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REVIEW

Biomedical Applications of Some Schiff Bases and Their Transition Metal Complexes: A Review

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A diverse class of compounds known as Schiff bases and their metal complexes are synthesized *via* condensation of amino and carbonyl compounds. Schiff bases and their metal complexes have several applications in analytical, pharmacological, organic, bioinorganic, and material research, which has increased interest in this class of molecule. In a variety of reactions, even in the presence of moisture, many Schiff base metal complexes have outstanding catalytic activity. Schiff bases serve as versatile pharmacophores due to their ability to bind with metals of different oxidation states to form complexes. Over the past few decades of metal-based drug research, Schiff base metal complexes have been the focus of much coordination chemistry research due to their utility across multiple scientific scenarios. As therapeutic agents, they may be beneficial in numerous circumstances, including infections, tumors, viruses, inflammation, pain and fungus. The focus of medicinal chemists is currently on the development of novel chemotherapeutic Schiff bases and their metal complexes. This review summarizes some of the most promising antimicrobial and anticancer activities of Schiff bases and their transition metal complexes. A possible relationship between structure and activity in some cases is also discussed.

Keywords: Schiff base, Transition metal complexes, Antimicrobial, Anticancer activity.

INTRODUCTION

The versatility of Schiff bases makes them essential chemical substances in many areas, including pharmaceutical, inorganic and analytical chemistry. When coordinated with a range of transition metal ions, these compounds can form stable complexes that exhibit a wide variety of structures and properties. Because of their wide range of chemical activity and potential uses, metal complexes with Schiff bases have recently attracted a lot of research interest. Schiff bases are formed with a variety of compounds, including aminothiazoles, pyrazolones, amino acids, 2-hydroxy-1-naphthylaniline, aminosugars, aromatic aldehydes, triazole rings, thiosemicarbazides and isatins [1-3]. Schiff bases can be found with bidentate, tridentate or tetradentate ligands and can form stable five- or six-membered metal chelate complexes with a variety of metal ions. Electron deficient groups, such as azomethine, can capture metal ions due to their large radii and high coordination number. It is unclear whether monodentate Schiff bases can form stable complexes. This may be due to the lack of energy of the imino nitrogen of the azomethine group. Bidentate or tridentate ligands of the Schiff base can coordinate to various metal ions through their azomethine and -OH/SH groups [4] and stabilize them in various oxidation states through chelation processes.

Schiff bases are the excellent building blocks for novel pharmaceuticals because their active groups contain active electrons and are produced when an amine moiety reacts with the carbonyl group of an aldehyde or beta diketone [5,6]. Extensive investigations have been conducted in the field of medicinal chemistry to develop robust and efficient pharmaceuticals. The broad spectrum of pharmacokinetic characteristics and their significance in drug discovery programmes have led to the various applications of Schiff base derivatives in therapeutic chemistry [7]. According to reports, Schiff base derivatives and their metal complexes exhibit a wide range of biological actions, including anti-inflammatory [8-11], antibacterial [12-16], antifungal [17-22], antiviral [21,22], antioxidant [23-27], antimalarial [28,29], DNA binding [30] and acute toxicity and resistance to gastropathy *in vivo* [31]. Moreover, metal complexes refined from the Schiff base are currently used as antitumor

agents [32,33] and anticancer agents [34-39]. Many structures derived from Schiff base complexes include macrocycles [40], dehydroacetic acid based hydrazines [41], hydrazinemetamides, 2-[3-methyl-2-thienylidene] [42], aroylhydrazone ligands and pyridine auxi-liary ligands [43] and thiadiazoline moieties [44] was stated as anticancer agents.

