Research Article

Medicinal Flavour of Macrocycles: Existing Scenario and Emerging Prospects

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Abstract

This review article focuses on the current state-of-the-art of macrocyclic chemistry. It collects writings in a comprehensive way and attempts to provide perspectives for this emerging field. Macrocyclic chemistry continues to the most exploited area due to the well characterized synthetic routes and ever improving library of precursors, many more of which are becoming commercially available. In such a large subject, this review encompasses the fields, namely those that involve different synthetic routes and medicinal evaluation of macrocyclic compounds. We only considered the synthetic macrocycles, with emphasis on metal complexation and their phenomenal applications in medicinal realm. The article integrates important concepts and chemistry of these macrocyclic supramolecules. It tries to demonstrate novel opportunities for investigators in terms of architectures and potential applications.

Keywords: Macrocyclic compounds, supramolecules, biomimmics, spectroscopic studies, enzymes, contrast agents.

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Introduction

Enthrallment with macrocyclic chemistry over the past few decades has led to the synthesis of an ever-increasing number of elegant and intricate functional structures with sizes that approach cyclization. Metal-macrocycle frameworks built on the principles of coordination chemistry combine the desirable properties of the individual organic and inorganic components, having applications in various fields [1-11]. There is a growing interest in the application of synthetic macrocycles to chemical biology, potentially leading to drug discovery. The techniques for the macrocycle synthesis have advanced steadily since the bronze and iron ages; it can be argued that the need to accelerate the pace of development of new technologies for their synthesis and applicability has never been greater if we are to respond to the rapidly increasing demand for medicines. Due to the diminishing supplies and the pressures governments worldwide are proposing policies to ensure that new technologies are developed in order to maintain supplies of these supramolecules that are becoming essential for world. A major goal of supramolecular chemistry is to achieve a greater understanding of nature through synthetic mimicking of biological structures and processes in the laboratory [12,13]. As a consequence, this structural type has now been successfully tested on most biological target classes. The goal of this article is to put new perspectives into the current applications, opportunities, and challenges associated with macrocycles [14].

To this end, a significant amount of research has been conducted into supramolecular recognition motifs and their assembly into functional constructs [15]. 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 [16,17]. A significant number of macrocyclic drugs are currently on the market, predominantly of natural product origin with complex structures [18]. In general, shape-persistent macrocycles were found to have a wide range of applications such as self-assembly on surfaces or self-aggregation into supramolecular channels. 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 [19]. A central tenet of supramolecular chemistry is preorganisation [20-21] and it was Pederson and Cram [22-26] who clearly demonstrated the concept using macrocyclic polyethers. The idea of macrocyclisation as a means to preorganise a host and in turn effect stronger binding has since been widely used in the field [27-30].

The design and study of synchronized metal containing macrocycles is an interesting field of chemistry [31]. Macrocyclic complexes are of great importance due to their resemblance to many naturally occurring macrocycles, such as porphyrins and cobalamines. A number of nitrogen donor macrocyclic derivatives have long been used in analytical, industrial and medical applications [32]. Macrocyclic metal chelating agents are useful for detecting tumor lesions [33]. Transition metal macrocyclic complexes have received much attention as an active part of metalloenzymes as biomimic model compounds [34] due to its resemblance with natural proteins like hemerythrin and enzymes. The chemistry of macrocyclic complexes is also important due to their use as dyes and pigments [35]. This remarkable growth is due to the synthesis of a large number and variety of synthetic macrocycles, which behave as coordinating agents for metal ions [36]. Template reactions have been widely used as the synthetic routes for macrocyclic complexes [37,38]. Nitrogen containing macrocycles have a strong tendencyto form stable complexes with transition metals and received a great attention because of their biological activities, including antiviral, anticarcinogenic [39], as well as antifertile [40].

Tetraaza macrocyclic ligands and their substituted derivatives are involved in diverse applications such as catalysis, enzyme mimics, chemical sensors, selective metal ion recovery, pharmacology and therapy [41]. Cyclams (1,4,8,11-tetraazacyclotetradecane) with C- and/or N-alkyl substituents and their metal complexes have received considerable attention because their structural and chemical properties can be quite different from those of the unsubstituted parent cyclam (1,4,8,11-tetraazacyclotetradecane) macrocycle [42-44]. Macrocyclic complexes of the transition metals have a number of unique properties offered by the macrocyclic environment, such as metal ion-selective reagents, the ability to access unusual oxidation states of the metal center, models for metalloenzyme active sites, applications in biology, medicine [45,46] and also as catalysts for the conversion of various organic substrates.

The basic reactions for synthesis of the macrocyclic compounds include the formation of the carbon–carbon bonds, heteroatom-carbon bonds such as, O–C, S–C, N–C and N-C and heteroatom-heteroatom bonds such as B–O [47]. 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 non-biological functions [48].

Diversity oriented synthesis

Template directed synthesis

Template directed synthesis is the organization of an assembly of atoms with respect to one or more geometric loci to achieve a particular linking of atoms [49,50]. The seminal [51,52] template macrocycle synthesis, as well as many more exotic examples [53], utilize metal ions as the “anchor” of the template complex. Lawrence, et al., extending a

technology previously developed for simple macrocycle synthesis [54], used a $Cu2^{+}$ template to produce ethylene side-bridged 15- membered macrobicycles from piperazine derivatives [55]. The advantages of this synthesis are the ease and high yield of the reaction. In 1989, a fascinating side-bridged ligand having a sulfur donor was described [56]. Few cross-bridged ligands have been made by these methods. These "simple" syntheses produce what are in terms of rigidity.

Protection/deprotection synthesis

When the more facile direct syntheses or template directed methods failed or were not feasible, protection/deprotection of functional groups, a more sophisticated, synthetically challenging synthesis of small bridged azamacrocycles has been applied. Ligands, like the crowns and simple cryptands, have been used mostly for the complexation of alkali and alkaline earth metals [57], but have also been applied to complexation of the NH^{4+} cation [58]. The more sophisticated protection/deprotection strategy has been invoked in order to place the bridging superstructures between nonadjacent nitrogen donors. This method has been quite successful, producing the prototypical cryptands and spherical cryptands, as well as several additional small azamacropolycycles that are complementary to transition metal ions. These ligands are invariably proton sponges, an indication of their rigidity. Directing and holding fixed multiple nitrogen lone pairs into a bi- or tricyclic cavity is responsible for this behavior, one that is seemingly indicative of strong binding for complementary metal ions as well. In conclusion, the protection/deprotection methods appear to be more effective in terms of the range of bridges they can produce, as well as in their ability to crossbridge the macrocycles. The latter characteristic is vital for synthesizing the most rigid ligands.

Condensation synthesis

Finally, the condensation reactions appear to simplify azamacrocycle bridging, although through rather complex mechanisms. This technique has thus far been limited to producing one- or twocarbon bridges between adjacent, nonadjacent, or sometimes both sets of nitrogen donors. But as these reactions become better understood, it is likely that their benefits will be retained while the range of macropolycycles they produce will expand. This synthetic route to bridged azamacrocycles is at once the most mechanistically complex and the easiest in terms of number of steps, physical labor, and yields. Reactions of formaldehyde with tetraazamacrocycles have yielded compounds with single carbon atom bridges between adjacent nitrogen atoms [59-62]. These macropolycycles have not been exploited for transition metal coordination, since it is believed the one-carbon bridges would prevent both aminal groups from binding the same ion [63]. Condensation of the dialdehyde glyoxal with tetraazamacrocycles has been more widely utilized to produce tetracyclic tetraamines varying in size and substitution pattern.

Medicinal Facets

Lessons from nature

Nature has evolved enzymes that are very efficient as oxidation catalysts. These include cytochrome P450 and peroxidases; enzymes that use an Iron(IV) oxoporphyrin radical cation intermediate to catalyze the oxidation of various organic substrates selectively and efficiently [64]. In recent years, several metal complexes that activate H_2O_2 or O_2 have been synthesized from biologically relevant transition metals and a myriad of electron donating ligands [65-71]. The literature clearly shows that the study of this diverse ligand system is linked with many of the key advances made in inorganic chemistry. Among these, metal complexes of porphyrins, sulfonated phthalocyanines and Fe(III) complexes based on a class of tetraamide macrocyclic ligands (Fe-TAMLs) have been shown to be functional mimics of peroxidases [72-74]. Designing metal complexes that activate H_2O_2 or O_2 but are themselves inert to oxidation is the key to the synthesis of efficient transition-metal oxidation catalysts [75]. An approach pursued by many chemists to achieve this goal has been to mimic enzymes that function as oxidation catalysts. An Fe(III)

complex of a biuret-amide based macrocyclic ligand (**Figure 1**) that exhibits both excellent reactivity for the activation of H_2O_2 and high stability, especially at low pH and high ionic strength, is reported [76].

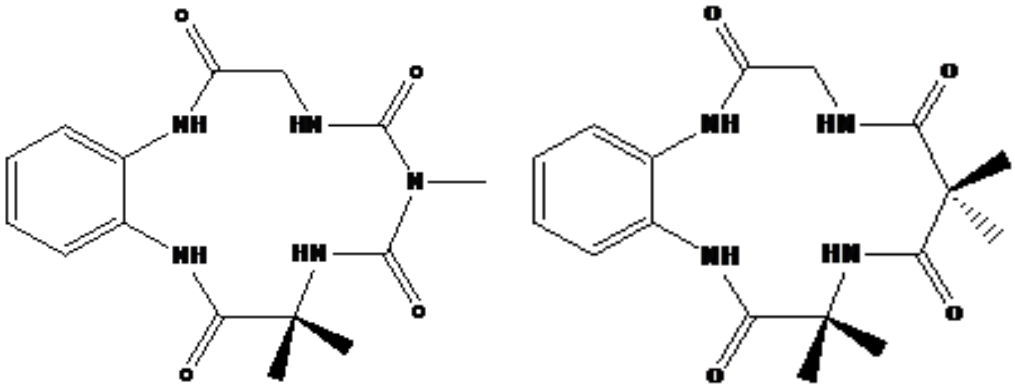


Figure 1 Molecular structure of Fe(III) complexes.

The development of agents for selective modulation of protein–protein interactions (PPIs) constitutes a prominent goal in drug discovery and chemical biology [77]. Since PPIs are often mediated by well-defined secondary structural elements, a promising strategy in this area has involved the stabilization or mimicry of these motifs via compact molecular scaffolds [78-80]. Reflecting their need, Jessica M. Smith and co-workers [81] reported the design of side-chain-to-tail linked organo-peptide hybrids incorporating a-helical protein-binding motif. Using this strategy, macrocyclic inhibitors interaction displaying increased proteolytic stability could be obtained (**Figure 2**).

