



# **Transition Metal Coordination Complexes with Diverse Schiff Base Ligands and Macrocyclic Systems: Synthesis and Structural Diversity**

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## **Authors' contributions**

*This article was written and compiled in collaboration between both authors. Author PG managed the literature survey, designed and wrote the draft of the review article. Author AAH performed the final analysis and gone through the entire manuscript for necessary modification and improvement. Both authors read and approved the final manuscript.*

## **Article Information**

DOI: 10.9734/AJOPACS/2017/34727

### Editor(s):

(1) Kuldeep Kholiya, Department of Applied Science, B. T. Kumaon Institute of Technology, Dwarahat, India.

### Reviewers:

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(2) O. Sobola Abdullahi, Lagos State University, Nigeria.

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Complete Peer review History: <http://www.sciencedomain.org/review-history/20493>

**Review Article**

**Received 8<sup>th</sup> June 2017**  
**Accepted 29<sup>th</sup> July 2017**  
**Published 14<sup>th</sup> August 2017**

## **ABSTRACT**

This review is intended to update the current advances in the fields of coordination chemistry of transition metals with the Schiff base ligands including the macrocyclic systems. Different methods were involved to synthesize different Schiff base ligands and were reported along with their biological activities. A number of transition metal coordination complexes containing diverse ligands are reported in this review along with a discussion on their structural features and field of potential applications.

**Keywords:** *Synthesis; coordination compounds; macrocyclic ligand; Schiff base; antibacterial activity; antifungal activity.*

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## 1. INTRODUCTION

Schiff bases and their metal complexes emerge as a diverse field of chemistry and play an important role in the development and progress of coordination chemistry [1]. There is an increasing effort to analyze the designing and preparation of materials and to study their chemical functionality, coordination pattern catenation catalysis and separation [2]. The literature clearly shows that the study of this diverse ligand system is linked with many of the key advances made in inorganic chemistry [3,4]. Non-covalent interaction such as dispersion forces [5], hydrogen bonding [6], coordination bonds [7], and aromatic interactions [8] routinely drive self-assembly processes on surfaces. The intense escalation in the research area of macromolecular metal complexes is due to the astonishing chemical and electronic properties of these materials like conductance, sensors, luminescence, and catalysis of reactions. There are various well described methods (template method) for the synthesis of such materials and the appropriate modifications and in the reactants, provides an alternative for the production of these macromolecular metal containing complexes. The incorporation of metal ions into the macromolecules can be done either by the formation of coordinate bond or by the organometallic bond of the metal ion to the heteroatoms present in the system. The variation in the properties of the metallated macromolecular systems are due to the variation in various aspects like oxidation state of metal, geometry of the complex formed and all these factors can be controlled during the synthesis of the macromolecular system.

Lehn et al has studied the host-guest chemistry and received the noble prize for the same which has opened the minds of scientists in this field. [9,10] and since then supramolecular chemistry has progressive as a renowned field of modern chemical research. Modern supramolecular chemistry has concerned the self-assembly [11] of those synthetic compounds which are related to natural systems [12]. There was an amalgamation of macromolecular systems and traditional polymer chemistry. The synthesis of supramolecular materials having higher ratios of polymer ratio, it was observed to produce materials having attention-grabbing characteristics and assemblies with distinguished polymeric properties. By varying the polymer ratio, the macroscopic characteristics can be

changed greatly. Meijers research group [13] has studied the formation of polymers which are stable and are prepared from low molecular weight materials like poly(ethylene/butylene) with telechelic-2-ureido-4[1H]-pyrimidinone end groups. The high molecular weight polymers are obtained by the interaction of end group through the hydrogen bonding.

## 2. METAL-LIGAND CHEMISTRY

Supramolecular chemistry is a field of study concerning the association of individual molecules into large-scale structures by interactions other than covalent bonds [14]. These supramolecular structures may be designed through a variety of interactions which comprise hydrogen bonding, electrostatic interactions,  $\pi$ - $\pi$  interactions, hydrophobic interactions and other host-guest effects, and metal-ligand interactions. Of these interactions, metal-ligand complexes are among the most well-studied, having first been brought to the consideration of the broader scientific community with Pedersen's work on the ability of cyclic polyether's to complex metal salts in the late 1960's [15,16].

In common terms, metal-ligand coordination orbits around the donation of electron density by the electron-rich ligand to the electron-poor metal center. The electron donation of the ligands may arise through a number of modes, such as a negative charge on the ligand, electron density in the  $\pi$ -electron cloud of  $sp$  and  $sp^2$ -hybridized bonds, and the electrons of lone pairs on an organic molecule. The interaction of electron lone-pairs with metal d-orbitals is witnessed in  $\sigma$ -donating ligands such as amines and phosphines. One particular example is  $Co(NH_3)_6Cl_3$ , a compound whose structure was first interpreted by Werner, laying the basis of the study of coordination chemistry. Upon coordination of the ligand with the metal, hybridized metal orbitals of the type  $d^xsp^y$  form accept electron density from the ligand, with the integers  $x$  and  $y$  depending on the extent of d-orbital filling, ligand properties, and other factors [17]. Often the partial hybridization of the d-subshell of the metal gives rise to a splitting of the orbital energies, resulting in higher energy antibonding hybridized orbitals, and lower energy bonding orbitals. This can overcome the pairing energy of the electrons in the orbital, resulting in paired electrons occupying lower energy orbitals [18].

### 3. SCHIFF BASE CHEMISTRY

Schiff bases have occupied an important position in coordination chemistry since they have been discovered [19-21]. Due to the ease of formation, stability and different oxidation states, they have played a great role in the chelation of transition metal and main metal coordination chemistry [22-24]. Inorganic chemistry has advanced greatly due to the presence of these diverse ligand systems. These schiff bases have also played a pronounced part in the construction of inorganic biochemistry, catalysis, medicine, optical properties etc. Transition metal coordination with these diverse ligand systems are also of great importance in the field of chemistry [25]. The constructions and properties of these Schiff base metal complexes can be improved by attaching different substituents to the ligand backbone [26]. Their influential role in the biological sciences has increased the interests of scientists and are greatly used as antibacterial, antifungal and antitumor [27-29].

Schiff bases are designed and synthesized by the reaction of amines with aldehydes and ketones under specific conditions discovered by Hugo Schiff [30]. Schiff base is a nitrogen containing compound also known as imine or azomethine. The functional group present in the Schiff base ligand is  $R_1HC=N-R_2$  where  $R_1$  and  $R_2$  are aryl, alkyl, cycloalkyl or heterocyclic group (Fig. 1).

The presence of lone pair of electron on nitrogen atom of the C=N group imparts excellent chelating ability to these compounds as are shown in the example given in Fig. 2. The chelating capability of the schiff baes makes it an

interesting ligand system in coordination chemistry particularly due to its flexibility and ease of formation.

Schiff bases can be synthesized in various ways by adopting different methods [31-33], while as an acid catalysed condensation of amines and aldehydes and ketones is the most common one. This is a two-step reaction in which the nucleophilic attack by nitrogen atom on carbonyl carbon is the first one resulting in the carbinolamine intermediate which is unstable. In the second step, the intermediate undergoes dehydration to form a carbon double bond which is known as a Schiff base [34,35]. (Scheme 1) All steps involved in this reaction sequence are reversible. Therefore, Schiff base condensation can be used for generating diverse materials if different starting materials are used [36].

There are various factors which disturb the condensation reaction, but the pH solution plays a vital role. Since the basic amine is protonated in acidic medium and cannot act as a nucleophile hence stops the reaction. Moreover, in basic medium sufficient number of protons are not available to eliminate the hydroxyl group from the unstable intermediate, hence makes it difficult to continue the reaction [37].

Schiff base metal complexes are commonly synthesized by reacting metal salts with Schiff base ligands under specific reaction conditions. Nevertheless, for the purpose of catalysis, some of the metal complexes are also synthesized during the reaction process in the system. Five synthetic routes have been described for the Schiff base metal complex synthesis and are given as follows in Scheme 2 [38].

