [**30, 62**]. The semisynthetic macrolactam analogue ixabepilone of epothilone B is used for the treatment of advanced breast cancer [**63**]. In addition, romidepsin, a histone deacetylase (HDAC) inhibitor generated from the bacteria Chromobacterium violaceum, is an antineoplastic prodrug used for the treatment of refractory cutaneous T-cell lymphoma and refractory peripheral T-cell lymphoma [**30, 64**] (Figure 5).

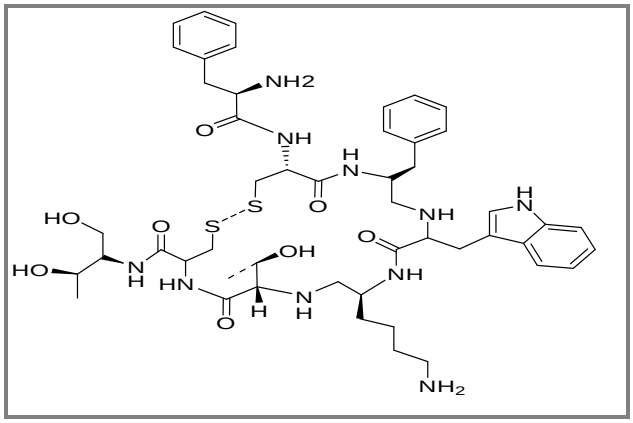


Epothilone B (X=O), Ixablepilone (X=NH)

Figure 5. Macrocycles used as cancer chemotherapeutic agents.

Macrocycles have also been clinically used as immunosuppressant agents, one such example, the cyclic polypeptide cyclosporine inhibits the production and release of interleukin-2 (IL-2), inhibits IL-2-induced activation of resting T-lymphocytes and thus inhibits T cell-mediated immune responses [30,65]. It is frequently used to prevent rejection in organ transplant recipients [10]. Another macrolide lactone class of immunosuppressive agents includes sirolimus (rapamycin) [66] and tacrolimus. Similar to cyclosporine, this macrolide class can also be used in organ transplantations to prevent organ rejection by inhibiting the response to IL-2 or the secretion of IL-2, and subsequently blocking activation of T and B cells [**30, 67**]. However, mechanistically, sirolimus inhibits T-lymphocyte activation and proliferation in response to antigenic and cytokine stimulation and inhibits antibody production **[30**]. In contrast, temsirolimus, a derivative of sirolimus, was approved by the U.S. FDA in 2007 and is used in the treatment of advanced renal cell cancer [**30, 68**]. Temsirolimus and its active metabolite, sirolimus, function as targeted inhibitors of mTOR (mammalian target of rapamycin) kinase activity [**30, 68**].

Macrocyclic Agents for Pituitary Disorders: Somatostatin, a 38-membered macrocyclic peptide hormone, regulates the release of human growth hormone from the pituitary. The synthetic cyclic octapeptide surrogate's octreotide and lanreotide were subsequently developed to mimic the pharmacological activity of endogenous somatostatin (Figure 5) [**69, 70**]. Notably, octreotide exhibits more potent inhibition of growth hormone, glucagon, and insulin relative to somatostatin. Similarly, lanreotide also displays a greater affinity for somatostatin receptors and has a much longer half-life than somatostatin [**30, 70**]. Both octreotide and lanreotide are used for the treatment of acromegaly; octreotide is also indicated for the treatment of severe diarrhea and flushing associated with carcinoid syndrome [**30, 71**] (Figure 6).



Octreotide

Figure 6. Macrocyclic agents related to pituitary disorders.

Cabtalytic Activity: Among these submissions' catalytic activity of these macrocyclic complexes has a major contribution to the green chemistry. Most of the transition metal macrocyclic complexes are synthesized to act as the catalyst for various reasons, due to their high thermal stability, unusual structural, electronic and electrochemical properties. Some natural macrocyclic complexes have shown the ability of using as catalysts for many transformations such as vitamin B12. Catalysis can be separated into a number of areas, depending on the substrate and the catalytic reaction. One of the prime areas of the initial effort in catalysis has been the small molecule activation, such as O_2, NO_2, NO, H_2S and CO_2 [72].