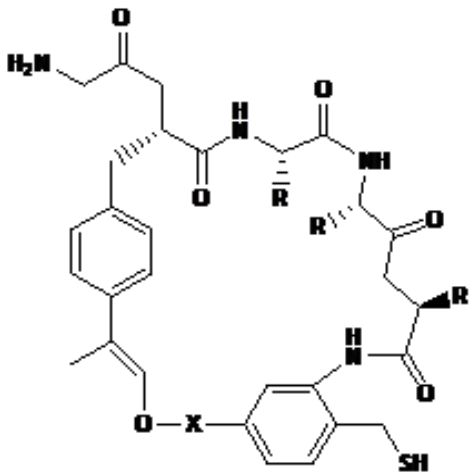


Figure 2 Macrocyclic inhibitors displaying increased proteolytic stability

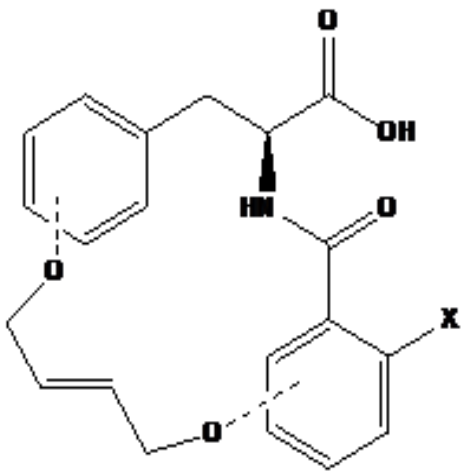


Figure 3 Low molecular weight 14−18 membered macrocycles

Integrins are a family of adhesion molecules responsible for transmembrane signaling by undergoing conformational rearrangements. They are involved in a wide range of biological processes, e.g., angiogenesis, inflammation, cancer, and hemostasis, and are therefore highly interesting drug targets. The amino acid derived low molecular weight 14−18-membered macrocycles (**Figure 3**) turned out to be highly active toward integrin α2β1 with IC_{50}s in the low nanomolar range. The conformation of the macrocycles was found to be highly important for the activity, and an X-ray crystal structure was obtained to clarify this. Subsequent docking into the metal-ion dependent adhesion site (MIDAS) of a β1 unit revealed a binding model indicating key binding features [82].

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 [28]. 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 like metalloporphyrins (hemoglobin, myoglobin, cytochromes, chlorophylls), corrins (vitamin B_{12}) and antibiotics (valinomycin, nonactin) etc. Antibiotic, antifungal, anticancer and immunosuppressive activities as seen for erythromycin (1), [83,84], amphotericin B (2) [85,86], epithilone B (3) [87-89] and rapamycin (4) [90-92] respectively (**Figure 4**).

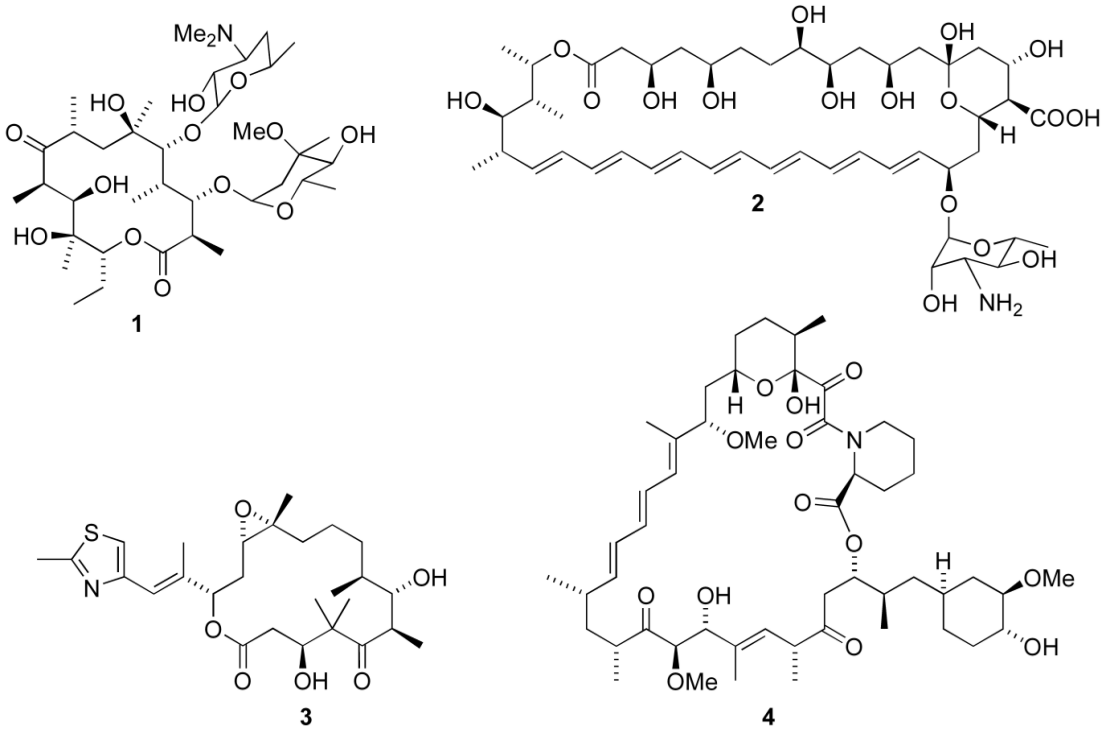
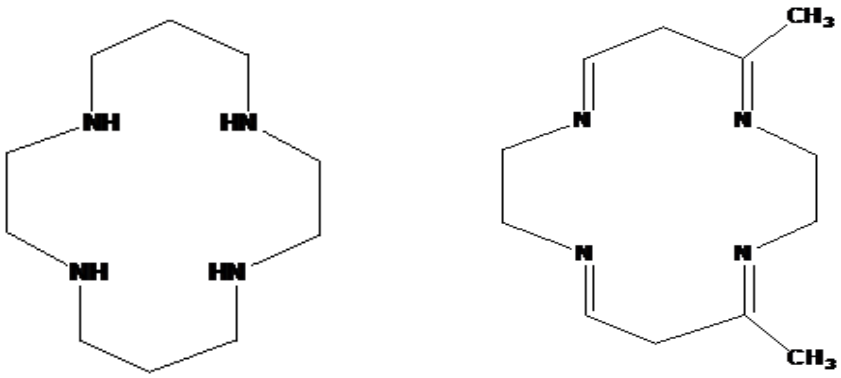


Figure 4 Structures of naturally occuring macrocyclic drugs: erythromycin (1), amphotericin B (2), epithilone B (3) and rapamycin (4)



a b

Figure 5 Tetraaza macrocycles.

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 [93-96]. Until recently, the tetraaza macrocycles, such as (cyclam) (a) and related ligands with extensive varieties of modifications including differing degrees of saturation and ring size (b), had been the most studied (**Figure 5**), 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 [97].

A recent study describes how the use of the α-diimine-containing macrocycles, 1–3, incorporating different ring sizes can be employed to moderate the degree of $(CuI)_n$ aggregation in the solid state (**Figure 6**). Reaction of an excess of CuI with 1, 2 or 3 in acetonitrile followed by slow diffusion of ether into the respective solutions yielded complexes [98].

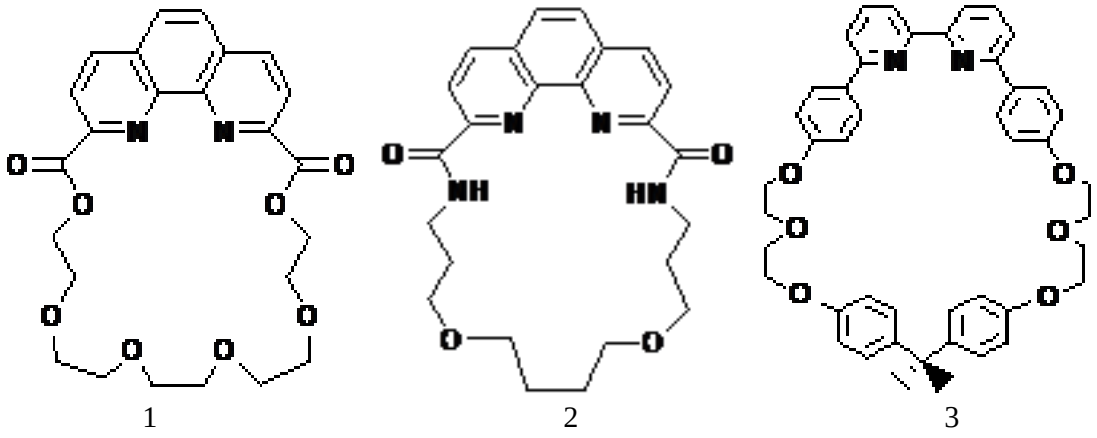


Figure 6 α-Diimine-containing macrocycles

Xiao-huan Huang and co-workers [99] in their work, two anthryl-appended macrocycles 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. Especially, 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 7**).

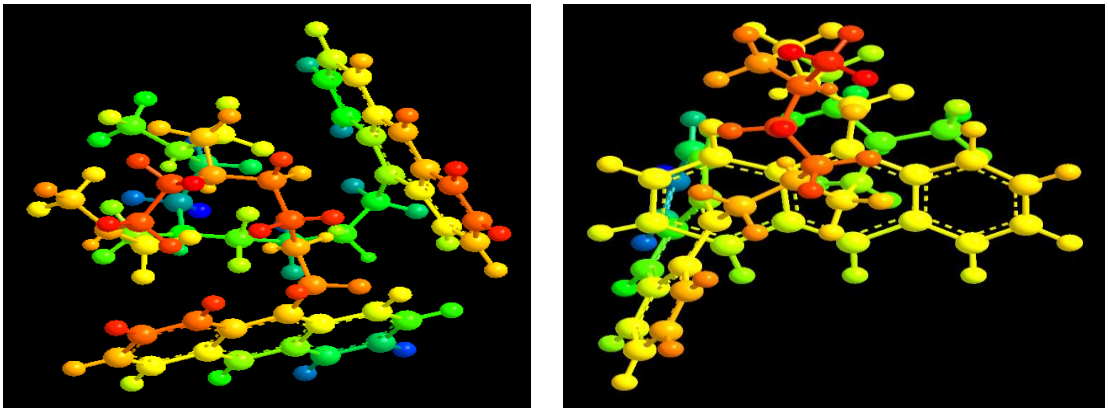


Figure 7 Anthryl-appended macrocycles

To mimick the natural enzymes [FeFe]-hydrogenases, some new porphyrin and metalloporphyrin moiety containing model complexes have been successfully prepared by Li-Cheng Song et. al [100] (**Figure 8**).

