

Biological applications of macrocyclic Schiff base ligands and their metal complexes: a survey of the literature (2005-2019)

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Abstract

This article aims to provide a survey of biological applications of Schiff base macrocycles and their metal complexes, with emphasis given to the synthesis of the compounds and to their uses as antibacterial and antifungal agents. The literature on the subject, published during the 2005-2019 period, is shortly reviewed. This is an informed report collecting information on the addressed topic in a concise systematic way, and can be expected to be useful as a fast literature catalogue for researchers working on this and related domains.

Keywords: Macrocyclic Schiff base ligands and their metal complexes; biological applications; literature survey (2005-2019).

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1. Introduction

1.1. Polyamines

Di- and polyamines are relatively simple organic substances that have two or more than two amino groups, respectively, in their structure. Low molecular weight linear di- and polyamines are found in all forms of life, including the human body, and they are involved in key biological processes in animals and plants [1–6]. The most abundant members of this type of compounds in living systems include the diamine putrescine (1,4-diaminobutane), the triamine spermidine (*N*-(3-aminopropyl)-1,4-butanediamine), and the tetraamine spermine (*N,N'*-bis(3-aminopropyl)-1,4-butanediamine). Other di- or polyamines occurring in lower concentration in living organisms comprise trimethylenediamine (1,3-diaminopropane), cadaverine (1,5-diaminopentane), homospermidine (*N*-(4-aminobutyl)-1,4-butanediamine), and norspermine (*N,N'*-bis(3-aminopropyl)-1,3-propanediamine), but the list includes a few dozens of compounds [7,8].

The first biogenic amine discovered was spermine, that was identified in the human semen by van Leeuwenhoek, in 1677, in the form of phosphate [9]. Interestingly, the correct structure of the compound was only determined in 1926 [10,11]. Spermidine was also discovered and isolated from semen, in the beginning of the 20th century [2]. Putrescine and cadaverine are likewise present in the semen, but they were discovered together, by the end of the 19th century, in decaying matter, where they appear as result of the breakdown of amino acids [12-14]. These compounds may occur in both *eukaryote* (e.g., animals, plants, algae) and *prokaryote* (bacteria) cells [1-14].

The usual amount of di- and polyamines present inside the cells of living systems is at the millimol level [15,16]. However, the concentration of free amines is small and maintained within a very narrow range (7-10% of the total amount) because the decrease in their concentration inhibits cell proliferation while excess is toxic [15,16]. Indeed, most of the di- and polyamines in

the cells are bound to different polyanionic molecules, especially nucleic acids, but also proteins and phospholipids [13-18].

It has been noticed that an increase in the concentration of polyamines may be associated with rapidly proliferating cancer cells (in particular in the case of breast, colon, lung, prostate and skin tumors) [19,20], and this has been used as basis for diagnosing cancer and monitoring progresses during cancer treatment [6,19,20-22]. In fact, the interaction of polyamines with nucleic acids and other biological molecules, in terms of their association with cancer, has become the focus of intensive research [1,19-24].

Another relevant use of di- and polyamines is in the synthesis of Schiff base compounds, which can then receive applications in coordination chemistry. Indeed, complexation of Schiff base ligands (in particular of macrocyclic Schiff base derivatives) with metal ions has been shown to give rise to a considerable number of chemical systems exhibiting unique properties for application in several domains, like catalysis, materials sciences and medicine, for example [25,26]. This fact has been giving increased importance to the investigation on this particular type of compounds.

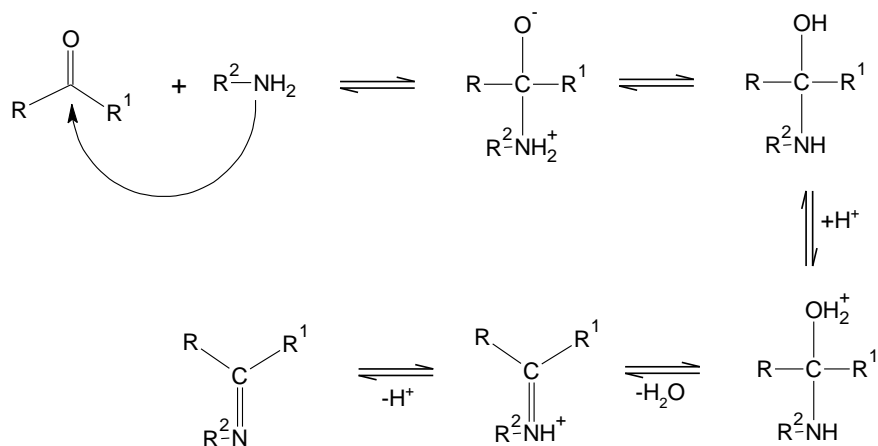
1.2. Schiff base ligands

Schiff bases are compounds with the general formula $RR'C=NR''$ ($R'' \neq H$), and can be considered a sub-class of imines [27,28]. Depending on its structure, a Schiff base can be either a secondary aldimine (when R or R' is an H atom) or a secondary ketamine (when both R and R' are different from H). Their general designation (Schiff base) originates from Hugo Schiff, who first discover this type of compounds [29]. A number of other specific usual names exist for Schiff bases having particular structural elements. For example, a Schiff base derived from an aniline (where R'' is a

phenyl or a substituted phenyl group) can be called an anil, while bis-Schiff base compounds are frequently designated as Salen-type compounds.

Schiff bases can be synthesized from an aliphatic or aromatic amine and a carbonyl compound by nucleophilic addition forming a hemiaminal, followed by dehydration to generate the imine.

(Scheme 1).

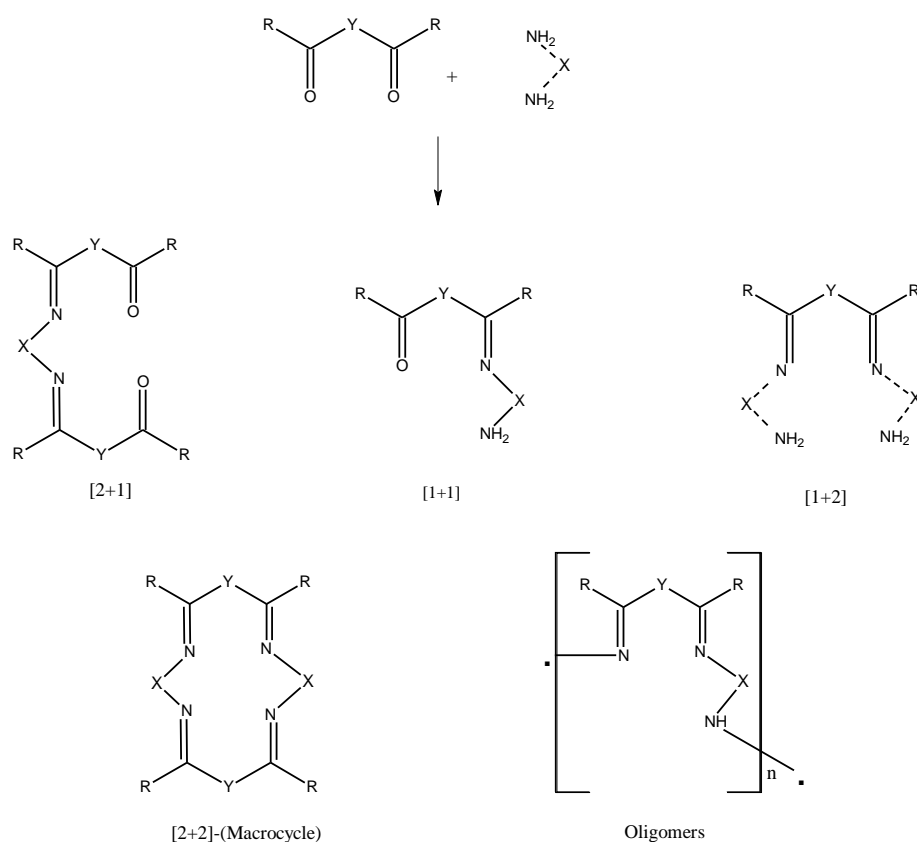


Scheme 1 – Synthesis of a Schiff base from condensation of a carbonyl and an amine precursor.

The literature on Schiff bases is extensive and it is not purpose of this article to address this general topic. In here, we will focus on a specific type of Schiff bases, the ones designated currently by macrocyclic Schiff bases, which are the members of this family of compounds bearing at least one large (7 membered or larger) ring. An example of a naturally occurring macrocyclic Schiff base derivative is corrin, which is the parent macrocycle related to the substituted derivative found in vitamin B₁₂ (cobalamine), but the majority of this type of compounds are produced in the laboratory.

Considerable effort has been made in the last two decades for developing metal-free methods for furnishing macrocycles starting from dicarbonyl compounds and diamines (Scheme 2) in addition to standard metal-templated protocols [30,31]. A large variety of [1+1] and [2+2]-

(macrocyclic) ligands has been synthesized in order to ascertain correctly the role of the different coordinating atoms and of their relative position on the structures resulting from coordination of these ligands to metal ions [30-41]. These studies also aimed to understand the factors that most contribute to determine the number and size of the chelating rings formed upon complexation of Schiff base macrocyclic ligands, as well as the effect of the flexibility and shape of the coordinating moiety on binding [31,42-45]. Progress on the chemistry for synthesis of these type of Schiff bases has allowed, for example, the preparation of macrobicyclic ligands *via* a one-step multiple condensation reactions procedure [30,42-45].



Scheme 2 – Main possible condensation products of dicarbonyl compounds with diamines in different proportions. The R groups may be distinct from each other and X and Y represent generic fragments (in general alkyl chains).

The macrocyclic Schiff bases can also be reduced to the related polyamine derivatives, containing the same cyclic complexity, by reaction with an appropriate reducing agent [30-33]. Similarly, the related complexes can undergo reductive decomplexation reactions when treated with appropriate reductants, with the consequent formation of the corresponding polyamine derivatives [30-33]. These polyamine compounds are less sensitive to hydrolysis and more flexible than their imine analogous, what can be of interest for certain applications.

Introduction of specific functionalities at the periphery of the coordinating moiety has allowed the synthesis of macrocyclic systems capable of multi-recognition, and that may be used, for example, in specific separation [46-48], transport processes across membranes [49,50], or activation and catalysis in eco-compatible solvents [51]. In these areas, the presence in the molecules of pendant arms (two or more) attached to the proper positions of the macrocycle framework appears particularly interesting, since it allows for the generation of a pseudo-enclosed environment suitable for modeling of supramolecular molecule-receptor systems [52]. On the other hand, for macrocycles acting as receptors, the hole size represents an additional parameter which may greatly influence the ability to discriminate among the different species to be recognized.

Macrocyclic Schiff base derivatives are in general good chelating agents and prone to form different types of complexes with metal ions. In fact, one of the most popular methods for the synthesis of macrocyclic Schiff bases requires the active participation of a metal ion in the process, *i.e.*, the metal-promoted one-step (template) condensation method [36-40]. In this synthetic procedure, a metal ion is used as template to induce orientation of the reacting groups of linear substrates in the required conformation for the ring to close [53]. In this way, one has direct access to macrocyclic Schiff base metal complexes, whose practical applications are, as already

mentioned, relevant in many different domains [14,17,33,52]. In this article we will focus on their uses as bioactive systems, in particular as antibacterial and antifungal agents.

1.3. Macrocyclic Schiff base metal complexes

The majority of therapeutic drugs are organic compounds and, because of this, less attention has been given in this field to inorganic and coordination compounds. Nevertheless, the number of inorganic and coordination compounds shown to exhibit beneficial bioactive properties has been growing considerably during the last decades. They have been noticed to be particularly effective in cancer therapy, as a result of their ability to specifically interact with DNA [1,6,19-24,54]. The prototype compound is cisplatin [*cis*-diaminedichloroplatinum(II)], which was approved as a chemotherapeutic drug for use in testicular and ovarian cancers by the U.S. Food and Drug Administration (FDA) in 1978 [55-57], and in Europe one year later [58]. Interestingly, despite the fact that thousands of cisplatin analogues have been synthesized since then, and tested as potential anticancer drugs, only two of them, carboplatin and oxaliplatin, have been used in the clinical treatment of neoplastic diseases, while the rest have remained inactive [54,59-64].

