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Review Article

Macrocyclic Assembly: A Dive into the Pecking Order and Applied Aspects of Multitalented Metallomacrocycles

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To aid in knowledge of macrocyclic complexes and biomedical scientists, we are presenting here a review article with compilation of work done so far along in relation to macrocyclic ligands and their metal complexes. The metal ion chemistry of macrocyclic ligands has now become a major subdivision of coordination chemistry. This overview focuses on developments in design, synthesis, and self-assembly of metal-based architectures and ligands related to macrocyclic chemistry.

1. Introduction and Scope

Macrocycles occupy a unique segment of chemical space. In the past decade, their chemical diversity expanded significantly, supported by advances in bioinformatics and synthetic methodology. As a consequence, this structural type has now been successfully tested on most biological target classes. The goal of this paper is to put into perspective the current applications and opportunities associated with macrocycles [1]. Macrocycles are defined herein as molecules containing at least one large ring composed of nine or more atoms. Macrocycles have several features that make them interesting in efforts to tackle "difficult" targets with extended binding sites [2]. Because of their size and complexity, they can engage targets through numerous and spatially distributed binding interactions, thereby increasing both binding affinity and selectivity. Furthermore, cyclization provides a degree of structural preorganization that may reduce the entropy cost of receptor binding compared to linear analogues [3, 4]. A significant number of macrocyclic drugs are currently on the market, predominantly of natural product origin with complex structures [5]. This paper is dedicated to explore the field of macrocycles and to highlight salient features of their versatile chemistry. Cyclization of a linear molecule into a macrocyclic ring constitutes a significant change in molecular shape. This transformation restricts the degrees of conformational freedom of the molecule and imposes structural organization which was absent in the linear precursor [6]. Since the birth of macrocycles as early as 1936 [7], the field only began to blossom in early 1960s with the pioneering work of Thompson and Busch [8]. In such a large subject, this paper can focus only on certain aspects of macrocyclic chemistry.

Medicinal chemists have long used macrocyclization as a tool in drug discovery. A classic illustration of this technique was the discovery of potent cyclic peptide somatostatin mimics three decades ago [9, 10]. The method of cyclization since then developed into a general paradigm in peptidomimetic drug design that has been widely used in the discovery of biologically active compounds for studying the cell. These macrocycles represent a new class of structures for further development and for future application in high-throughput screening against a variety of biological targets [11]. Recognition of the importance of complexes containing macrocyclic ligands has led to a considerable effort being invested in developing reliable inexpensive synthetic routes for these compounds. These macrocycles which contain varying combinations of aza (N), oxa (O) phospha (P), and sulfa (S) ligating atoms can be tailored to accommodate specific metal ions by the fine-tuning of the ligand design features, such as the macrocyclic hole size, nature of the ligand donors, donor set, donor array, ligand conjugation, ligand substitution, number and sizes of the chelate rings, ligand flexibility, and nature of the ligand backbone. A large amount of data has been

published on macrocyclic ligands containing only nitrogen, only sulphur, or both as donor atoms, namely, tetraaza [12], thiadiaza [13], thiatriaza [14], dithiadiaza [15, 16], or dithiatriaza [17]. However, there is scarce information on thiatetraaza compounds. In fact, only one thiatetraaza macrocycle, 1-thia-4,7,11,14-tetraazacyclohexadecane, was studied [18]. The different types of macrocyclic ligands are particularly exciting because of the importance in generating new areas of fundamental chemistry and many opportunities of applied chemistry. The majority of macrocycles represent creative and focused efforts to design molecules which will have particular uses.

The significance of macrocyclic compounds extends from large number of life composing and naturally occurring complexes with enormous biological functions to vast numbers of synthetically made ones for diverse biological and nonbiological functions [19]. These compounds have been explored for their antibacterial [20], fungicidal [21], anticonvulsant [22], and catalytic [23] activities. The available literature has also evidenced about their antioxidant [24] and anti-HIV activities [25]. These are also used as MRI contrast agents [26]. The thermodynamic and kinetic inertness of transition metal complexes of polyazamacrocyclic ligands have significant industrial application [27].

The family of complexes with macrocyclic ligands has remained a focus of scientific attention for many decades [28]. The chemistry of macrocyclic complexes provide a huge area of research ranging over many areas of chemistry and biochemistry. This review compiles advances in the synthesis and application of macrocyclic ligands and their metal complexes that comprise a linkage between chemistry and biological sciences.

2. Aza Macrocycles

Important chemical, biological, and medicinal problems have been assaulted using azamacrocycles and their metal complexes as useful tools, with significant advances made in a number of these areas. Interest in the smaller triaza macrocycles, ([9]aneN$_3$) (Table 1, Compound 1a) and its variations, has also accelerated in recent years. Added to the simple polyaza macrocycles has been the effort to achieve functionalized macrocycles in order to expand the chemistry of these ligands by combining the rigid structural aspects of the macrocyclic ring with the more flexible and kinetically labile properties of pendant chains. The design and development of artificial receptors able to recognise and sense selectively anionic species has become a prominent and active field of research within the realm of "supramolecular chemistry." A new quinoline pendant arm derivative of [9]aneN3 and its optical response in the presence of transition and posttransition metal ions has been studied. In particular ligand behaves as an efficient OFF-ON fluorescent chemosensor for Zinc(II) in MeCN/H_2O 1 : 1 (v/v) and in pure H_2O at pH 7.0 (Table 1, Compound 1b) [29].

As more advanced chelator design is achieved by Burke and Archibald [30]. Lanthanide(III) complexes of the tacn based ligand (Table 1, Compound 2a) have been shown to be the first fully characterised examples of discrete f-block complexes which can bind sulphur dioxide. Encapsulation occurs with gaseous SO_2 at room temperature and the coordination process was analysed using DFT calculations. The uranium(III) complex of the related hexadentate chelator (Table 1, Compound 2b) can reduce CO_2 to CO and CO_3 using KC_8 as a reductant to engage the catalytic cycle. Nickel(II) and copper(II) complexes of bis-triaza derivatives induce B- to Z-DNA transition by the formation of a macrochelate compound between the dinuclear complexes and the DNA strand, properties which do not occur with the analogous mononuclear triazacyclododecane derivative. Studies of copper(II) tacn derivatives (Table 1, Compound 2c) with a pendant guanidine group show increased rates of DNA cleavage compared with those of the parent tacn complex. Functionalisation of technetium(VII) tacn complex (Table 1, Compound 2d) through a (3+2)-cycloaddition reaction of the technetium-oxide compound has been performed to form M–O–R bonds. This opens up possibilities to form dual functional BFCs when combined with macrocycle N-functionalization. Trisphosphinic acid NOTA derivatives (Table 1, Compound 2e) have been prepared and their complexation properties with gallium(III) explored. Replacement of carboxylic acid arms with phosphinic arms increased selectivity for binding and forms complexes more efficiently. Iron(II) complexes (Table 1, Compound 2f) convert from low spin to high spin upon addition of dithionite and the spin change operates in an aqueous solution altering from a diamagnetic solution to a paramagnetic one with the associated change in longitudinal relaxation of the water molecules that can be observed by MRI experiments.

A series of mono- and di-[12]aneN3 ligands (Table 1, Compound 3a, 3b and 3c) which contain different substituents on the coordinating backbone, different linkers between two [12]aneN3 units, and different *N*-methylation on the [12]aneN3 units have been synthesized and fully characterized by Guo and coworkers. The catalytic activities of their metal complexes on the cleavage of RNA model phosphate 2-hydroxypropyl-*p*-nitrophenyl phosphate (HPNPP) varied with the structures of the ligands and metal ions. Click reactions afforded an efficient method to prepare a series of [12]aneN3 ligands. The results clearly indicate that the structures of the linker between two [12]aneN3 units play very important role in their catalytic synergistic effects [31].

Until recently, the tetraaza macrocycles, such as (cyclam) and related ligands with extensive varieties of modifications including differing degrees of saturation and ring size, had been the most studied (Table 1, Compound 4a and 4b), primarily because of the relationship of these molecules to naturally occurring tetraaza macrocycles, such as the porphyrins and corrins. Currently, with interest in metal-metal interactions, increased activity has occurred in the area of larger macrocycles capable of incorporating more than one metal ion [32].

Naturally occurring azamacrocyclic metal complexes such as haems, chlorophyll, vitamin B_{12}, and the factor F430 carry pendent ring substituents and axial coligands that act as functional components in these important biological systems. Design of related systems with structural features related

Table 1: Aza macrocycles.

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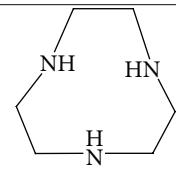
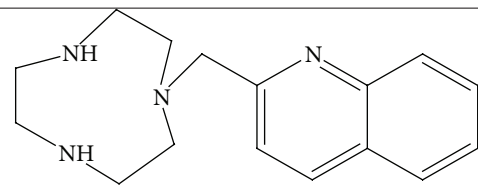
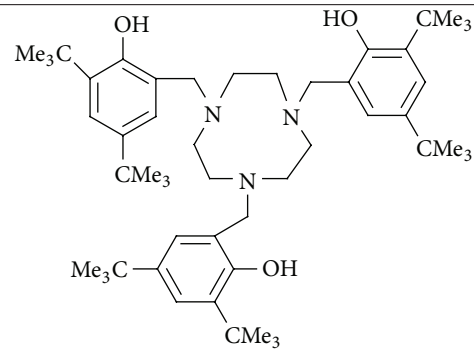
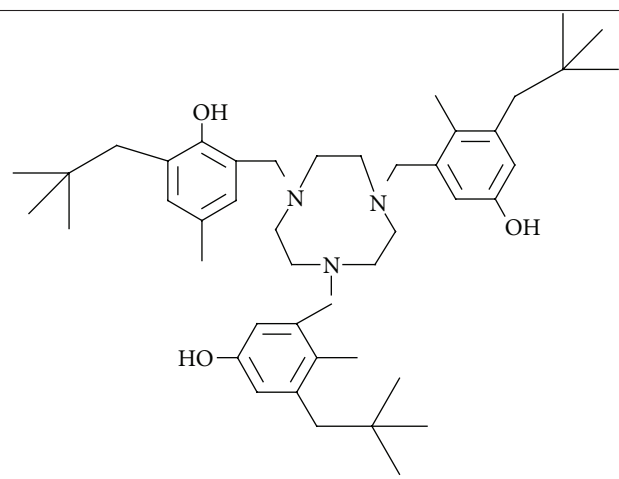
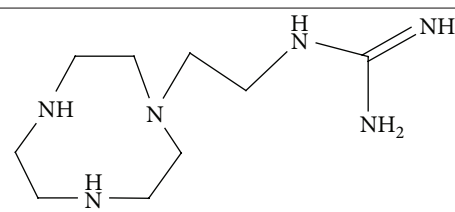
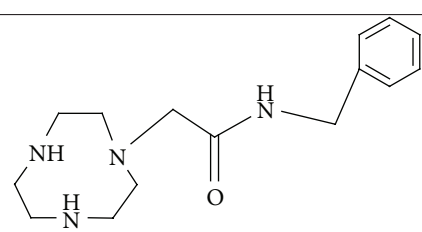
1		1a
2		1b
3		2a
4		2b
5		2c
6		2d

Table 1: Continued.