The threat of microbial infections to human civilization dates back to ancient times and this is significant since these diseases have killed off huge numbers of people in different parts of the world. The Infectious Diseases Society of America noted in their report that certain microbial species, such as *Pseudomonas aeruginosa* and *Klebsiella pneumonia*, along with species from the genera *Staphylococcus*, *Enterococcus*, *Enterobacter* and *Acinetobacter*, pose a significant risk of infection [45]. The biological activities of Schiff bases and their transition metal complexes have been shown in numerous published studies to be effective against various bacterial and fungal species as well as tumours. Another group of devastating diseases is cancer, which poses a threat to people all over the globe, both in developed and developing nations, due to the lack of effective treatments [35]. The transition metals can create a wide variety of complexes with Schiff base ligands.

Several reseachers reported the study of Schiff base complexes using various human tumor cell lines, including human liver cancer (Hep-G2) cells [46,47], human breast adenocarcinoma (MCF-7) cell [48,49], SKOV-3 [50-52], prostate cancer cell (PC-3) [53,54], cervical cancer cell (HeLa) [55-57], adenomacarcinoma human alveolar basal epithelial cell (A 549) [58], human colon cancer cell line (HCT-116) [59] and renal cell carcinoma (A498) [60] cancer properties. In addition to their usefulness as catalysts [61,62], industrial chemicals [63, 64] and environmental friendly molecules [65,66], Schiff bases have a long history of use as effective sensors [67,68] and other similar roles. Complexes including mixed ligands [69], porphyrins [70-74], Schiff bases [75], *etc.*, are all within their capabilities. These transition metal complexes have important uses as catalysts in chemical synthesis, biology and medicinal chemistry [69-72,74-87]. In last few years, there have been many reports on the use of antibacterial, antifungal, antioxidant, anticancer, anti-inflammatory, antiviral and antimalarial activities, especially in biology. Therefore, a review shows the need for Schiff base ligands and their transition metal complexes. In this review biomedical information about new Schiff bases and their transition metal complexes published from 2019 to 2023 are highlighted.

Schiff bases and their transition metal complexes: Schiff base is one of the most widely used families of organic compounds and is a complex reaction between carbonyl groups and primary amines. This class of compounds is generally defined by the presence of an active imine (-CH=N) group that can bind to metal ions *via* neutral electrons attached to the nitrogen atom [88]. The structure of Schiff base also contains many heteroelements such as oxygen and sulphur, which can form chelates with metals. The nature of the donor atoms as coordination sites, their electronegativities and steric factors generally determine the potential of the ligands. Due to the presence of a lone electron pair on the N atom, electron donation of the double bond and the low electronegativity of nitrogen, the N atom of azomethine group (>C=N) is a very good donor site and the Schiff base is considered an active ligand [89,90]. For the synthesis of Schiff bases, the basic carbonyl group can be an aldehyde (aromatic or aliphatic) or a ketone. The stability of imine group is controlled by the presence of substituents attached to the (>C=N) bond. Schiff base is a multifunctional pharmacophore in which metal ions in the unit structure are precipitated due to the large number of donor atoms [91,92]. Transition metal complexes of Schiff bases are usually formed by chelation of Schiff base ligands with metal ions of different oxidation states. The empty *d*-orbital of the metal ion provides the site for easy bonding between the unpaired electrons of the ligand donor atom and in some cases this bonding occurs through deprotonation. A general rule in coordination chemistry is that chelation makes the process more stable and changes the physical properties of the complex due to electron recycling in the ring [93,94]. Their stability increases when the chelating rings have five or six membered ring. The aryl group attached to the nitrogen or carbon of the azomethine group prevents their rapid decomposition and polymerization. Azomethine is an important element in chemistry and biology because the two single electrons in the sp^2 hybridized orbital of the nitrogen are easy to process with metal. Changes in the denticity of Schiff base can control the stereochemistry of metal complexes, thereby affecting their physical properties. Several medicinal products contain metal ions that play an important role in the effectiveness of biological activity [95]. Many studies describe the effectiveness of metals by comparing them with free ligands. Recently, many research articles on Schiff bases have mentioned their ability to act as antibiotics and to enhance their effects by forming chelation with metal [96-98]. Chelation causes significant changes in the biological properties of the ligand and the metal moiety [99].