Being common ligands in coordination chemistry, Schiff bases have been used extensively in this field, giving rise to a plethora of different types of complexes. Their coordination ability results mainly from the π -acceptor properties of their constituting imine nitrogen atom. Accordingly, the coordination versatility of Schiff bases strongly increases when the ligand bears several imine groups, which may act as multiple coordination sites. Procedures have been developed successfully for preparation of mono-, di- or polymacrocycles, catenands, compartmental ligands and calixarenes based on Schiff bases [65].

An interesting observation is that complexation with a metal often improves the stability of the Schiff base ligand, while the majority of macrocyclic complexes have also been noticed to be both kinetically and thermodynamically more stable than the analogous compounds with non-cyclic ligands [66]. These facts have contributed to stimulate research on this type of compounds, which in turn has allowed elucidating aspects of the reactivity of Schiff base coordination compounds that would not be possible to investigate using the less stable analogous complexes of non-cyclic ligands. The interest in exploring metal ion complexes with macrocyclic Schiff base type ligands has received strong stimulus also owing to the recognition of the role played by this kind of structures in metalloproteins [65], and a broad variety of Schiff base macrocycles have been used for metal-biosites modeling of cationic, anionic or neutral receptors [30]. In addition, the progress on synthetic macrocyclic chemistry has also resulted in an increased understanding of the properties and function of naturally occurring biological macrocycles and their complexes [52,67].

Among the general type of systems considered in this review, those formed by functionally substituted macrocyclic Schiff bases ligands bearing additional donor groups are of particular interest. Such ligands represent one of the most important classes of heteropolydentate ligands capable of forming not only mononuclear complexes of different types with transition and/or non-transition metal ions, but also diverse bi- and polynuclear complexes with potential for application in several areas. The progressive availability of larger and more multifarious ligands exhibiting such structural characteristics has been facilitating also the design of macrocyclic Schiff base metal complexes with specific properties resulting from the simultaneous presence of metal ions in close proximity within the same coordinating moiety. For example, using compartmental ligands, binuclear complexes have been synthesized where the two metal centers, if paramagnetic, interact with each other through the bridging donor atoms of the ligands in a ferromagnetic or

antiferromagnetic way; by introducing modifications in the ligands, one can adjust the distance between the two chambers and/or the paramagnetic centers as well as the chemical environment around them, thus allowing for the modulation of the magnetic interactions in order to achieve the desired materials' magnetic properties [66].

These types of complexes can be obtained by self-condensation of suitable formyl- or keto-precursors and primary (poly)amines followed by coordination to the metal center *via* reaction with an appropriate metal salt [30,66]. Alternatively, they can be obtained in a single step by the already mentioned metal-template procedure [36-40,53]. In some cases, the initially synthesized complexes can be converted in other species through transmetalation reactions, leading to species otherwise not accessible to synthesis [66]. Template and transmetalation reactions quite often give rise to the desired complexes in high-yield and in a satisfactory purity grade.

As shown in the next section, the potential biomedical applications of macrocyclic Schiff bases and of their metal complexes as antimicrobial agents are very relevant, and some drugs based on this type of pharmacophore are indeed already on the market or in advanced phases of clinical trials. Mimosipil {IUPAC name: (5R,9R,E)-5-(((E)-5-chloro-2-hydroxy-3-methoxybenzylidene)amino)-11-ethylidene-7-methyl-5,6,9,10-tetrahydro-5,9-methanocycloocta[b]pyridin-2(1H)-one}, for example, is an acetylcholinesterase (AChE) inhibitor that has demonstrated potential use in the treatment of Alzheimer's disease [68], while the drug known by dBET57 {IUPAC name: 2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)ethyl)acetamide} is a cancer PROTAC (proteolysis-targeting chimeras) type active agent [69]. Nevertheless, in spite of all accumulated favorable data, and the large list of publications stressing the potential of this type of compounds as medicines, the practical use of macrocyclic compounds in general as drugs is yet

rather limited. Indeed, there is still a considerable resistance to the acceptance of macrocycles as pharmaceutical agents mostly because they did not fit the usual structural paradigm followed by the industry: small heterocyclic molecules with a reduced number of functional groups that most of times conformed to the Lipinski's rule of five [70]. Also, the synthetic challenge for macrocyclic structures is just recently been partially overcome and time is still required to fulfil the necessities of the library formats needed for the high throughput screening efforts essential to the majority of contemporary drug discovery programs. These facts give additional relevance to publications gathering together the most prominent recent results on the bioactivity of macrocyclic compounds (as those considered in this article), which appear as a privileged way to stimulate further fundamental research in this field and, in particular, market-targeted research by the specialized R&D laboratories of the pharmaceutical companies.

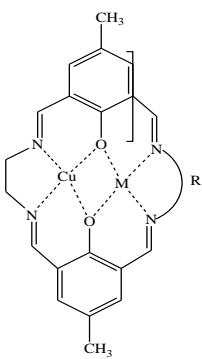
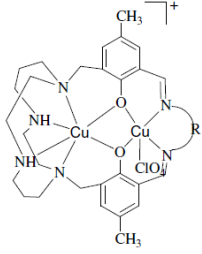
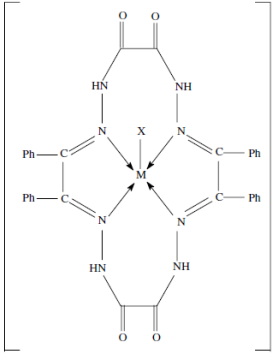
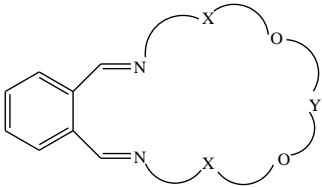
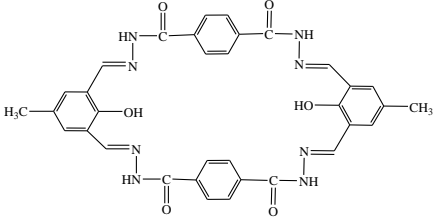
2. Literature survey (highlights 2005-2019)

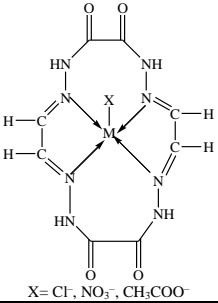
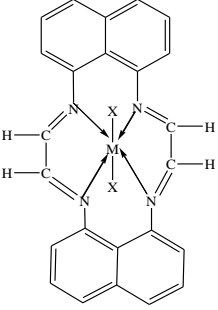
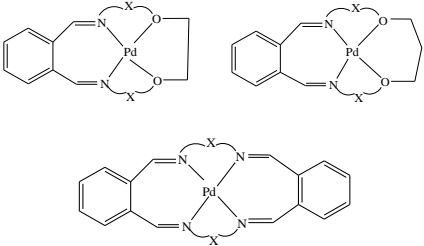
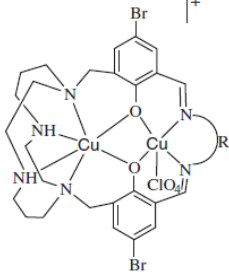
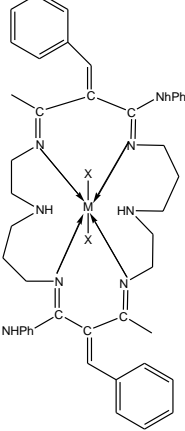
In this section, the most relevant literature on biological applications of macrocyclic Schiff base ligands and their metal complexes appearing during the period 2005-2019 is reviewed in brief. The data have been arranged in the format of a table (Table 1), where the most relevant results and the systems investigated in the surveyed studies are concisely described. To facilitate the search for a specific chemical system, for each article mentioned in the Table an illustration is provided, which shows the schematic structure of a representative compound or type of compounds addressed in the cited publication. The articles are organized by year of publication instead of by subject. Though the alternative possibility has also some advantages, the presentation of the articles by chronological order permits to follow in an easier way the progress over the time on a given matter and, more importantly, to interconnect this progress with developments taking place on related

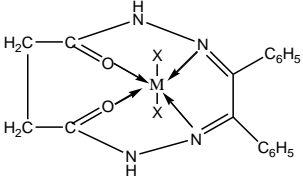
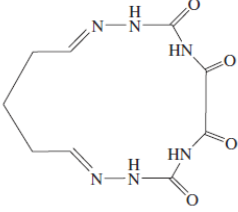
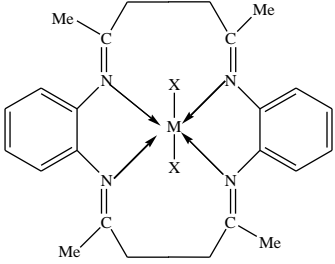
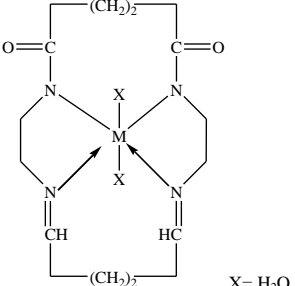
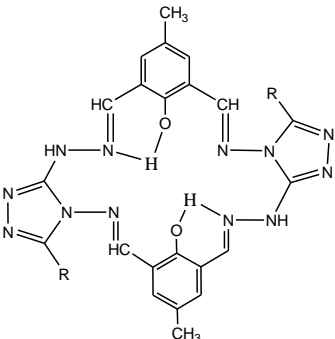
subjects. On the whole, 84 articles (besides those cited in the introduction) dealing with biological applications (in many cases better designated as biological *potential* applications) of macrocyclic Schiff base ligands and their metal complexes are described in this review, in particular those related to their ability to act as antibacterial or/and antifungal agents. This is an informed report gathering information on this topic in a concise systematic way, and will certainly be of great value for the researchers working on this and related domains.

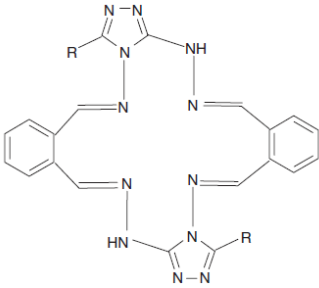
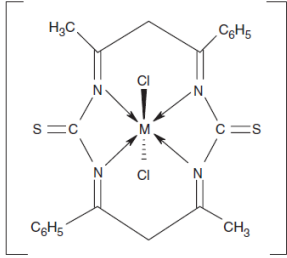
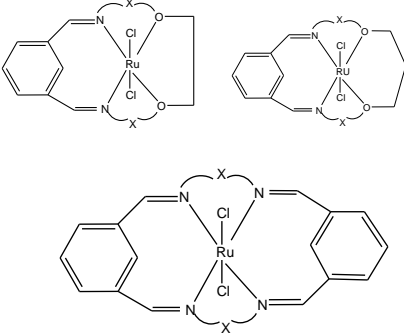
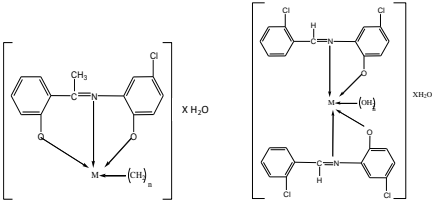
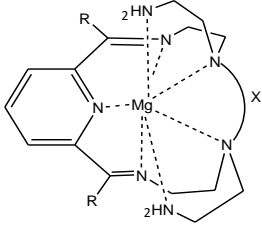
Table 1. Biological applications of macrocyclic Schiff base ligands and their metal complexes: literature highlights 2005-2019.