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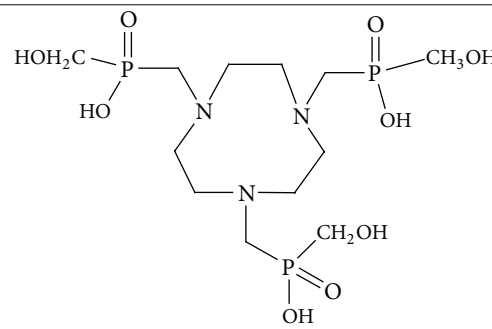
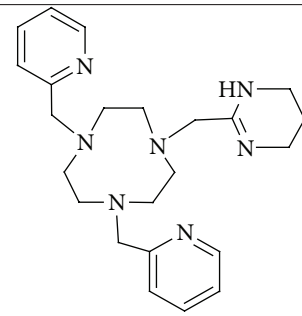
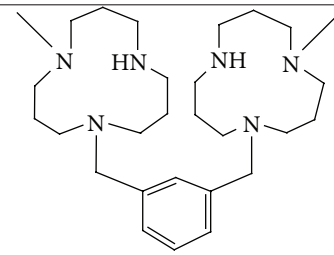
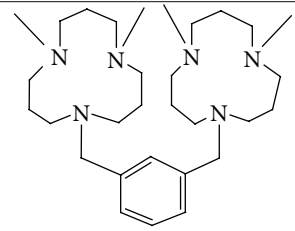
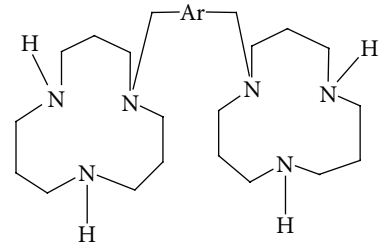
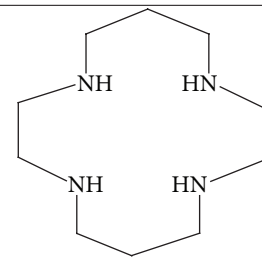
7		2e
8		2f
9		3a
10		3b
11		3c
12		4a

Table 1: Continued.

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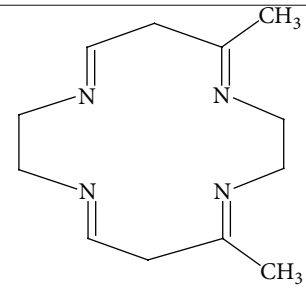
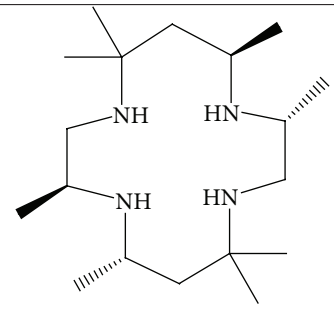
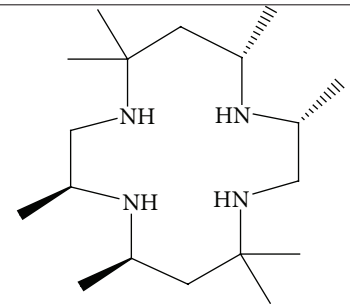
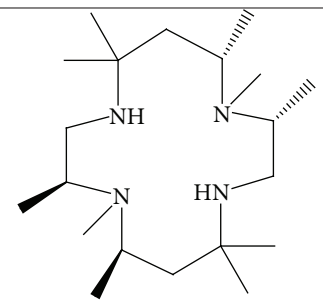
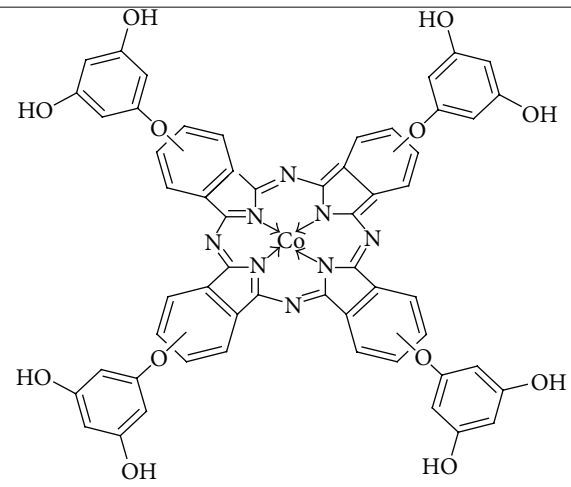
13		4b
14		5a
15		5b
16		5c
17		9a

Table 1: Continued.

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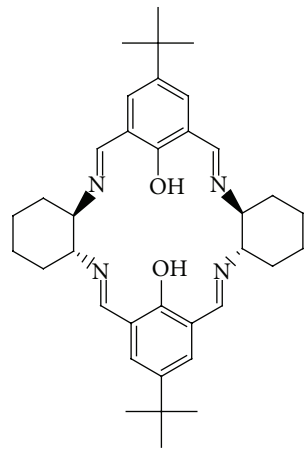
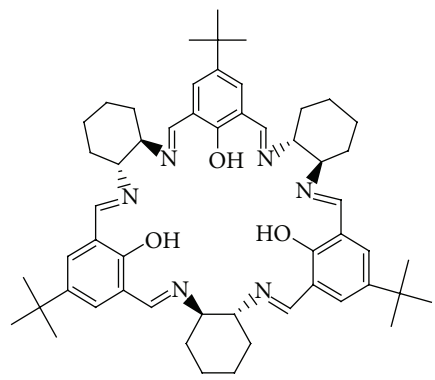
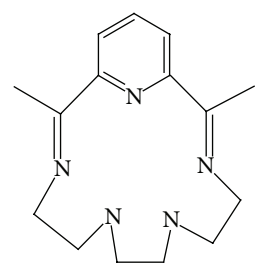
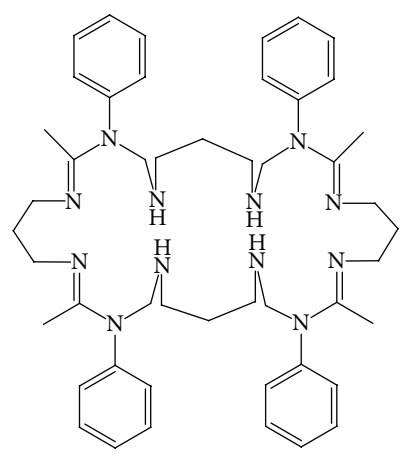
18		7a
19		7b
20		8a
21		8b

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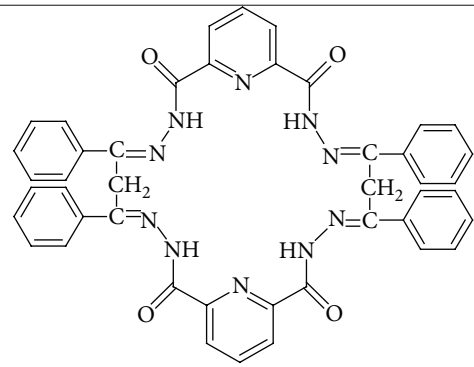
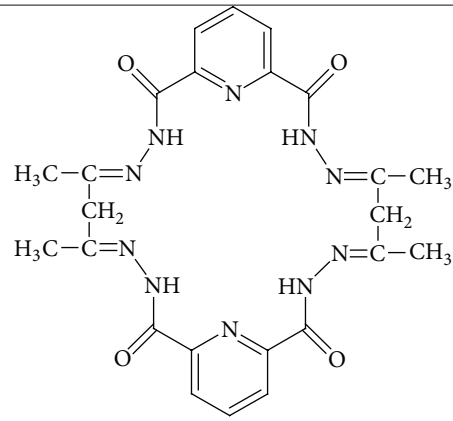
22		6
23		9b

to their natural counterparts has been reported recently. Chen and coworkers [33] characterized the copper complexes of these ligands (Table 1, Compound 5a, 5b and 5c). The compounds exhibit pronounced antimicrobial activity.

Phthalocyanines(Pcs) are 18 p-electron containing macrocyclic conjugated systems consisting of four isoindole units that attract huge interest due to their diverse applications in medicinal and materials chemistry [34]. Metal-free and Co(II)-phthalocyanines carrying eight dodecaborate substituents (96 boron atoms) on the peripheral positions were synthesized in a multistep reaction sequence (Table 1, Compound 6) [35]. Moreover, selective macrocycle formation which has been carried out by reaction of 4-tert-butyl-2,6-diformylphenol with (1R,2R)- or (1S,2S)-1,2-diaminocyclohexane in the presence of 1 equivalent of Zn^{2+} ions leads to selective formation of a chiral 2+2 macrocycle. Application of 0.5 equivalent of Zn^{2+} ions under the same conditions leads to selective formation of a chiral 3+3 macrocycle, which forms a cavitand-shaped trinuclear double-decker complex with Zn(II) (Table 1, Compound 7a and 7b) [36].

A new macrocyclic complex $DyCl_3(LN_5)\cdot 4H_2O$ has been prepared in which the Dy(III) ion is equatorially bound by an N_5-donor macrocycle. Gavey and coworkers implemented the 15-membered macrocyclic ligand LN_5 to promote axial anisotropy in a Dy(III) complex $DyCl_3(LN_5).4H_2O$ and showed that it exhibits SMM-like (single molecule magnets) behaviour in zero field [37]. The metal-templated cyclocondensation reaction of diacetylpyridine with triethylenetetramine in the presence $DyCl_3\cdot 6H_2O$ afforded the desired 15-membered N_5 macrocycle (Table 1, Compound 8a). As reported by Khan [38], reactions of the macrocyclic ligand $[L_2HClO_4]$ with the reactants $[Ir(CO)(Ph_3P)_2Cl]$ and $[RuCl_3(AsPh_3)_2\text{-}CH_3OH]$ produce bimetallic complexes with the stoichiometries $[Ir_2L(Ph_3P)_2Cl(ClO_4)]$ (I) and $[Ru_2LCl_4(ClO_4)_2]$ (II), respectively. The macrocyclic ligand has accommodated both the lower, Ir(I), and higher, Ru(III), oxidation states of metal ions, which shows the flexible nature and capability of macrocycle to form stable complexes (Table 1, Compound 8b). Physicochemical and spectroscopic data of the complexes confirms the encapsulation of two metal ions in the macrocyclic cavities via coordination through nitrogen atoms of the unsymmetrical aza groups, which results in homodinuclear macrocyclic complexes. Schiff bases have also been widely studied and used in the fields of organic synthesis and metal ion complexation for a number of reasons [39, 40]. Macrocyclic hydrazone Schiff bases were synthesized and used as organic chelating agents to extract some metal cations from their aqueous to another organic phase (Table 1, Compound 9a and 9b). The results have established the feasibility of using simple and inexpensive extractants based on hydrazone Schiff bases to extract the heavy metal ions like Cu(II) by controlling their structure from aqueous medium [41]. It is our perspective

that these developments will continue and even intensify, with azamacrocycles assuming an ever more important role in chemistry.

3. Oxa Macrocycles

First group of macrocyclic compounds are crown ethers, which contain oxygen, sulfur, and nitrogen as donor atoms. The first crown ether was synthesized in 1967 by Pedersen, who obtained dibenzo-18-crown-6, which has gained attention for its ability to form stable complexes with metal ions within their central cavity [42]. The recent advances of the crown ethers chemistry were reviewed by few authors [43]. Also acyclic polyethers were found as extractants or ionic carriers. The macrocycle types tend to form stable complexes with metal ions. Such complexes contain species incorporated in the macrocyclic cavity.

Over the past few decades, mechanically interlocked molecules [44–48], such as rotaxanes and catenanes, have become typical candidates in the design of artificial molecular machines. Bistable rotaxanes [49–51], which can change their shapes and properties in response to external stimuli, have important potential to function as molecular switches [52], molecular logic gates [53], and stimuli-responsive materials when functional units are introduced into the rotaxane molecule.

Zhou and coworkers [54] reported the design, preparation, characterization, and properties of a bis-spiropyran-containing [2]rotaxane in which intercomponent transfer interactions can be altered in response to the combination of chemical and photochemical stimuli, along with remarkable UV/Vis absorption and fluorescence spectral changes. The chemical structure of the multistable bis-spiropyran-containing crown ether 2-SP (Table 2, Compound 10).