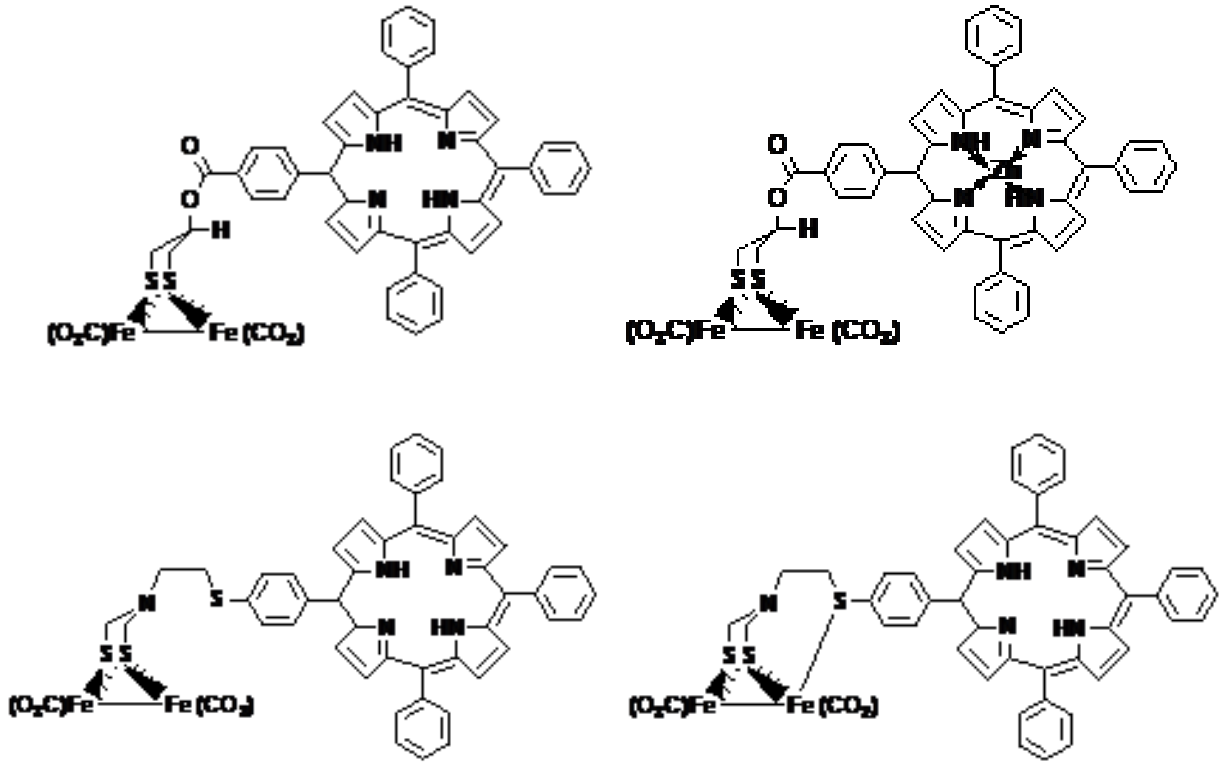


Figure 8 Porphyrin and metalloporphyrin moiety to mimick the natural enzymes [FeFe]-hydrogenases.

Significant efforts have been made to explore the reaction mechanisms of the solvolytic cleavage of phosphate esters mediated by natural enzymes [101-106] and some metal complexes [107-116]. 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 Xuepeng Zhang and co-workers [117] (**Figure 9**).

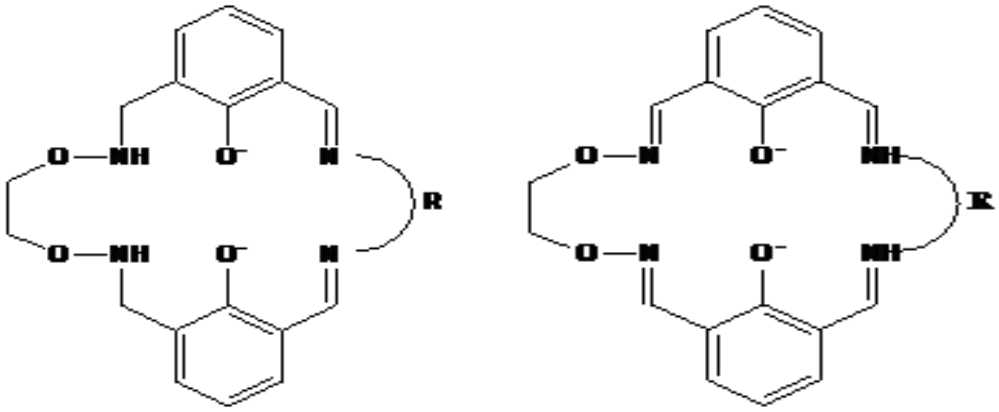


Figure 9 Bivalent dinuclear complexes.

Tools for chemical biology

The design of new metal-based cancer chemotherapeutic agents is in the forefront research area of inorganic medicinal chemistry. It is well known that medicinal inorganic chemistry is a multidisciplinary field combining elements of chemistry, pharmacology, toxicology and biochemistry [118]. 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 [119]. Metal-free and Co(II)-phthalocyanines carrying eight dodecaborate substituents (96 boron atoms) on the peripheral positions were synthesized in a multistep reaction sequence [120] (**Figure 10**).

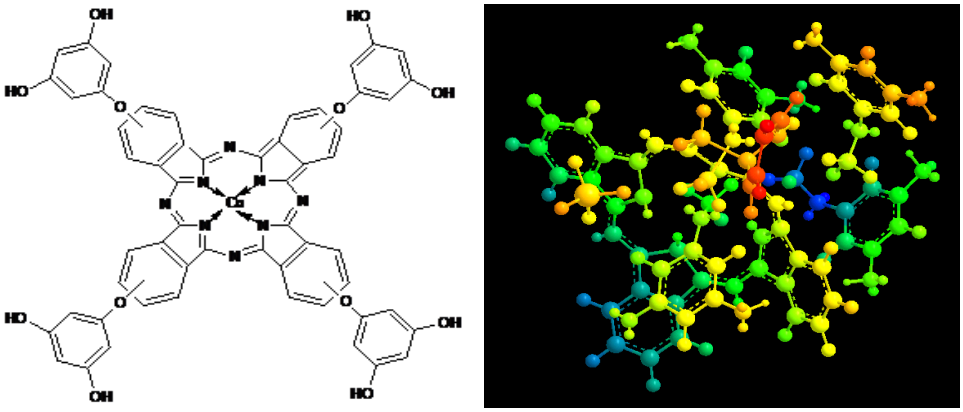
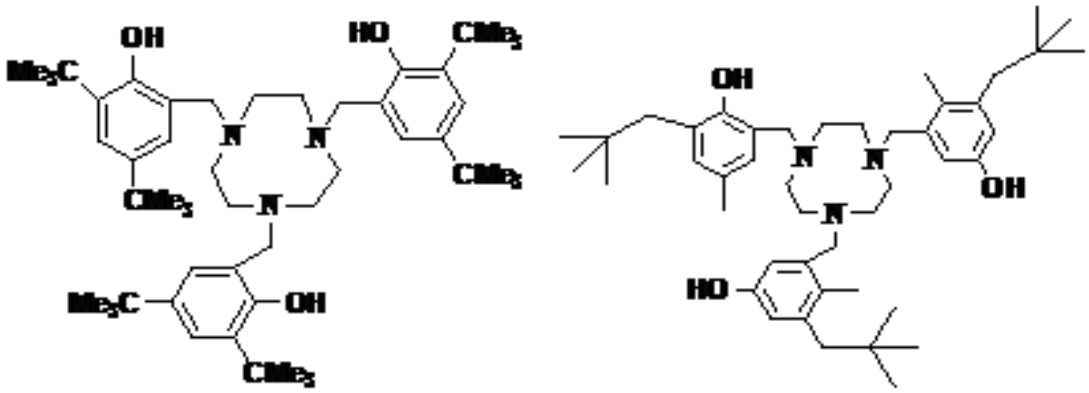


Figure 10 Co(II)-phthalocyanines.

As more advanced chelator design is achieved by Benjamin P. Burke and Stephen J. Archibald [121]. Lanthanide(III) complexes of the tacn based ligand L1 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 L2 can reduce CO_2 to CO and CO_3 using KC_8 as a reductant to engage the catalytic cycle (**Figure 11**).

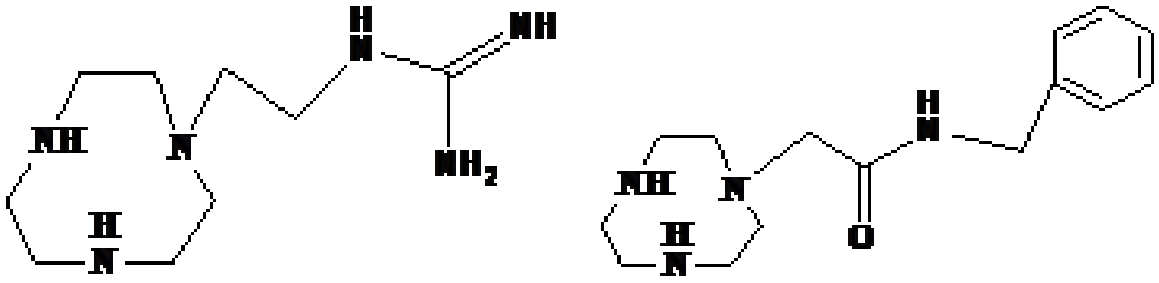


L1 L2

Figure 11 Tacn based ligand L1 and L2

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 such as L3 with a pendant guanidine group show increased rates of DNA cleavage compared with those of the parent tacn complex.

