Chapter-1

Review of literature
INTRODUCTION

The study of macrocyclic complexes represents a major area of activity which impinges on a range of other area in both chemistry and biochemistry. Coordination chemistry of macrocyclic ligands has been a fascinating area of current research interest to the inorganic chemists all over the world. The synthesis and study of macrocycles have undergone tremendous growth and their complexation chemistry with a wide variety of metal ions has been extensively studied [1]. Macrocyclic ligands are polydentate ligands containing their donor atoms either incorporated in or, less commonly, attached to a cyclic backbone. “The word macrocycle may be defined as a cyclic molecule with three or more potential donor atoms in a heteroatom ring of at least nine atoms”.

Macrocyclic compounds continue to attract considerable interest due to their countless possible applications arising from their ability to bind different kinds of substrates. They are able to form stable and selective complexes with a variety of inorganic and organic cations, and by reaction with some anionic and neutral organic and biological substrates give supramolecular compounds with specific properties and applications [2]. A very large number of synthetic, as well as many natural macrocycles have now been studied in considerable depth, thereby investigating the unusual coordination properties frequently associated with cyclic ligand complexes. The fact that macrocyclic ligand complexes are involved in a number of fundamental biological systems has long been recognized. The importance of such complexes, for example to the mechanism of photosynthesis of plants and bacteria or for transportation of oxygen in mammalian and other respiratory systems, has provided motivation for the investigation of metal-ion chemistry of these systems as well as of
cyclic ligand systems [3]. Owing to the presence of a central cavity, macrocyclic ligands have long been employed as selective hosts for a wide range of guest molecules and ions. Thus, macrocyclic systems have been employed as selective extractants/ionophores for transition and post-transition metal ions in a range of solvent extraction and bulk membrane transport studies [4]. Macrocyclic complexes find extensive biomedical applications as contrast enhancing agents in magnetic resonance imaging [5,6], as NMR shift reagents for biological systems [7] and as catalysts for the cleavage of RNA [8,9]. Macrocyclic ligands have received special attention because of their mixed soft-hard donor character, versatile coordination behavior [10], and of their pharmacological properties, i.e. toxicity against bacterial/fungal growth [11], anticancerous [12], antitumor [13] and anti-inflammatory [14]. Apart from the biological implications, aspects of the chemistry of macrocyclic ligands are of relevance to a diverse number of other areas such as metal ion catalysis, organic synthesis, metal ion discrimination in addition to a number of potential industrial and other applications. More recently the interest in the chemistry of macrocyclic ligands has been reborn due to their applications in supramolecular chemistry and new materials [15].

In 1886, Baeyer [16] synthesized the first documented macrocycle possessing a pyrrole heterocyclic ring (Figure 1), resembling the porphyrin, via an acid catalysed condensation between pyrrole and acetone. The first macrocyclic compound prepared from a diacid was dimeric ethylene succinate reported [17] by Vorlander in 1894 (Figure 2).
Prior to 19th century there existed only well established category of synthetic macrocyclic ligands containing nitrogen atoms, which were the highly conjugated phthalocyanines. Phthalocyanine [18-20] (Figure 3) and its derivatives bear a strong structural resemblance to the natural porphyrin systems. Phthalocyanines and their symmetrically substituted derivatives have been an important class of dyes and pigments since their first synthesis early last century. They have also been used as catalysts for desulfurization processes in the oil industry. Recently, these macrocyclic compounds have been applied as photoconducting agents in photocopiers, laser printers, and optical read/write disks. They are expected to play a more versatile role in material chemistry due to their potential applications in molecular electronics and photonics, electrochromic displays, nonlinear optics, electrocatalytic reagents, and medical applications [21].
Until the 1960’s only the phthalocyanines and various isolated compounds such as Alphen’s cyclam (Figure 4) and the polyethers of Luttinghan [22] were available (Figure 5).