Recently, Zheng and coworkers [55] have applied the concepts of social self-sorting to pseudorotaxane assemblies and supramolecular pseudorotaxane polymers based on the crown ether/secondary ammonium ion binding motifs. Four monomeric building blocks equipped with one crown ether and one secondary ammonium ion are synthesized and studied with respect to their ability to form daisy chain dimers. Two crown ethers with different cavity sizes, that is, [21]crown-7 (Table 2, Compound 11a) and [24]crown-8 (Table 2, Compound 11b), and two ammonium ions substituted with either a thin alkyl group or a more bulky benzyl group are used as the binding motifs.

Five oxonium tetrahalogenaurate(III) (Hal = Cl, Br) benzo-crown ether (BCE) complexes (Table 2, Compound 12a and 12b) are prepared and reported by Pluzhnik-Gladyr and coworkers [56]. All compounds form the laminated structures with alternation of cationic and anionic layers. The robustness of the anionic sheets is sustained by the halogen-halogen interactions and makes crucial impact on extraction of stoichiometric products in the case of tetrabromoaurate(III) salts.

Zhou et al. [57] developed new efficient method for synthesizing macrocyclic aryl ethers from diiodoarenes (dibromoarenes) and diphenols catalyzed by copper/iron in one step because such kind of macrocycles (Table 2, Compound 13a–13i) may be used as new electron-rich receptors for molecular recognition or for assembling new interlocked supramolecular architectures. The new methodology has the advantages of higher yields, more generality, and simpler and cheaper catalyst system [58].

4. Polythia, Polyphospha, and Polyarsa Macrocycles

The transport of cations through supported liquid membrane mediated by neutral carriers can be regarded as a sequential process including phase transfer of salt, complexation/decomplexation, and diffusion steps. Nezhadali and Akbarpour [59] reported the preparation of polymer membrane and its selectivity to silver(I) ion from an aqueous solution containing seven metal cations, Co(II), Ni(II), Cu(II), Zn(II), Ag(I), Cd(II), and Pb(II), was studied. The effect of variation in the number of the macrocyclic sulfur atom donor set and the size of ring 9 (Table 3, Compound 14a) and 16 member macrocycles (Table 3, Compound 14b) on transport efficiency is presented. Silver(I) ion transport occurred (at 25°C) from the aqueous source phase across the polymer membrane (derived from cellulose triacetate) containing ligands 9-membered, S3-donor, and 16-membered S4-donor macrocycles as the ionophores in separate experiments to the aqueous receiving phase. Clear transport selectivity for silver(I) ion was observed using both thioether donor macrocycles. The efficiency of transport rate for silver(I) ion with using 9-membered S3-donor macrocycle as carrier was better than 16-membered S4-donor.

As dynamic covalent components, disulfides are ubiquitous in nature and have been shown to be effective partners in template supramolecular systems (Table 3, Compound 15) [60]. Cyclic disulfide macrocycles were rapidly synthesized cleanly and selectively from rigid dithiols via oxidation with iodine when activated by pnictogen additives (As and Sb) [61].

Polythia macrocycles have been found to complex a variety of transition metals but have not received the same attention as the more readily accessible polyaza and polyoxa macrocycles. Polythia macrocycles [62] are the thioether analogs of the crown ethers (Table 3, Compound 16). These are the most extensively studied macrocycles in line after the polyoxa and polyaza macrocycles.

Phosphorus macrocycles can exist in a variety of conformations, a number of which are stable. The barrier for inversion of phosphate is 146.4 kJ mol^{-1}; hence there are five conformations possible for the tetraphosphorus macrocycle (Table 3, Compound 17) [63]. The polyarsa macrocycles (Table 3, Compound 18) comprise one of the least common types of macrocycles.

5. Mixed Macrocycles

There is a growing interest in a large macrocyclic ligand system that can form binuclear complexes exhibiting electron

Table 2: Oxa macrocycles.

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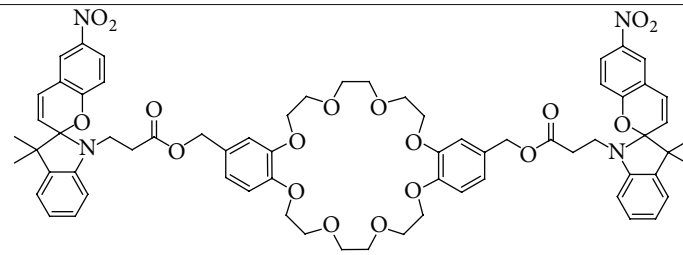
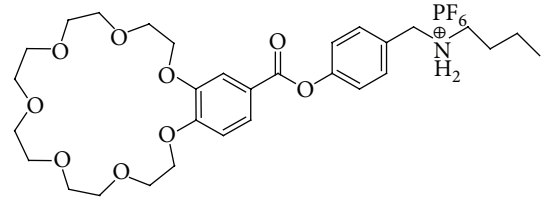
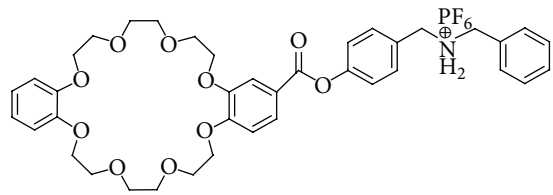
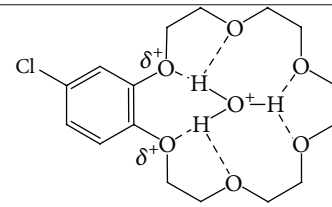
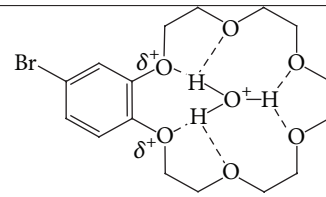
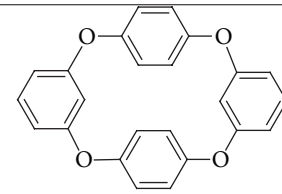
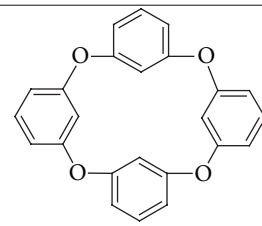
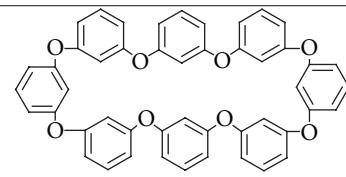
1		10
2		11a
3		11b
4		12a
5		12b
6		13a
7		13b
8		13c

Table 2: Continued.

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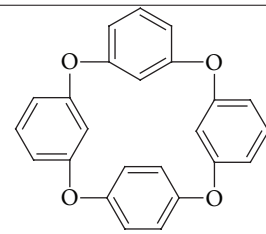
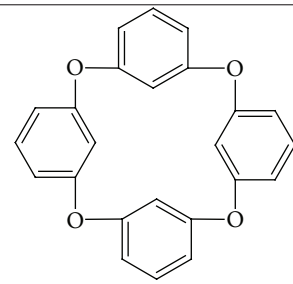
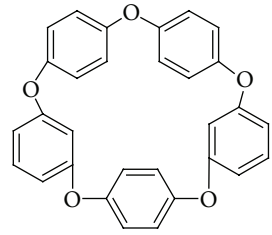
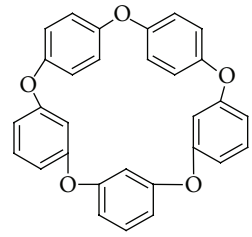
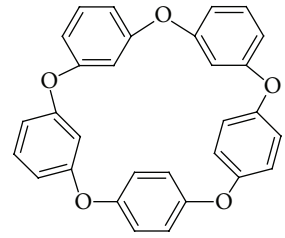
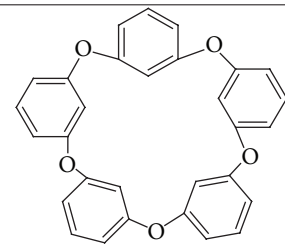
9		13d
10		13e
11		13f
12		13g
13		13h
14		13i

transport, charge transfer, and allosteric behaviour. Hydrazones are special group of compounds in the Schiff bases family. They are characterized by the presence of (C=N–N=C). The presence of two interlinked nitrogen atoms was separated from imines, oximes, and so forth and hydrazone Schiff bases of acyl, aroyl, and heteroaroyl compounds have additional donor sites like C=O. The additional donor sites make them more flexible and versatile (Table 4, Compound 19a–19c). This versatility has made hydrazones good polydentate chelating agents that can form a variety of complexes

Table 3: Polythia, polyphospha, and polyarsa macrocycles.

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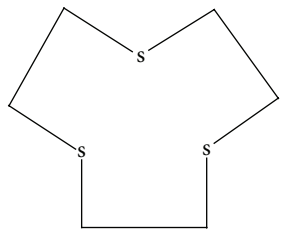
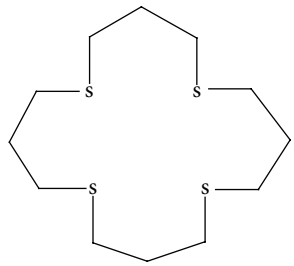
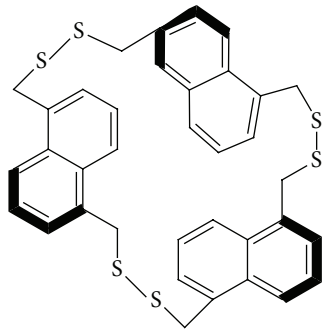
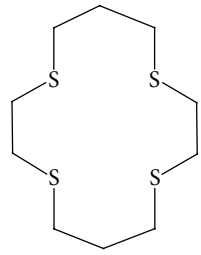
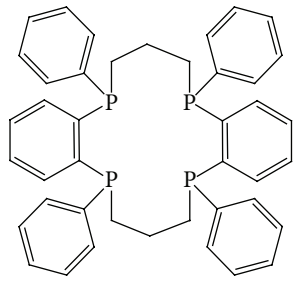
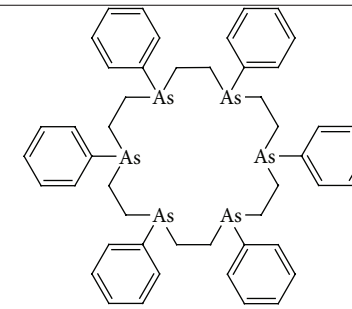
1		14a
2		14b
3		15
4		16
5		17

Table 3: Continued.

S. no.	Structure	Compound
6		18

with various transition and inner transition metals and have attracted the attention of many researchers. Such complexes have been presented [64].

A new system made of cerium ion(III) and an aza-crown ether ligand was constructed and used as catalyst or the phosphate ester hydrolysis. An aza-crown ether ligand, 4,7,13,16-tetraethoxycarbonylmethyl-1,10-dioxa-4,7,13,16-tetraaza-18-C-6 (Table 4, Compound 20) was synthesized and characterized in this work by Lee and coworkers [65].

Design and synthesis of new macrocyclic ligand systems capable of forming binuclear complexes have received considerable attention. A 20-membered $N_2O_2S_2$ macrocycle (L^1) (Table 4, Compound 21a) and a 40-membered $N_4O_4S_4$ macrocycle (L^2) (Table 4, Compound 21b) obtained from the mixed products via respective [1:1] and [2:2] cyclization are employed and a comparative investigation of the coordination behaviour of these macrocyclic ligands with nickel(II), cadmium(II), and silver(I) is reported [66].