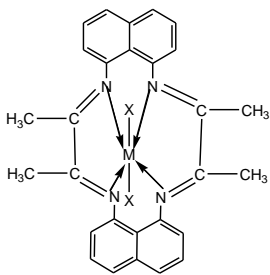
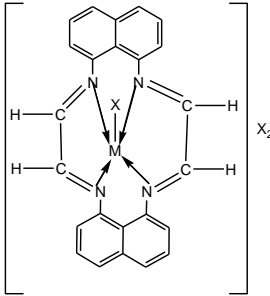
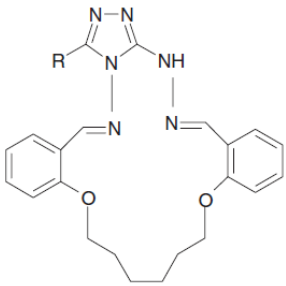
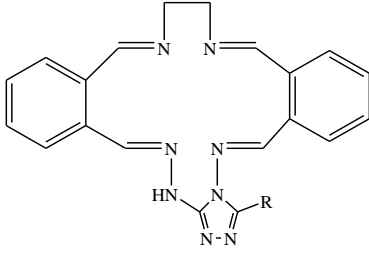
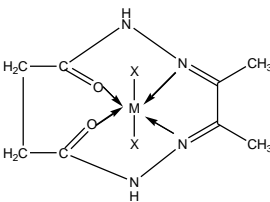
Authors	Summary	Illustrative studied compounds	Refs.
J. Gao, F.R.Woolley, R.A. Zingaro	The first δ -conjugated macrocyclic diimine and triaza DNA-binding intercalators and their Pt(II) conjugates have been synthesized by direct Schiff base cyclocondensation. This paper describes a new class of platinum-based antitumorals.		[71]
B.H. Mruthyunjayaswamy, Y.J. Omkar, B. Ijare, S.G. Patil, S.M. Kudari	A series of di- and tetra-nuclear complexes based on two new macrocyclic phenoxo-bridged ligands were reported. The compounds were synthesized through the template method by using the precursors 2,6-diformyl-4-methylphenol, succinoyldihydrazide/sebacoyldihydrazide and their respective metal chlorides. The Cu(II), Co(II) and Zn(II) complexes of both the ligands have shown good antifungal activity against <i>A. niger</i> and <i>F. oxysporum</i> and medium to weak antibacterial activity against <i>E. coli</i> and <i>S. aureus</i> .		[72]
H.I. Ugras, I. Basaran, T. Kilic, U. Cakir	A new macrocyclic Schiff base has been prepared by condensation of triethylene glycol diamine with terephthalaldehyde. The synthesized ligand has been shown to possess high activity against the studied microorganisms (<i>E. coli</i> , <i>S. epidermidis</i> , <i>B. subtilis</i> , <i>S. aureus</i> , <i>S. Typhimirum</i> , <i>K. pneumonia</i> , <i>P. aeruginosa</i> and <i>E. fecalis</i> bacterial strains and the <i>C. albicans</i> fungi).		[73]
N. Nishat, M.M. Haq, T. Ahamad, V. Kumar	A new macrocycle, 1,16-diaza-7,10-diamino-6,11-dioxo-1,17-bis[20-hydroxy-50-aminobenzyl] piperazine-4,12-cyclododecadiene, has been synthesized by a multistep process. The related complexes (with M= Mn(II), Co(II), Ni(II), Cu(II) or Zn(II)) show significant inhibitory activity against bacteria (<i>B. subtilis</i> , <i>B. megaterium</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> and <i>S. boydii</i>) and fungi (<i>C. albicans</i> , <i>Trichophyton</i> sp., <i>A. flavus</i> , <i>Fucarium</i> sp., <i>Mucor</i> sp. and <i>Penicillium</i> sp.).		[74]
P.M. Reddy, A.V.S.S. Prasad, K. Shanker, V. Ravinder	Ten novel macrocyclic Co(II) compounds have been synthesized by treating four N ₄ and six N ₂ O ₂ donor macrocycles with cobalt chloride in methanol. All of them along with existing antibacterial drugs were screened for antibacterial activity against Gram positive and Gram negative bacteria. All these compounds were found to be more active when compared to streptomycin and ampicillin.		[75]

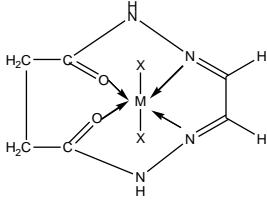
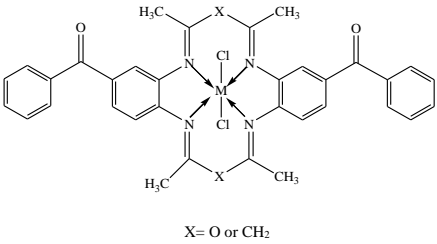
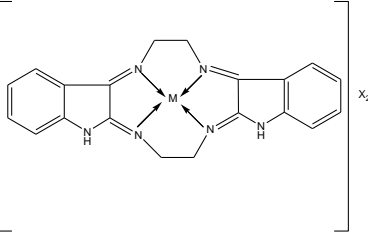
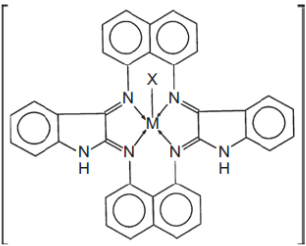
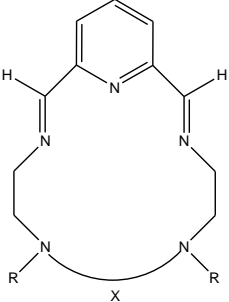
<p>H. Khanmohammadi, R. Arabahmadi, M.H. Abnosi, H.R. Khavasi</p>	<p>Eight new heterodinuclear Cu(II)–M(II) (M = Pb and Zn) complexes of four new phenol-based compartmental macrocyclic ligands were synthesized. All complexes were screened for their antibacterial and antifungal activity (against <i>E. coli</i> and <i>S. aureus</i>, and <i>C. albicans</i>, respectively).</p>		<p>[76]</p>
<p>S. Sreedaran, K.S. Bharathi, A.K. Rahiman, L. Jagadish, V. Kaviyaranan, V. Narayanan</p>	<p>A series of novel unsymmetrical dicompartmental binuclear Cu(II) complexes has been prepared by Schiff-base condensation. All the studied complexes were screened for antifungal (<i>C. albicans</i>) and antibacterial (<i>S. aureus</i>, <i>B. cereus</i>, <i>K. pneumonia</i>, <i>P. aeruginosa</i> and <i>E. coli</i>) activities.</p>		<p>[77]</p>
<p>D.P. Singh, R. Kumar, J. Singh</p>	<p>A new series of complexes has been synthesized by template condensation of oxalyldihydrazide and benzil. The biological activities of the metal (M=Cr(III), Fe(III) and Mn(III)) complexes have been tested <i>in vitro</i> against a number of pathogenic bacteria (<i>B. cereus</i>, <i>S. typhi</i>, <i>E. coli</i> and <i>S. aureus</i>) to assess their inhibiting potential.</p>		<p>[78]</p>
<p>P.M. Reddy, Y.P. Ho, K. Shanker, R. Rohini, V. Ravinder</p>	<p>A series of novel macrocyclic compounds were synthesized by the condensation of <i>o</i>-phthalaldehyde with aromatic amino alcohols, followed by treatment with 1,2-dibromoethane or 1,3-dibromopropane <i>via</i> non-template method. The compounds were found to exhibit potential antibacterial activity. The macrocycles were also tested <i>in vitro</i> to evaluate their activity against fungi <i>A. flavus</i> and <i>Fusarium</i> species.</p>	 <p>X= alkyl, aryl or N-containing heterocyclic substituents.</p>	<p>[79]</p>
<p>P.G. Avaji, C.H.V. Kumar, S.A. Patil, K.N. Shivananda, C. Nagaraju</p>	<p>A macrocyclic hydrazone Schiff base was synthesized by reacting 1,4-dicarbonyl phenyl dihydrazide with 2,6-diformyl-4-methyl phenol, and a series of metal (Co(II), Ni(II) and Cu(II)) complexes with this new Schiff base was synthesized. The Schiff base and its complexes have also been screened for their antibacterial (<i>E. coli</i>, <i>S. aureus</i>, <i>S. dysentery</i>, <i>Micrococcus</i>, <i>B. subtilis</i>, <i>B. cereus</i> and <i>P. aeruginosa</i>) and antifungal (<i>A. niger</i>, <i>Penicillium</i> and <i>C. albicans</i>) activities. Brine shrimp bioassays were also carried out to study the <i>in vitro</i> cytotoxic properties of the compounds.</p>		<p>[80]</p>

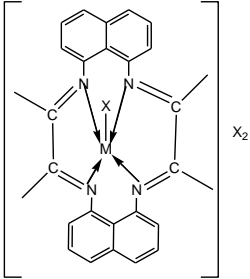
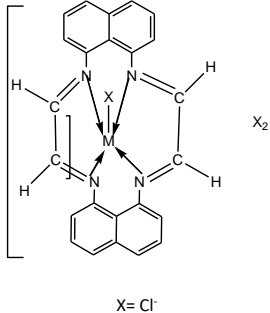
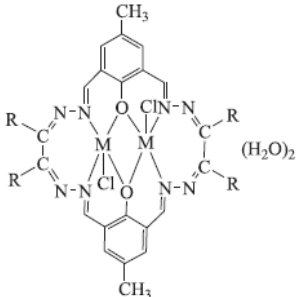
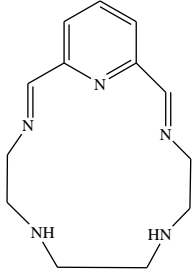
<p>D.P. Singh, R. Kumar, J. Singh</p>	<p>A new series of complexes was synthesized by template condensation of oxalyldihydrazide and glyoxal in methanolic medium in the presence of M=Cr(III), Mn(III) and Fe(III) salts. The biological activities of the metal complexes were tested <i>in vitro</i> against a number of pathogenic bacteria (<i>B. cereus</i>, <i>S. typhi</i>, <i>E. coli</i> and <i>S. aureus</i>), some of the complexes exhibiting remarkable antibacterial activities.</p>	 <p>X= Cl⁻, NO₃⁻, CH₃COO⁻</p>	<p>[81]</p>
<p>D.P. Singh, K. Kumar, S.S. Dhiman, J. Sharma</p>	<p>A novel series of complexes of the type [M(C₂₄H₁₆N₄)X₂] (M = Co(II), Ni(II), Cu(II), Zn(II) and Cd(II); X= Cl⁻, NO₃⁻, CH₃COO⁻) has been synthesized by template condensation of 1,8-diaminonaphthalene and glyoxal in the presence of salts of the different metals, in methanolic medium. These metal complexes were also tested for <i>in vitro</i> antibacterial (<i>B. subtilis</i>, <i>B. stearothermophilus</i>, <i>E. coli</i> and <i>P. putida</i>) and antifungal (<i>A. flavus</i> and <i>A. niger</i>) activities to assess their inhibiting potential.</p>		<p>[82]</p>
<p>K. Shanker, P.M. Reddy, R. Rohini, Y.P. Ho, V. Ravinder</p>	<p>New macrocyclic Schiff base Pd(II) compounds were synthesized by treating N₄ and N₂O₂ coordinating macrocycles with palladium chloride. The biological activities of all the macrocycles and macrocyclic Pd(II) compounds have been tested (<i>B. subtilis</i>, <i>S. aureus</i>, <i>E. coli</i> and <i>K. pneumonia</i>). The compounds were found to be more active than commercially available antibacterial drugs like streptomycin and ampicillin.</p>	 <p>X= alkyl, aryl or N-containing heterocyclic substituents.</p>	<p>[83]</p>
<p>S. Sreedaran, K.S. Bharathi, A.K. Rahiman, R. Prabu, R. Jegadeesh, N. Raaman, V. Narayanan</p>	<p>A series of unsymmetrical dicompartmental binuclear Cu(II) complexes has been prepared by Schiff base condensation of 1,8-[bis(3-formyl-2-hydroxy-5-bromo)benzyl]-1,4,8,11-tetraazacyclotetradecane with aliphatic and aromatic diamines, Cu(II) perchlorate and trimethylamine. All the complexes show good antimicrobial and antifungal activities against <i>E. coli</i>, <i>P. aeruginosa</i>, <i>B. subtilis</i>, <i>K. Pneumonia</i> and <i>S. aureus</i>, and <i>C. albicans</i>, respectively.</p>		<p>[84]</p>
<p>N. Raman, S.J. Raja, J. Joseph, A. Sakthivel</p>	<p>Macrocyclic complexes of Cu(II), Ni(II), Co(II) and Zn(II) of a tetradentate Schiff base ligand derived from 3-benzalideneacetoacetanile and N-(2-aminoethyl)1,3-propanediamine were synthesized. The <i>in vitro</i> biological testing of the compounds against <i>E. coli</i>, <i>S. aureus</i>, <i>S. typhi</i> and <i>K. pneumonia</i> was performed. It was also shown that the copper complex prefers to bind within DNA in oxidation state II instead of I.</p>	 <p>X= Cl⁻</p>	<p>[85]</p>