Since then, lot of advances have taken place considerably in the late 60’s and early 70’s in the field of coordination chemistry of polyazamacrocycles by the pioneering and independent contributions [23-25] of eminent scientists like Curtis, Busch, Jager
and Pedersen (Figure 6). Charles J. Pedersen’s publication [25] (1967) “Synthesis
and Characterization of over 30 new cyclic polyether macrocycles” initiated
tremendous and continuing interest in scientific community. These discoveries led to
more systematic studies of macrocycles and their metal complexes and as such
provided the corner stones on which supramolecular chemistry has been built.

a. Curtis (1961)  
b. Busch (1964)  
c. Jager (1964)  
d. Pedersen (1967)

Figure 6

During the past decades macrocyclic ligands have attracted widespread attention due
to two unique properties: (a) their ability to discriminate among closely related metal
ions based on the metal ion radius (ring size effect); (b) the significant enhancement in complex stability constant which is generally exhibited by optimally fitting macrocyclic ligands relative to their open-chain analogues (macrocyclic effect) [26]. The formation of macrocyclic complexes depends significantly on the dimension of internal cavity, on the rigidity of macrocycles, on the nature of its donor atoms and on the complexing properties of the anion involved in the coordination [27]. The interest in such species stems from the applications of these complexes ranging from modeling the active sites of many metalloenzymes [28,29], to hosting and carrying small molecules [30] or catalysis [31]. As most of the applications of macrocycles are associated with their ability to complex with ions, the main target in macrocyclic ligand design is to synthesize compounds that are able to discriminate between ions. The ability to control metal ion selectivity is clearly of great interest in many areas and this selection is influenced by the nature, arrangement of donor atoms and also the ring size. There is at present a need for the investigation of selective coordination properties in novel systems [32].

The synthesis of macrocycles is an art in itself. There are four main approaches to prepare macrocyclic ligand systems:


b. Metal ion promoted reactions, involving condensation of noncyclic components in the presence of suitable metal ion (Template effect).

c. Modification of a compound prepared by methods (a) and (b).

d. High dilution technique.

The preparation of the free macrocycles has certain advantages in many cases. The purification of the organic product may be more readily accomplished than
purification of its complexes, and further the characterization by physical techniques becomes easier. But the free macrocycles are often of low yield for the desired product and may have side reactions. To overcome this problem the ring closure step in the synthesis may be carried out under conditions of high dilution [33] or another way is that a rigid group may be introduced to restrict rotation in the open chain precursors [34,35] which facilitates cyclization. One of the most effective methods for the synthesis of macrocyclic complexes involves an in-situ approach where the presence of metal ion in the cyclization reaction markedly increases the yield of the cyclic product. The metal ion plays an important role in directing the steric course of the reaction and this effect is termed “metal template effect” [36]. The metal ion may direct the condensation preferentially to cyclic rather than the polymeric products. The metal ion and the anion are important to the template process because the balance between the size of the cation and anion will determine the degree of dissociation of the metal salt in the reaction medium [37].

Synthesis of multidentate macrocyclic ligands by the metal template method has been recognized as offering high-yielding and routes to new ligands and their complexes [38, 36, 39, 40]. The template effect can be divided into two slightly more specific effects. The kinetic template effect describes the directive influence of the metal ion and controls the steric course of a sequence of stepwise reactions. In cases where the thermodynamic template effect operates, the metal ion perturbs an existing equilibrium in an organic system and the required product is produced often in high yield as a metal complex. In most cases, the kinetic template effect is operative, however, an assignment can not be made in all cases. The first example of the deliberate synthesis of a macrocycle using this procedure was described [41] by
Thompson and Busch (Scheme 1), although Curtis had previously demonstrated the potential of template assembly by the reaction of \([\text{Ni(en)}_3] \ (\text{ClO}_4)_2 \) \((\text{en} = 1,2\text{-diaminoethane})\) and acetone yielding isomeric tetraazamacrocyclic complexes [42] (Scheme 2).

![Scheme 1](image1)

![Scheme 2](image2)

Metal ions also facilitate the self-condensation of o-phthalonitrile to give metal-phthalocyanin complexes [43] (Scheme 3). Shakir and co-workers have reported [44] the self-condensation reaction of o-aminobenzoic acid in the presence of transition metal ions as templates.
In the last few years a great deal of research has been aimed to design macrocyclic complexes highly selective and sensitive to metal ions [45]. Among the various synthetic strategies proposed, the template condensation is one of the most highlighted. Metal template condensation often provides selective routes towards products that are not obtainable in the absence of metal ion [46]. The capability of metal ions to promote the template synthesis of macrocyclic ligands has been studied extensively and depends on several factors related to the ligand characteristics, as well as on the nature of the metal ion [47]. Metal ions typically interact with molecules displaying binding tendencies (ligands) and place them in the space around themselves, according to a definite geometrical order. The metal addresses the synthetic pathway to a chemical object of a predetermined geometry and is said to act as a template [48]. The term template was first used in chemistry by Busch and Thompson, to illustrate the role of nickel (II) in the synthesis of macrocyclic complexes (Scheme 1) [41].
However, template synthesis of the macrocyclic Schiff bases on metal ions has two substantial disadvantages. First, rather often it does not allow one to synthesize metal-free macrocyclic Schiff bases. Usually the more complete and unambiguous the template condensation, the stronger the metal ion bound in the macrocyclic cavity. Therefore, in many cases it is rather difficult to isolate the free ligand, and then when performing demetalation of the complex the imino groups –C=N–R are reduced to the amine groups –CH₂–NHR with simultaneous demetalation. Second, template synthesis from dicarbonyl compounds and diamines usually affords symmetric macrocyclic complexes. Other starting building blocks have to be used to obtain nonsymmetric macrocyclic Schiff bases. During the last two decades, considerable efforts have been made for developing metal-free methods for furnishing macrocycles starting from various dicarbonyl compounds and diamines in addition to standard metal-templated protocols [49].