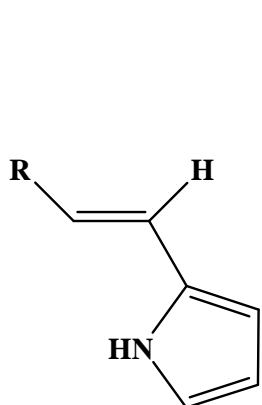


Fig. 1. Synthesis of Schiff base ligand

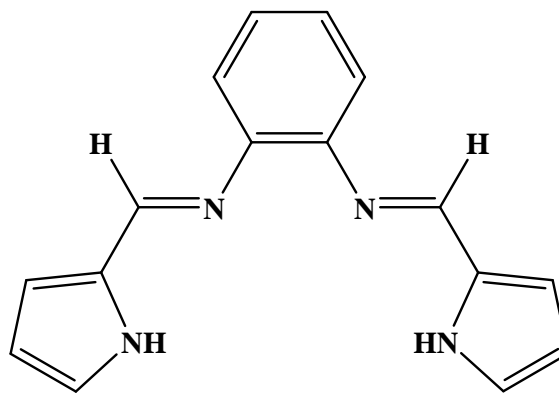
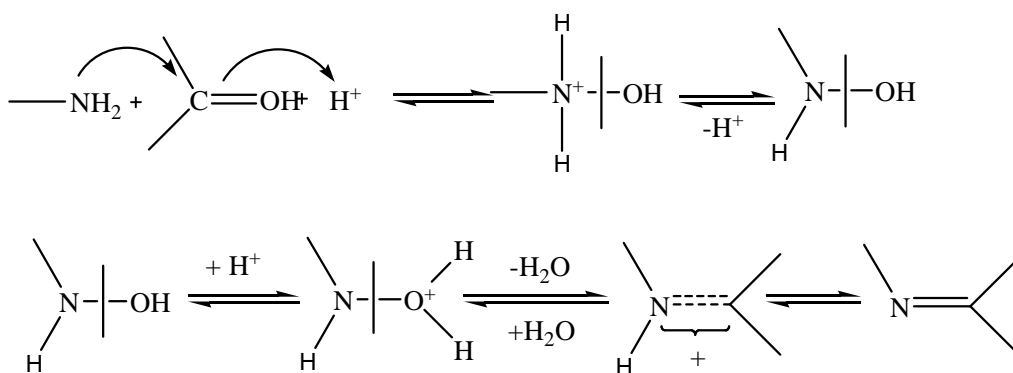
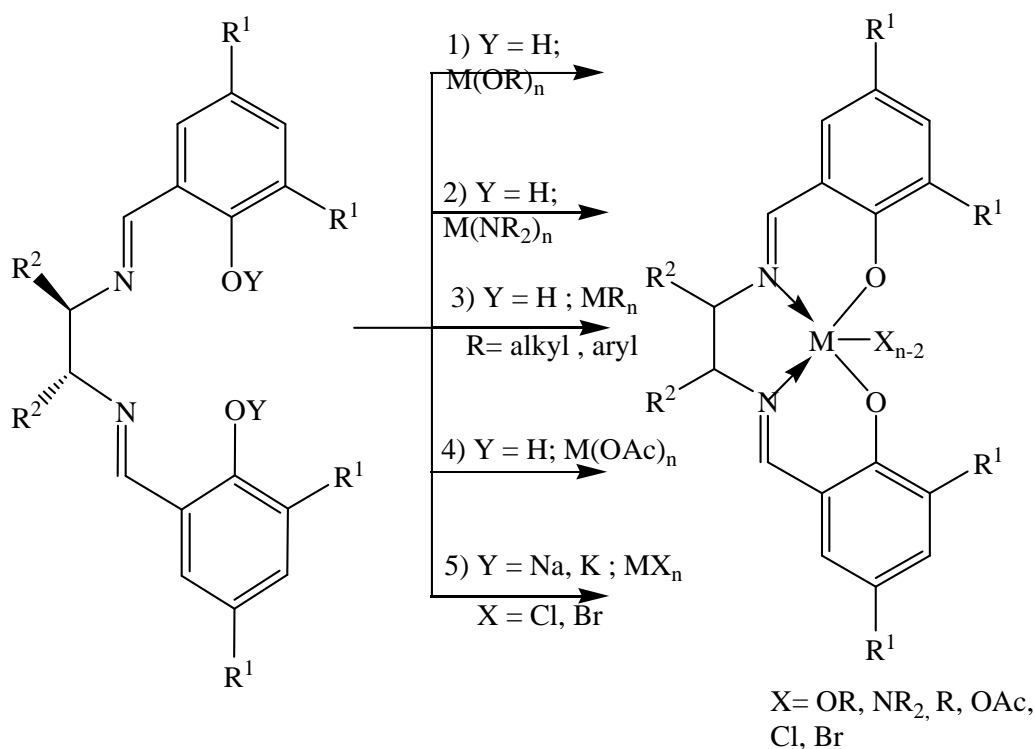


Fig. 2. Synthesis of chelating Schiff base ligand



Scheme 1. Synthesis of Schiff base



Scheme 2. Synthetic routes for metal complex synthesis

Route 1 uses the metal alkoxides  $[M(OR)_n]$  which are easily available to use particularly of transition metals. In Route 2 Metal amides, are used as the precursors in the synthesis of metal complexes based on schiff bases. Various other routes utilised as synthetic routes consists of direct reaction of Schiff base and the metal ion. (Route 3) or reaction of the Schiff bases with the corresponding metal acetates with refluxing (Route 4). The scheme described in Route 5 which is somewhat effective in synthesizing salen-type metal complexes comprises of a two-

step reaction, the deprotonation of the Schiff bases and the reaction with metal salts. The Phenolic hydrogens can be deprotonated effectively by using sodium hydride or potassium hydride in coordinating solvents and the surplus NaH or KH can be removed by filtration.

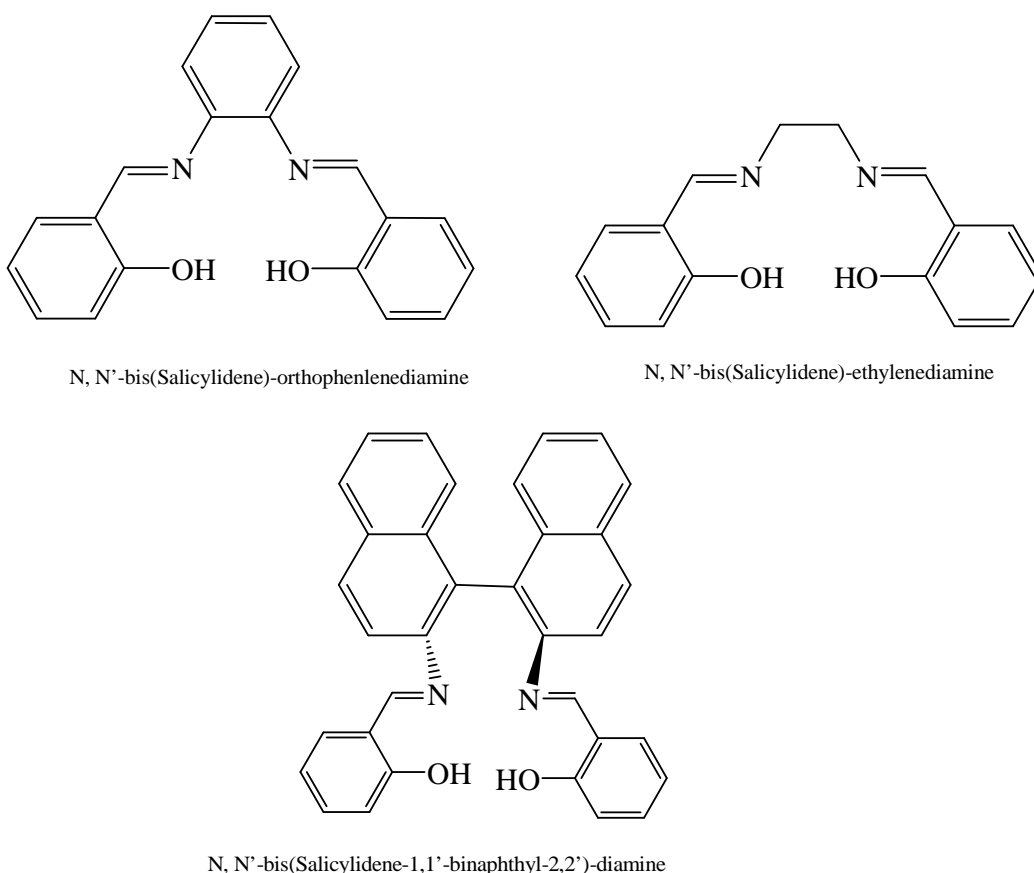
The word salen was used only to designate the tetradentate Schiff bases obtained from salicylaldehyde and ethylenediamine, and is reported in the literature to represent the class of (O, N, N, O) tetradentate ligands (Fig. 3). As

numerous achiral and chiral Schiff base ligands and by-products are synthetically obtainable, a widespread diversity of metal-tetradentate Schiff base complexes bearing  $N_2O_2$  has been produced as well. Schiff base metal complexes frequently assume octahedral configuration, even though with a limited exception and they normally carry two ancillary ligands [39,40].