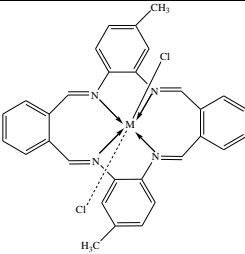
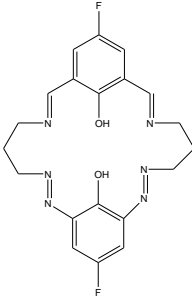
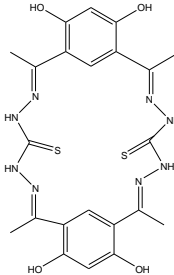
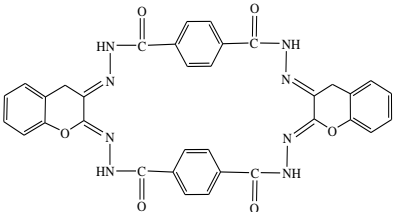
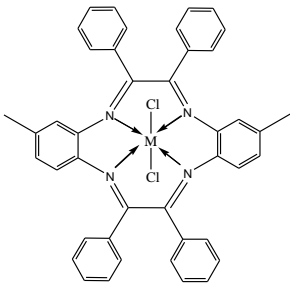
<p>D.P. Singh, V. Malik, R. Kumar, K. Kumar, J. Singh</p>	<p>A series of new macrocyclic complexes of type $[M(C_{18}H_{16}N_4O_2)X_2]$ ($M = Co(II), Ni(II), Cu(II), Zn(II)$ and $Cd(II)$; $X = Cl^-, NO_3^-, CH_3COO^-$) was synthesized by the condensation of succinyl dihydrazide with benzil in the presence of the metal ions. The complexes were tested for <i>in vitro</i> antibacterial activity against <i>B. cereus</i>, <i>S. typhi</i>, <i>E. coli</i> and <i>S. aureus</i>, some of them showing promising results.</p>		<p>[86]</p>
<p>N. Nishat, R.U. Din, S. Dhyani</p>	<p>New derivatives of semicarbazone have been prepared by reaction of semicarbazides and glutaraldehyde. All the synthesized compounds have been screened against bacterial strains <i>S. aureus</i> and <i>E. coli</i>, and fungi strains <i>C. albicans</i> and <i>A. niger</i>. The results were compared with those obtained for the reference drugs kanamycin (antibacterial) and miconazole (antifungal).</p>		<p>[87]</p>
<p>D.P. Singh, R. Kumar, M. Kamboj, K. Jain</p>	<p>A new series of macrocyclic complexes $[M(C_{24}H_{28}N_4)X_2]$ ($M = Co(II), Ni(II), Cu(II)$ and $Zn(II)$; $X = Cl^-, NO_3^-, CH_3COO^-$) has been synthesized by condensation of <i>o</i>-henylenediamine with acetonylacetone (diacetonyl) in the presence of the metal ions. The complexes were tested for <i>in vitro</i> antibacterial activity against <i>B. cereus</i>, <i>S. typhi</i>, <i>E. coli</i> and <i>S. aureus</i> bacteria strains.</p>		<p>[88]</p>
<p>N. Nishat, A.S. Dhyani</p>	<p>$Co(II), Ni(II), Mn(II), Cu(II)$ and $Zn(II)$ complexes with a new macrocyclic ligand, 1,4,11,14-tetraaza-cyclonodeca-5,10-dioxo-1,14-diene were synthesized. All studied complexes were screened against bacterial (<i>S. aureus</i>, <i>E. coli</i>, <i>B. subtilis</i> and <i>S. typhimurium</i>) and fungal (<i>F. oryzae</i> and <i>C. albicans</i>) strains. Preliminary results showed that the complexes inhibited bacterial/fungal growth to a greater extent than the free ligand.</p>		<p>[89]</p>
<p>P.G. Avaji, S.A. Patil</p>	<p>A series of $Co(II), Ni(II)$ and $Cu(II)$ complexes has been obtained by template condensation of 2,6-diformyl-4-methylphenol and 3-substituted-4-amino-5-hydrazino-1,2,4-triazole in the presence of $CoCl_2 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$ and $CuCl_2 \cdot 2H_2O$. All the studied Schiff base ligands and their complexes were evaluated for their microbiological properties, and some of the compounds shown to exhibit promising antibacterial and antifungal activities against <i>S. aureus</i>, <i>E. coli</i>, <i>B. subtilis</i> and <i>P. aeruginosa</i>, and <i>A. niger</i> and <i>A. fumigates</i>, respectively.</p>		<p>[90]</p>

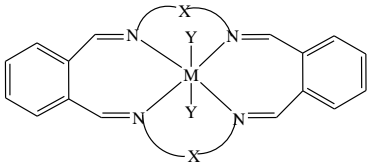
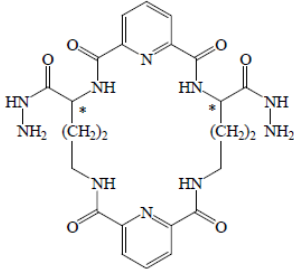
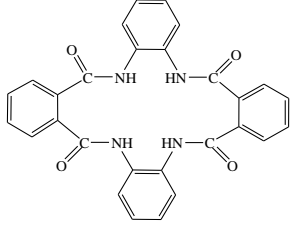
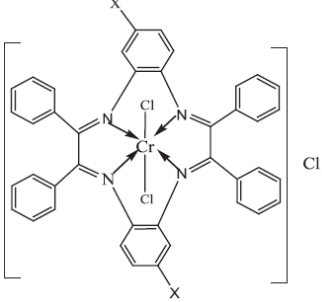
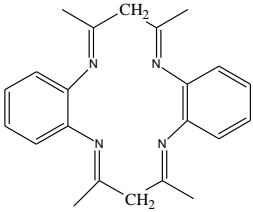
<p>G.B. Bagihalli, S.A. Patil</p>	<p>A series of metal complexes has been synthesized with newly-derived biologically active ligands. The Schiff bases and their Co(II), Ni(II), Cu(II), and Zn(II) complexes have been screened for antibacterial (<i>E. coli</i>, <i>S. aureus</i>, <i>S. pyogenes</i>, and <i>P. aeruginosa</i>), and antifungal (<i>A. niger</i>, <i>A. flavus</i>, and <i>Cladosporium</i>) activities by the minimum inhibitory concentration method. DNA cleavage studies were also carried out.</p>		<p>[91]</p>
<p>S. Chandra, S. Verma, U. Dev, N. Joshi</p>	<p>A macrocyclic ligand, 1,3,7,9-tetraaza-2,8-dithia-4,10-dimethyl-6,12-diphenylcyclododeca-4,6,10,12-tetraene has been synthesized. Complexes of this ligand with Mn(II), Co(II), Ni(II), and Cu(II) was been synthesized too. The ligand and its complexes were screened <i>in vitro</i> against two pathogenic fungi (<i>F. moniliformae</i> and <i>R. solani</i>) and bacteria (<i>S. aureus</i> and <i>P. aeruginosa</i>) to assess their growth inhibiting potential.</p>		<p>[92]</p>
<p>K. Shanker, R. Rohini, V. Ravinder, P. M. Reddy, Y.P. Ho</p>	<p>A series of nitrogen and oxygen heterocyclic macrocyclic ligands and their Ru(II) complexes were synthesized. All the investigated ligands and the Ru(II) complexes, along with existing antibacterial drugs (streptomycin and ampicillin) were screened for antibacterial activity against (<i>B. subtilis</i>, <i>S. aureus</i>, <i>E. coli</i> and <i>K. pneumonia</i>) bacteria, the new compounds being found to be more active than the reference drugs. The representative macrocyclic Schiff bases and their complexes were also tested <i>in vitro</i> to evaluate their activity against fungi (<i>A. flavus</i> and <i>Fusarium</i>) and compared with the amphotericin and bavistin commercial drugs.</p>	 <p>X= alkyl, aryl or N-containing heterocyclic substituents.</p>	<p>[93]</p>
<p>A.P. Mishra, R.K. Mishra, S.P. Shrivastava</p>	<p>Structural and antimicrobial studies of coordination compounds of M= VO(II), Co(II), Ni(II) and Cu(II) with some Schiff bases derived from 2-amino-4-chlorophenol were synthesized. The <i>in vitro</i> biological screening effects of the investigated compounds were tested against the bacteria <i>E. coli</i>, <i>S. aureus</i> and <i>S. fecalis</i>, and the fungi <i>A. niger</i>, <i>T. polysporum</i> and <i>C. albicans</i>.</p>		<p>[94]</p>
<p>H. Khanmohammadi, H. Keypour, M. Salehi Fard, M.H. Abnosi</p>	<p>The synthesis and characterization of four Mg(II) complexes prepared <i>via</i> cyclocondensation of 2,6-diformylpyridine and 2,6-diacetylpyridine with two hexadentate hexaamines, in the presence of Mg(II) ion, were reported. Their antibacterial and antifungal properties against <i>E. coli</i> and <i>S. aureus</i>, and <i>C. albicans</i>, respectively, were also described.</p>	 <p>R= H or CH₃; X= alkyl chain</p>	<p>[95]</p>