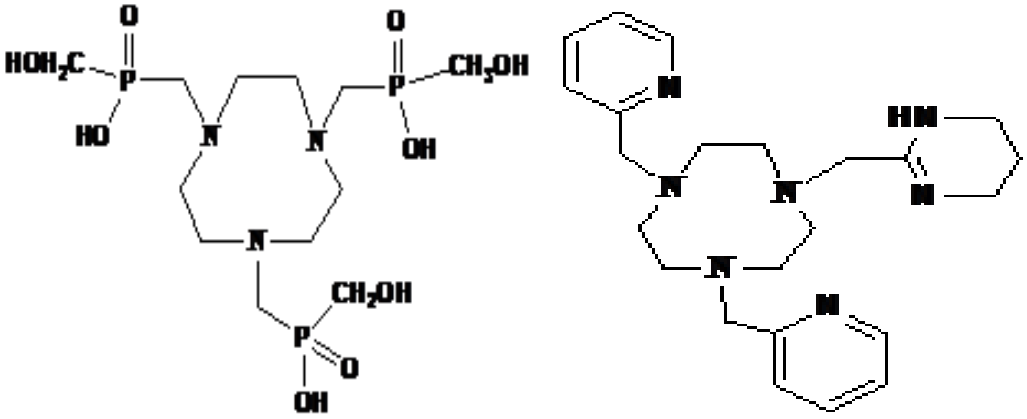
Functionalisation of technetium(VII) tacn complex of L4 through a (3+2)-cycloaddition reaction of the technetium-oxide compound has been performed to form M–O–R bonds (**Figure 12**).



L3 L4

Figure 12 Copper(II) tacn complex of L3 and technetium(VII) tacn complex of L4

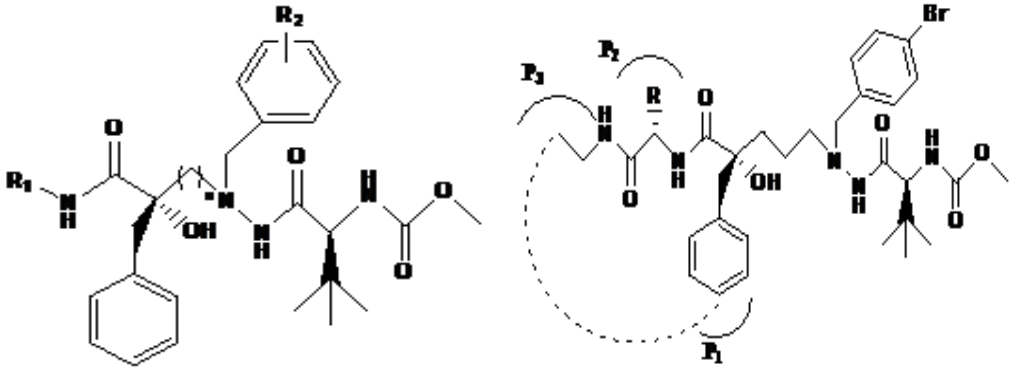
This opens up possibilities to form dual functional BFCs when combined with macrocycle N-functionalisation. Trisphosphinic acid NOTA derivatives such as L5 have been prepared and their complexation properties with gallium(III) explored. Replacement of carboxylic acid arms with phosphinic arms increased selectivity for binding and forms complexes more efficiently. Iron(II) complexes of L6 convert from low spin to high spin upon addition of dithionite, 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 (**Figure 13**).



L5 L6

Figure 13 Trisphosphinic acid derivatives

The development of new pharmaceuticals has undergone a substantial change over the past decade and continues to change rapidlyHIV-1 protease inhibitors (PIs) are essential components in highly active antiretroviral therapy (HAART) but are associated with severe side effects such as dyslipidaemia, hypersensitivity and lipodystrophy [122]. Considering the fast development of resistant viral strains in general [123], 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 [124] (**Figure 14**).

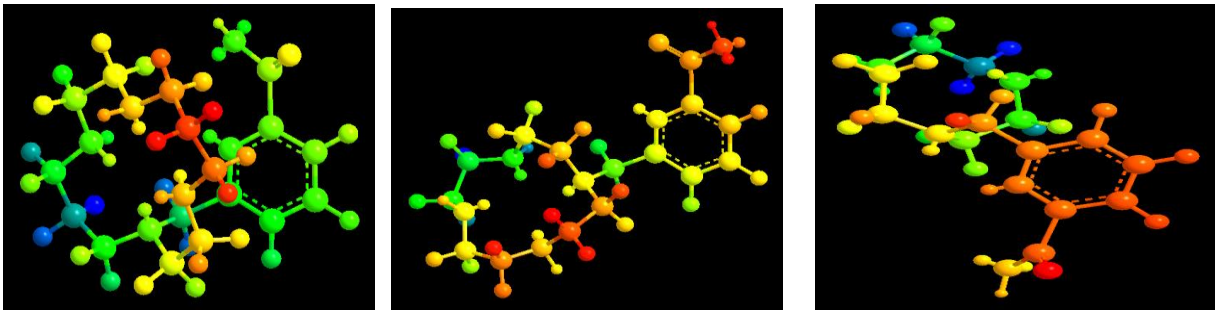


a b

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

Lack of non-invasive methods to track cells with whole-body and real-time capability is therefore an 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 pre-identified site, e.g. engrafted tumor, it lacks the sensitivity for systemically infused cells and whole-body assessment. 64Cu-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 [125].
The synthesis of the ligand Hnompa (6-((1,4,7-triazacyclononan-1-yl)methyl)picolinic acid) and a detailed characterization of the Mn2+ 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 15**) have been emerged by Eniko Molnar and co-workers [126].



Htempa Hdompa Hnompa

Figure 15 Mn2+ complexes formed by 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)

Naturally occurring azamacrocyclic metal complexes such as haems, chlorophyll, vitamin B_{12}, and the factor F430 carry pendent ring substituents and axial co-ligands that act as functional components in these important biological systems. Design of related systems with structural features related to their natural counterparts has been reported recently. Tapashi G. Roy and co-workers [127] and characterized the copper complexes of these ligands (L_A, L_B, L_{BZ}, L_{CZ} and L_{CZ1}) (**Figure 16**). The compounds exhibit pronounced antimicrobial activity.

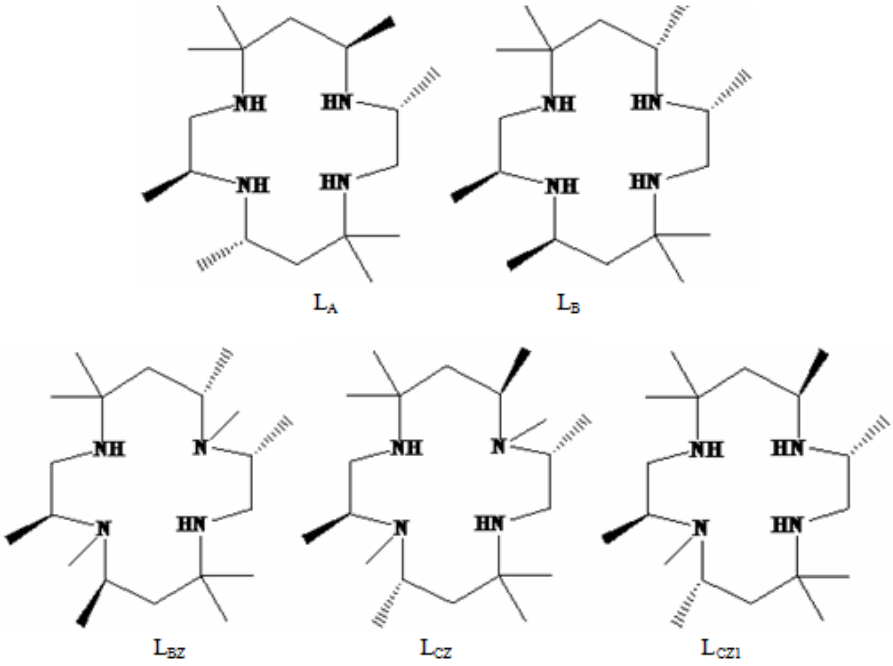


Figure 16 Ligands (L_A, L_B, L_{BZ}, L_{CZ} and L_{CZ1}).

Synthetic, structural and biological aspects of tetraazamacrocyclic complexes of Tin(II) have been described (**Figure 17**). 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 bio-chemicals parameters of reproductive organs have been examined in male albino rats in vivo [128].

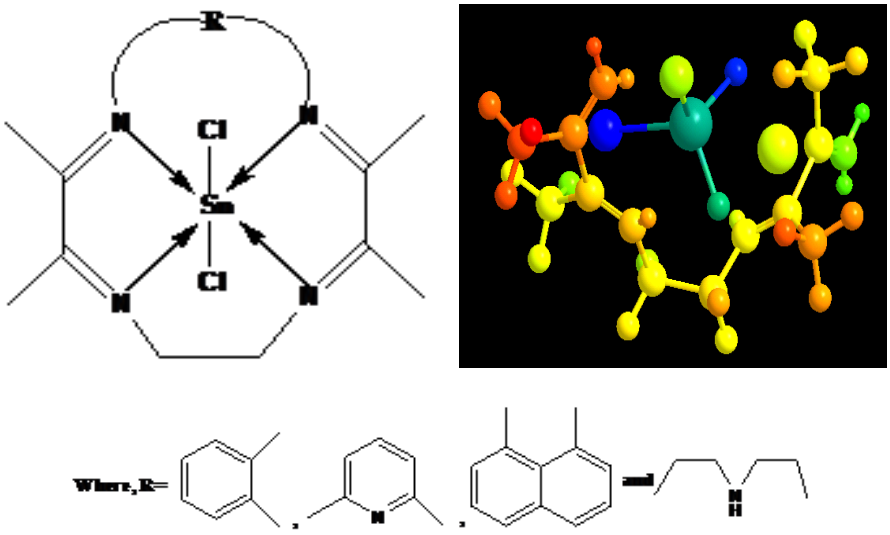
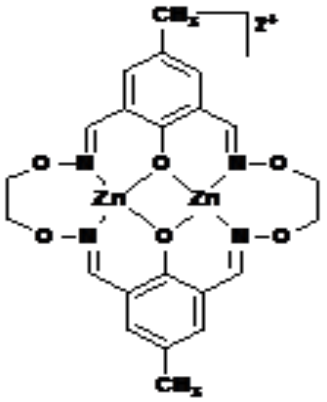


Figure 17 Tetraazamacrocyclic complexes of Tin(II).

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 Zn(II) 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 18**). 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 cells. Cytotoxicity of the complexes was further confirmed by the lactate dehydrogenase enzyme level in HepG2 cell lysate and content media [129].