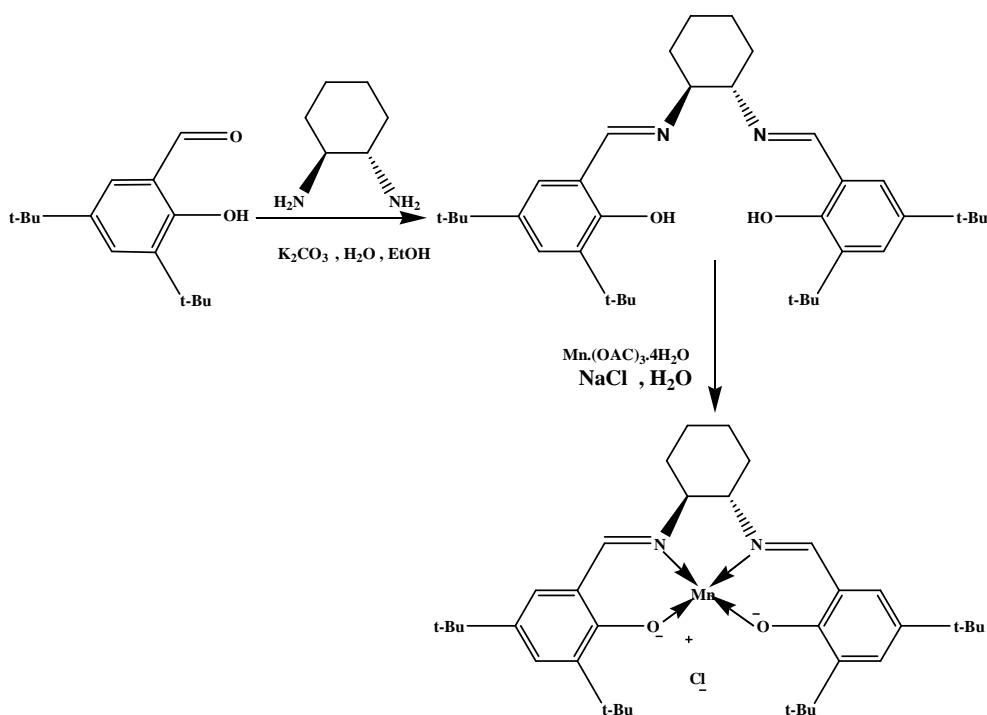
The chemistry of multimetallic complexes is presently an extensive and interdisciplinary research area. Dinucleating metal complexes have been attention-grabbing field of research because of their importance because they act as catalysts in the process of oxygenation [41]. Innovations of dinuclear cores at the prominent sites of some metalloproteins have awakened attentiveness in the investigation of multimetallic systems [42]. Many mono and dialdehyde / ketones have been engaged to condense with amines or amino acid to determine multidentate binucleating Schiff bases to synthesize a diversity of binuclear transition metal complexes

[43]. Trinuclear metal complexes can be synthesized from the ligands having azomethine nitrogen and phenolic oxygen. The cavity present in the tetradentate ligands presents a suitable place for complexation for divalent metal ions. Schiff bases complexes also form homo or hetero trinuclear complexes by acting as bidentate ligands [44]. The proficiency of these complexes to coordinate via cis oxygen atoms leads to the development of trinuclear metal complexes [45].

There are number of uses of Schiff base complexes which are discussed briefly. The development of the distinguished Schiff base complex, N, N'-bis(3, 5-di-tertbutylsalicylidene) - 1, 2-cyclohexanediaminomanganese (III) chloride is presented in Scheme 3 [46,47]. This metal complex of manganese is called as Jacobsen's catalyst which is prepared efficiently by the reaction of *trans*- 1,2-diaminocyclohexane and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde and manganese metal followed by the oxidation.



**Fig. 3. Synthesis of achiral and chiral Schiff base ligands**



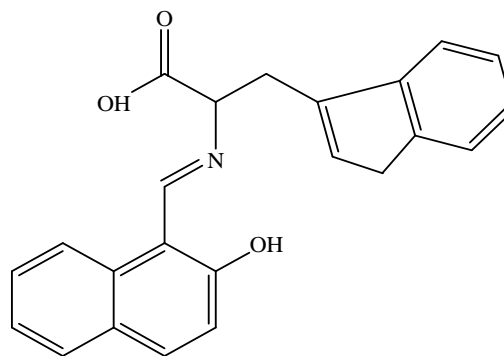
**Scheme 3. Synthesis of Jacobsen's catalyst**

Bhunia et al. prepared a catalyst by the hybridization of a Ni(II) complex with the mesoporous silica, MCM-41 by modification. The ligand has been obtained from the condensation of salicylaldehyde and 3-aminopropyltriethoxysilane which was then attached with the MCM-41 chemically via silicon alkoxide pathway. The properties of this synthesized catalyst has been checked in the epoxidation of alkenes using tert-butylhydroperoxide as an oxidant and the catalyst can be recycled several times without any activity loss [48].

Li and co-workers have designed a new zinc containing chemosensor namely 2-((2-hydroxynaphthalen-1-yl)methyleneamino)-3-(1H-indol-3-yl) propanoic acid (Fig. 4), which has the easy procedure for synthesis and have high selectivity to Zn ions with complete solubility in aqueous solvent. In addition to this sensor, they also incorporated the inexpensive and water-soluble tryptophan with 2-hydroxy-1-naphthaldehyde to make available the chelation sites for the metal ions and the assembly was interpreted spectroscopically [49].

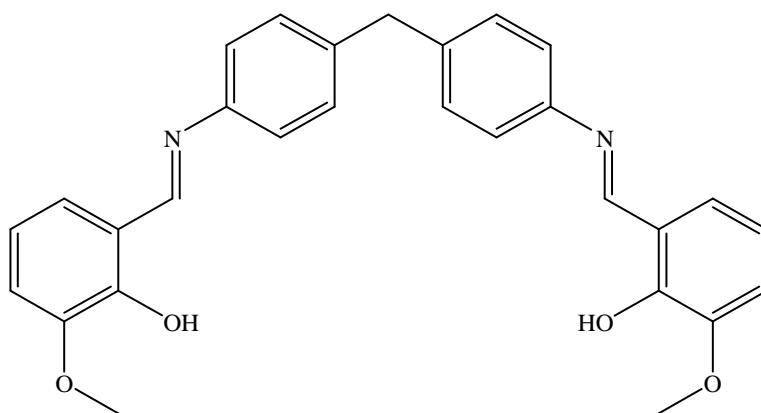
Schiff bases based on the fluorescence used for the finding of Zn(II) has been synthesized by Liu

et al. (Fig. 5). This confident ligand system is employed for the progress of new fluorescent probe for the discovery of Zn(II) cation [50].

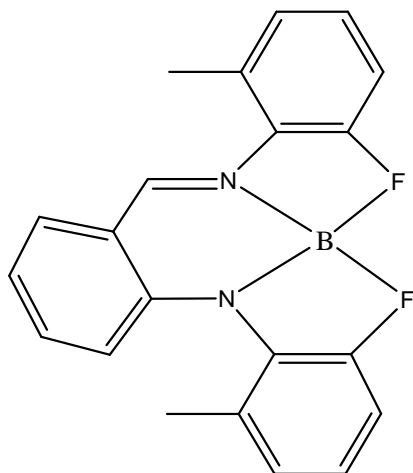


**Fig. 4. Synthesis of chemosensor ligands**

Luminescent metal complexes have received noble consideration in the current era owing to their budding applications in the fields of optoelectronic devices and sensors [51,52]. The most central concern in organic LED is the synthesis of molecules having extraordinary emission efficiency and selection of metal ions via the modification [53,54]. Organic boron compounds have worthy luminescent properties and electron-transporting properties (Fig. 6) [55].