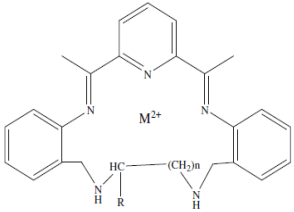
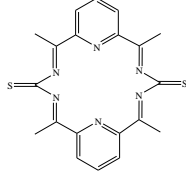
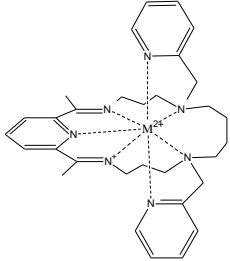
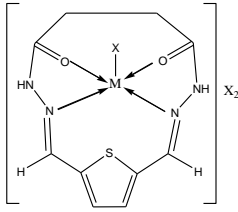
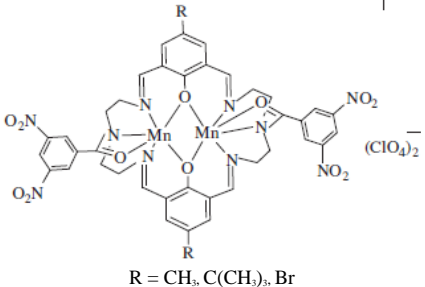
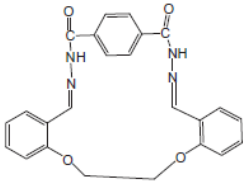
<p>D. Singh, K. Kumar, R. Kumar, J. Singh</p>	<p>A novel series of complexes of the type $[M(C_{28}H_{24}N_4)X_2]$, where $M = Co(II), Ni(II), Cu(II), Zn(II)$ and $Cd(II)$, $X = Cl^-, NO_3^-$ and CH_3COO^-, was synthesized by template condensation of 1,8-diaminonaphthalene and diacetyl in the presence of divalent metal salts, in methanolic medium. The macrocyclic complexes were tested for <i>in vitro</i> antibacterial activity against some pathogenic bacterial strains (<i>B. cereus</i>, <i>S. typhi</i>, <i>E. coli</i> and <i>S. aureus</i>). The MIC values shown by the complexes against were compared with the values shown by the standard antibiotics linezolid and cefaclor.</p>		<p>[96]</p>
<p>D.P. Singh, K. Kumar, S.S. Dhiman, J. Sharma</p>	<p>A new series of complexes of the type $[M(C_{24}H_{16}N_4)X]X_2$, where $M = Cr(III), Fe(III)$ and $Mn(III)$, and $X = Cl^-, NO_3^-$ and CH_3COO^-, was synthesized by template condensation of 1,8-diaminonaphthalene and glyoxal in the presence of metal salts, in methanolic medium. All the synthesized metal complexes were tested for <i>in vitro</i> antimicrobial activities against bacteria (<i>B. subtilis</i>, <i>B. stearothermophilus</i>, <i>E. coli</i>, and <i>P. putida</i>) and fungi (<i>A. flavus</i> and <i>A. niger</i>). The results were compared with those of antibiotics chloramphenicol and streptomycin, and the antifungal drug cyclohexamide.</p>		<p>[97]</p>
<p>S.A. Patil, U.V. Kamble, P. S. Badami</p>	<p>A novel series of N_2O_2 diazadioxo macrocyclic complexes $[MLCl_2]$ ($M = Co(II), Ni(II)$ and $Cu(II)$) was synthesized. The ligands were synthesized by the condensation of 1,6-bis(2-formylphenyl) hexane and 3-substituted-4-amino-5-hydrazino-1,2,4-triazole. All the studied complexes have been screened for their antibacterial (<i>E. coli</i>, <i>S. aureus</i>, <i>S. typhi</i>, <i>P. aeruginosa</i>) and antifungal (<i>A. niger</i>, <i>A. flavus</i> and <i>Cladosporium</i>) activities by the MIC method. DNA cleavage studies were also reported.</p>		<p>[98]</p>
<p>U.V. Kamble, S.A. Patil, P.S. Badami</p>	<p>A series of 17-membered complexes $[MLCl_2]$ ($M = Co(II), Ni(II)$ and $Cu(II)$) was prepared with newly derived biologically active ligands. These ligands were synthesized by condensation of 3-substituted-4-amino-5-hydrazino-1,2,4-triazole with bis(phthalaldehyde) ethylene-diamine. The compounds were screened for their antibacterial (<i>E. coli</i>, <i>S. aureus</i>, <i>S. typhi</i>, <i>P. aeruginosa</i>) and antifungal (<i>A. niger</i>, <i>A. flavus</i> and <i>Cladosporium</i>) activities. DNA cleavage studies using these complexes were also reported.</p>		<p>[99]</p>
<p>D.P. Singh, K. Kumar</p>	<p>The condensation of succinyldihydrazide with diacetyl in the presence of the appropriate divalent metal ions resulted in the formation of $[M(C_8H_{12}N_4O_2)X_2]$, where $M = Co(II), Ni(II), Cu(II), Zn(II)$, and $X = Cl^-, NO_3^-, CH_3COO^-$. The complexes were tested for <i>in vitro</i> antibacterial activities (<i>S. aureus</i>, <i>B. subtilis</i>, <i>E. coli</i>, and <i>P. aeruginosa</i>) and compared with the standard antibiotic ciprofloxacin.</p>		<p>[100]</p>

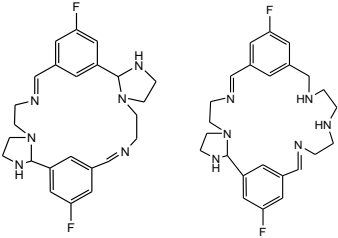
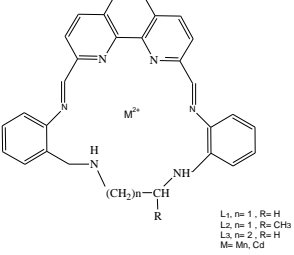
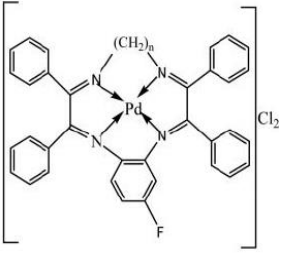
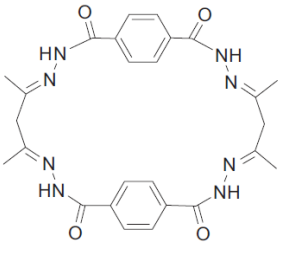
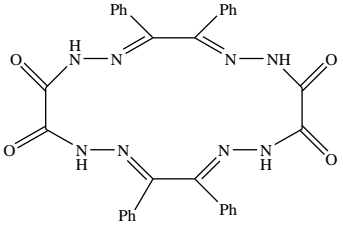
<p>D.P. Singh, V. Malik, R. Kumar, K. Kumar</p>	<p>The condensation reaction of succinyldihydrazide with glyoxal in the presence of the relevant divalent metal ions results in the formation of the complexes of type $[M(C_6H_8N_4O_2)X_2]$ where $M = Co(II), Ni(II), Cu(II), Zn(II)$ or $Cd(II)$, and $X = Cl^-, NO_3^-$ or CH_3COO^-. The complexes were tested for <i>in vitro</i> antibacterial activity. Some of the complexes showed remarkable antibacterial activities against <i>B. cereus</i>, <i>S. typhi</i>, <i>E. coli</i> and <i>S. aureus</i> bacterial strains.</p>		<p>[101]</p>
<p>F. Firdaus, K. Fatma, M. Azam, M. Shakir</p>	<p>Two Schiff bases bearing functionalized pendant arms have been synthesized by cyclocondensation of 3,4-diaminobenzophenone with 2,3-butanedione and 2,4-pentanedione, respectively. Mononuclear macrocyclic complexes were then prepared by reacting $M = Fe(III), Co(II)$ and $Cu(II)$ with the pre-formed Schiff bases. The ligands and complexes were screened <i>in vitro</i> against bacteria (<i>S. mutans</i>, <i>S. pyogenes</i>, <i>S. aureus</i>, <i>P. aeruginosa</i>, <i>S. typhimurium</i> and <i>E. coli</i>), and fungi (<i>C. albicans</i>, <i>C. krusei</i>, <i>C. parapsilosis</i> and <i>Cr. neoformans</i>).</p>	 <p style="text-align: center;">$X = O \text{ or } CH_2$</p>	<p>[102]</p>
<p>D. P. Singh, V. Grover, R. Kumar, K. Jain</p>	<p>A new series of macrocyclic complexes of type $[M(TML)X]X_2$, where $M = Cr(III), Fe(III)$, TML is a tetradentate macrocyclic ligand, and $X = Cl^-, NO_3^-$ or CH_3COO^-, was synthesized by condensation of isatin and ethylenediamine by both conventional and microwave methods. The complexes were tested for <i>in vitro</i> antibacterial activity against bacterial strains <i>B. cereus</i>, <i>S. typhi</i>, <i>E. coli</i> and <i>S. aureus</i>.</p>		<p>[103]</p>
<p>D.P. Singh, K. Kumar, C. Sharma, K.R. Aneja</p>	<p>A novel series of complexes $([M(C_{36}H_{22}N_6)X]X_2)$, where $M = Cr(III), Mn(III)$ or $Fe(III)$; $X = Cl^-, NO_3^-, CH_3COO^-$ has been synthesized by condensation of 1,8-diaminonaphthalene and isatin in the presence of trivalent metal salts in methanolic medium. All synthesized macrocyclic complexes have been tested for <i>in vitro</i> antimicrobial activities against pathogenic bacteria strains, viz. <i>S. aureus</i>, <i>B. subtilis</i>, <i>E. coli</i>, <i>P. aeruginosa</i>, and two fungi strains, (<i>A. niger</i> and <i>A. flavus</i>). The MICs of the new complexes were compared with those of the standard antibiotic ciprofloxacin and the antifungal amphotericin-B.</p>		<p>[104]</p>
<p>H. Khanmohammadi, S. Amani, M.H. Abnosi, H.R. Khavasi</p>	<p>A new asymmetric heptaaza Schiff base macrocyclic bis (pendant donor) $Mn(II)$ complex has been prepared and tested against <i>E. coli</i>, <i>S. aureus</i> and <i>C. albicans</i>. The optimized geometry of the prepared complex has been obtained from density functional method, using B3LYP/6-31G* basis set, and its structure discussed.</p>		<p>[105]</p>

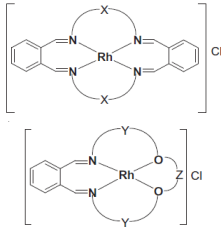
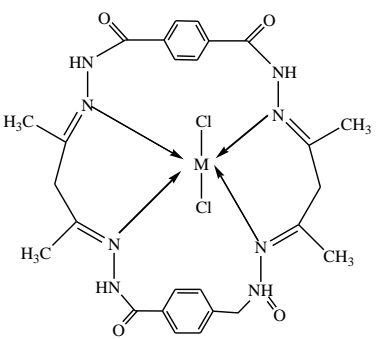
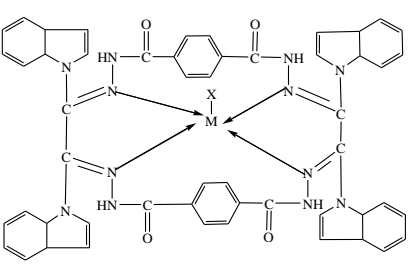
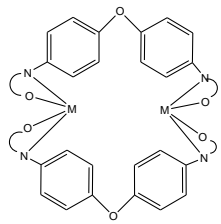
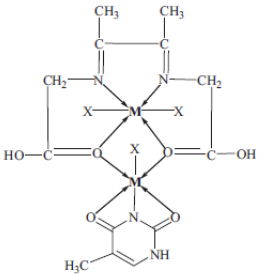
<p>D. Singh, K. Kumar</p>	<p>A novel series of complexes of the type $[M(C_{28}H_{24}N_4)X]X_2$, where $M = Cr(III), Fe(III)$ or $Mn(III)$, $X = Cl^-, NO_3^-, CH_3COO^-$ and $(C_{28}H_{24}N_4)$ was synthesized by the template condensation of 1,8-diaminonaphthalene and diacetyl in the presence of trivalent metal salts, in methanolic medium. All the synthesized macrocyclic complexes were tested for <i>in vitro</i> antifungal activity against <i>A. niger</i> and <i>A. fumigatus</i>. The obtained results were compared with those obtained for the standard antifungal drug fluconazole.</p>		<p>[106]</p>
<p>D. P. Singh, K. Kumar, S.S. Dhiman, J. Sharma</p>	<p>A new series of complexes ($M = Cr(III), Mn(III)$ and $Fe(III)$) has been synthesized by template condensation of 1,8-diaminonaphthalene and glyoxal in the presence of the metal salts in methanolic medium. All the synthesized complexes were tested for <i>in vitro</i> antimicrobial activities against the bacterial strains <i>B. subtilis</i>, <i>B. stearotherophilus</i>, <i>E. coli</i> and <i>P. putida</i>, and the fungi <i>A. flavus</i> and <i>A. niger</i>. The obtained results were compared with those for the standard antibiotics chloramphenicol and streptomycin, and the antifungal drug cyclohexamide.</p>	 <p style="text-align: center;">X = Cl</p>	<p>[107]</p>
<p>B. Lakshmi, P.G. Avaji, K.N. Shivananda, P. Nagella, S.H. Manohar, K.N. Mahendra</p>	<p>A series of binuclear $M = Co(II), Ni(II)$ and $Cu(II)$ complexes was synthesized by the template condensation of glyoxal, biacetyl or benzil bis-hydrazide and 2,6-diformyl-4-methylphenol. The obtained Schiff bases and their metal complexes have also been screened for their antibacterial (<i>S. aureus</i>, <i>S. dysentery</i>, <i>Micrococcus sp.</i>, <i>B. subtilis</i>, <i>B. cereus</i> and <i>P. aeruginosa</i>) and antifungal (<i>A. niger</i>, <i>Penicillium sp.</i> and <i>C. albicans</i>) activities by the MIC method.</p>		<p>[108]</p>
<p>G.G. Mohamed, M.M. Omar, M.S. Abou El-Ela, A.M.M. Hindy</p>	<p>A macrocyclic Schiff base ligand was prepared <i>via</i> condensation of 2,6-pyridine dicarboxaldehyde with triethylene tetramine. The Schiff base and some metal complexes of the compound were screened against both Gram positive and negative bacteria. The $Cr(III)$ and $Cu(II)$ complexes show good inhibitory activities against Gram positive bacteria, which are also inhibited in a smaller extent by the $Fe(III)$ and $UO_2(II)$ complexes. The $Co(II)$ complex was found to inhibit both the tested Gram positive and negative bacteria. On the other way, the complexes of $Ni(II)$, $Cd(II)$ and $Th(IV)$ completely missed antibacterial activity.</p>		<p>[109]</p>
<p>M. Shakir, S. Khanam, M. Azam, M. Aatif, F. Firdaus</p>	<p>Template condensation between <i>o</i>-phthalaldehyde and 3,4-diaminotoluene resulted in a novel mononuclear 16-membered tetraimine complexes of general formula $[MLCl_2]$ [with $M = Co(II), Ni(II), Cu(II)$ and $Zn(II)$]. Interaction of these complexes with calf-thymus DNA has been examined using fluorescence quenching experiments, which revealed that the complexes bind effectively to the DNA.</p>		<p>[110]</p>