Biomedical applications: The sp^2 hybridized nitrogen of azomethine group interacts with cellular processes by forming hydrogen bonds between functional sites of cellular components [100]. Bacteria caused infections with a large number of antibiotics, leading to increased mortality. The incidence of fungal infections has increased recently and can be life threatening [101]. Fig. 1 shows the comparison of different biomedical applications.

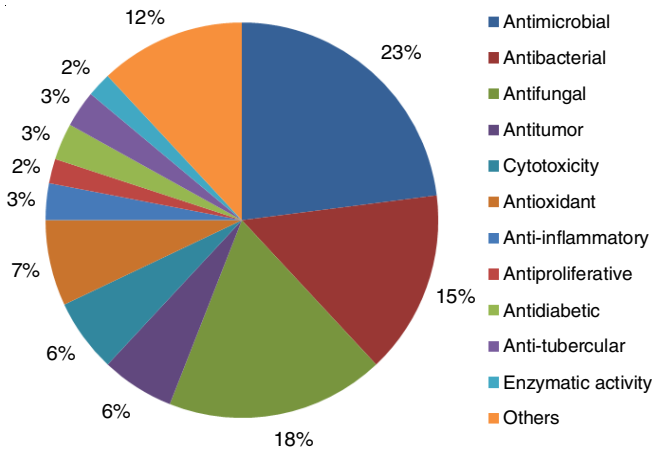


Fig. 1. Comparison of publications on different biomedical activities

The presence of methoxy and halogen groups contributes to the fungicidal activity of the ligands. Chelation can enhance immunity by promoting the ability of the pathway to cross cell membranes. Chelation reduces the polarity of the metal ion due in part to its positive charge on the donor group and delocalization of electrons in the chelating ring. Schiff bases and their metal complexes are toxic to bacteria due to the presence of lipophilic groups (-OCH_3, CH_3CH_2CH-, -C_6H_5). The lipophilicity of the complex increases after the delocalization of the π-electrons in the chelating ring facilitates entry into the lipid bilayer of the cell membrane. Most metal chelates have polar and non-polar properties, making them suitable for entry into cells and tissues [102-105]. Enzymes that rely on free hydroxyl groups for their activity seem to be more impacted by the metal ions in polychelates, since they are inhibited when ligands and their metal chelates contain N and O donors. All the metal polychelates are more toxic as compared to ligands. Cancer or malignancy, a class of diseases in which a group of cells exhibit uncontrolled growth, invasion and sometime metastasis, remains a significant societal problem. Treatment options include surgery and chemotherapy, but current chemotherapy has many side effects [106,107]. Although platinum based complexes such as cisplatin have been used to treat cancer, they are not effective chemotherapy. Therefore, researchers have attempted to develop non-platinum based compounds [108]. Schiff base derivatives have recently been shown to have good anticancer properties.

Aroua *et al.* [109] reported the synthesis of Schiff base metal complexes [$Cr(L_1)(H_2O)Cl_2$] (**C_1**), [$Zn(HL_1)(H_2O)Cl_2$], (**C_2**) and [$Mn(L_1)(H_2O)_2Cl$] (**C_3**), which were formed *via* condensation of the Schiff base ligand **L_1** with their respective metal salts. By mixing 2-amino methyl benzimidazole with 2-hydroxy in ethanol, the Schiff base ligand was prepared. The synthesized compounds are likely to have an octahedral geometry. Using diffusion method, the pathogenic bacteria *E. coli*, *B. subtilis* and the fungus *A. niger* were used to test the antibacterial and antifungal activity of **L_1** and **C_1-C_3** [110]. Like its metal complexes (**C_1-C_3**), **L_1** had potent antimicrobial and antifungal activities. Perhaps the ligand's enhanced activity relative to its metallic complexes as a result of the free movement of electrons, which might be because of the presence of free hydroxyl group in ligand. The SRB assays were used to examine the complex **C_1-C_3**'s *in vitro* anticancer activity against the human cell lines colorectal adenocarcinoma (HCT 116), hepatocellular carcinoma (HepG2) and breast adenocarcinoma (MCF-7). The IC_{50} values for HCT 116, MCF-7 and HepG2 cells were 6.7, 1.1 and 0.7 µg, respectively, indicating that complex **C_3** has strong cytotoxic effects. The IC_{50} values for HCT 116 and HepG2 cells were 46.1 and 36.6 µg, respectively, indicating minimum cytotoxic effects of complex **C_2**, while the corresponding values for complex **C_1** are in the range of 10.2 to 30.5 µg and 1.6 µg, respectively indicating moderate cytotoxic effect of this complex. From this study, it is revealed that complexes **C_1** and **C_2** have no cytotoxic effect against breast carcinoma MCF-7 cells. Complex **C_3** exhibited high toxicity to *Aedes aegypti* larvae, according to the results of the biological tests conducted on the pest, with LC_{50} values of 4.764 ppm.