**Fig. 5. Synthesis of Schiff bases base on fluorescence**



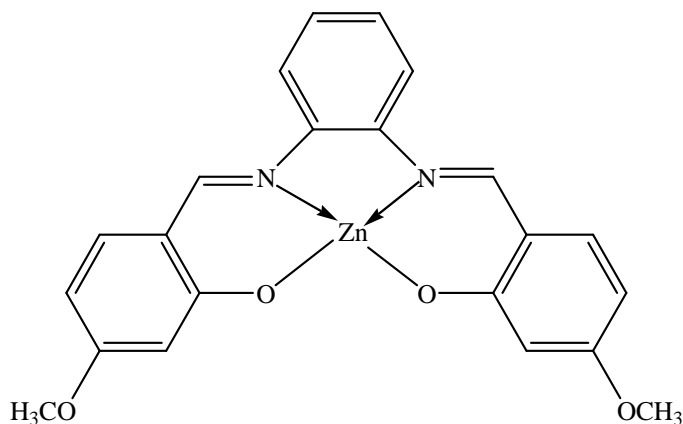
**Fig. 6. Synthesis of luminescent metal complexes**

Bhattacharjee et al. [56] synthesized a series of novel photo luminescent hemi disc like distorted

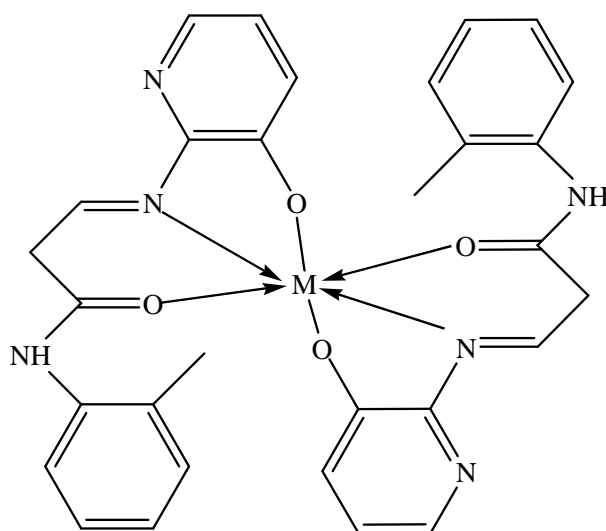
square planar Zn(II) Schiff base complexes having 4-substituted alkoxy chains on the side aromatic ring (Fig. 7).

The applications of organic chromophore as nonlinear optical materials in the fields of optical signal processing, optical data acquisition, optical computing and optical communications have increased the interest of scientists in designing and synthesizing of such materials [57]. Azomethines having imine group demonstration wide applications such as nonlinear optical materials, corrosion inhibitors, catalyst transporters, heat resistant materials and in biological systems [58-60].

Tanga and co-workers [61] has synthesized cyanide based salen type Schiff base electronic acceptors with a series of asymmetric donor acceptor substituents (Fig. 8).



**Fig. 7. Synthesis of novel photo luminescent Zn(II) Schiff base complexes**



**Fig. 8. Synthesis of salen type Schiff base electronic acceptors**

Schiff bases are also known to exhibit biological properties and are mostly used as drugs in medicinal [62,63]. Experimental studies have shown that the incorporation of metal ion increases the biological activity of Schiff bases upon chelation [64,65].

S. Hasnain et al. [66] synthesized Schiff base N, N' bis(Salicylidene) thiosemicarbazide obtained from thiosemicarbazide and salicylaldehyde and its Cu(II), Ni(II), Mn(II) and Co(II) complexes which displayed effective antimicrobial activities against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and against *Aspergillus niger*, *Candida albicans*, and *Aspergillus flavus* (yeast) respectively. Schiff base obtained from 2'-methyleacetoacetanilide and 2-amino-3-hydroxypyridine and its Zn(II), Cu(II), Ni(II) and Co(II) complexes have been tested for their antimicrobial activities against various strains of bacteria and fungi and the statistics shows that the complexes have greater activity than the ligand [67].

Various biological investigations have proved that DNA is the main target of anticancer drugs as the drugs interact with the DNA of the cancer cells and damage it, hence blocking the cell division which leads to the death of cells [68,69]. The transition metal complexes have emerged as great probes for the DNA studies and potential therapeutic agents [70-72]. To specifically target DNA sites will create novel chemotherapeutics and also magnify capability for scientists to probe DNA and to synthesize exceedingly profound diagnostic agents [73].

DNA binding of metal complexes is an important issue and it is compulsory to comprehend over the various binding modes while synthesizing the antitumor drugs. Mostly, the metal complexes interact either in covalent way or in non-covalent way with the DNA, whereas the non-covalent interaction has three binding modes that is intercalation, groove binding and external static electronic effects. Amongst these binding modes, intercalation is of great importance as it increases the planarity of the ligands [74,75]. Furthermore, the complex geometry, type of metal ion, valency of the metal ion and type of donor atoms present play an essential part in determining the binding magnitude of metal complexes to DNA [76-78].

The anticancer activity of Schiff base ligands and its metal complexes have been investigated broadly and the complexation of the metal ions increases the activity of the Schiff bases [79,80]. Nickel complexes of 1, 2-bis (salicylideneamino) ethane in presence of monoperoxyphthalic acid show the cleavage of plasmid DNA [81]. Griffin et al. [82] have observed DNA binding of twenty-six (26) salen complexes of Mn(III) and observed that the structure and the stereochemistry of the substituents are mainly responsible for the changing DNA cleavage.

The interaction of chromium(III) Schiff base complexes,  $[\text{Cr}(\text{salen})(\text{H}_2\text{O})_2]^+$  where salen = N,N' ethylene bis (salicylideneimine) and  $[\text{Cr}(\text{salprn})(\text{H}_2\text{O})_2]^+$  where salprn = N,N' propylene bis (salicylideneimine) (Fig. 9) with calf thymus DNA (CT-DNA) has been reported



[83,84]. Binuclear Cu(II) complexes of N, N' bis(3,5-tert-butylsalicylidene-2-hydroxy)-1,3-propanediamine, are effective in cleaving DNA of the plasmid in the presence of H<sub>2</sub>O<sub>2</sub> at pH = 7.2 and 37 °C [85].

Wu and co-workers synthesized a binuclear complex, [(phen)Cu(lbipp) Cu(phen)](ClO<sub>4</sub>)<sub>4</sub> (Fig. 10) (phen = 1, 10-phenanthroline and lbipp = 2,9-bis(2-imadazo [4,5-f] [1,10] phenanthroline) - 1, 10-phenanthroline). Photophysical and viscometry have shown that binuclear copper (II) complex binds strongly to CT-DNA by intercalation of the two phenanthroline copper (II) terminals [86].

Raman et al. have reported the DNA binding properties of the Cu(II) and VO(IV) complexes derived from Schiff base ligand 4-(3',4'-dimethoxybenzaldehyde) 2-3-dimethyl-1-phenyl-3-pyrazolin-5-one with polypyridyl ligand(s) as co-ligand(s) binding to CT-DNA by partial intercalation into the base pairs of DNA

and stimulate the photo cleavage of plasmid DNA pBR322 under irradiation at 365 nm [87].

Schiff base metal complexes [88] derived from amino acids have properties which are essential for the understanding several biochemical reactions *in vivo* [89]. Amino acids establish the construction of proteins and are vital for carrying out vast quantity of biological roles as demonstrated by the part played by enzymes [90-93]. O-phthalaldehyde plays essential role in amino acid assay as the residues in numerous enzymes and biological fluids have been determined by using O-phthalaldehyde [94]. It is used at the clinical level as a best disinfectant [95]. Currently, great attention is paid for the development of copper Schiff base complexes because as they act as models for copper proteins, where a diverse set of donor atoms is present [96]. Zinc containing carboxylate-bridged complexes [97] are used in bio systems as phosphatases and amino peptidases and cobalt complexes to mimic cobalamine (B<sub>12</sub>) coenzymes [98].