Reduction of such Schiff base species sometimes provides the synthesis of large flexible macrocycles comprising di- or multinuclear binding sites. For the non-Schiff base type macrocycles including the cyclam and related large ring types, a number of dinuclear transition metals and silver(I) complexes have been known [67].

The increasing interest in the molecular recognition properties of naturally occurring macrocycles has attracted much attention in the design and synthesis of new cyclic polyaza and polyoxa macrocycles [68]. Some new oxygen-sulfur, multibenzo macrocyclic ligands (Table 4, Compound 22a–22e) containing amide groups have been prepared using the macrocyclization process with the reaction of 2, 2-thiobis-[4-methyl(2-aminophenoxy)phenyl ether] as a symmetrical diamine with appropriate dicarboxylic acid dichlorides in moderate yields. This macrocyclization led to the formation of di- and tetramide macrocycles. These reactions were routinely carried out at ambient temperature in CH_2Cl_2 as solvent in high dilution without template effect conditions. It is found that sulfur atom affects the rigidity of the macrocycles and diastereotopicity of nuclei in the ring of these series of macrocyclic compounds [69].

Studies on complexes with synthetic macrocyclic ligands have received a new impetus since the discovery of the natural molecules. Nasman [70] has synthesized a novel series of 15-membered diaza-dithiamacrocyclic complexes

Table 4: Mixed macrocycles.

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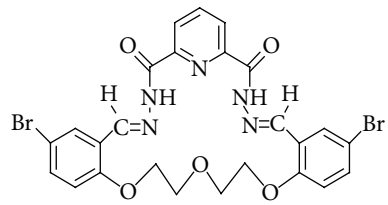
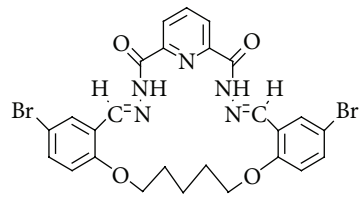
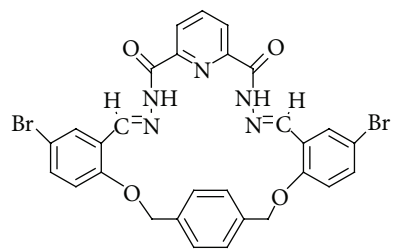
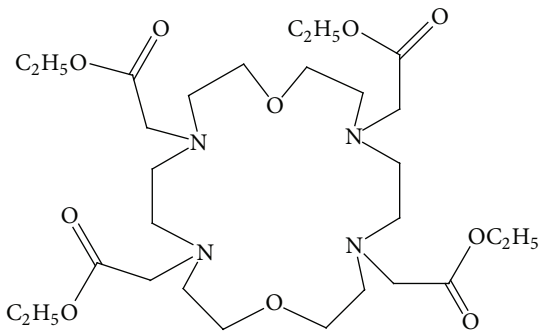
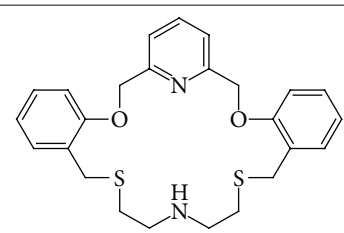
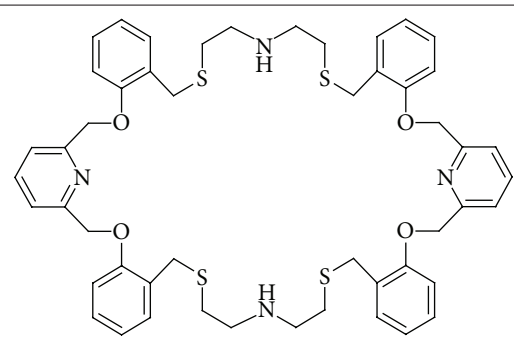
1		19a
2		19b
3		19c
4		20
5		21a
6		21b

Table 4: Continued.

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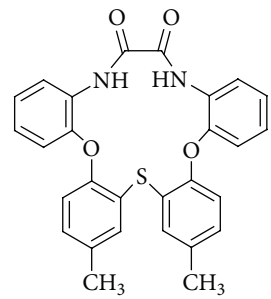
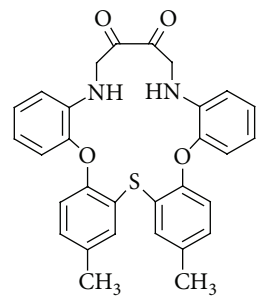
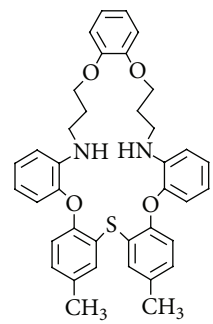
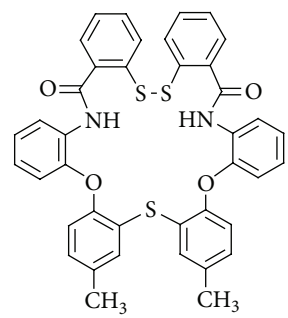
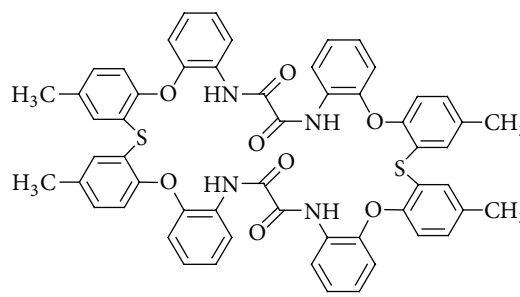
7		22a
8		22b
9		22c
10		22d
11		22e

Table 4: Continued.

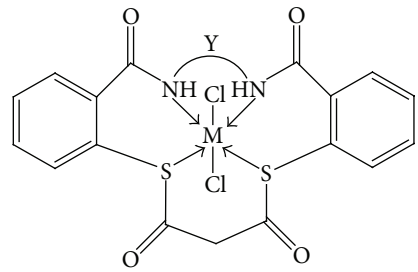
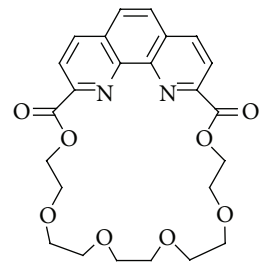
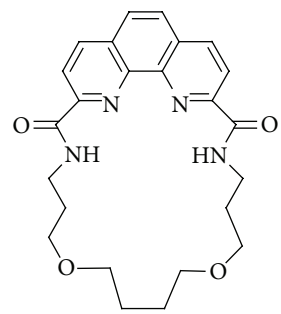
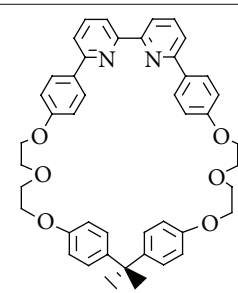
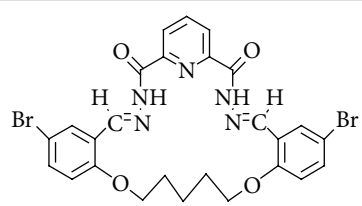
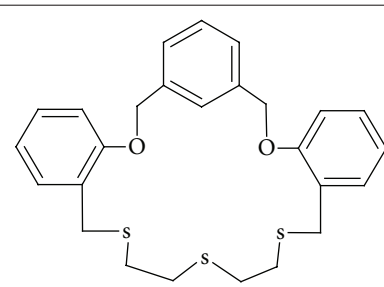
S. no.	Structure	Compound
12		23
13		24a
14		24b
15		24c
16		25a
17		25b

Table 4: Continued.

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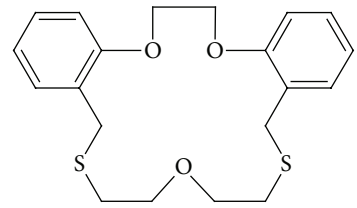
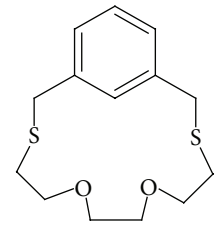
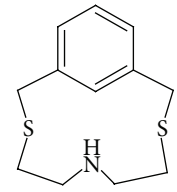
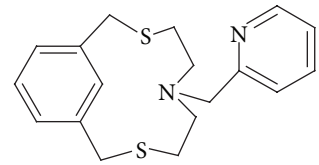
18		25c
19		25d
20		26a
21		26b

(ML_1Cl_2) and (ML_2Cl_2) (M = Fe, Co, Ni, Cu, and Zn) by the template condensation reaction of o-thiosalicylic acid with aliphatic or aromatic diamines and diethyl malonate in the presence of transition metal ions in alcoholic medium (Table 4, Compound 23). The resultant complexes may have wide applicability. It should prove useful for investigating complexes of a range of other ligand types, as well as for the study of metal-containing biological molecules such as metalloenzymes, in addition to their catalytic activity for important industrial applications.

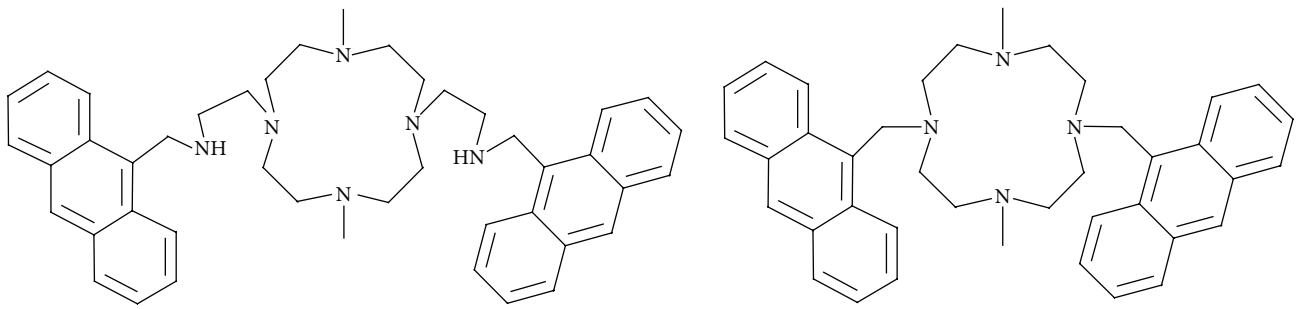
A recent study describes how the use of the α-diimine-containing macrocycles (Table 4, Compound 24a–24c), incorporating different ring sizes, can be employed to moderate the degree of $(CuI)_n$ aggregation in the solid state. Reaction of an excess of CuI with 24a, 24b, or 24c in acetonitrile followed by slow diffusion of ether into the respective solutions yielded complexes [71].

Two silver(I) complexes, $[Ag_2(L^3)_2(ClO_4)_2]\cdot CH_2Cl_2\cdot CH_3OH$ [18] and $[Ag_2(L^3)_2(NO_3)_2]\cdot 2CH_3CN$ [19] incorporating the respective 18-membered (Table 4, Compound 25a) and 20-membered (Table 4, Compound 25b) tribenzo-O_2S_2 macrocycles, have been reported; both complexes exhibit cyclic dimer structures. Two exo-coordinated cyclic dimer platinum(II) complexes incorporating the mixed oxa-thia macrocycles (Table 4, Compound 25c and 25d), incorporating 17- and 15-membered rings, respectively, have also been reported. In each complex thiaphilic platinum adopts its preferred square-planar coordination geometry and both complexes are unusual in that their structures incorporate hydrogen bonded solvent molecules that link the macrocycle pairs [72].

Three NS_2-donor macrocycle isomers including a metai-somer (Table 4, Compound 26a) which show a leaf-shaped 1D network structure on complexation with mercury(II) halides have been reported. Metallosupramolecules based on compound 26a and the limited research in the area of the N-pivot thiamacrocycles so far has prompted Park et al. [73] to investigate the coordination behaviors of L_2 (Table 4, Compound 26b) in which one *ortho*-type pyridine side arm is attached to tertiary amine nitrogen (N_{tert}) of the parent macrocycle. They have reported the synthesis and structural characterization of the three mercury and one copper complexes of 26b.