			
<p>Y.F. Chen, L. Wei, J.L. Bai, H. Zhou, Q.M. Huang, J.B. Li, Z.Q. Pan</p>	<p>Two complexes were synthesized by [2+2] cyclocondensation of 2,6-diformyl-4-fluorophenol with 1,3-propyldiamine in the presence of Zn(II) and Mn(II). The antibacterial activity of the compounds against <i>S. aureus</i> was investigated using penicillin as reference system.</p>		[111]
<p>A.A.A. Abou-Hussein, W. Linert</p>	<p>Mono- and bi-nuclear acyclic and macrocyclic complexes with hard-soft Schiff base ligands obtained from reaction of 4,6-diacetylresorcinol and thiocarbonylhydrazide have been prepared. The ligands and the metal complexes were screened for antimicrobial activity against <i>S. aureus</i> as Gram positive bacteria and <i>P. fluorescens</i> as Gram negative bacteria, as well as for antifungal activity against <i>F. oxysporum</i>. Most of the studied complexes were shown to exhibit mild antibacterial and antifungal activities against these organisms.</p>		[112]
<p>G. Kumar, S. Devi, R. Johari, D. Kumar</p>	<p>A Schiff base ligand was synthesized, by reacting 1,4-dicarbonyl-phenyl-dihydrazide and chromene-2,3-dione, and a series of metal complexes with this new ligand was prepared by reaction with Cr(III), Mn(III) and Fe(III) salts, in methanolic medium. The complexes were tested as growth inhibitors of <i>S. aureus</i>, <i>B. subtilis</i>, <i>P. aeruginosa</i>, <i>E. coli</i> and <i>S. typhi</i> bacteria as well as <i>Rizoctonia sp.</i>, <i>Aspergillus sp.</i> and <i>Penicillium sp.</i> fungi, and shown to exhibit good antibacterial and antifungal properties.</p>		[113]
<p>M. Shakir, S. Khanam, F. Firdaus, A. Latiff, M. Aatif, S.I. Al-Resayes</p>	<p>Template condensation of benzil with 3,4-diaminotoulene resulted in mononuclear 12-membered tetraimine macrocyclic complexes of the type [MLCl₂] [with M = Co(II), Ni(II), Cu(II) and Zn(II)]. Studies of interaction of these complexes with calf thymus DNA showed that the complexes are avid binders to the DNA. In addition, <i>in vitro</i> screening against <i>S. aureus</i>, <i>S. mutans</i>, <i>S. pyrogenes</i>, <i>S. epidermidis</i>, <i>B. cereus</i>, <i>C. xerosis</i>, <i>E. coli</i>, <i>K. pneumoniae</i>, <i>P. vulgaris</i> and <i>P. aeruginosa</i> proved that they are good growth inhibiting agents of these pathogenic bacteria.</p>		[114]

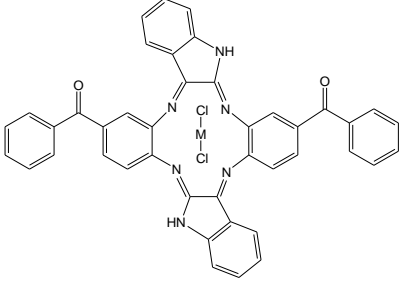
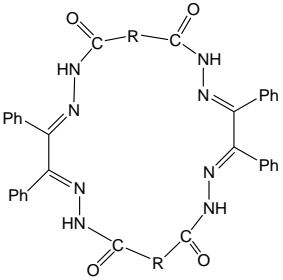
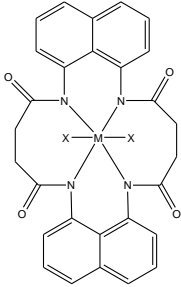
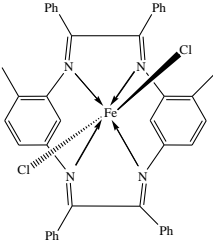
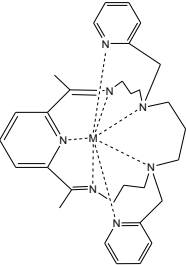
<p>E.R. Krishna, P.M. Reddy, M. Sarangapani, G. Hanmanthu, B. Geeta, K.S. Rani, V. Ravinder</p>	<p>Several tetraaza macrocyclic ligands were prepared by condensation of ophthalaldehyde with several substituted aromatic amines/azides and subsequently used to synthesize a series of metal complexes of Ru(II), Pd(II) and Pt(II). Both the ligands and complexes were screened for their antibacterial activities against Gram positive (<i>S. aureus</i> and <i>B. subtilis</i>) and Gram negative (<i>E. coli</i> and <i>K. pneumonia</i>) bacteria using the MIC method.</p>	 <p>X= substituted (diamide, triazole or pyridine groups. Y= Cl⁻.</p>	<p>[115]</p>
<p>O.I. Salam, M.A. Al-Omar, A. A. Fayed, E.M. Flefel, A.E. Amr</p>	<p>A series of macrocyclic imides and Schiff-bases has been prepared <i>via</i> the cyclocondensation of pyridine-2,6-dicarbonyl dichloride with L-ornithine methyl ester, to give the corresponding macrocyclic bis-esters. Microorganisms screening showed that most of the newly synthesized compounds have antimicrobial activities against <i>B. subtilis</i>, <i>S. aureus</i> and <i>E. coli</i> bacteria and <i>C. albicans</i> and <i>A. niger</i> fungi that are comparable to those of the reference drugs ampicillin and ketaconazole.</p>		<p>[116]</p>
<p>S.C. Ruchi</p>	<p>Mn(II), Co(II), Ni(II) and Cu(II) complexes with the new tetradentate macrocyclic ligand 1.2.5.6-tetraoxo-3,4,7,8-tetraaza-(1,2,3,4,5,6,7,8)-tetrabenzene(L) were synthesized. The antimicrobial activities and LD50 values of both the ligand and complexes, as growth inhibiting agents against <i>B. subtilis</i> and <i>X. compestris</i> bacteria and plant pathogenic fungi <i>R. solani</i> and <i>R. blast</i> were investigated <i>in vitro</i> with good results.</p>		<p>[117]</p>
<p>I. Masih, N. Fahmi, R. kumar</p>	<p>Cr(III) macrocyclic complexes were obtained by template condensation of substituted 1,2-diphenyl-ethanones with 1,2-phenylenediamine, 4-chloro-1,2-phenylenediamine and 4-fluoro-1,2-phenylenediamine in the presence of CrCl₃.6H₂O. The newly synthesized ligands and complexes were screened for antimicrobial (against bacterial strains <i>E. coli</i> and <i>B. subtilis</i>, and fungi strain <i>F. oxysporum</i>), nematicidal (<i>M. incognita</i>) and pesticidal (<i>C. cephalonica</i>) activities, with promising results.</p>		<p>[118]</p>
<p>S. Rani, S. Kumar, S. Chandra</p>	<p>A novel tetradentate nitrogen donor [N₄] macrocyclic ligand has been synthesized from condensation of acetyl acetone with <i>o</i>-phenylene diamine. The antimicrobial activities of the ligand and its Pd(II), Pt(II), Ru(III) and Ir(III) complexes against plant pathogenic fungi <i>A. porri</i> and <i>F. oxysporum</i>, and bacteria <i>X. compestris</i> and <i>P. aeruginosa</i> have been screened <i>in vitro</i>, the results indicating that the Ru(III) complex is highly active while the other metal complexes show only moderate activity as compared to the free ligand.</p>		<p>[119]</p>
<p>H. Keypour, M. Liyaghati-Delshad,</p>	<p>Six new M= Cd(II) and Zn(II) complexes with a macrocyclic Schiff base ligand produced by cyclo-</p>		<p>[120]</p>