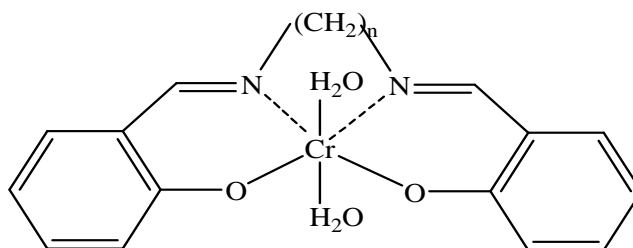


Fig. 9. Synthesis of chromium(III) Schiff base complex

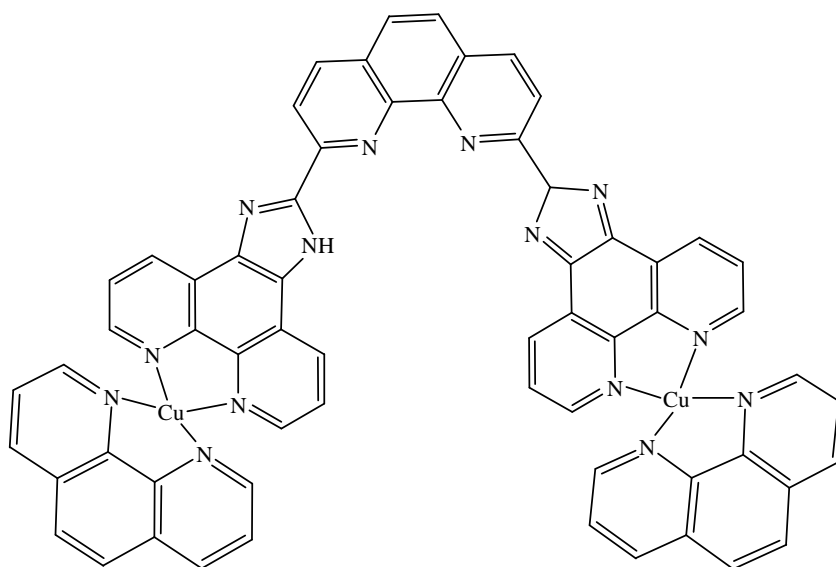


Fig. 10. Synthesis of a binuclear copper complex

Sakiyan et al. [99] have synthesized the Schiff base Mn(III) complexes (Fig. 11) obtained from amino acids and 2-hydroxy-1-naphthaldehyde. The coordinating behavior has shown that Schiff base binds through the ONO donor set derived from the carboxyl, imino and phenoxy groups of the ligands.

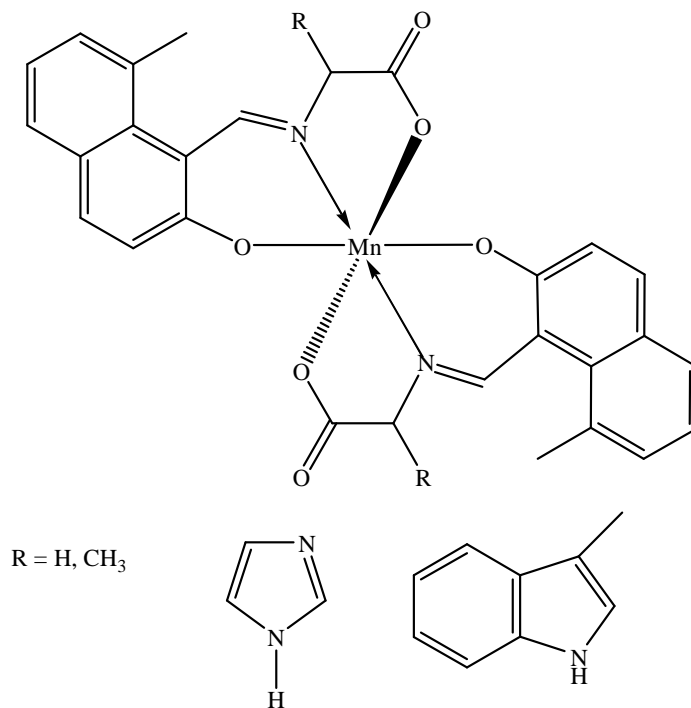
Boghaei et al. [100] synthesized a sequence of new ternary zinc (II) complexes [Zn (L) (phen)] (Fig. 12) where phen = 1, 10-phenanthroline and L = ligands obtained from the amino acids and sodium salicylaldehyde-5-sulfonate and sodium 3-methoxy-salicylaldehyde-5-sulfonate. The Schiff base ligand act as tridentate ONO moiety, coordinating to the metal through oxygen, nitrogen, carboxyl oxygen and nitrogen's of 1, 10-phenanthroline.

Dong and co-workers have designed and synthesized a ternary Cu(II) complex with Schiff base obtained from salicylaldehyde and L-valine and 1, 10-phenanthroline. The DNA-binding properties of the complex have been studied by UV-visible, fluorescence, circular dichroism spectroscopies and thermal denaturation measurements [101].

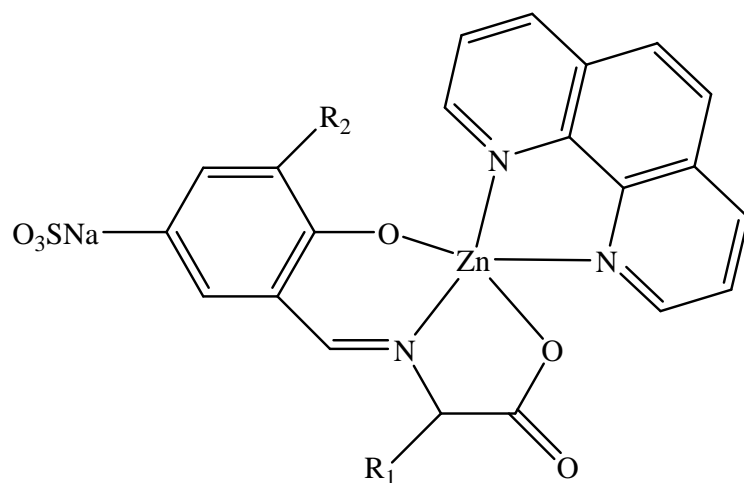
Sharma et al. [102] reported silicon metal complexes of amino acid based ligands (Fig. 13) obtained from the condensation of furfuraldehyde and indole-3- carbaldehyde with alanine, glycine, valine, isoleucine and tryptophan and the synthesized compounds were characterised and tested for antifungal activities.

Abdallah et al. [103] reported a new Schiff base ligand (Fig. 14) by the reaction of *o*-phthaldehyde and 2-aminophenol and its complexes with various metal ions and were screened for antimicrobial activities. The synthesized compounds inhibited the growth of the tested fungi at different rates. However, the metal complexes of Mn (II) and Fe (II) were tested for antibacterial activity and exhibited weak growth of inhibition against *Escherichia coli* and *Staphylococcus aureus*.

Sinha et al. [104] have reported heterocyclic Schiff base ligands from the condensation reactions of indole-3-carboxaldehyde with different L-amino acids and have studied their radio imaging, radiolabeling and antimicrobial activity.