6. Synthetic Routes

The introduction and literature survey parts revealed that synthetic macrocycles and their macrocyclic complexes in



1 2

Figure 1: Anthryl-appended macrocycles.

general and polyazamacrocycles in particular could play essential roles in diverse chemical and biological processes [74, 75]. Macrocyclic ligands or their complexes can be generally synthesized by three general methods developed so far. These are

(i) the high dilution technique under a high dilution apparatus with solvents under high temperature and inert atmosphere,

(ii) the use of rigid groups such as dicyclohexylcarbodiamide, DCC, and DMAP to restrict the rotation in open chain precursors,

(iii) the metal template effect method in which the presence of especially transition metal ions promotes the macrocyclic formation by its orthogonal d-orbital directing effect.

The first two methods are used for synthesis of free macrocyclic ligands. The metal template effect method is an effective and more effective and more selective method than the other for the synthesis of macrocyclic complexes and involves an in situ approach where in the presence of metal ions in the cyclisation reaction markedly increases the yield of the products [76, 77]. The metal ion plays an important role in directing the steric course of reaction preferentially toward cyclic than oligomeric or polymeric and stabilized the macrocycles once formed.

7. Applications

Research and clinical applications for metallomacrocycles are bound to their broad biological presence, including light-gathering processes, metal catalyzed reductions, and semiconductive properties. The biological applications have been well documented in numerous reviews. The literature clearly shows that the study of this diverse ligand system is linked with many of the key advances made in inorganic chemistry.

7.1. Biomimmics. The great interest in synthetic macrocycles and their corresponding metal complexes is related to the fact that they can mimic naturally occurring macrocyclic molecules in their structural features. The formation of macrocyclic complexes depends significantly on the dimension of the internal cavity, on the rigidity of the macrocycle, on the nature of its donor atoms, and on the complexing properties of the counter ion [78].

There is a tremendous interest in exploring new ligand environments for transition and main group metal chemistry as well as for developing synthetic mimics of biological systems. The study of synthetic macrocyclic compounds is an important area of chemistry in view of their presence in many biologically significant naturally occurring metal complexes. Macrocyclic complexes have received special attention because of their presence in many important biological systems, for example, metalloporphyrins (hemoglobin, myoglobin, cytochromes, chlorophylls), corrins (vitamin B12), antibiotics (valinomycin, nonactin), and so forth. The design and synthesis of anion-selective sensors have received considerable attention owing to the presence of multiple and various anionic species in both inorganic applications and biological systems [79–82]. Huang and coworkers [83], in their work, two anthryl-appended macrocycles 1 and 2 were synthesized, and their binding abilities toward transition metal ions were studied. Both of them show selectivity for Zn(II) over other metal ions (Cd(II), Co(II), Ni(II), and Cu(II)) by observed changes in their fluorescent spectra. In particular, ligand 1 exhibits a remarkable enhancement in excimer emission by coordination with Zn(II), whereas for 2, no excimer emission evolved. So, 1-Zn(II) was chosen as an anion receptor to study its recognition ability in neutral aqueous solution, as the unique excimer behavior can be exploited during anion sensing. Complex 1-Zn(II) was chosen as a fluorescent sensor for anion recognition, as it exhibits excellent selectivity for ATP in neutral aqueous solution (Figure 1).

Significant efforts have been made to explore the reaction mechanisms of the solvolytic cleavage of phosphate esters mediated by natural enzymes [84–89] and some metal complexes [90–98]. The hydrolysis mechanisms of phosphate monoester NPP promoted by unsymmetrical bivalent dinuclear complexes have been explored. The form of the active catalyst has been verified, and the metal-bound ion acts as the nucleophilic reagent. The binding modes of the catalyst substrate complexes were also explored by Zhang and coworkers [99] (Figure 2).

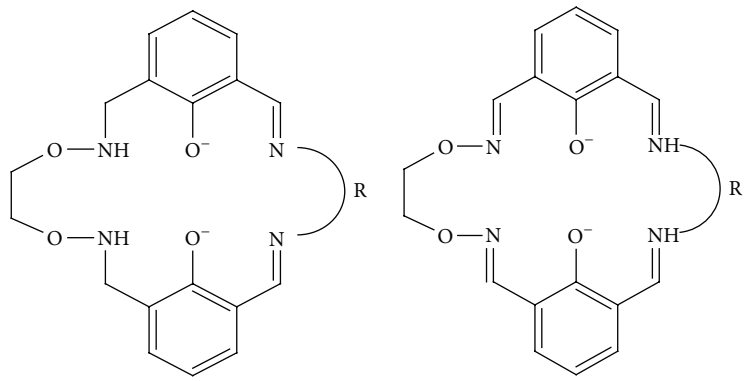


Figure 2: Bivalent dinuclear complexes.

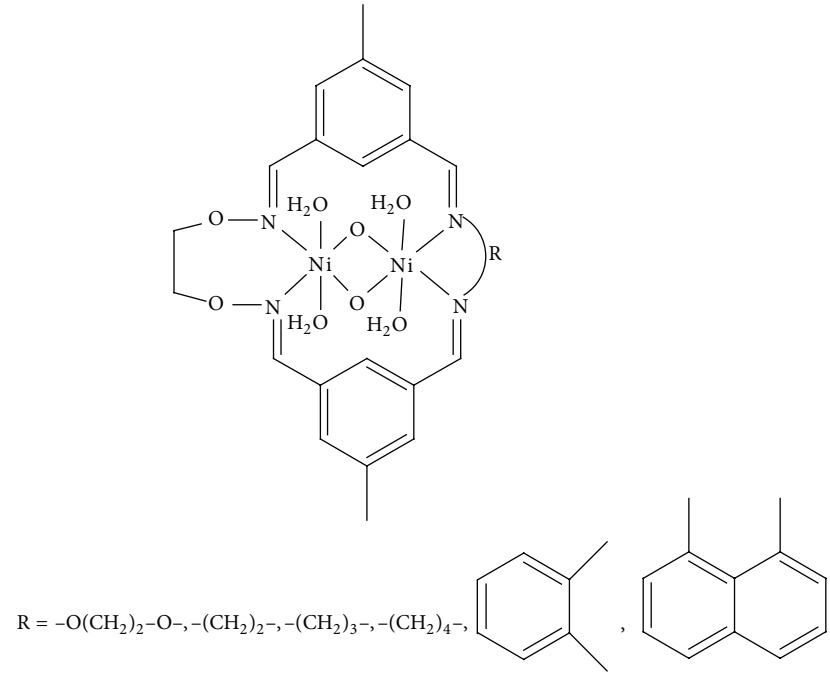


Figure 3: Macrocyclic binuclear nickel(II) complexes.

Nickel(II) complexes of a macrocyclic ligand containing mixed donors have attracted much attention because they are used as a model for nickel centred enzymes such as bifunctional carbon monoxide dehydrogenase/acetyl-CoA synthase, nickel containing superoxide dismutase, urease, and phosphatase. New macrocyclic binuclear nickel(II) complexes (Figure 3) have been synthesized by using the bicompartmental mononuclear complex with various diamines. The complexes can cleave the DNA through hydrolytically, because a classical radical scavenger, such as dimethyl sulfoxide (DMSO), was completely ineffective in the cleavage activity [100].

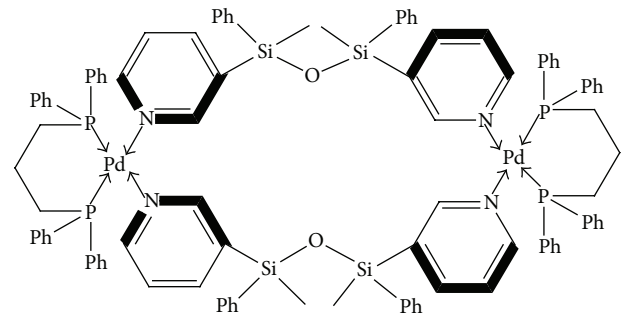


Figure 4: Ionic macrocyclodimeric palladium(II) complex.

7.2. Ion Transport. Three dimensional cation binding with the armed macrocycles is one of the important topics not only in the area of the ion transport but also in the construction of new metallosupramolecules [101]. Ionic macrocyclodimeric palladium(II) complex, $[(dppp)Pd(m\text{-}pmps)]_2(CF_3SO_3)_4$ (dppp = 1,3-bis(diphenylphosphino)propane; m-pmps = 1,3-bis(3-pyridyl)-1,3-dimethyl-1,3-diphenyldisiloxane) (Figure 4), was synthesized. Metallacyclodimer was constructed and it is sensitive to metallophilicity of the polyatomic

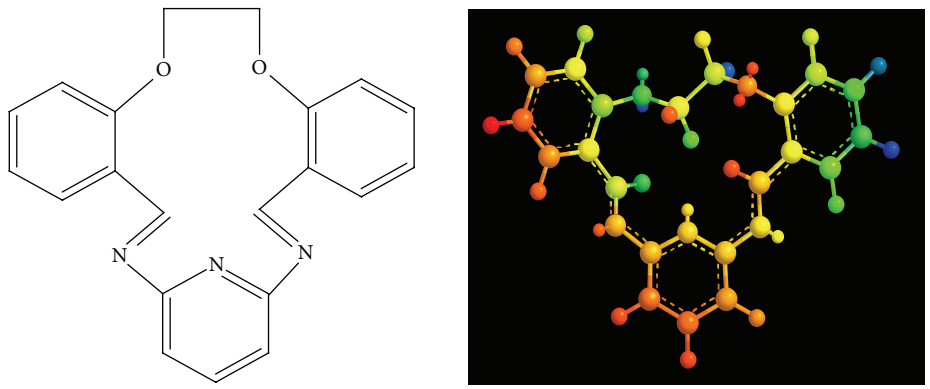


Figure 5: 1,12,14-Triaza-5,8-dioxo-3(4),9(10)-dibenzoyl-1,12,14-triene.

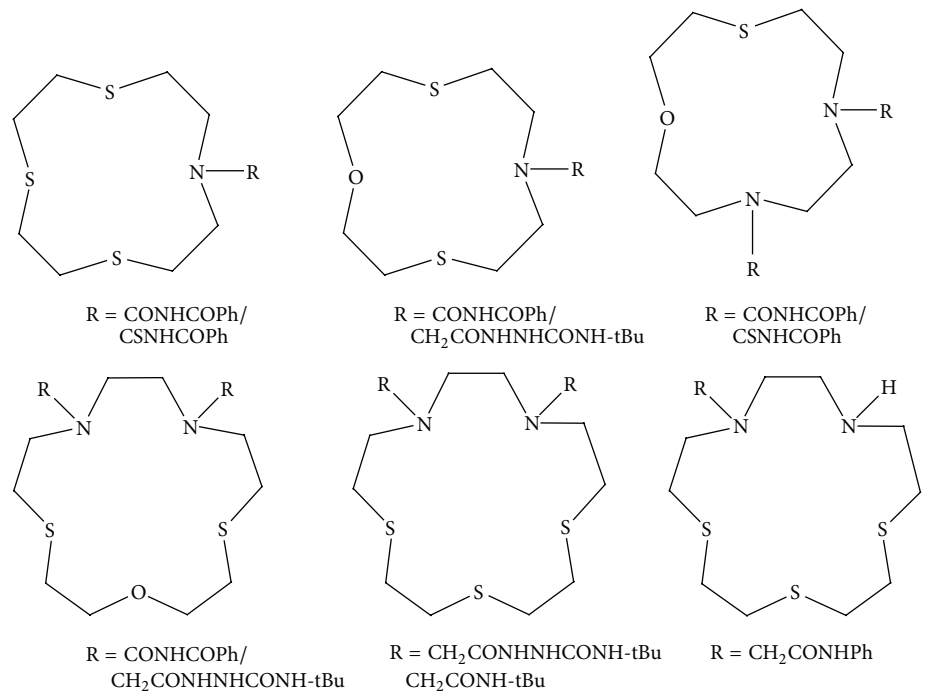


Figure 6: Pendant arm aza-thioether macrocycles.

anion. These results contribute to the delicate modulation of metallacyclic receptors and anion recognition, in addition to anion sensor, anion transport, and molecular switching [102].