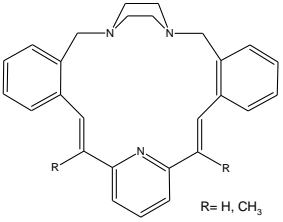
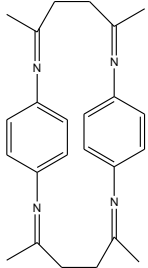
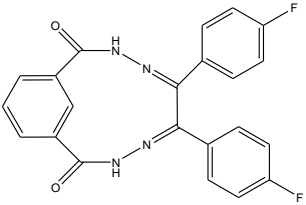
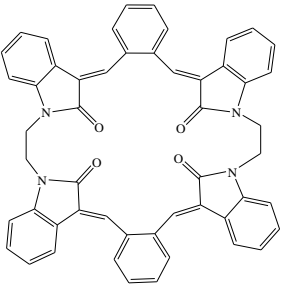
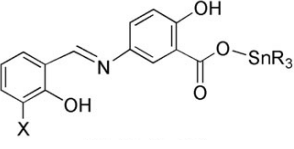
M. Rezaeivala, H.R. Khavasi	condensation of 2,6-diacetylpyridine with three different linear aromatic amines were investigated. The compounds were found to exhibit antibacterial activity against both Gram positive (<i>S. aureus</i> , <i>B. cereus</i> , <i>C. xerosis</i>) and Gram-negative bacteria (<i>E. coli</i> , <i>K. pneumonia</i> , <i>P. vulgaris</i>). It was also shown that the antibacterial activity of the investigated Cd(II) complexes is greater compared to that of the corresponding Zn(II) complexes.		
S. Chandra, S. Agrawal	Complexes of Ce(III), Nd(III), Sm(III) and Eu(III) with a macrocyclic ligand obtained by the condensation of 2,6-diacetylpyridine with thiourea were prepared and characterized. The compounds were shown to exhibit <i>in vitro</i> moderate antifungal behavior against <i>A. niger</i> and <i>F. oxysporum</i> .		[121]
H. Keypour, M.H. Zabarjadian, M. Rezaeivala, A. Chehreghani, H. Amiri-Rudbari, G. Bruno	Two new branched hexadentate amines were prepared. Condensation with 2,6-diacetylpyridine in methanol, in presence of M= Mn(II), Zn(II) or Cd(II) ions, led to the production of a series of novel Schiff base macrocyclic complexes with two 2-pyridylmethyl pendant arms. The synthesized complexes were screened for their antibacterial activities against four bacterial strains (<i>E. coli</i> , <i>B. cereus</i> , <i>S. subrogation</i> and <i>S. aureus</i>) and the complexes were shown to be good growth inhibitors for the considered microorganisms.		[122]
P. Rathi, D.P. Singh	Macrocyclic Schiff base derived complexes of general formula [MLX] ₂ , where L is C ₁₀ H ₁₀ N ₄ O ₂ S, M= Cr(III) or Fe(III), and X = Cl ⁻ , CH ₃ COO ⁻ or NO ₃ ⁻ , were synthesized <i>via</i> the template condensation method. All the metal complexes were explored for <i>in vitro</i> antimicrobial effects against <i>B. subtilis</i> , <i>E. coli</i> , <i>S. cerevisiae</i> and <i>C. albicans</i> , as well as for their antioxidant activities.		[123]
P. Arthi, S. Shobana, P. Srinivasan, L. Mitu, A.K. Rahiman	A series of bis(phenoxo)-bridged binuclear Mn(II) complexes was synthesized by cyclocondensation of 2,6-diformyl-4-R-phenols with 2,20-3,5 dinitrobenzoyliminodi(ethylamine) trihydrochloride in the presence of Mn(II) perchlorate. The antibacterial efficacy of the complexes was screened against bacterial strains <i>E. faecalis</i> , <i>P. aeruginosa</i> , <i>V. cholerae</i> , <i>V. harveyi</i> , <i>S. aureus</i> and <i>S. mutans</i> . DNA interaction studies suggested that these complexes bind to CT-DNA by intercalation.		[124]
E.M. Zayed, M.A. Zayed	Novel bisaldehyde-hydrazide Schiff bases were prepared as new macrocyclic compounds <i>via</i> condensation reactions of (2,2'-(ethane-1,2-diylbis(oxy))dibenzaldehyde) bisaldehyde and terephthaloyl or benzohydrazide. Their biological activities were tested <i>in vitro</i> against <i>E. coli</i> , <i>P. vulgaris</i> , <i>B. subtilis</i> and <i>S. aureus</i> bacteria, in order to assess their antimicrobial potential.		[125]

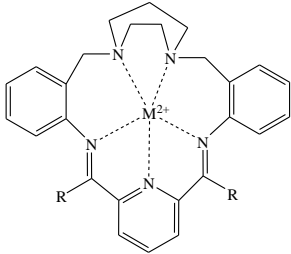
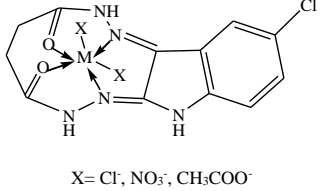
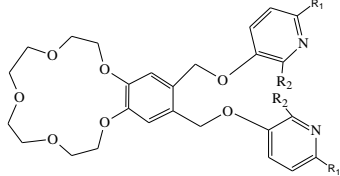
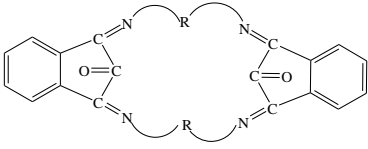
<p>Q.R. Cheng, L. Yu, P. Li G.Y. Liao H. Zhou Z.Q. Pan</p>	<p>Three dinuclear complexes of Ni(II) and Mn(II) with a macrocyclic ligand resulting from condensation of 2,6-diformyl-4-fluorophenol with diethylenetriamine or <i>N,N</i>-bis(3-aminopropyl)-2-thiopheno-ethylamine were synthesized and characterized. All three complexes have been found to promote cleavage of plasmid pBR322 DNA. The antibacterial activities of the complexes against <i>S. aureus</i> and <i>E. coli</i> bacteria were also investigated.</p>		<p>[126]</p>
<p>H. Keypour, M. Liyaghati-Delshad, M. Rezaeivala, M. Bayat</p>	<p>Three new hexaaza (N_6) macrocyclic Schiff base ligands containing a phenanthroline moiety have been synthesized. The synthesized complexes (of Mn(II) and Cd(II)) were screened for their antibacterial activity against six bacterial strains (<i>S. aureus</i>, <i>B. cereus</i>, <i>C. xerosis</i>, <i>E. coli</i>, <i>K. pneumoniae</i> and <i>P. vulgaris</i>) and showed promising results.</p>		<p>[127]</p>
<p>N. Fahmi, I. Masih, K. Soni</p>	<p>A new class of unsymmetrical Pd(II) macrocyclic complexes was reported. The complexes were synthesized by template condensation reaction of 1,2-diphenyl-ethanone derivatives with a series of diamines in the presence of PdCl₂. The newly prepared compounds were screened for their antibacterial and antifungal activities against <i>E. coli</i> and <i>B. subtilis</i>, and <i>F. oxysporum</i> and <i>R. nigricans</i>, respectively, which were compared with those of the free ligand. The complexes were also screened for their nematocidal (<i>M. incognita</i> eggs) and pesticidal (<i>C. cephalonica</i>) activities.</p>		<p>[128]</p>
<p>P. Gull, A.A. Hashmi</p>	<p>A macrocyclic Schiff base ligand derived from 1,4-dicarbonyl-phenyl-dihydrazide and pentane-2,4-dione and its Co(II), Cu(II) and Ni(II) complexes were prepared. The antimicrobial activities of the ligand and complexes, as growth inhibiting agents, were screened <i>in vitro</i> against different species of bacteria (<i>E. coli</i>, <i>B. subtilis</i>, <i>P. aeruginosa</i> and <i>S. aureus</i>) and fungi (<i>C. albicans</i>, <i>Fusarium</i> sp., <i>Trichosporon</i> sp. and <i>A. flavus</i>).</p>		<p>[129]</p>
<p>H. Zafar, A. Kareem, A. Sherwani, O. Mohammad, M. A. Ansari, H.M. Khan, T.A. Khan</p>	<p>The condensation between 1,2-diphenyl-ethane-1,2-dione dihydrazone and dimethyl or diethyloxalate in methanol resulted in a novel Schiff base octaazamacrocyclic ligand. The ligand and its complexes of general formula of the type [MLX₂] and [CuL]X₂ (with M = Mn(II), Co(II), Ni(II) and Zn(II), and X = Cl⁻ or NO₃⁻) were screened for <i>in vitro</i> activity against <i>S. aureus</i> and <i>E. coli</i> bacteria, and also for their anticancer activity against the human cervical carcinoma, human breast adenocarcinoma and human hepatocellular carcinoma cell lines. Moderate to good cytotoxicity against the studied cancer cell lines was observed.</p>		<p>[130]</p>

<p>P.M. Reddy, K. Shanker, V. Srinivas, E.R. Krishna, R. Rohini, G. Srikanth, A. Hu, V. Ravinder</p>	<p>Ten mononuclear Rh (I) complexes with different macrocyclic ligands having N₄ and N₂O₂ donor sites were synthesized and investigated as catalysts in hydrolysis of nitrile group containing pharmaceutical drug letrozole.</p>	 <p>X, Y = alkyl, aryl or N-containing heterocyclic substituents.</p>	<p>[131]</p>
<p>P. Gull, A.A. Hashmi</p>	<p>A macrocyclic Schiff base ligand derived from 1,4-dicarbonyl-phenyl-dihydrazide and pentane-2,4-dione and its M= Co(II), Cu(II) and Ni(II) complexes were synthesized. The antimicrobial activities of the synthesized compounds were screened <i>in vitro</i>, as growth inhibiting agents. The antibacterial and antifungal screenings were carried out for <i>E. coli</i>, <i>B. subtilis</i>, <i>P. aeruginosa</i> and <i>S. aureus</i> bacterial and <i>C. albicans</i>, <i>Fusarium sp.</i>, <i>Trichosporon sp.</i> and <i>A. flavus</i> fungal strains, respectively. It was shown that the macrocyclic ligand possesses mild activity against the studied organisms, while the complexes exhibit moderate to significant activities.</p>		<p>[132]</p>
<p>G. Kumar, S. Devi, D. Kumar</p>	<p>The synthesis of macrocyclic complexes of M= Cr(III), Mn(III) and Fe(III) with a Schiff base ligand obtained through the condensation of 1,4-dicarbonyl phenyl dihydrazide with 1,2-di(1<i>H</i>-indol-1-yl)ethane-1,2-dione was reported. The antifungal and antibacterial activities of the complexes against <i>Aspergillus sp.</i>, <i>Rizoctonia sp.</i> and <i>Penicillium sp.</i>, and <i>S. aureus</i>, <i>B. subtilis</i>, <i>P. aeruginosa</i>, <i>E. coli</i> and <i>S. typhi</i>, respectively, were found to be considerably higher than those of the free ligand and of the reference drugs phenylbutazone (anti-inflammatory), imipenem (antibacterial) and miconazole (antifungi).</p>	 <p>X= Cl⁻, NO₃⁻, CH₃COO⁻</p>	<p>[133]</p>
<p>V.K. Singh, R. Kadu, H. Roy, P. Raghavaiah, S.M. Mobin</p>	<p>A series of xanthate [2:2] binuclear <i>N,O</i>-bidentate Schiff base macrocyclic complexes of M= Cu(II) and Co(II) was synthesized. The copper complexes were shown to exhibit high <i>in vitro</i> anticancer activity against HEP 3B (hepatoma) and IMR 32 (neuroblastoma) cell lines. The obtained IC₅₀ values for these compound confirm their better anticancer potency compared to the reference drug, cisplatin.</p>		<p>[134]</p>
<p>A.N. Srivastva, N.P. Singh, C.K. Shrivastaw</p>	<p>Novel binuclear metal complexes of general formula [M₂(PymL)X₃] (where M= Cu(II), Ni(II), Co(II) or Zn(II); X= Cl⁻ or CH₃COO⁻ and PymL= C₁₃H₁₇N₄O₆) were synthesized by template condensation of a Schiff base derived from glycine using 2,3-butanedione, 5-methyl-2,6-pyrimidine-dione and the proper metal chloride/acetate salt. The compounds were evaluated for their antimicrobial activity against bacteria <i>S. aureus</i>, <i>B. subtilis</i>, <i>E. coli</i> and <i>S. typhi</i> and fungi <i>C. albicans</i> and <i>C. parapsilosis</i>. The results indicate that the new metal complexes exhibit better</p>		<p>[135]</p>