The octahedral complexes [$V(HL_2)(L_2)Cl_2$] (**C_4**), [$Cr(HL_2)(L_2)Cl_2$] (**C_5**), [$Mn(HL_2)(H_2O)_2Cl_2$] (**C_6**), [$Fe(L_2)_2(H_2O)Cl$] (**C_7**), [$Co(L_2)_2(H_2O)Cl$] (**C_8**), [$Ni(HL_2)(L_2)(H_2O)Cl$] (**C_9**), [$Cu(HL_2)(H_2O)_2Cl_2$] (**C_{10}**) and [$Zn(HL_2)_2Cl_2$] (**C_{11}**) were synthesized by Alorini *et al.* [111] using ligand **L_2** in a 1:1 molar ratio of L to M. The ligand was synthesized by reflux condensation reaction of 2-hydroxy-1-napthaldehyde and benzaldehyde with *p*-phenylenediamine. The metal complexes were prepared by reacting the ligand with metal(II) chlorides. The ligand and its complex were tested for antibacterial and antifungal properties using the whole plate diffusion method. Among the synthesized complexes, only **C_8** and **C_{11}** show moderate antibacterial effects and ligand, **L_2** do not show any antibacterial effects. **C_4** shows the highest antifungal effects against *C. albicans* (IZ 13 mm) when tested in 30, 20 and 10 µL, while **C_5** and **C_7** show high inhibition zone (IZ 11 mm, 12 mm), but **C_6**, **C_9** and **C_{11}** show intermediate antifungal effect (4-9 mm) at the same concentration (Table-1). The inhibition zone data demonstrated that

TABLE-1
ANTIMICROBIAL RESULTS OF BACTERIAL AND FUNGAL STRAINS IN INHIBITION ZONE (IZ) DIAMETERS (mm) AND MIC VALUES (µg/mL)

Compounds	Bacterial strains				Fungal strains		Conc. (µg mL^{-1})	Ref.
	Gram-positive bacteria		Gram-negative bacteria					
	S. aureus	*B. substilis*	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*		
	Results in diameter (mm)							
L_1	–	32	30	–	25	–	10^{-3} M	[109]
C_1	–	24	26	–	25	–		
C_2	–	15	20	–	20	–		
C_3	–	24	24	–	25	–		
L_7	6-11	6-13	7-12	6-12	–	–	6×10^2	[114]
L_8	6-8	8-13	7-12	6-11	–	–		
L_9	6-11	8-13	7-12	6-11	–	–		
L_{10}	6-10	6-13	7-12	6-11	–	–		
C_{22}	8-14	10-15	10-15	8-13	–	–		
C_{23}	8-14	8-13	10-14	8-13	–	–		
C_{24}	12-17	13-22	10-17	11-16	–	–		
C_{25}	12-18	14-22	13-18	12-16	–	–		