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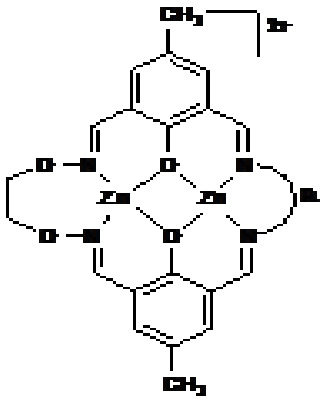


2-6

Where,

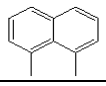
Ligand	R	Complex
L^2	$-(CH_2)_2-$	2
L^3	$-(CH_2)_3-$	3
L^4	$-(CH_2)_4-$	4
L^5		5
L^6		6

Figure 18 Dizinc(II) complex with potent antiproliferative activity

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 [130]. Herein, we desribe 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 Anthony D. William and co-workers [131] (**Figure 19**).

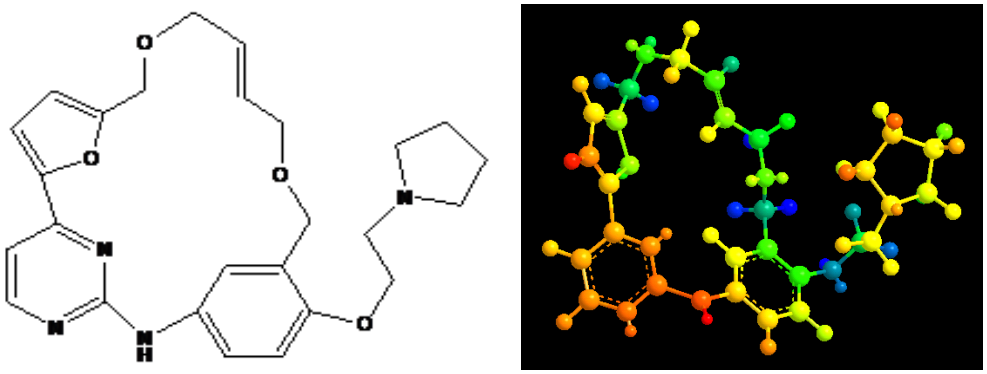


Figure 19 Structure of macrocycles that selectively inhibit JAK2 kinase within the JAK family and FLT3 kinase.

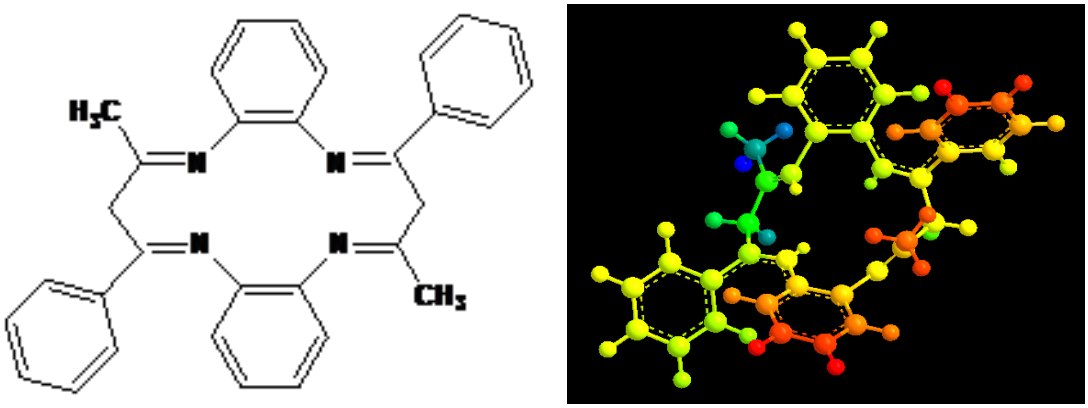
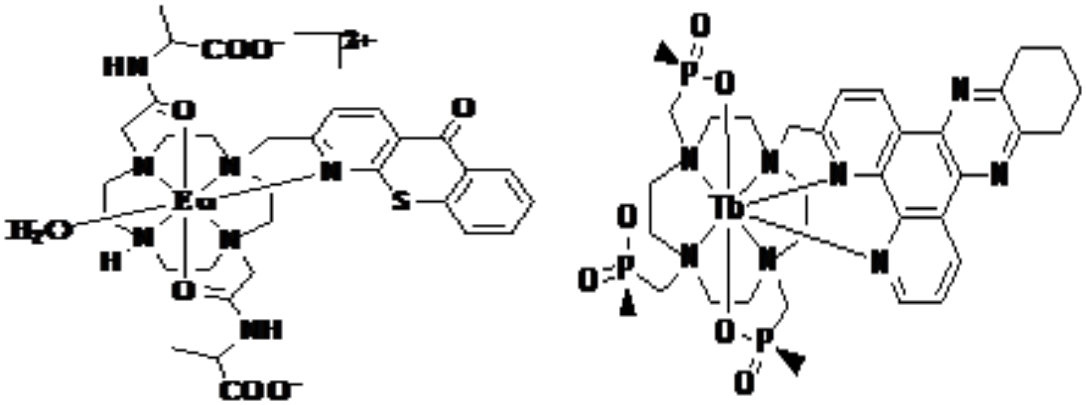


Figure 20 Tetradentate macrocyclic ligand

A novel tetradentate macrocyclic ligand viz. 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 were synthesized (**Figure 20**). Youla S. Tsantrizos and co-workers [132] have synthesized a novel class of inhibitors which could potentially provide a therapeutic agent for the treatment of hepatitis C in humans.

Magnetic Resonance Imaging (MRI) has witnessed enormous growth in the last few years and emerged as one of the most powerful techniques in diagnostic clinical medicine and biomedical research [133]. 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 [134]. Parker et al. reported Eu(III) and Tb(III) complexes having tetraazatriphenylene chromophores (**Figure 21**) which show remarkable properties for the ratiometric detection of bio-analytes in living cells [135-139].



(a) Thiaxanthone (b) Tetraazatriphylene

Figure 21 Eu(III) and Tb(III) complexes having tetraazatriphenylene chromophores.

The biggest change in drug development, particularly in the anticancer field, has been the move away from cytotoxic to molecularly targeted agents, though related changes have occurred in most areas of drug development [140]. Although highly effective in treating a variety of cancers, the cure with *cis*-platin 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 [141].
The three globally approved complexes- cis-platin, oxaliplatin and carboplatin-play a major role in cancer chemotherapy [142]. However their effectiveness is still hindered by clinical problems, including acquired or intrinsic resistance, a limited spectrum of activity, and high toxicity leading to side effects [143-148]. The search for anticancer agents with improved properties has focused on the synthesis of a new generation of platinum compounds [149]. Apoptosis as a form of programmed cell death is one of the major mechanisms of cell death in response to cancer therapies. Its deregulation, i.e. either loss of pro-apoptotic signals or gain of anti-apoptotic signals, can lead to a variety of pathological conditions such as cancer initiation, promotion and progression or results in treatment failures [150]. Lanhong Zheng et. al. [151] summarizes several marine peptides, based on their effects on apoptotic signaling pathways (**Figure 22**).

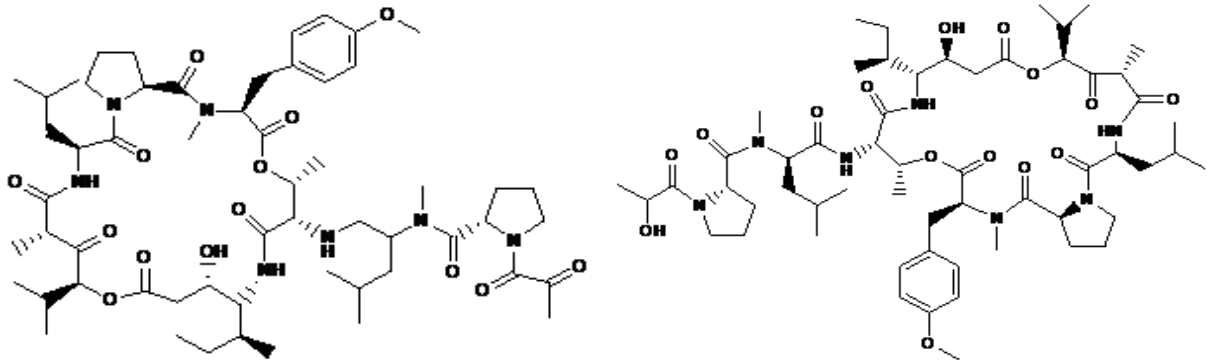


Figure 22 Structure of marine peptides, based on their effects on apoptotic signalling pathways.

Catalysis

The macrocycle types tend to form stable complexes with metal ions. Such complexes, which contain species incorporated in the macrocyclic cavity. A series of molecular materials that are structurally similar to the Ni(II) macrocycle $[Ni(cyclam)]^{2+}$(cyclam=1,4,8,11-tetraazacyclotetradecane) have been used as electrocatalysts for the reduction of CO_2 at a mercury pool working electrode in aqueous solution (**Figure 23**). At pH 5, with an applied potential of −0.96 V *vs.* NHE (over potential of −0.55 V), the complexes are highly efficient, having both high rate constants and Faradaic efficiencies (F.E.s) for the selective reduction of CO_2 to CO [152].

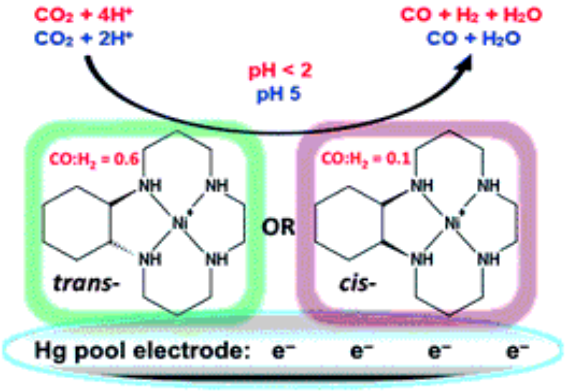


Figure 23 Ni(II) macrocycle structurally similar to the $[Ni(cyclam)]^{2+}$ used as electrocatalysts

A series of mono- and di-[12]ane N3 ligands (**Figure 24**), 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 Zhi-Fo Guo and co-workers. 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 [153].