Chandra and Singh [103] have used 1,12,14-triaza-5,8-dioxo-3(4),9(10)-dibenzoyl-1,12,14-triene as an excellent ion carrier to construct a highly selective electrode for determination of zinc ion (Figure 5).

A series of pendant arm aza-thioether macrocycles containing hydrogen-bonding amide functionalities have been synthesised of [12]aneS_3N–CONHCOPh, [12]aneS_3N–CSNHCOPh, [12]aneS_2ON–CONHCOPh, [12]aneS_2ON–CH_2CONHCONH– tBu, [15]aneS_2ON_2–(CH_2CONHCONH–tBu)$_2$, and [15]aneS_3N_2–(CH_2CONHPh)$_2$ which are presented in Figure 6. Membrane and liquid-liquid extraction experiments have shown that these systems are highly selective for Ag(I) over a range of other metal ions [104].

Two new macrocyclic ligands, containing nitrogen and sulfur donor atoms, were designed and synthesized in a multistep reaction sequence (Figure 7). The macrocycles with amide group were used in solvent extraction of picrates of metals such as Ag^+, Hg^{2+}, Cd^{2+}, Zn^{2+}, Cu^{2+}, Ni^{2+}, Mn^{2+}, Co^{2+}, and Pb^{2+} from aqueous phase to the organic phase. Ligand A and B showed high transfer of Ag^+, Hg^{2+} ions from the aqueous phase to the dichloromethane and chloroform phase, when compared to the other ions. However, compound B shows higher selectivity than compound A towards Ag^+ and Hg^{2+} ion [105].

7.3. Catalysis. Transition metal complexes in which the ligands are able not only to influence the physicochemical properties, the reactivity, and the stability of the metal centre but also to exert a function in their own right have nowadays

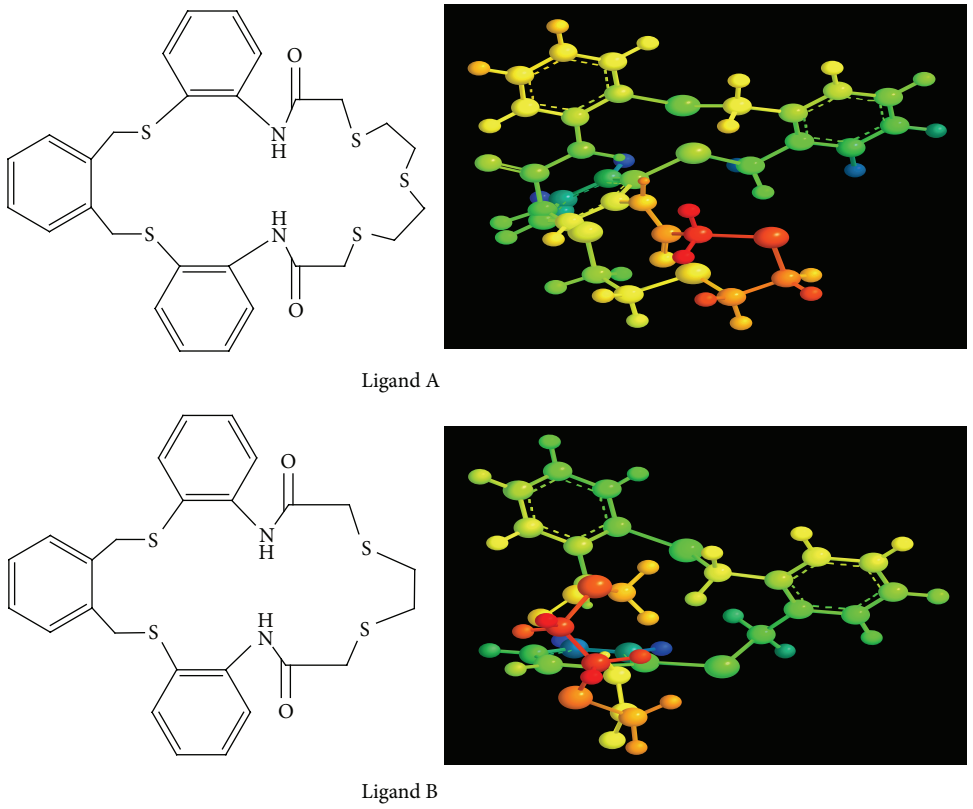


Figure 7: Macrocyclic ligands, containing nitrogen and sulfur donor atoms.

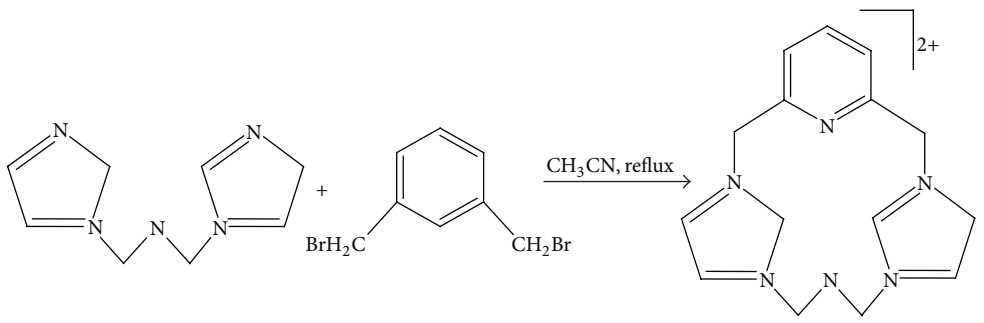


Figure 8: The pyridyl group exerts a positive effect on the catalytic efficiency of the complexes in standard Sonogashira reactions.

come to the forefront of organometallic and coordination chemistry research. Such "noninnocent" ligands can, for example, act as an electron relay toward the metal centre (redox-active ligands), take up an active role in a catalytic event promoted by the metal complex (cooperative catalysis), or more simply provide a handle for the construction of more complicated structures such as higher nuclearity metal complexes and clusters, supramolecular systems, or metal organic frameworks [106–110].

Palladium(II) and platinum(II) complexes of the title ligands have been prepared (Figure 8), the two carbene moieties of the ligand coordinate to the metal in cis fashion, while the bridging pyridyl group remains outside the metal coordination sphere but close to the metal centre. The presence of the pyridyl group exerts a positive effect on the catalytic efficiency of the complexes in standard Sonogashira reactions [111].

A new tri-linked aza-crown macrocycle (L2) was synthesized from monomacrocycle analogue (L1) by Williamson etherification (Figure 9). This work is a good example of the design of multinuclear complexes for artificial nucleases and DNA cleavage. The trinuclear zinc(II) complex displayed good hydrolytic activity for phosphate diester [112].

A new fourth-generation poly(propylene imine) dendrimer (G4-M) containing 32 triolefinic 15-membered macrocycles on the surfaces has been reported. Using new

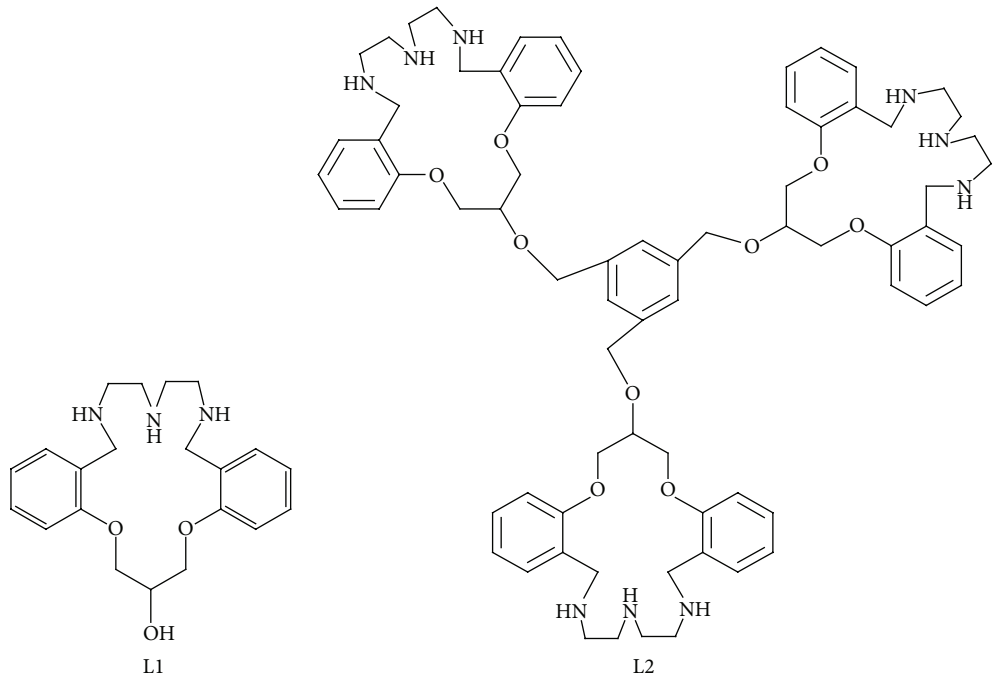


Figure 9: Tri-linked aza-crown macrocycle (L2) was synthesized from monomacrocycle analogue (L1) by Williamson etherification.

dendrimers with triolefinic 15-membered macrocycles at the end of the dendron as stabilizers for preparing metallic nanoparticles provides the advantage of minimal surface deactivation for catalytic applications [113].

7.4. Magnetic Resonance Imaging. Magnetic resonance imaging (MRI) is a diagnostic technique widely used in radiology to obtain detailed images of the body. The so-called contrast agents (CAs) are paramagnetic compounds that increase the contrast between the specific tissue or organ of interest and the surrounding tissues of the body. There is increasing interest in paramagnetic coordination complexes that create magnetic resonance imaging (MRI) contrast through their effect on ligand proton chemical shifts. Such contrast agents include paraCEST (paraCEST = paramagnetic chemical exchange saturation transfer) agents as well as paramagnetic complexes that have temperature or pH sensitive proton resonances used for chemical shift imaging (paraCSI = paramagnetic chemical shift imaging) [114–117]. Fe(II) macrocyclic complexes are a relatively new addition to the class of MRI contrast agents that function through paraCEST (paramagnetic chemical exchange saturation transfer) or paraCSI (paramagnetic complex chemical shift imaging) [118] (Figure 10).

Lack of noninvasive methods to track cells with whole-body and real-time capability is therefore unmet clinical needs. Super Paramagnetic Iron-Oxide Nanoparticles (SPION) have been successfully used as magnetic resonance imaging (MRI) contrast agents for high resolution imaging of cells without substantial impact on cell viability. While MRI of SPION-labeled cells have been used for investigating preidentified site, for example, engrafted tumor, it lacks the sensitivity for systemically infused cells and whole-body assessment. 64 Cu-based PET has been used to track cells up to 48 hrs.

Most of the compounds that entered into clinical practice as CAs are Gd^{3+} complexes of poly(aminocarboxylate) ligands. Indeed, increasing attention has been devoted recently to Mn^{2+} complexes of certain macrocyclic polyamines and their acetate, phosphonate, or phosphinate derivatives as possible substitutes for Gd^{3+} complexes [119].