Substitution of the coordinated metal ion by other metal ions which are not effective as templates has also been achieved by the transmetallation [50-53] (metal exchange) reaction. In this way a wide range of mono- and dinuclear complexes have been prepared. A metal which cannot serve as a template for particular macrocycle can effectively coordinate to form stable complexes if reacted with the free macrocycles. For the larger Schiff base macrocycle, transition metal ions are ineffective as templates. Consequently the kinetic lability of the metal ions present in the macrocyclic complexes of the s- and p- block cations enable the generation of the corresponding transition and inner-transition metal complexes by transmetallation reactions. On treating the kinetically labile complexes with a second metal ion, the liberated macrocycle is captured and stabilized by coordination to the new metal ion before decomposition [54-58].
The transmetallation is the resultant of the stability differentials of the parent complex and the complex of the transmetallating ion. Thus, for the transmetallation to be feasible the stability of the complex of the transmetallating ion should be greater than that of the parent complex. Transmetallation has been exploited to synthesize a range of dinuclear complexes of [2+2] macrocycles from the corresponding mononuclear complexes. The sequence of reaction involving ring closure by transmetallation with a concomitant ring contraction and reduction in ligand denticity and subsequent ring expansion in the presence of larger metal ions (Scheme 4). Thus it has been observed that when the metal ion is too small for the macrocyclic cavity, ring contraction takes place by transmetallation with a concomitant reduction in ligand denticity and ring size. The complex of the ring contracted macrocycle undergoes ring expansion in presence of large metal ions.

Scheme 4
Schiff base macrocycles have been of remarkable versatility in macrocyclic and supramolecular chemistry [49,59]. They were among the first artificial macrocyclic complexes to be synthesized. These macrocycles have played a vital role in the development of synthetic macrocycles. Condensation of carbonyl compounds with primary amines was discovered in 1864 by Hugo Schiff [60]. Macrocyclic Schiff base complexes have attracted much attention since early 1980s. The diamine Schiff base macrocycles obtained by the condensation of one molecule each of the dicarbonyl and diamine precursors have been termed [1+1] macrocycles and the tetraimine macrocycles obtained by the condensation of two molecules of the dicarbonyl compounds with the two molecules of the diamine moiety have been termed as [2+2] macrocycles as a consequence of the number of head and lateral units present [61]. Macrocyclic Schiff-bases have been of great importance in macrocyclic chemistry because they can selectively chelate certain metal ions depending on the number, type and position of their donor atoms, the ionic radius of the metal centers, and the coordinating property of the counterions [62]. The instant and enduring popularity of Schiff base ligands undoubtedly stem from the ease with which they can be synthesized, their bewildering versatility and their wide ranging complexing ability once formed. The literature clearly shows that the study of this diverse ligand system is linked with many of the key advances made in inorganic chemistry. Not only have they played a seminal role in the development of modern coordination chemistry, but they can also be found at key points in the development of inorganic biochemistry [63]. They have also been extensively employed in the understanding of molecular processes occurring in biochemistry, material science, catalysis, encapsulation, activation, hydrometallurgy, transport and separation phenomena [64, 65]. A broad variety of Schiff base macrocycles can be utilized for metal biosites modeling [49],
catalyst for many organic reactions, models of reaction centers of metalloenzymes [66], non-linear optical materials [67,68], effective catalysts in asymmetric synthesis [69], luminescence materials [70,71], DNA binding and cleavage reagents etc.