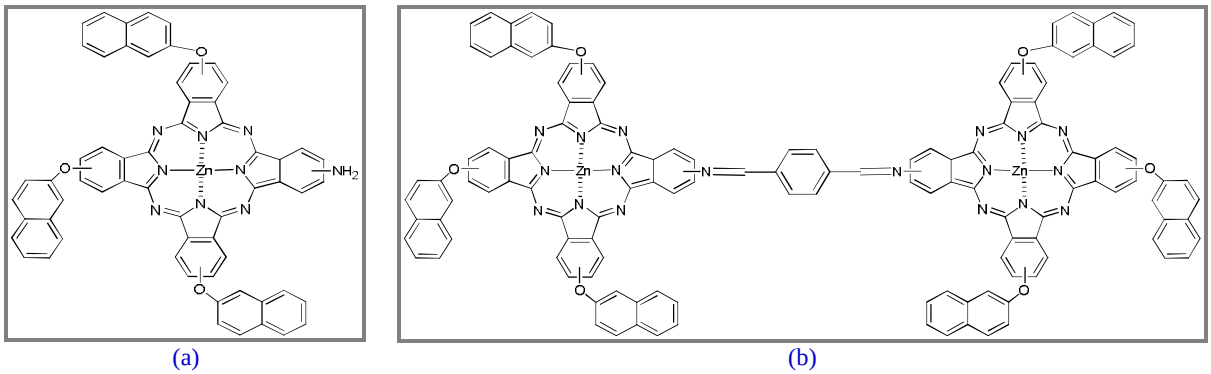
Transition metals such as Cu, Ni, V, and Fe also act as catalysts itself, but these metal catalysts have numerous drawbacks. These metals show the catalytic activity only when it is in 100% pure form, but the pure metals such as Pt are highly. Another thing is, in higher potentials these metals can undergo oxidations that can changes their surface properties. Moisture, dust, higher and lower temperatures will directly influence the catalytic activity of the metal. Many of these disadvantages can be eliminated by using these metals in the macrocyclic form. The communal transition metals used in macrocyclic catalysts are Fe, Co, Ni, and Cu, and the macrocyclic ligands include chelating atoms N_4, N_2O_2, N_2S_2, O_4, and S_4. This can be further explicated by considering the interaction between small molecules and a transition metal. Electron transition occurs first from small molecules such as oxygen and carbon dioxide into the empty dz^2 orbital, forming a π bond, lowering the anti-bonding π orbital's and rising the energy of the dyz and dxzorbitals of the transition metals. This permitsthe electron transition from these filled orbitals to the anti-bonding π orbital, and resulting in catalytic activity. These transition metal macrocyclic complexes are also very popular in the medicinal field [73] due to their resistivity towards the gram (-) and gram (+) bacteria, fungal growth and as the virusinhibitors.

Imaging Agents: The utility of macrocyclic ligands and their metal complexes as MRI agents is well established. Several macrocyclic ligands and their metal complexes have been reported in literature as potential imaging agents [73]. This is attributed to the sharp emission and long luminescence lifetime at room temperature offered by lanthanoid ions along with high stability and biological compatibility of aza-macrocyclic ligands. Number of studies on macrocyclic chelates designated that the combination of heterocyclic core like pyridine, bipyridine or terpyridine with diethylenetriaminetriacetic acid core (DTTA) generates ligands, which form highly stable and emissive complexes. [74, 75]. These complexes could be used as biolabeling and other imaging agents. Due to the extrarigidity imposed by pyridine moiety macrocyclehas been reported to form complexes with stable transition and lanthanide ions. They showed that the mechanism of formation of the complexes with ligand 39a were analogues to that of DOTA and