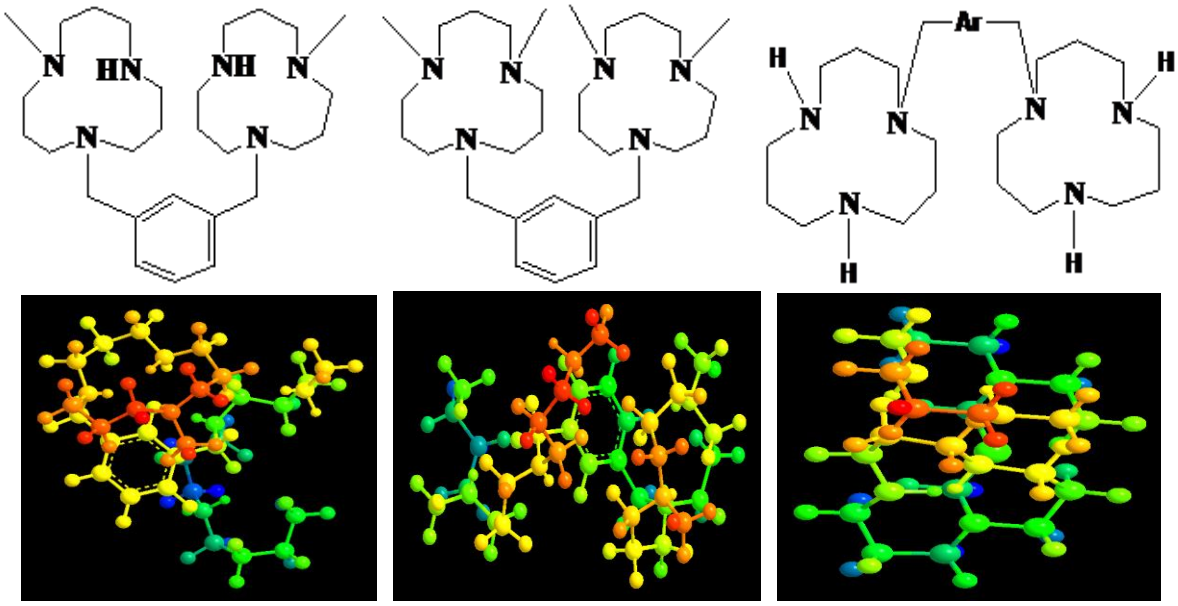
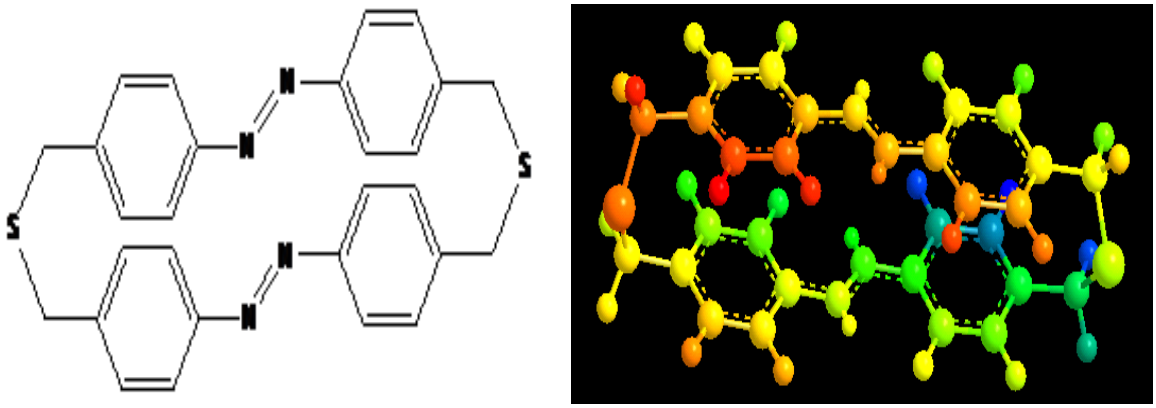


Figure 24 Series of mono- and di-[12]ane N3 ligands.

Controlling the structure at the molecular level in a defined and reversible way promises tremendous opportunities in the area of molecular materials, for example as data storage devices [154-156], sensors [157] or molecular machines [158,159], but also for life science applications [160-164]. Especially light induced molecular switches have gained huge attention during the last decade due to their fast, selective and reversible switching properties [165,166]. Well-known scaffolds are for example diarylethenes, spiropyrans [168] or azobenzenes [169-172]. The latter have emerged from classical dyes and have become powerful molecular switches due to their ability to alter the geometry by photochemical or thermal isomerization. Herein, an extensive isomerization study on a fully characterized macrocycle containing four azo units (**Figure 25**) is presented by Luca Schweighause and co-workers [173].



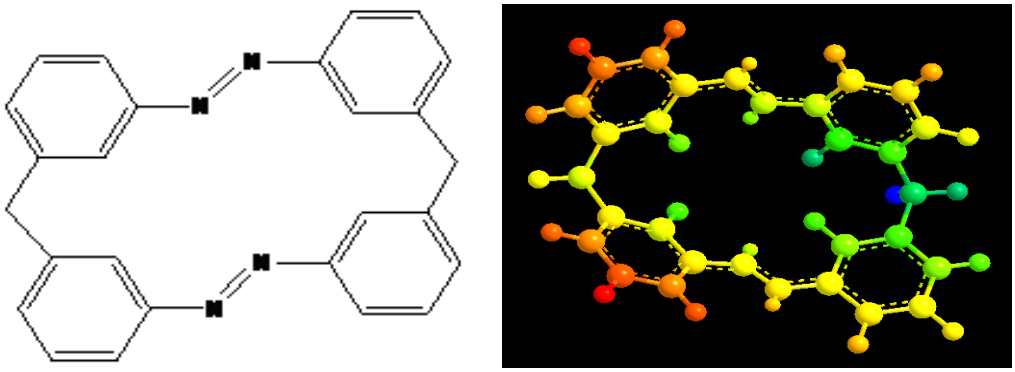


Figure 25 Macrocycle containing four azo units

Studies on complexes with synthetic macrocyclic ligands have received a new impetus since the discovery of the natural molecules. Omar S. M. Nasman [174] have synthesized a novel series of 15-membered diaza-dithiamacrocyclic complexes (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 (**Figure 26**). 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 metallo-enzymes, in addition to their catalytic activity for important industrial applications.

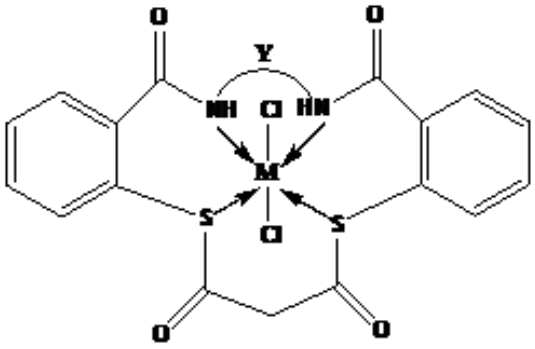


Figure 26 15-membered diaza-dithiamacrocyclic complexes

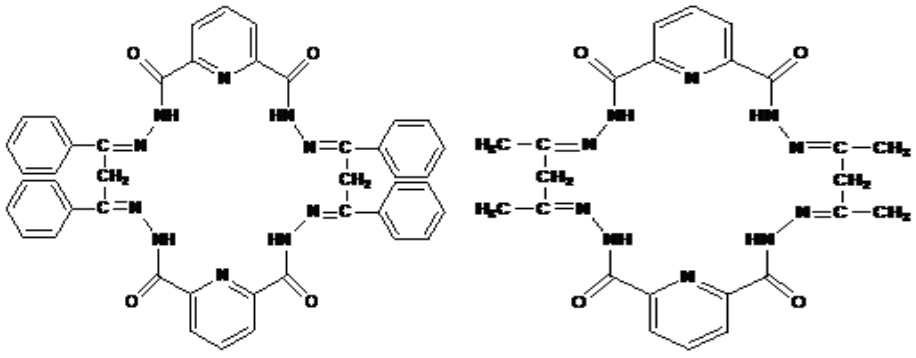


Figure 27 Schiff bases to extract the heavy metal ions

Schiff bases are widely studied and used in the fields of organic synthesis and metal ion complexation for a number of reasons [175,176]. A macrocyclic hydrazone Schiff bases were synthesized and used it as an organic chelating agent to extract some metal cations from their aqueous to another organic phase (**Figure 27**). 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 [177].

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, was synthesized and characterized in this work by Bingying Jiang and co-workers [178] (**Figure 28**).

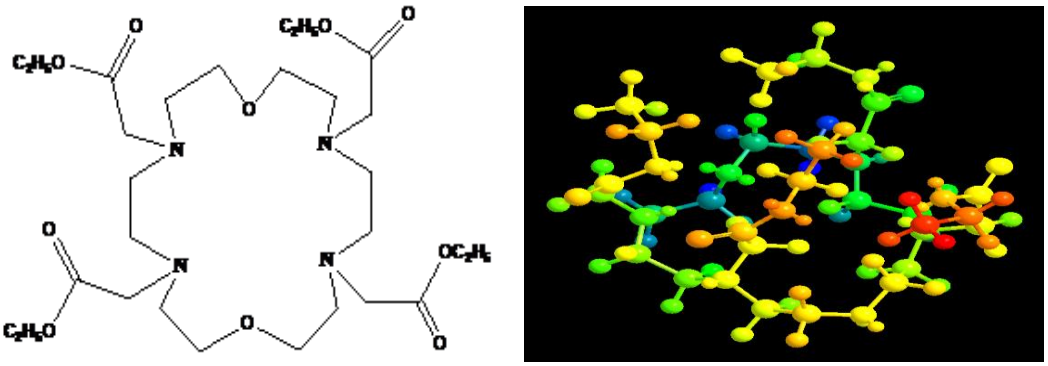
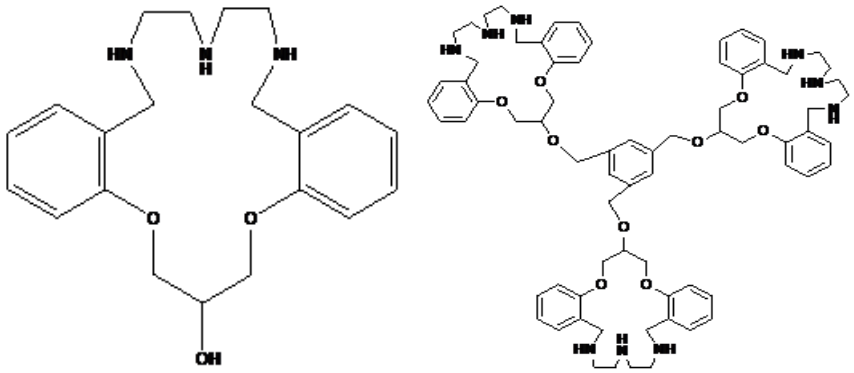


Figure 28 Aza-crown ether ligand.

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 come to the forefront of organometallic and coordination chemistry research. Such "non-innocent" 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 [179-183].