Schiff base macrocycles are formed by condensation between a dicarbonyl and a diamine resulting in imine linkage and the presence of $\text{N=C-C=N}$ structure unit responsible for the formation of a strong chelate ring resulting in possible electron delocalization associated with extended conjugation affecting the nature of the complex formed. The effective method for the synthesis of Schiff base macrocyclic complexes which involves the condensation reaction between suitable dicarbonyl compounds and primary diamines carried out in the presence of appropriate metal ions which serve as templates in directing the steric course of the reaction. In this metal template effect the metal ion-through coordination organizes the linear substrates to facilitate the condensation process which may lead toward either [1+1] or [2+2] macrocyclic products (Figure 8). Whether the cyclization proceeds through an intramolecular condensation to give a [1+1] macrocycle or through the bimolecular steps leading to a [2+2] macrocycle depends on the relative proportions of linear substrates, the nature of the cation and reactants (chain length number and position of donor atoms), the ratio of the template ionic radius to the cavity size, conformation of acyclic intermediates and coordination properties of counterions [72].
The preference for the formation of “1+1” and “2+2” macrocycles in metal template condensation also depends upon the following factors:

- If the diamine has insufficient chain length to span the two carbonyl groups then “1+1” macrocycle cannot be formed [73].
- If the template ion is large with respect to cavity size of the “1+1” ring, a “2+2” condensation may occur [74].
- The electronic nature of metal ion such as charge, polarizability and the required geometry of the complex.
- Conformation of “1+1” acyclic chelate.
The template potential of a metal ion in the formation of a Schiff base macrocycle depends on the preference of the cations for stereochemistries (octahedral, tetragonal, square planar or square pyramidal) in which the bonding d-orbital are in orthogonal arrangements. The size of the cation is important to direct the Schiff base condensation, as there should be compatibility between the radius of the templating cation and the hole or cavity of the macrocyclic framework. As indicated by Cation-Cavity “Best fit” the smaller metal ion favors the formation of “1+1” macrocycle while a larger metal ion favors the “2+2” macrocycle. Recently, H. Khanmohammadi et al. have reported [75] the synthesis of asymmetric heptaaza Schiff base macrocyclic complex of Mn(II) ion by templated [1 + 1] cyclocondensation of \( \text{N,N,N',N'-tetrakis(2-aminoethyl)propane-1,2-diamine} \) with \( \text{2,6-diacetylpyridine} \) (Scheme 5).

![Scheme 5](image)

The synthesis of aza-macrocyclic compounds received considerable attention during the last decades because of their relationship to biomimetic and catalytic systems and the applications of this type of chelating agents to biology and medicine. They have applications in modern chemical techniques such as magnetic resonance imaging,
imaging with radioisotopes and radiotherapy, i.e. techniques where metal complexes with extreme kinetic and thermodynamic stability toward metal release are required [76]. Aza type ligands appear as very promising to be used as antifertile, antibacterial, antifungal agents and for other biological properties [77-81]. Macrocyclic Schiff base nitrogen donor ligands have received special attention because of their mixed hard-soft donor character and versatile coordination behavior. Macrocyclic complexes with basic nitrogen donors could also form protonated moieties, which can interact with simple as well as with more complex inorganic and organic anions [82]. Because of the numerous areas of chemistry where aza-macrocyclic complexes have found a niche, the preparation of new macrocyclic ligands with ever more elaborate structures is also a vital area of research.

Polyazamacrocycles have been studied extensively because they exhibit a variety of special characteristics, especially the highly organized binding site for complex formation with both cations and host molecules [83]. Polyazamacrocycle–metal complexes have been studied as MRI contrast agents in medicinal chemistry and as fluorescence probes in chemical biology [84], they have also been utilized as metalloenzyme mimics and catalysts as well [85-89]. The large polyazamacrocyclic molecules, containing six or more nitrogen atoms, are known to form stable metal complexes, with one or more metal ions, due to their large number of nitrogen atoms [90]. The complexation capabilities of polyaza macrocycles are mainly governed by the macrocyclic ring size [91]. Transition metal complexes of polyaza macrocyclic ligands with functional groups have been synthesized in order to investigate how the functional groups affect their coordination geometry and chemical properties [92].