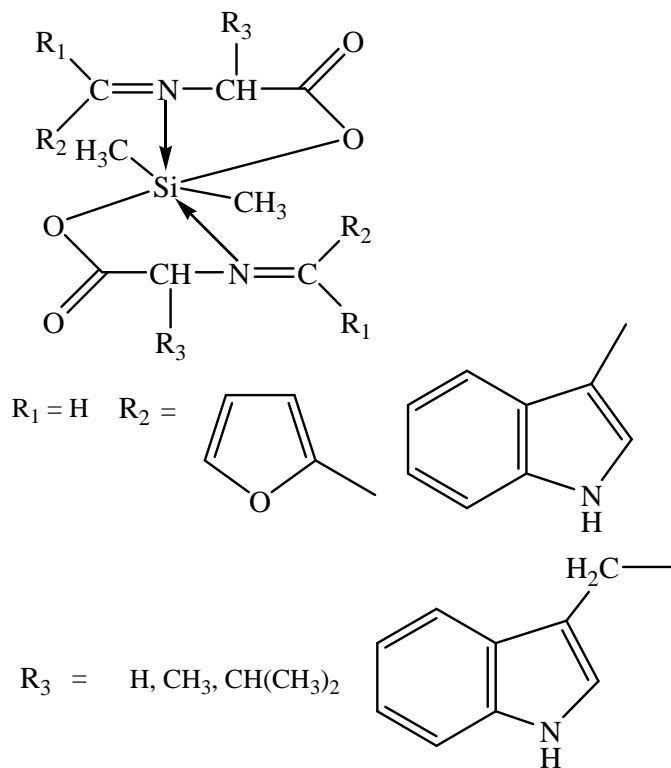
**Fig. 11. Synthesis of the Schiff base Mn(III) complex**



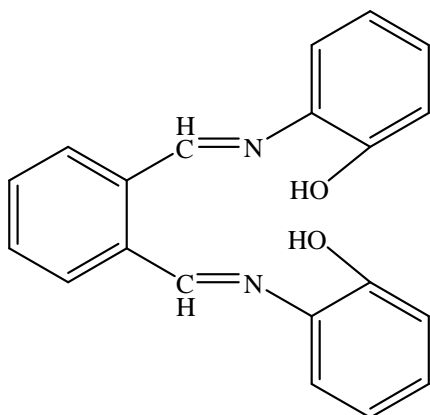
$R_1 = \text{H, CH}_2\text{Ph, CH(CH}_3)_2, \text{CH}_3, \text{CH}_2\text{CH(CH}_3)_2$

$R_2 = \text{H, OCH}_3$

**Fig. 12. Synthesis of a sequence of ternary zinc (II) complexes**



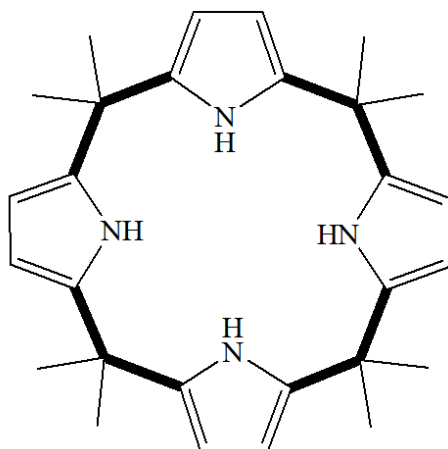
**Fig. 13. Monomeric complexes of amino acid Schiff base ligands**



**Fig. 14. Synthesis of antimicrobial Schiff base ligand**

#### 4. MACROCYCLIC CHEMISTRY

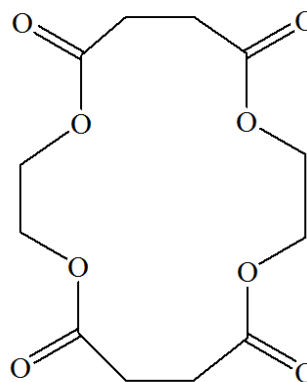
The study of macrocycle synthesis has gone through wonderful development and their complexation with variety of metal ions has been systematically studied [105]. Macrocyclic ligands are polydentate ligands having their donor atoms either incorporated in or attached to a cyclic backbone. Macrocyclic compounds have attracted interest because of their unlimited applications in various fields of research. Macrocyclic compounds are stable and form different compounds of both organic and inorganic nature and by reaction with some anionic and neutral organic and biological substrates give supramolecular compounds with particular properties and applications [106]. A great number of synthetic, as well as many natural macrocycles have now been investigated.



**Fig. 15. Synthesis of the pyrrole based macrocycle**

The involvement of macrocyclic ligands and their metal complexes in a number of essential biological processes has long been documented. They have shown vital day-to-day functions like photosynthesis, transportation of oxygen and motivated the scientists in deep study of metal ion chemistry of macrocyclic systems [107]. Macrocyclic ligands have been used as selective hosts for wide-ranging guest molecules and ions due to their central cavity, therefore these are engaged as selective extractants for transition and post-transition metal ions in a range of solvent extraction and bulk membrane transport studies [108]. Macrocyclic complexes have the applications in the biomedical field as contrast enhancing agents in magnetic resonance imaging, NMR shift reagents and catalysts for the cleavage of RNA [109-111]. Macrocyclic ligands have mixed soft-hard donor character, multipurpose coordination behavior and pharmacological properties due to which they have received special attraction in the chemical research [112-116]. The macrocyclic chemistry shows applications in other areas such as metal ion catalysis, organic synthesis, metal ion discrimination and in supramolecular chemistry [117].

Baeyer synthesized the first documented macrocycle possessing a pyrrole heterocyclic ring [118] (Fig. 15), similar to the porphyrin, via an acid catalyzed condensation between pyrrole and acetone. The first macrocyclic compound synthesized from a diacid was dimeric ethylene succinate reported [119] by Vorlander in 1894 (Fig. 16).



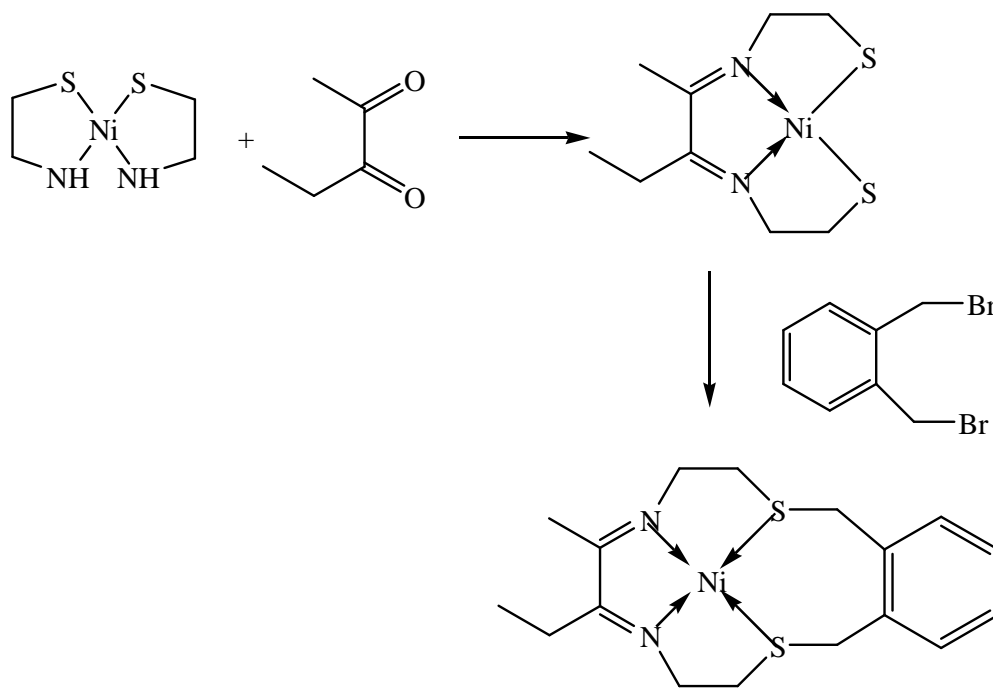
**Fig. 16. Synthesis of dimeric ethylene succinate**

Macrocyclic ligands have two matchless properties: (a) their capability to differentiate between two metal ions based their ion radii; (b) the important improvement in complex stability constant which is usually shown by macrocyclic ligands relative to their open-chain analogues (macrocyclic effect) [120]. Synthesis of macrocyclic complexes is influenced by the size of the internal cavity, by the rigidity of macrocycles, nature of its donor atoms and by the complexing properties of the anion involved in the coordination [121]. The applications shown by such compounds ranging from modeling the active sites of many metalloenzymes [122], to hosting and carrying small molecules [123] or catalysis [124] has raised the interest in this field of study. Presently the examination of selective coordination properties in novel systems is the need of an hour [125].

One of the best and effective methods for the development of macrocyclic complexes consists of an *in-situ* methodology where the metal ion in the cyclization reaction increases the yield of the cyclic product greatly. The metal ion plays an important part role in the completion of the reaction and this effect is known as “*metal template effect*” [126]. The metal ion directs the condensation favorably to cyclic rather than the

polymeric products. The metal ion and the anion are important because the equilibrium among the size of the cation and anion will control the dissociation of the metal salt in the reaction medium [127]. Multidentate macrocyclic ligand synthesis by the metal template effect has been documented as offering higher-yields [128,129]. The first instance of the development of a macrocycle using this technique was described [130] by Thompson and Busch (Scheme 4).