its derivatives, and had comparable stability constant values [**73**]. Fifteen membered bipyridine-based macrocyclic ligand 39b and18-membered pyridyl hexaaza macrocycle and their respective lanthanide complexes have been assessed as MRI component [**75**]. The use of pyridine appended 12-and14-membered tetraaza macrocycles with and without acetic acid or phosphonic acid arms and their lanthanide complexes as imaging agents is known for two decades or so these complexes have been 4 for cancer imaging, and detection of lesions etc. However, some of the complexes possess stability constant lower than corresponding DOTA-type species and were not kinetically stable *in vivo*. This is a negative indication for such ligands as they might harm normal and healthy tissues. Kiefer and Woods isolated DOTA-based ligand to probe the coordination of lanthanide ions to the phosphonate pendant groups within this more rigid macrocycle. The presence of the pyridine ring constrains the conformation of the macrocycle to the achiral (dkdk) form, while the more flexible chiral DOTA can be either (kkkk) or (dddd). The ligand readily forms 1:1 complex with lanthanide ions. Hexaaza macrocyclic pyridinophane 45 having no pendant arm was reported as a new alternative to cyclin for complexation.

APPLICATION

Metal ions typically interact with molecules displaying binding tendencies (ligands) and place them in the space around themselves, according to a definite geometrical order. This property lies at the basis of coordination chemistry and, over the last hundred years, gave rise to thousands and thousands of compounds of interest for medical care, diagnostics, industrial catalysis, optics and electronics, solar energy harvesting, hydrometallurgical extraction, etc. [**76, 77**]. In view of the variety of potential applications of pyrazolate–bridged multi–metal coordination macrocyclic and cage–like hosts, Jiang and co–workers have devoted their great efforts to develop the self–assembly of metallo–macrocycles with bi– or poly–pyrazolate–bridged ligands. They have reported macrocycles by employing di–palladium complex $[(bpy)_2Pd_2(NO_3)_2](NO_3)_2$, (where, bpy=2,2´–bipyridine) as corners and tetrapyrazolate calix[4]arene–based ligand (L_4^-) as linkers, a novel cavity–containing high–positively–charged polypyrazolate–bridged metallo–macrocycle $[Pd_{16}L4]^{16+}$ [**78, 79**].A planar binuclear zinc phthalocyanine was newly synthesized for use in dye–sensitized solar cells, based on Schiff base and asymmetric amino zinc phthalocyanine by Baiqing Zhu and co–workers [**80**] (Figure 7).



(a) (b)

Figure 7. Zinc phthalocyanines based on extended π–conjugation.

Binding and sensing of phosphorylated substrates by synthetic receptors with high selectivity in aqueous medium is still one of the greatest challenges of supramolecular chemistry. Among them, pyrophosphate (PPi) has been one of the most pursued targets because it plays crucial roles in numerous biological processes, such as energy storage, signal transduction, DNA/RNA polymerization, and muscle contraction, and it controls metabolic processes through participation in various enzymatic reactions [**81**]. A new diethylenetriamine–derived macrocycle reported by Mesquita and co–workers, bearing 2–methylquinoline arms and containing *m*–xylyl spacers (Figure 8), was prepared in good yield by a one–pot [2+2].

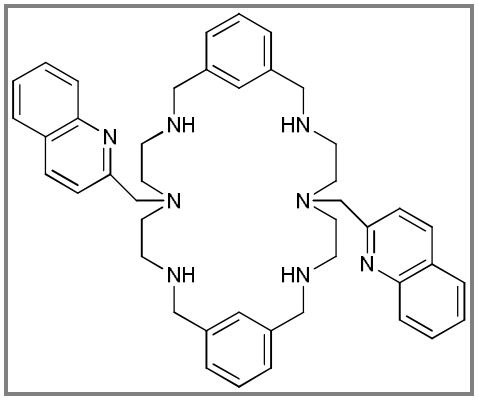


Figure 8. First hexaazamacrocycle with appended 2–methylquinoline arms.

CONCLUSION

As macrocyclic chemistry has established, the variety and space of the applications of these molecules have continued to multiply. These applications paint out a principled picture that macrocycles belong to "privileged" class of molecules for therapeutic intervention, the kind that holds clear answers to the challenges facing modern drug discovery. This review frames out the requests of macrocyclic complexes in world of medicinal chemistry.

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