The synthesis of the ligand Hnompa (6-((1,4,7-triazacyclononan-1-yl)methyl)picolinic acid) and a detailed characterization of the Mn^{2+} complexes formed by this ligand and the related ligands Hdompa (6-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)picolinic acid) and Htempa (6-((1,4,8,11-tetraazacyclotetradecan-1-yl)methyl)-picolinic acid) Figure (11) have emerged by Molnár and coworkers [120].

7.5. Antitumour Agents. The biggest change in drug development, particularly in the anticancer field, is moving away from cytotoxic to molecularly targeted agents, though related changes have occurred in most areas of drug development [121]. Though highly effective in treating a variety of cancers, the cure with cisplatin is still limited by dose-limiting side effects and inherited or acquired resistance phenomena, only partially amended by employment of new platinum drugs. Therefore, attempts are being made to replace these platinum-based drugs with suitable alternatives and numerous metal complexes are synthesized and screened for their anticancer activities [122].

Apoptosis as a form of programmed cell death is one of the major mechanisms of cell death in response to cancer therapies. Its deregulation, that is, either loss of proapoptotic

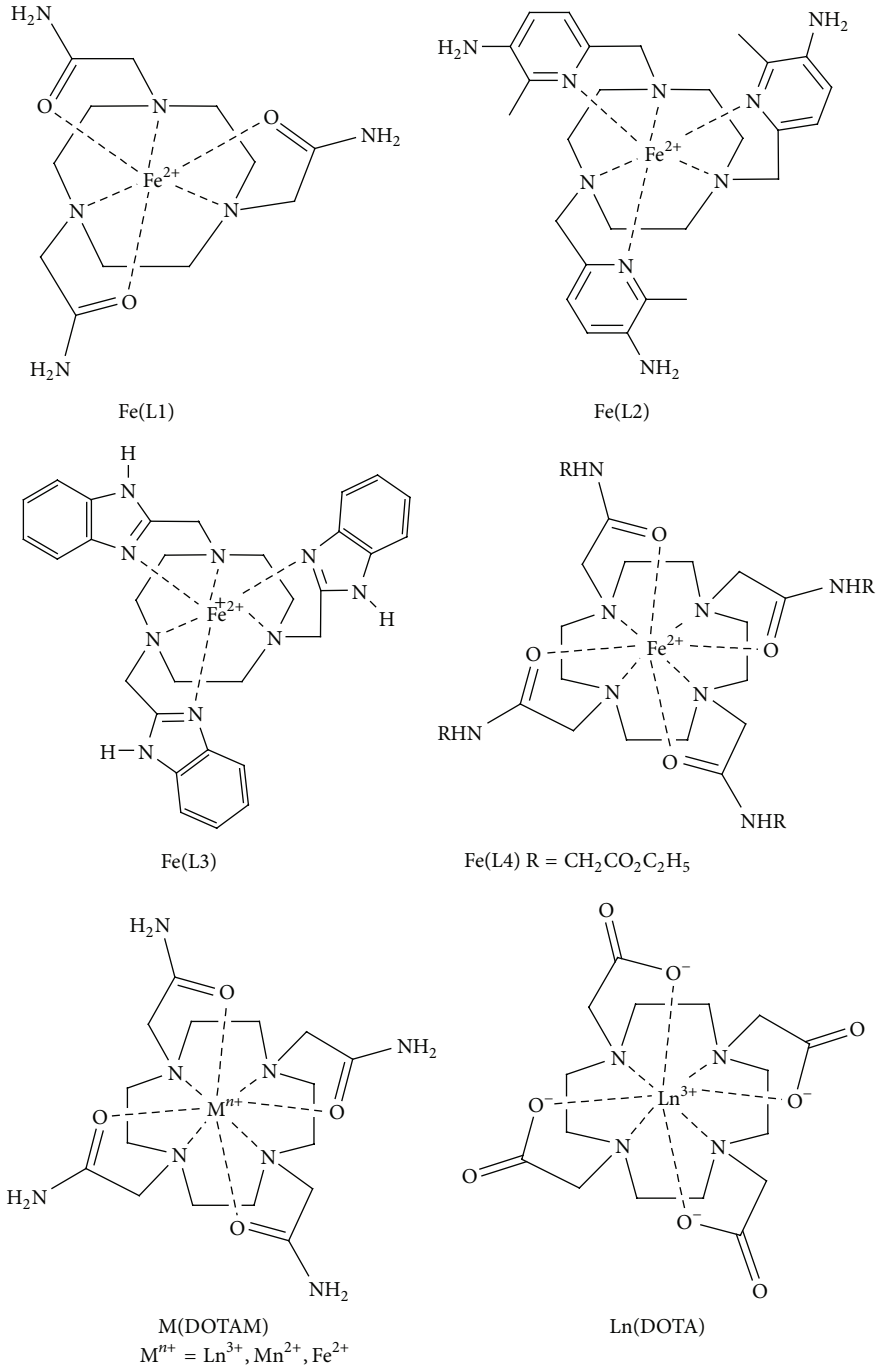
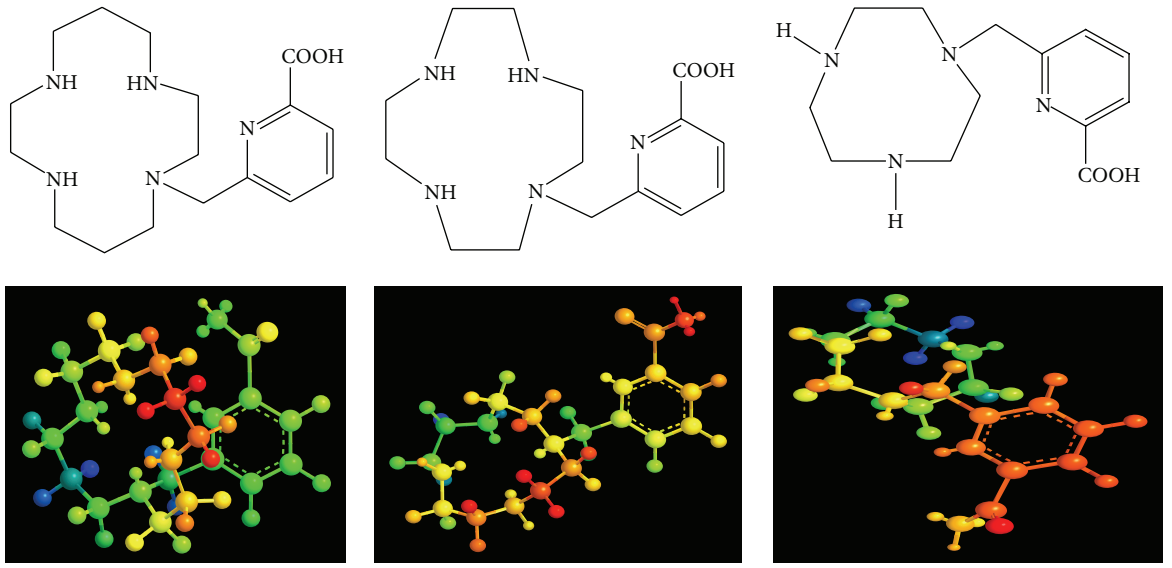


Figure 10: Class of MRI contrast agents that function through paraCEST.

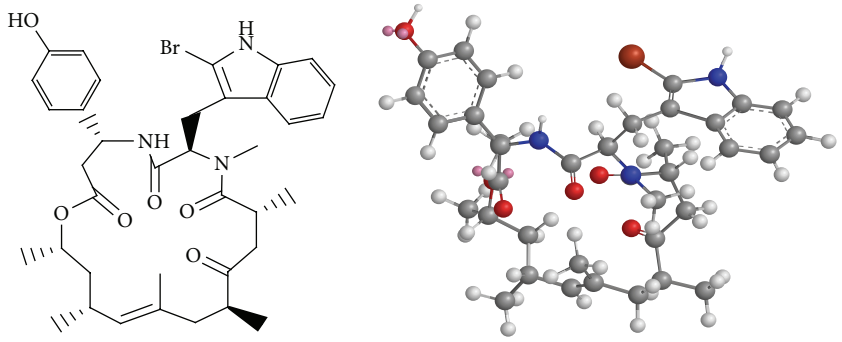
signals or gain of antiapoptotic signals, can lead to a variety of pathological conditions such as cancer initiation, promotion, and progression or results in treatment failures [123]. Zheng et al. [124] summarizes several marine peptides, based on their effects on apoptotic signaling pathways (Figure 12).

A wide repertoire of Zn(II) complexes have been utilized as radioprotective agents, tumor photosensitizers, antidiabetic insulin-mimetic, and antibacterial or antimicrobial agents. Also, certain ZnII complexes, which strongly bind and cleave DNA, exhibit prominent anticancer activities and regulate apoptosis. A symmetrical macrocyclic dizinc(II) complex has been synthesized by using the ligand (L1). A series of unsymmetrical macrocyclic dizinc(II) complexes (2–6) has been synthesized (Figure 13). The ligand L1, dizinc(II) complexes 1, 3, and 6 showed cytotoxicity in human hepatoma HepG2 cancer cells. The results demonstrated that 6, a dizinc(II) complex with potent antiproliferative activity, is able to induce caspase-dependent apoptosis in human cancer



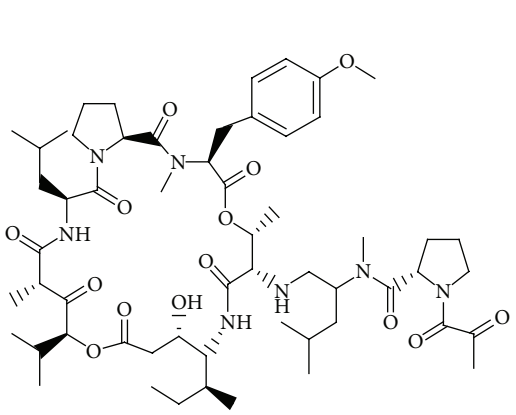
Htempa Hdompa Hnompa

FIGURE 11: Ligand Hnompa (6-((1,4,7-triazacyclononan-1-yl)methyl)picolinic acid), Hdompa (6-((1,4,7,10-tetraazacyclododecan-1-yl)methyl)picolinic acid), and Htempa (6-((1,4,8,11-tetraazacyclotetradecan-1-yl)methyl)-picolinic acid).

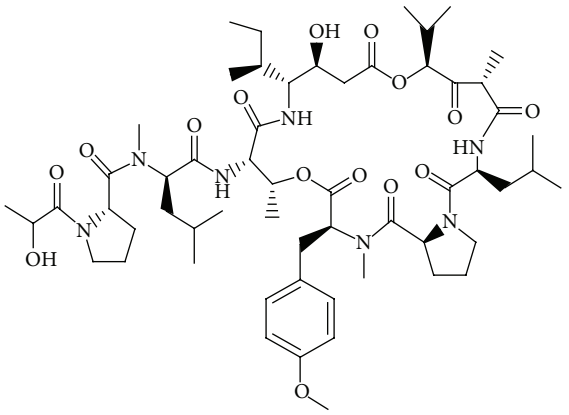


MM2 structure of jasplankinolide

(a) Jasplankinolide

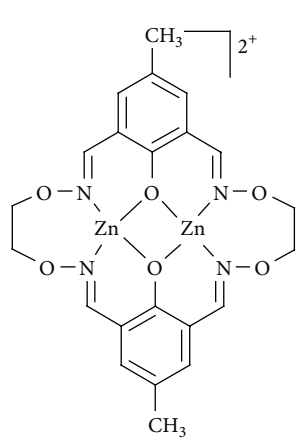


(b) Aplidine



(c) Didemin

FIGURE 12: Structure of marine peptides, based on their effects on apoptotic signaling pathways.