Nowadays designing of macrocyclic complexes which are highly selective and sensitive to metal ions has becoming an important branch of research [131]. Although various strategies were employed for the development of macrocyclic complexes, but template method has gained the importance among all which offers selective pathways to the products that are not available without the metal ion [132]. The ability of metal ions to synthesis of macrocyclic ligands by the template method depends both on the ligand and metal characteristics [133,134]. Metal ions bind with the molecules i.e. ligand systems having donor group of atoms and place them around themselves to form a particular geometry. The metal ions act as a template and direct the ligand system to take appropriate geometry through a proper pathway [136].



**Scheme 4. Synthesis of a macrocycle using template effect**

In addition to template method of synthesis significant struggle have been made to develop macrocycles without metal ions starting from various dicarbonyl compounds and diamines [135,136]. The macrocycles derived by the reaction of one molecule each of the dicarbonyl and diamine compounds have been designated as [1+1] macrocycles and the macrocycles achieved by the reaction of two molecules of the dicarbonyl compounds with the two molecules of the diamine moiety have been designated as [2+2] macrocycles as a result of the number of head and lateral units present [137,138].

The inclination for the development of "1+1" and "2+2" macrocycles in metal template condensation also depends upon the following factors:

- A "1+1" macrocycle cannot be formed, when the diamine has not enough chain length between the two carbonyl groups [139].
- A "2+2" condensation prefers over "1+1" condensation, if the metal ion has large ionic radii [140].
- Nature of metal ion such as charge, polarizability and geometry of the complex.
- Conformation of "1+1" acyclic chelate.

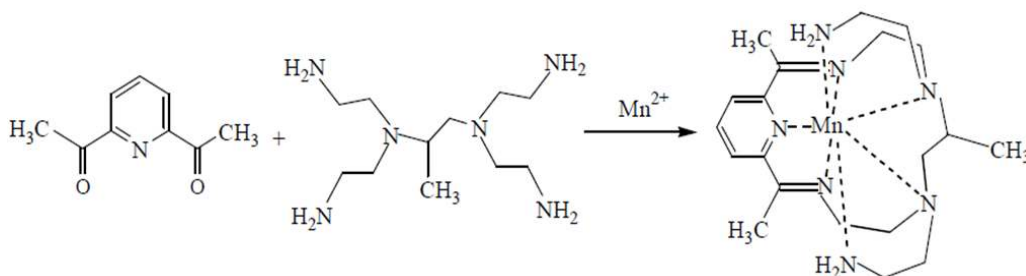
H. Khan mohammadi and co-workers have the developed of asymmetric heptaaza Schiff base macrocyclic complex of Mn(II) ion by templated [1 + 1] cyclocondensation of N,N,N',N'-tetrakis(2-aminoethyl)propane-1,2-diamine with 2,6-diacetylpyridine [141] (Scheme 5).

Due to the increasing applicability of aza-macrocyclic compounds in biomimetic, catalytic, biology and medicine, these compounds have gained much consideration. They have found great significance in the arenas where metal complexes with exciting kinetic and

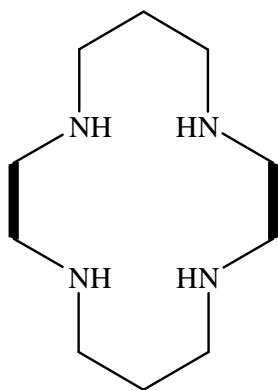
thermodynamic stabilities toward metal release are necessary such as techniques like magnetic resonance imaging, imaging with radioisotopes and radiotherapy [142]. Aza-macrocyclic ligands are also dynamically used as antimicrobial agents and other biological properties [143-146].

The tetraaza macrocyclic ligands and their metal complexes have been largely studied and fascinated coordination chemists [147]. The significance of tetraaza macrocycles [14] and  $N_4$  (Fig. 17) and [12] and  $N_4$  (Fig. 18) have been acknowledged for several years and their complexation chemistry with a large variety of metal ions has been investigated comprehensively [148-151]. Sulekh Chandra et al. have reported the synthesis and characterization of a large number of tetraazamacrocyclic complexes. The applications of the tetraaza macrocyclic ligands and their metal complexes range from the elimination of toxic metals from unwanted streams, radiotherapy to contrast agents for magnetic resonance imaging [152-154].

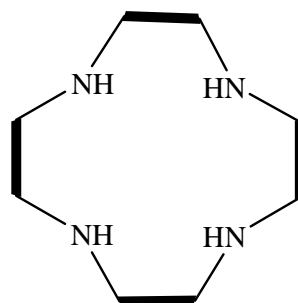
The hexaazamacrocycles are motivating and multipurpose compounds having capability to bind one or two metal ions and can also encapsulate anionic guests through electrostatic interactions [155]. (Figs. 19, 20 and 21) Rothermel and co-workers have [156] synthesized hexaazamacrocycles (Fig. 20) showing the role of metal ion in describing the conformation of macrocycle [157]. Hexaazamacrocycles as reported by Martell et al. [158] have the capacity to bind a wide variety of anions together with halides, nitrate and phosphate, and even in chelating the biological anions like carboxylates and nucleotides [159]. M. del C. Fernandez and co-workers have synthesized the Ni(II) nitrate and perchlorate complexes with two stereo-isomeric hexaazamacrocyclic ligands [160] (Fig. 22).



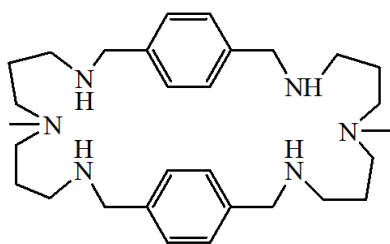
**Scheme 5. Developed of asymmetric Schiff base macrocyclic complex of Mn(II)**



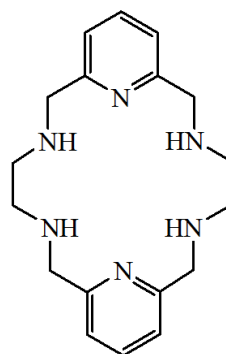
**Fig. 17. Synthesis of tetraaza macrocyclic ligand**



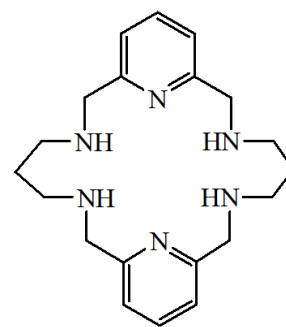
**Fig. 18. Synthesis of tetraaza macrocyclic ligand**



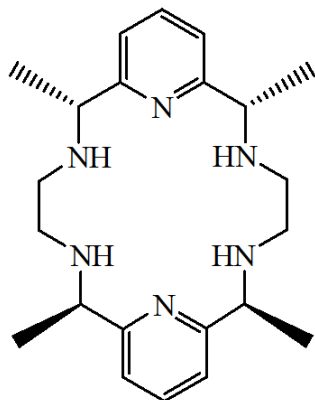
**Fig. 19. Synthesis of hexaaza macrocyclic ligand**



**Fig. 20. Synthesis of hexaaza macrocyclic ligand**



**Fig. 21. Synthesis of hexaaza macrocyclic ligand**



**Fig. 22. Synthesis of the stereo-isomeric hexaazamacrocyclic ligand**

Octaazamacrocycles having the huge cavity size formed by the macrocycle backbone form the mono and di-nuclear metal complexes and also display fascinating co-ordination properties. They

are capable to stabilize many anions in their hexaprotonated form [161].

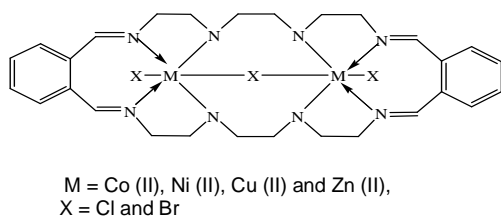
Polyazamacrocycles display exceptional features, particularly the highly systematized binding position for complex formation with both cations and host molecules [162]. Polyazamacrocyclic-metal complexes as MRI contrast agents in medicinal chemistry, metalloenzyme mimics, and catalysts as well as fluorescence probes in chemical biology are well documented [163,164]. The large polyazamacrocyclic molecules form stable metal complexes, with various metal ions, owing to their number of donating nitrogen atoms [165]. The chelation abilities of polyaza macrocycles are usually due to the ring size of the molecule [166]. The effect of functional groups on the geometry and chemical properties of polyaza macrocycles have been investigated by incorporating the functional groups in the macrocycles [167].