	activity than the free Schiff base against the investigated bacteria and fungi.		
A.E. Amra, M.A. Al-Omara	A series of macrocyclic tripeptides and linear dipeptide Schiff base derivatives was synthesized from pyridine-3,5-dicarboxylic acid and L-phenylalanine methyl ester. The antimicrobial activities (against <i>B. subtilis</i> , <i>S. aureus</i> and <i>E. coli</i>) of some of the novel compounds were found to be comparable with that of streptomycin, chosen as control.		[136]
H.A. El-Boraey, M.A. El-Salamony, A.A. Hathout	A novel penta-azamacrocyclic 21-membered [N ₅] ligand and its complexes with Co(II), Ni(II), Cu(II), Ru(III) and Pd(II) were prepared and characterized. The ligand and some of the complexes were tested for their inhibitory effect on the growth of bacteria strains <i>S. pyogenes</i> and <i>E. coli</i> , the activity data showing that most of the tested compounds exhibit remarkable antibacterial activity against these organisms.		[137]
Z. Parsaee, K. Mohammadi	Several new macrocyclic bridged dianilines tetradentate with N ₄ coordination sphere Schiff base ligands and their Ni(II) complexes were synthesized. All the Schiff bases and their complexes have been assayed <i>in vitro</i> as antibacterial agents against two Gram negative (<i>E. coli</i> and <i>P. aeruginosa</i>) and two Gram positive (<i>S. aureus</i> and <i>S. epidermidis</i>) bacteria. The Ni(II) complexes were found to be more active than the parent free macrocycle Schiff bases.		[138]
H. Keypour, M. Mahmoudabadi, A. Shoostari, L. Hosseinzadeh, F. Mohsenzadeh, R.W. Gable	A new diamine ligand, 2,20-(piperazine-1,4-diylbis(methylene)dianiline, was synthesized by reaction of 2-nitrobenzyl chloride and piperazine. Its M= Mn(II) and Zn(II) complexes were prepared <i>via</i> the metal template cyclocondensation method and tested for <i>in vitro</i> antibacterial properties against <i>B. subtilis</i> , <i>B. thuringiensis</i> , <i>S. Aprophyticus</i> , <i>Pectobacterium</i> sp. and <i>P. fluorescens</i> . The complexes show appreciable antibacterial properties, in some of the cases better than those of tobramycin and tetracycline drugs, which were selected as standards.		[139]
P. Gull, B.A. Babgi, A.A. Hashmi	A macrocyclic Schiff base ligand derived from 1,4-dicarbonyl-phenyl-dihydrazide and glyoxal, and its Ni(II), Cu(II) and Co(II) complexes were synthesized. All the synthesised compounds were screened for their antimicrobial properties against some strains of bacteria (<i>S. aureus</i> , <i>B. subtilis</i> , and <i>E. coli</i>) and fungi (<i>C. albicans</i> , <i>A. flavus</i> and <i>A. niger</i>). The antioxidant activity of the compounds was also studied through scavenging effect on radicals, with the copper complex showing enhanced antioxidant activity when compared with the other studied metal complexes.		[140]
M. Shakir, N. Bano,	12-membered ring Schiff base macrocyclic complexes of dichloro[5,6;11,12-dibenzophenone-		[141]

M.A. Rauf, M. Owais	1,4,7,10-tetraazacyclododeca-1,3,7,9-tetraene-2,3,8,9-diindole] with divalent metals [M = Co(II), Ni(II), Cu(II) and Zn(II)] were synthesized <i>via</i> template condensation of isatin and 3,4-diaminobenzophenone. The comparative <i>in vitro</i> antibacterial study of the metal complexes against different pathogenic microbes (<i>S. aureus</i> , <i>E. coli</i> and <i>C. albicans</i>) revealed enhanced activity for the Cu(II) complex, which was further certified by its efficacy to resist biofilm formation, as investigated by XTT proliferation assays.		
K. Soni, R.V. Singh, N. Fahmi	The condensation reaction between benzyl-dihydrazone and pyridine 2,3-dicarboxylic acid, pyridine 3,4-dicarboxylic acid or pyridine 2,4-dicarboxylic acid led to novel Schiff base macrocyclic ligands. Metal complexes of the type [MLCl ₂] [with M = Co(II) or Ni(II)] were then prepared. The ligands and the complexes were screened for their antibacterial (against <i>S. aureus</i> and <i>E. coli</i>), antifungal (against <i>F. semitectum</i> and <i>A. flavus</i>) and DNA cleavage activities. The studies showed that the complexes possess antimicrobial and DNA cleavage activities better than the free ligands.		[142]
M. Shakir, N. Bano, A. Rauf, S. Kazmi, M. Alam	The macrocyclic ligand, 2,4:11,13-dinaphthyl-1,5, 10,14 tetraazacyclooctadecane-6,9,15,18-tetraone obtained from condensation of 1,8-diaminonaphthalene and succinic acid, was used to synthesize complexes of general formula [MLCl ₂] [with M = Mn(II), Co(II), Ni(II), Cu(II) or Zn(II)]. CT-DNA interaction and circular dichroism studies indicated a greater binding ability in the case of the Cu(II) complex, <i>via</i> groove binding. The <i>in vitro</i> cytotoxicity towards the cancer cell lines HeLa and MCF-7 has been evaluated, with the novel Cu(II) complex appearing as an alternative candidate to traditional chemotherapeutic agents.	 <p style="text-align: center;">X = H₂O</p>	[143]
A. Kumar, V.K. Vashistha, P.Tevatia, R. Singh	Tetraazamacrocyclic complexes of Mn(II), Fe(III), Co(II) and Ni(II) have been synthesized by the template method. Macrocyclic complexes exhibit high interaction affinity towards CT-DNA by intercalation binding. Biological studies of the macrocyclic complexes compared with standard the drug gentamycin, have shown increased antibacterial activity against <i>E. coli</i> , <i>P. aeruginosa</i> , <i>B. cereus</i> , <i>S. aureus</i> and antifungal activity against <i>C. albicans</i> .		[144]
M. Bordbar, F. Tavoosi, A. Yeganeh-Faal, M.H. Zebarjadian	The interaction of complexes of M= Cd(II), Zn(II) and Mn(II) bearing the (4,8-bis(2-pyridylmethyl)-4,8-diazaundecane-1,11-diamine) macrocycle ligand with CT-DNA was investigated. Changes in the circular dichroism spectra and in the DNA melting temperature showed that the studied complexes exhibited good DNA interaction ability <i>via</i> partial intercalation mode.		[145]

<p>H. Keypour, M. Mahmoudabadi, A. Shoostari, M. Bayat, F. Mohsenzadeh, R.W. Gable</p>	<p>New Cd(II) macrocyclic Schiff-base complexes were prepared <i>via</i> metal template cyclocondensation of 2,2'-(piperazine-1,4-diylbis(methylene) dianiline and 2,6-pyridinedicarbaldehyde or 2,6-diacetylpyridine. The complexes were tested for <i>in vitro</i> antibacterial properties against <i>B. anthracis</i>, <i>B. thuringiensis</i>, <i>B. subtilis</i>, <i>S. griseus</i>, <i>S. enteritidis</i>, <i>S. maltophilia</i>, <i>P. fluorescens</i>, <i>S. typhi</i> and <i>Ralstoniasolanacearum</i>. Some of the compounds were found to exhibit better biological activity than the standard antibiotics chlortetracycline and penicillin.</p>		<p>[146]</p>
<p>O.A. El-Gammal, A.F. Al-Hossainy, S.A. El-Brashy</p>	<p>The macrocyclic ligand, (2<i>E</i>)-3,6,10,13-tetramethyl-2,7,9,14-tetraaza-1,8 (1,4)-dibenzenacyclotetradecaphane-2,6,9,13-tetraene and its Co(II), Ni(II) and Cu(II) complexes were isolated and characterized. The compounds were screened <i>in vitro</i> against pathogenic bacteria, and concluded to have better inhibition proprieties against Gram positive (<i>S. pyogenes</i> and <i>S. epidermidis</i>) than against Gram negative (<i>P. vulgaris</i> and <i>Klebsiella</i> sp.) bacteria. The complexes were also found to have some protective effect on DNA.</p>		<p>[147]</p>
<p>P. Jain, V. Singh, S. Ali, V. Tripathi, U. Saraswat</p>	<p>A macrocyclic Schiff base ligand was prepared by condensation of 1,3-dicarbonyl-phenyl-dihydrazide with 4,4-difluorobenzil, and its Co(II), Ni(II), Cu(II) and Zn(II) complexes were subsequently synthesized. The bacterial growth inhibiting potential of the synthesized ligand and all prepared metal complexes was assessed against Gram positive (<i>S. aureus</i> and <i>B. subtilis</i>) and Gram negative (<i>E. coli</i>, <i>P. aeruginosa</i> and <i>S. typhi</i>) bacterial strains. The anticancer activity of the synthesized compounds against squamous cell carcinoma (SCC4), head and neck cancer cell lines was also evaluated.</p>		<p>[148]</p>
<p>A.G.B. Dileepan, T.D. Prakash, A.G. Kumar, P.S. Rajam, V.V. Dhayabaran, R. Rajaram</p>	<p>A new class of macrocyclic compounds with promising antioxidant and antibacterial activity was reported. The biological properties and possible pharmacological applications of the compounds were explored by performing antioxidant and antibacterial tests. The antimicrobial potencies of the newly synthesized compounds were examined by performing <i>in vitro</i> antibacterial evaluation. <i>E. faecalis</i>, <i>B. megaterium</i>, <i>S. epidermidis</i>, <i>S. aureus</i>, <i>V. cholera</i>, <i>E. coli</i>, <i>S. typhi</i> and <i>S. flexneri</i> were used as test bacteria.</p>		<p>[149]</p>
<p>J. Liu, Y. Lin, M. Liu, S. Wang, Y. Li, X. Liu, L. Tian</p>	<p>Six new triorganotin complexes were synthesized by one-pot reaction of 5-aminosalicylic acid, salicylaldehyde and triorganotin hydroxide. Bioassay results against two human tumor cell types (A549 and HeLa) demonstrated that the complexes are efficient cytostatic agents and may be explored as potential antitumor drugs.</p>	 <p>X = H, CH₃O; R = Ph, cyclohexyl, CH₂C(CH₃)₂Ph</p>	<p>[150]</p>

<p>M. Aidi, H. Keypour, A. Shoostari, M. Bayat, L. Hosseinzadeh, H.A. Rudbari, R.W. Gable</p>	<p>Several macrocyclic Schiff base complexes with the homopiperazine skeleton were prepared <i>via</i> template approach, based on the condensation reaction of an amine containing homopiperazine moiety and 2,6-diacetylpyridine or 2,6-pyridine dicarboxaldehyde, in the presence of M= Cd(II), Mn(II) and Zn(II) ions. The cytotoxic activity of the compounds was found to be stronger than that of doxorubicin, used as standard. Also, the bonding situation in the complexes, were analyzed by NBO and energy-decomposition analyses.</p>		<p>[151]</p>
<p>S. Ali, V. Singh, P. Jain, V. Tripathi</p>	<p>Macrocyclic complexes of M= Co(II), Ni(II), Cu(II) and Zn(II) were synthesized <i>via</i> template method by condensation of succinic acid dihydrazide with 5-chloroisatin in alcoholic medium. The compounds were found active against <i>B. subtilis</i>, <i>S. aureus</i>, <i>P. aeruginosa</i> and <i>E. coli</i> bacteria. The Zn(II) complex was also shown to exhibit significant anticancer activity against squamous cell carcinoma cells tested by the MTT assay method.</p>	 <p>X= Cl, NO₃⁻, CH₃COO⁻</p>	<p>[152]</p>
<p>S. Koçoğlu, H. Ogutcu, Z. Hayvalı</p>	<p>New double-armed crown ether ligands linked to pyridine derivatives were synthesized and characterized. The macrocyclic ligands were synthesized by the reactions of 4',5'-bis(bromomethyl)benzo-15-crown-5 with 3-hydroxy pyridine derivatives. A series of Na(I), K(I) and Ag(I) complexes of the macrocyclic ligands was then prepared. The antimicrobial activity of the synthesized compounds against a large number of microorganisms was evaluated.</p>	 <p>R₁= H, CH₃; R₂= H, Cl, Br, NO₂</p>	<p>[153]</p>
<p>S. Sharma, P.M.N. Chopra, V. Chugh</p>	<p>The synthesis, characterization and antimicrobial properties of some novel macrocyclic complexes with general formula [M(C₂₂H₁₆N₄O₂)X]X₂, where M= Fe(III), Co(III) and Cr(III), and X is either bromine or chlorine, were reported. The complexes were prepared by template condensation of ethylenediamine and 2,2-dihydroxyindane-1,3-dione using salts of the considered trivalent metals. The antimicrobial properties against Gram positive (<i>B. subtilis</i> and <i>B. stearo thermophiles</i>) and Gram negative (<i>P. putida</i> and <i>E. coli</i>) bacteria were investigating in comparison with standard antibiotics (streptomycin and chloramphenicol). The novel cobalt bromide and chromium chloride complexes were concluded to have significant antimicrobial activity.</p>	 <p>R= CH₂-CH₂</p>	<p>[154]</p>

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