A new tri-linked azacrown macrocycle (L2) was synthesized from mono macrocycle analogue (L1) by Williamson etherification (**Figure 29**). This work is a good example of the design of multinuclear complexes for artificial nucleases and DNA cleavage. The trinuclear zinc(II) complex 5 displayed good hydrolytic activity for phosphate diester [184].

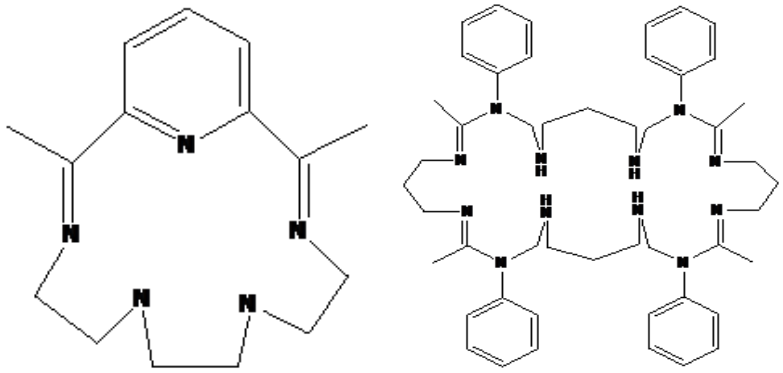


L1 L2

Figure 29 Tri-linked azacrown macrocycle (L2) was synthesized from mono macrocycle analogue (L1) by Williamson etherification.

A new fourth-generation poly(propylene imine) dendrimer (G4-M) containing 32 triolefinic 15-membered macrocycles on the surfaces has been reported. Using new 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 [185].

A new macrocyclic complex $DyCl_3(LN_5).4H_2O$ (**Figure 30a**) has been prepared in which the Dy(III) ion is equatorially bound by an N_5-donor macrocycle (LN_5). As susceptibility data reveal slow relaxation of the magnetisation in zero fields below 15 K with a distribution of relaxation rates as reported by Emma L. Gavey and co-workers [186]. The metal-templated cyclo-condensation reaction of diactetylpyridine with triethylenetetramine in the presence of DyCl3.6H2O afforded the desired 15-membered N_5 macrocyle.



a b

Figure 30 (a) Macrocyclic complex $DyCl_3(LN_5).4H_2O$ (b) Homo-dinuclear macrocyclic ligand can accommodate both the lower, Ir(I), and higher, Ru(III).

As reported by M. M. Khan [187], reactions of the macrocyclic ligand [L_2HClO_4] with the reactants [$Ir(CO)(Ph_3P)_2Cl$] and [$RuCl_3(AsPh_3)_2$-CH_3OH], produces bimetallic complexes with the stoichiometries [$Ir_2L(Ph_3P)_2Cl(ClO_4)$] (I) and [$Ru_2LCl_4(ClO_4)_2$] (II), respectively. Physico-chemical 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 homo-dinuclear macrocyclic complexes. 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 (**Figure 30 b**).

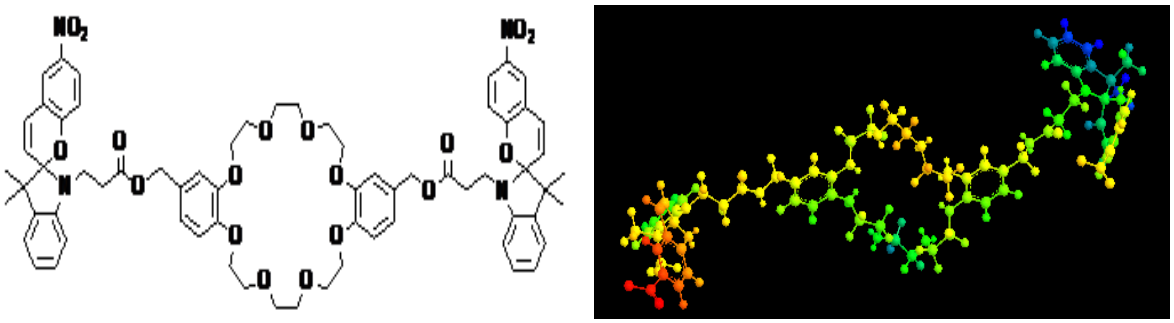


Figure 31 Multistable bis-spiropyran-containing crown ether 2-SP

Over the past few decades, mechanically interlocked molecules [188-192], such as rotaxanes and catenanes, have become typical candidates in the design of artificial molecular machines. Bistable rotaxanes [193-195], which can change their shapes and properties in response to external stimuli, have important potential to function as molecular

switches [115], molecular logic gates [196] and stimuli-responsive materials when functional units are introduced into the rotaxane molecule. Wei Zhou and co-workers [197] reported the design, preparation, characterization, and properties of a bisspiropyran- 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 structures of the multistable bis-spiropyran-containing crown ether 2-SP (**Figure 31**)

Qizhong Zhou et. al. [198] 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 may be used as new electron-rich receptors for molecular recognition or for assembling new interlocked supramolecular architectures (**Figure 32**). The new methodology has the advantages of higher yields, more generality, simpler, and cheaper catalyst system [199].

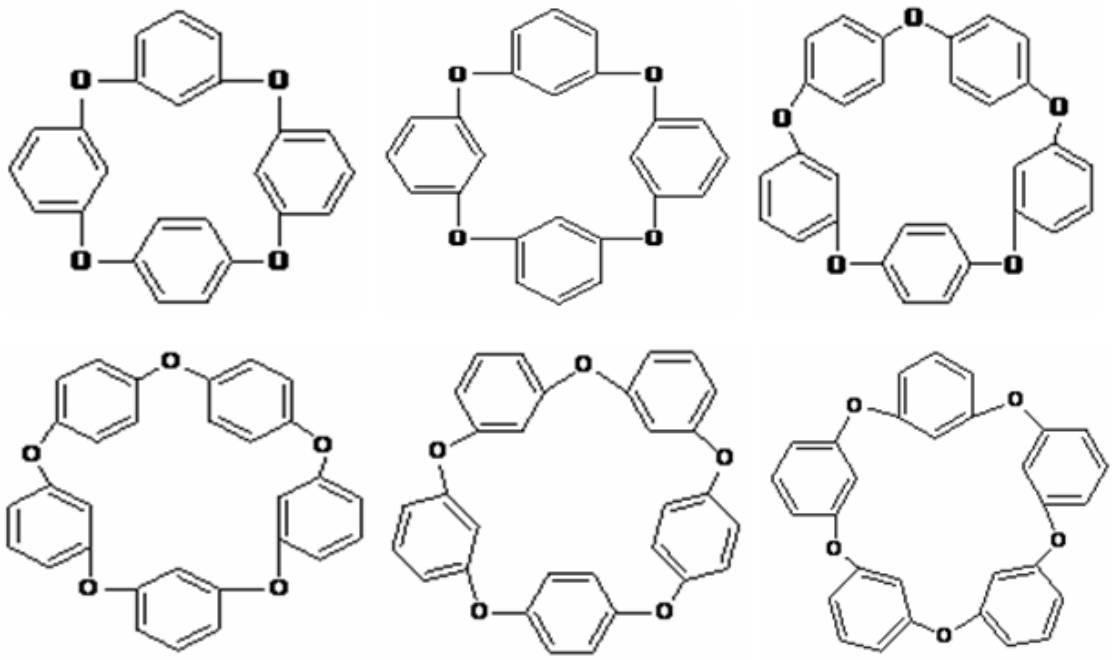


Figure 32 Macrocyclic aryl ethers

Selectivity and Transport

Interest in the smaller triaza macrocycles, such as ([9]aneN_3) 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’’.

Selective macrocycle formation 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) [200] (**Figure 33**).

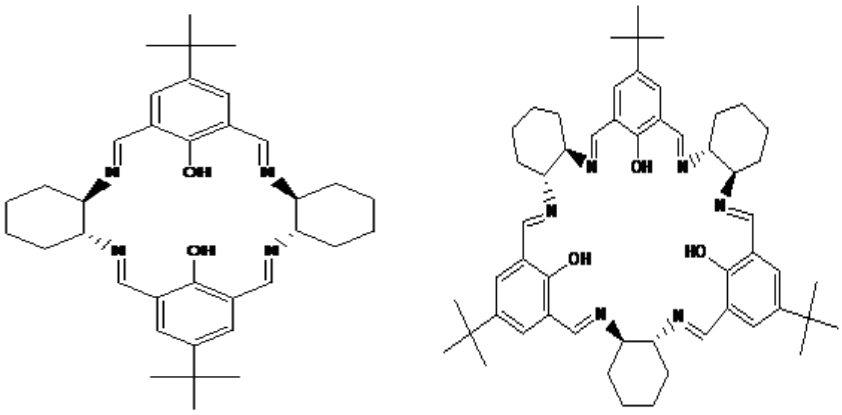


Figure 33 Cavitand-shaped trinuclear double-decker ligands.

A new quinoline pendant arm derivative of [9]aneN3 and its optical response in the presence of transition and post-transition metal ions has been studied. In particular ligand behaves as an efficient OFF–ON fluorescent chemosensor for Zinc(II) in MeCN/H2O 1 : 1 (v/v) and in pure H2O at pH 7.0 [201] (**Figure 34**).

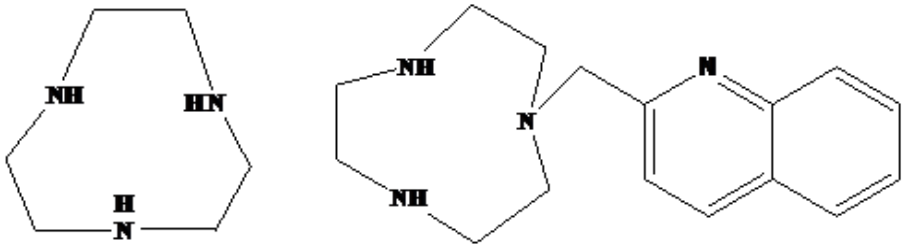


Figure 34 Triaza macrocycles.

The 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 [51]. 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 35**), was synthesized. Metallacyclodimer was constructed and it is sensitive to metallophilicity of the polyatomic anion. These results contribute to the delicate modulation of metallacyclic receptors and anion-recognition, in addition to anion sensor, anion transport and molecular switching [202].