Among the polyazamacrocycles, the tetraaza macrocyclic ligands and their metal complexes have attracted interest among the coordination chemists [93]. The
importance of tetraazamacrocycles [14]aneN₄ (Figure 9) and [12]aneN₄ (Figure 10) have been realized for several decades and their complexation chemistry with a large variety of metal ions has been studied thoroughly [94-97]. Tetraazamacrocyclic ligands have been the subject of a significant number of studies exploiting their metal ion size selectivity, strong binding constants, and ease of functionalization [98-100]. Among potential applications of the metal complexes of these ligands are the selective removal of toxic metals from waste streams [101], radiotherapy [102], and contrast agents for magnetic resonance imaging [103]. Tetraazamacrocycles with 14- and to a lesser extent 16- membered predominate. The metal complexes of [14]aneN₄ and [12]aneN₄ represent reference systems [104] in the coordination chemistry of azamacrocycles and they are of great practical importance because the knowledge gained might be most easily transferable to the understanding of the natural products. Sulekh Chandra and co-workers have reported [105,106] the synthesis and characterization of a large number of tetraazamacroyclic complexes.

![Figure 9](image1.png) ![Figure 10](image2.png)

The majority of all nitrogen donor macrocycles that have been studied were tetraazamacrocycles but later on a large number of pentaazamacroycles have also
been studied. H. Keypour and co-workers have recently reported [107,108] a novel series of pentaaza macrocyclic complexes.

The hexaazamacrocycles are interesting and versatile receptor molecules being capable to coordinate one or two metal ions and in addition their protonated forms can also encapsulate anionic guests via electrostatic interactions or/and hydrogen bonds [109,110] (Figure 11, 12 and 13). Rothermel et al. [111] synthesized and studied hexaazamacrocycles (Figure 12) and it has been shown that the role of the metal ion size is essential in controlling the conformation of this type of macrocycle [112]. Hexaazamacrocycles that are readily obtainable from Schiff base condensation reactions reported by Martell and co-workers [113], are capable of binding a wide range of anions including halides, nitrate and phosphate, and even in complexing biological anions like carboxylates and nucleotides [114]. Recently, M. del C. Fernandez-Fernandez et al. have reported the Ni(II) nitrate and perchlorate complexes with two stereo-isomeric hexaazamacrocyclic ligands [115] (Figure 14).

Figure 11  Figure 12  Figure 13
Octaazamacrocycles also exhibit interesting co-ordination properties in spite of the large cavity size formed by the macrocyclic backbone, they are capable of forming stable mono- and di-nuclear metal complexes, as well as stabilize various anions in their hexaprotonated form [116].

A variety of macrocyclic complexes which have adjacent nitrogen atoms (cyclic hydrazines, hydrazone or diazines) are formed by condensation of hydrazine, substituted hydrazines or hydrazones with carbonyl compounds. Tetridentate and pentadentate aza macrocycles are formed [117] by condensation of 2,6-diacetylpyridine with hydrazine (Figure 15) or with dihydrazines (Figure 16). A variety of macrocyclic complexes have been reported [118,119] derived from hydrazine.
There has been considerable interest in the chemistry of binucleating macrocycles capable of holding two transition metal ions in close proximity. A number of such complexes have been reported earlier due to their potential relevance in bioinorganic chemistry [120-122], magneto chemistry [123], coordination chemistry [124-127] and homogeneous catalysis [128]. These macrocycles with a large cavity, accommodating two metal ions can be used to bind the metal centre at fixed distances. In these systems there is often an additional internal or external bridging group, which completes the structure of the binuclear species which has the advantage of being relatively rigid and thus gives structurally well defined moieties [129]. Many metalloenzymes contains two copper ions in their active site that operate cooperatively [130,131]. In physicochemical aspects these binuclear copper complexes have noteworthy significance as new inorganic materials showing various magnetic properties with anti-ferromagnetic coupling depending upon the bridge angle and degree of distortion [132,133]. Dinuclear copper containing proteins play an
important role in biology, including dioxygen transport or activation, electron transfer, reduction of nitrogen oxides and hydrolytic chemistry [134]. Metal complexes of binucleating macrocyclic ligands can be used as general models to understand the reactivity changes caused by the proximity of both metal centres. Binuclear macrocyclic complexes having similar and dissimilar coordination sites are of particular interest because such macrocyclic complexes are thermodynamically stabilized and kinetically retarded with regard to metal dissociation and metal substitution relative to metal complexes of acyclic ligands [135,136]. A group of researchers have reported [137-139] wide variety of binuclear macrocyclic complexes. In order to obtain binuclear macrocyclic complexes, three main synthetic strategies have been pursued (i) synthesis of large macrocycles or macrobicycles able to incorporate two metal ions [140], (ii) synthesis of bis macrocycles [141] and (iii) use of chelating agents bridging two macrocyclic units [142]. Each metal centre can interact with the other one directly by electrostatic forces or chemical bonding and indirectly via electron delocalization through the macrocyclic framework or bridging ligands. A variety of binuclear macrocyclic ligands with two similar and dissimilar metal centers have been reported [143,144] (Figure 17 and 18).