The chemistry of binucleating macrocycles has emerged as an interesting field for the chemists of present era because of the capability of keeping two transition metal ions in close vicinity. Such compounds were also designed early because of their wide range of applications ranging from bioinorganic chemistry [168,169], magneto chemistry [170], coordination chemistry [171,172] to homogeneous catalysis [173]. Macrocycles accommodating two metal ions because of their large cavity size can be utilised to bind the metal centre at fixed distances having an extra internal or external bridging group, which gives the macrocyclic system rigidity and also completes the structure of the binuclear species thus gives structurally well-defined compounds [174]. A lot of metalloenzymes contains two copper ions in their active site that operate cooperatively [175]. These binuclear copper complexes have extraordinary prominence as novel inorganic resources bestowing innumerable magnetic characteristics with anti-ferromagnetic coupling depending upon the bridge angle and degree of distortion [176]. Di-copper containing proteins are of biological importance performing various important functions like dioxygen transport, electron transfer, reduction of nitrogen oxides and hydrolytic chemistry [177]. Binucleating macrocyclic complexes can be used as models to recognise the reactivity changes caused by the proximity of both metal centres. Binuclear macrocyclic complexes having similar and dissimilar coordination sites are of great importance since these are thermodynamically stabilized and kinetically retarded with respect to metal dissociation [178,179]. The three main synthetic approaches have been followed while designing binuclear macrocyclic complexes, (i) synthesis of large macrocycles or macro bicycles capable to fit in two metal ions [180], (ii) synthesis of bis macrocycles [181] and (iii) use of chelating agents bridging two macrocyclic units [182]. Metal ions can co-operate directly through electrostatic forces or indirectly via electron

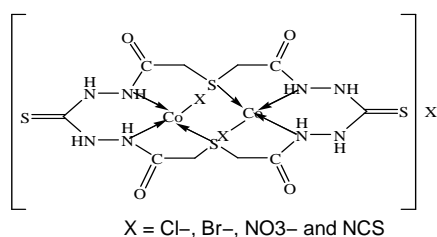
through the macrocyclic background. A wide range of binuclear macrocyclic ligands with two similar and dissimilar metal centers have been stated [183] (Figs. 23 and 24).

The macrocyclic polyamine ligands having pendant arms with functional groups and their metal complexes has been an emerging area of research [184-186]. Due to the presence these pendant arm groups, the attached groups offer additional donating groups which bring about the change in the structure of the macrocycle like stability, selectivity, stereochemistry and thermodynamic factors [187]. Thus, the chemical properties of such complexes are intensely altered by the nature and number of functional groups [188]. The ligating groups and the pendant arms control the metal binding capability of the macrocycle, thus other structures can also be designed by substituting the groups at the carbon and nitrogen atoms of the ring [189]. The compounds obtained by the substitution at carbon atom do not change the nature of the heteroatomic donor groups while as the groups attached to the nitrogen atom produce five or six numbered chelate rings, but both the functionalization's offer advantages and perform various functions at the same time. A group of researchers [190] have investigate the design and synthesis of a pendant arm hexaazamacrocyclic ligand (Fig. 25) L bearing four ethyldioxolane pendant groups and its metal complexes with various transition, post transition and lanthanide metal ions.

Farha and co-workers have reported the synthesis of a hexaazamacrocyclic ligand and its metal complexes [191] having pendant arm by reaction of 1, 2-phenylenediamine and 1, 4-phenylenediamine and formaldehyde (Fig. 26). Also Hassan Keypour et al. [192] have the synthesized of three  $Mn^{2+}$  macrocycles with two 2-pyridylmethyl pendant arms by the condensation of 2, 6- diacetylpyridine with three hexadentate amines with altered branches.

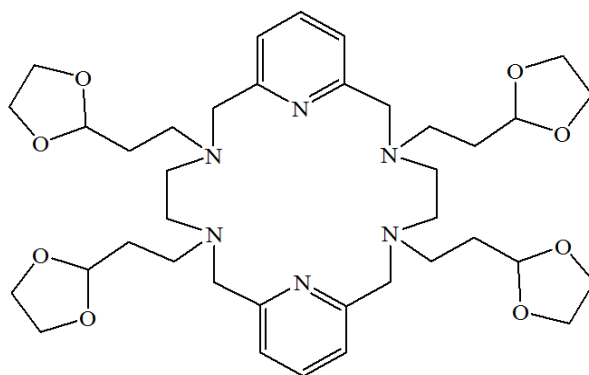


**Fig. 23. Synthesis of the binuclear macrocyclic ligand**

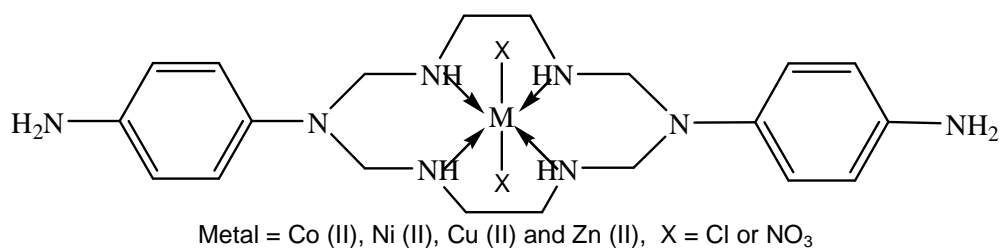


**Fig. 24. Synthesis of the binuclear macrocyclic ligand**





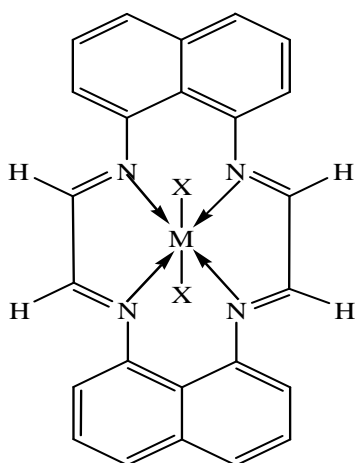
**Fig. 25. Synthesis of a pendant arm hexaazamacrocyclic ligand**



**Fig. 26. Synthesis of a pendant arm hexaazamacrocyclic ligand and its metal complexes**

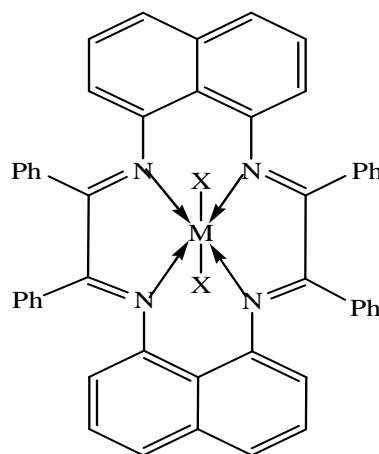
Macrocycles containing aromatic moieties form charge transfer complexes with various guest molecules and are used to investigate the complexation of host guest molecules to deliver new considerations into non-covalent binding interaction, chiefly cation  $\pi$ -interaction which include the stabilization of a positive charge by

the face of an aromatic ring [193]. There are abundant macrocycles having aromatic moieties [194,195] with 1, 8 diamionaphthalene (Fig. 27) and benzil (Fig. 28) subunits as the central part of the structural backbone of the macrocyclic structure.



M = Co(II), Ni(II), Cu(II) and Zn(II) X = Cl or NO<sub>3</sub>

**Fig. 27. Synthesis of macrocycles having aromatic moieties**



Where M = Co(II), Ni(II), Cu(II), Zn(II) X = Cl, NO<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>COO

**Fig. 28. Synthesis of macrocycles having aromatic moieties**

## 5. CONCLUSION

In this attempt the discovery, progress and the applications of the diverse Schiff bases, macrocyclic systems and their transition metal complexes have been widely sightseen. However, the biological activity of these class of compounds needs advance exploration. Schiff base transition metal complexes have emerged as one of the promising moieties for the design of antibacterial and antifungal agents. Further investigations in this field will address the structure –activity relation of the compounds and the mode of mechanism of action of these compounds.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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