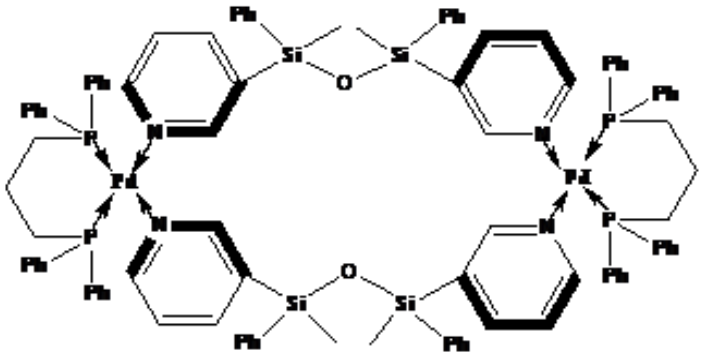


Figure 35 Ionic macrocyclodimeric palladium(II) complex.

Sulekh Chandra and Dev Raj Singh [203] 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 36**).

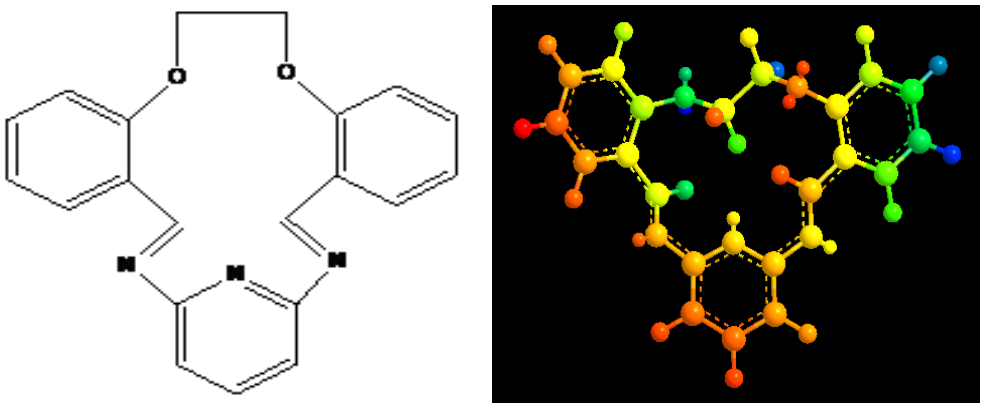
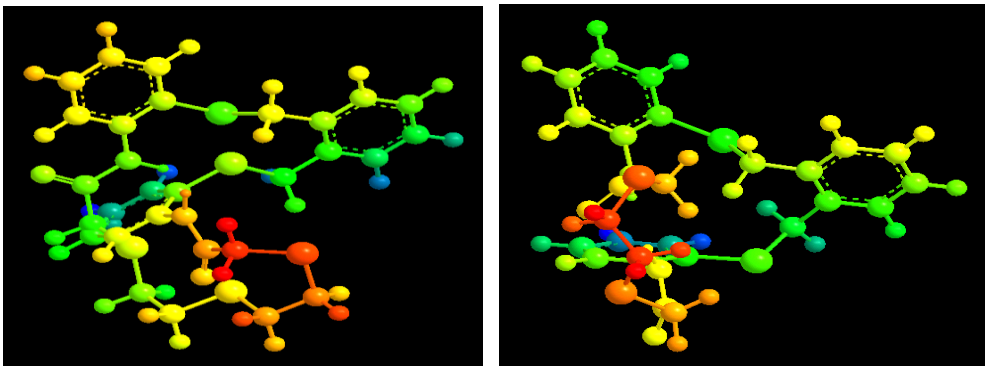


Figure 36 1,12,14-triaza-5,8-dioxo-3(4),9(10)-dibenzoyl-1,12,14-triene.

Two new macrocyclic ligands, containing nitrogen and sulfur donor atoms were designed and synthesized in a multi-step reaction sequence (**Figure 37**). 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^{+}, Hg^{2+} ion [204].



Ligand A Ligand B

Figure 37 Macrocyclic ligands, containing nitrogen and sulfur donor atoms.

Recently, Bo Zheng and co-workers [205] 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 i.e. [21]crown-7 and [24]crown-8 and two ammonium ions substituted with either a thin alkyl group or a more bulky benzyl group are used as the binding motifs (**Figure 38**).

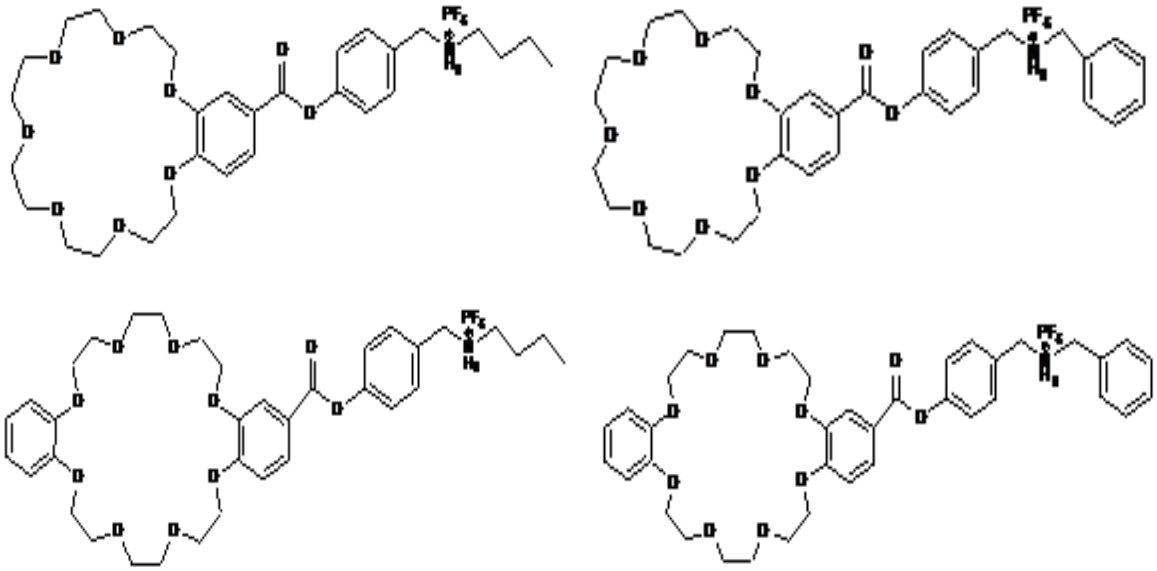
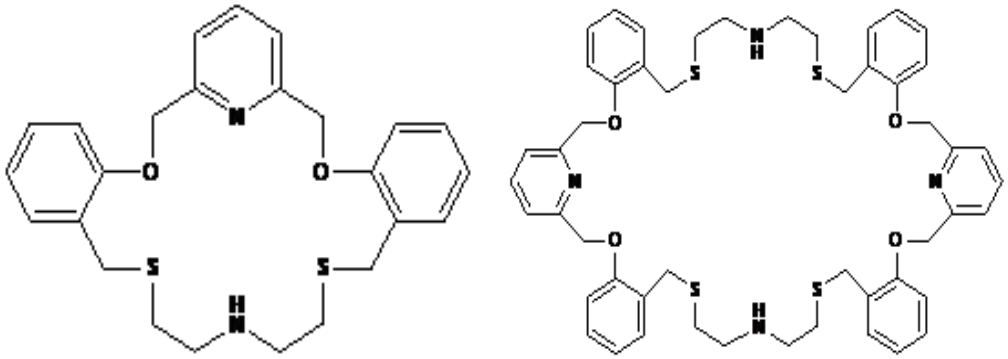


Figure 38 Supramolecular pseudorotaxane polymers based on the crown ether/secondary ammonium ion binding motifs.

There is a growing interest in a large macrocyclic ligand system that can form binuclear complexes exhibiting electron transport, charge transfer, and allosteric behavior. Therefore, 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) and a 40-membered $N_4O_4S_4$ macrocycle (L^2) obtained from the mixed products via respective [1:1] and [2:2] cyclization are employed (Figure 39) and a comparative investigation of the coordination behaviour of these macrocyclic ligands with nickel(II), cadmium(II), and silver(I) is reported [206].



L^1 L^2

Figure 39 A 20-membered $N_2O_2S_2$ macrocycle (L^1) and a 40-membered $N_4O_4S_4$ macrocycle (L^2).

Oxonium tetrahalogenaurate(III) (Hal = Cl, Br) benzo-crown ether (BCE) complexes are prepared and reported by Sergei M. Pluzhnik-Gladyr and co-workers [207]. 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 (**Figure 40**).

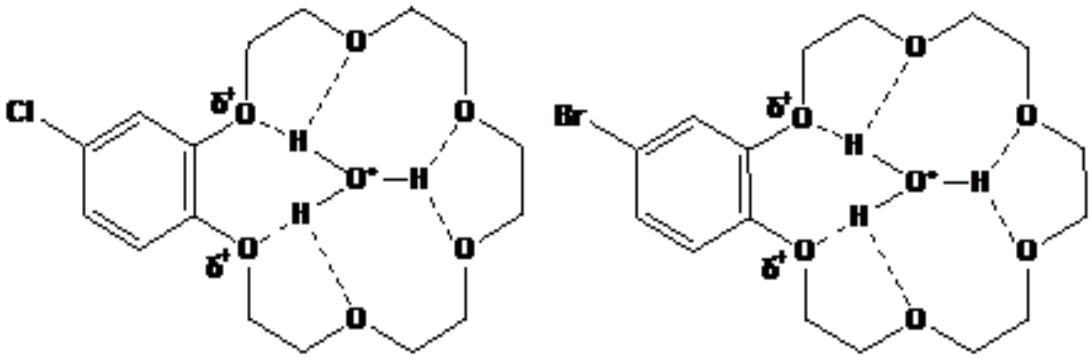


Figure 40 Oxonium tetrahalogenaurate(III) benzo-crown ether.

Conclusion

As described above, macrocyclic chemistry is a coordination-driven self-assembly, vibrant, and active field. It is evident that considerable progress has been made since the beginnings of the field few decades ago. Early work involved the self-assembly of helicates, grids, and other infinite ensembles. Out of these area evolved the self-assembly of finite closed systems, both two-dimensional and three-dimensional with well-defined shapes and sizes. Early work in this field focused on the development of rational methodologies for the self-assembly of predesigned systems along with their characterization. We hope that this review will stimulate further research into the chemistry and application of macrocyclic complexes. There has been a resurgence of interest in macrocylic field as shown by the recent chemistry described above, but there seems also to have been a tendency for rediscovery of matters described by past workers. We have tried to bring some of these points to the fore in the hope that progress may be facilitated in areas that are really novel. We look forward to further developments in this field of chemistry as well as a continuation of the steady increase in applications of these interesting and attractive complexes.

Acknowledgements

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