Shakir et al. [145,146] have reported a wide variety of polyazamacrocyclic Schiff base binucleating complexes with different bridging atoms or groups.
The preparation of macrocyclic polyamine ligands bearing functional pendant donor groups and their subsequent ligation to various metal ions has been an active area of research for many years [136, 147, 148]. The design and preparation of new functionalized macrocyclic ligands and complexes have received much attention because of their interesting chemical properties and potential applications in various fields [149]. The presence of pendant-arms into the macrocyclic skeleton have attracted a great deal of interest owing to the fact that the ligating groups attached to the macrocyclic backbone can offer additional donor groups to produce important changes in the control of the stability, selectivity, stereochemistry and certain thermodynamic parameters [150]. In general, chemical properties and structures of such compounds are strongly influenced by the nature and number of functional groups [151]. Since the cation-binding ability of the pendant-armed macrocycles is essentially controlled by the nature of the macrocyclic skeleton and ligating pendant
arms, structural combinations suitable for new and specific carriers can be designed. Thus, the substitution over N-donor atoms has the potential to generate the biggest steric and electronic effects due to the proximity of the site of substitution to the metal ions introduced [152]. Functionalization can be achieved either using a carbon or a nitrogen atom of a ring as attaching point. The carbon substituted derivatives have the advantage of not influencing the nature of the heteroatomic donor group and are ideal for side chains, which do not coordinate. A pendant chain attached to a nitrogen, on the other side, can be designed so that five or six-membered chelate rings are formed, when the side chain donor group bind to the metal ion, without a strong deformation of the macrocycle. Of course a combination of both type of functionalization offers all the advantages and allows to fulfill several functions at the same time.

A new pendant-arm hexaazamacrocyclic ligand, L bearing four ethyldioxolane pendant groups has been reported recently by a group of researchers [153] (Figure 19). The complexation capability of L in a 1:1 metal-ligand molar ratio towards the transition (Co(II), Ni(II), Cu(II)), post-transition (Zn(II), Cd(II)) and lanthanide (La(III), Ce(III), Nd(III), Sm(III), Eu(III), Ho(III), Er(III)) metal ions has been investigated.
Farha et al. have reported [154] the synthesis of hexaazamacrocyclic complexes bearing pendant arm by template condensation of 1,2-phenylenediamine and 1,4-phenylenediamine through formaldehyde in the presence of transition metal ions. (Figure 20). Hassan keypour and coworkers have reported [155] the synthesis of three Schiff base Mn$^{2+}$ macrocycles with two 2-pyridylmethyl pendant arms by the metal ion-templated [1+1] cyclocondensation of 2,6- diacetylpyridine with three different branched hexadentate amines
Macrocycles especially the ones possessing aromatic moieties are known to form charge transfer complexes with a variety of guests. These macrocycles were used to study complexation of diverse guests to provide new insights into non-covalent binding interaction, chiefly cation π-interaction which involve the stabilization of a positive charge by the face of an aromatic ring \[156\]. These molecular interactions are formed between the electron rich π-orbital of an aromatic ring and a cation. Incorporation of aromatic rings within the macrocyclic ligand, besides improving their optical properties, increases their rigidity and hence their potential preorganization. Several macrocycles containing aromatic moieties have been reported \[59,157,158\] having o-phthalaldehyde (Figure 21) 1,8 daminonaphthalene (Figure 22) and benzil (Figure 23) subunits as the main part of the structural backbone of the macrocyclic framework.
Where $M = \text{Co(II), Ni(II), Cu(II), Zn(II)}$;

$X = \text{Cl, NO}_3$, CH$_3$COO
Chapter 1

The brief introduction in the area of macrocyclic chemistry discussed in the above paragraphs does not enumerate the holistic coverage. It is rather impossible to condense the work reported in thousands of publications, articles as well as in reviews in few lines and pages. Therefore, only the relevant and parallel work has been included in introduction of the Ph.D. thesis.

In view of the fact that macrocyclic chemistry still forms the basis of extensive research due to multiple applications particularly in the areas like biology, catalysis and industry. It was therefore thought worth to develop this research area by designing and synthesizing a few novel macrocyclic compounds to explore their structural features and to investigate their potential biological applications.
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