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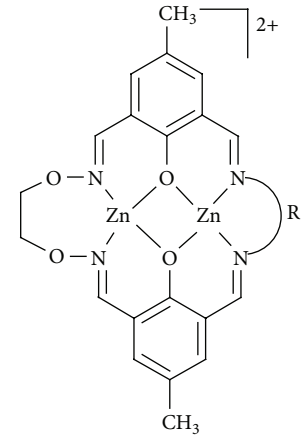


2–6

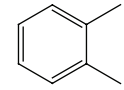
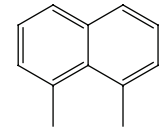
Ligand	R	Complex
L^2	$-(CH_2)_2-$	2
L^3	$-(CH_2)_3-$	3
L^4	$-(CH_2)_4-$	4
L^5		5
L^6		6

Figure 13: Dizinc(II) complex with potent antiproliferative activity.

cells. Cytotoxicity of the complexes was further confirmed by the lactate dehydrogenase enzyme level in HepG2 cell lysate and content media [125].

7.6. Therapeutics. In a total look, macrocyclic complexes display, along with other kinds of applicability, a wide range of pharmaceutical applications. The development of new pharmaceuticals has undergone a substantial change over the past decade and continues to change rapidly. HIV-1 protease inhibitors (PIs) are essential components in highly active antiretroviral therapy (HAART) but are associated with severe side effects such as dyslipidemia, hypersensitivity, and lipodystrophy [126]. Considering the fast development of resistant viral strains in general [127], there is a need for new, unique structural entities that could provide alternatives for use in future anti-HIV. Series of potent HIV-1 PIs related to both atazanavir and indinavir but encompassing a shielded tertiary alcohol as part of the transition-state-mimicking scaffold and different lengths of the central carbon spacer ($n = 1–3$) where tertiary alcohols were used as part of transition-state mimics in aspartyl PIs have been synthesized [128] (Figure 14).

Tsantrizos and coworkers [129] have synthesized a novel class of inhibitors which could potentially provide a therapeutic agent for the treatment of hepatitis C in humans. Lanthanide complexes have recently received considerable attention in the field of therapeutic and diagnostic medicines. Among many applications of lanthanides, gadolinium complexes are used as magnetic resonance imaging (MRI) contrast agents in clinical radiology and luminescent lanthanides for bioanalysis, imaging, and sensing [130]. New et al. reported that Eu(III) and Tb(III) complexes have tetraazatriphenylene chromophores (Figure 15) which show remarkable properties for the ratiometric detection of bioanalytes in living cells [131–135].

Synthetic, structural, and biological aspects of tetraazamacrocyclic complexes of Tin(II) have been described (Figure 16). Ligand and their unsymmetrical complexes have been tested for their antimicrobial effects on several pathogenic fungi and bacteria. The testicular sperm density, testicular sperm morphology, sperm motility, density of cauda epididymal spermatozoa, and fertility in mating trails and biochemicals parameters of reproductive organs have been examined in male albino rats in vivo [136].

An estimated 1% of the world's population is afflicted by rheumatoid arthritis (RA), a chronic, systemic inflammatory disorder leading to the destruction of articular cartilage and ankylosis of the joints [137]. The synthesis and SAR of a series of small molecule macrocycles that selectively inhibit JAK2 kinase within the JAK family and FLT3 kinase has been described by William and coworkers [138] (Figure 17).

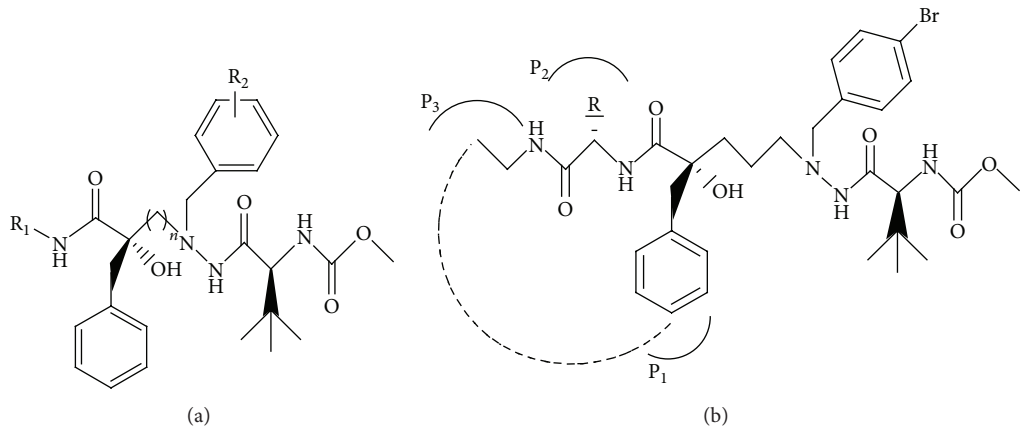


Figure 14: Generic structure of (a) linear HIV-1 protease inhibitor (n = 1–3). (b) New P1–P3 cyclized tertiary-alcohol-containing HIV-1 protease inhibitors (n = 3).

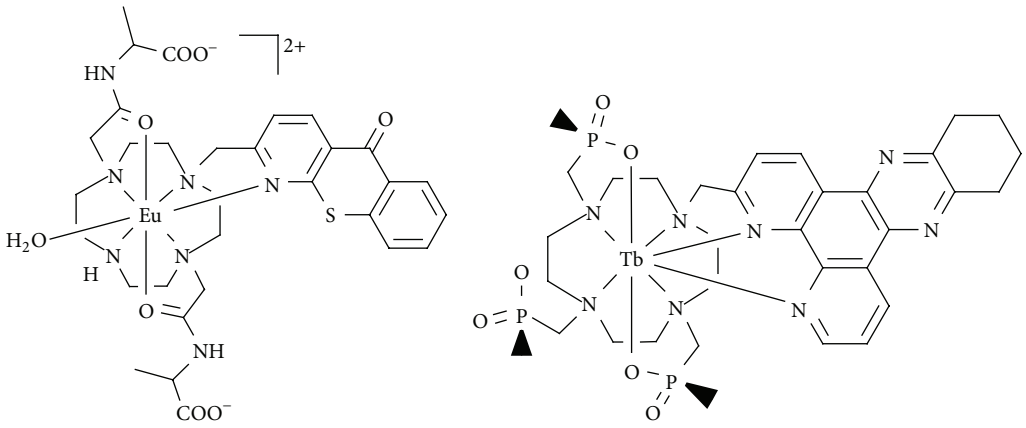


Figure 15: Eu(III) and Tb(III) complexes having tetraazatriphenylene chromophores.

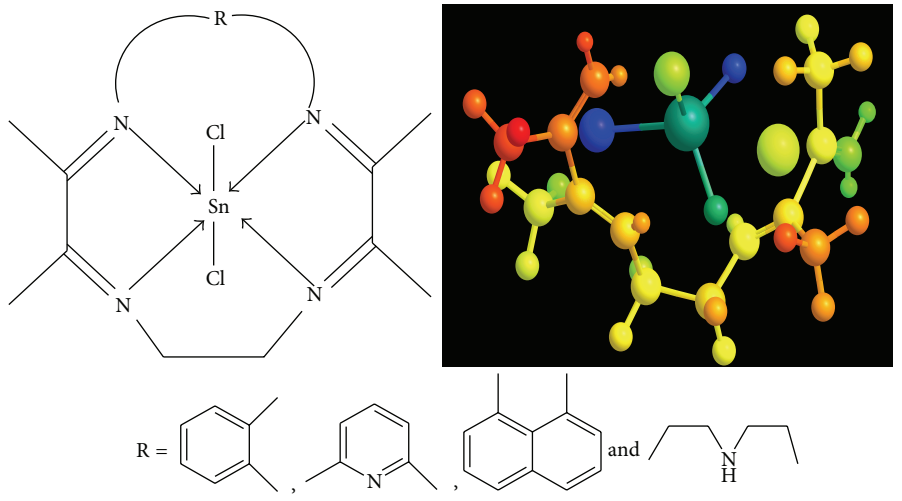


Figure 16: Tetraazamacrocyclic complexes of Tin(II).

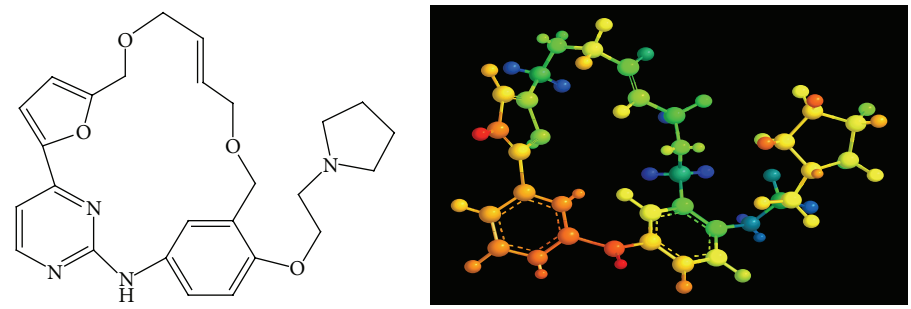


Figure 17: Structure of macrocycles that selectively inhibit JAK2 kinase within the JAK family and FLT3 kinase.

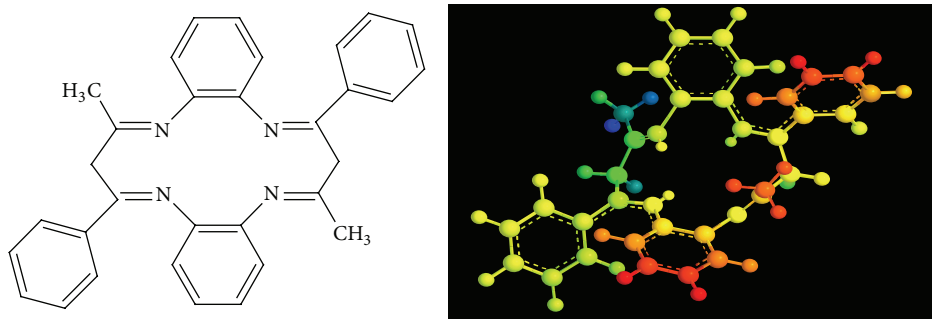


Figure 18: Tetradentate macrocyclic ligand.

A novel tetradentate macrocyclic ligand, namely, 1,5,8,13-tetraaza-2,9-dimethyl-4,11-diphenylcyclotetradeca-2,4,9,11-tetraene (L) and its complexes with Pd(II), Pt(II), Rh(III), and Ir(III) metal ions, was synthesized (Figure 18). The antimicrobial data reveal that the metal complexes act more as bactericidal and fungicidal agents [139].

8. Conclusion and Perspectives

Enormous work has been done so far for improvising and developing new macrocycles. Still, the macrocyclic world is in its adolescence. It is a fact that the demand for new and better macrocycles has never ended. Macrocycles possess applications in number of areas such as catalysis, bioinorganic, biomimetic, coordination chemistry and medical region such as antimicrobial and antibiotic. Drug developers continue to explore new approaches and molecular modalities in their continued efforts to identify modulators of the extremely well validated targets. It has been shown how we can utilise these stable frameworks to graft and engineer pharmaceutically interesting epitopes to increase their selectivity and bioactivity, opening up new possibilities for addressing "difficult" pharmaceutical targets. The complexity of the interlocking ring system will also have a profound influence on the behaviour of the molecule. The present report is particularly illustrative of this general trend.

Despite such a huge exploration of macrocycles, an inherent challenge is associated both with synthesis and analysis.

Conflict of Interests

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

Acknowledgment

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