L_{11}	–	5-10	5-10	–	10-20	–	1×10^3	[115]
C_{26}	–	10-20	10-20	–	10-20	–		
C_{27}	–	> 20	> 20	–	> 20	–		
C_{28}	–	10-20	> 20	–	10-20	–		
L_{12}	5	–	–	9	–	–	1×10^3	[116]
C_{29}	14	–	–	9	–	–		
C_{30}	23	–	–	9	–	–		
C_{31}	27	–	–	10	–	–		
C_{32}	25	–	–	14	–	–		
C_{33}	9	–	–	11	–	–		
C_{34}	16	–	–	11	–	–		
C_{35}	25	–	–	20	–	–		
C_{36}	34	–	–	25	–	–		
L_{13}	7.5	–	7	–	–	9	1×10^2	[117]
L_{14}	13	–	10	–	–	12		
L_{15}	11	–	12	–	–	14		
C_{37}	12	–	15	–	–	15		
C_{38}	22	–	18	–	–	17		
C_{39}	16	–	22	–	–	18		
L_{16}	1-3	7-10	7-10	–	7-10	–	1×10^2	[121]
C_{40}	4-6	7-10	7-10	–	ND	–		
C_{41}	7-10	1-3	1-3	–	4-6	–		
C_{42}	1-3	1-3	1-3	–	1-3	–		
C_{43}	ND	4-6	1-3	–	4-6	–		
L_{17}	12	14	13	–	11	13		[122]
C_{44}	24	27	24	–	20	21		
C_{45}	26	28	18	–	30	29		
C_{46}	28	30	20	–	25	27		
C_{47}	24	28	25	–	18	22		
C_{48}	31	32	33	–	34	28		
C_{49}	29	24	30	–	28	30		
L_{20}	< 7	–	< 7	–	–	–	2.0 mM	[124]
L_{21}	< 7	–	< 7	–	–	–		
C_{52}	< 7	–	< 7	–	–	–		
C_{53}	< 7	–	< 7	–	–	–		
L_{26}	13	–		14	15	15	2×10^3	[128]
C_{61}	8	–		ND	10	19		
C_{64}	8.87 ± 0.42	10.73 ± 0.42	ND	–	–	8.97 ± 0.21		[129]
C_{65}	12.83 ± 0.42	15.77 ± 0.42	11.93 ± 0.35	–	–	12.90 ± 0.26		
C_{66}	13 ± 0.46	18.70 ± 0.44	13.90 ± 0.26	–	–	15.80 ± 0.36		
C_{67}	10.87 ± 0.31	12.0 ± 0.40	10.80 ± 0.52	–	–	12.77 ± 0.40		
L_{28}	12	13	9.5	–	–	–	2×10^1	[130]
L_{29}	6	8	2	–	–	–		
C_{68}	16	18	13	–	–	–		
C_{69}	17	18	7	–	–	–		
C_{70}	15	15	14	–	–	–		
C_{71}	14	17	5	–	–	–		
Results in MIC values (µg/mL)								
L_{13}	100		50			100	1×10^2	[117]
L_{14}	30		50			50		
L_{15}	50		30			50		
C_{37}	30		17			30		
C_{38}	5		17			18		
C_{39}	30		10			10		
L_{18}	37.5	18.8	> 75				1.5×10^2	[123]
L_{19}	18.8	9.4	18.8					
C_{50}	9.4	4.7	37.5					
C_{51}	4.7	1.2	9.4					
L_{22}	25	> 50	> 50	> 50			5×10^1	[125]
L_{23}	6.25	25	12.5	25				
C_{54}	6.25	12.5	> 50	25				
C_{55}	0.78	1.56	6.25	3.12				

ND = Not detectable; Note: Only those bacterial and fungal strains that were commonly discussed in most articles were marked in the table. While other numerous microbial strains that are rarely studied, have been discussed in the main text.

ligands and its metal complexes exhibited a moderate suppression of fungal and bacterial growth at low concentrations (10 µL). Complexes in particular showed a multifold increase in inhibition at higher doses (30 µL), which may be attributed due to the presence of halogen group in complex **C_2**. According to the SRB assay, complex **C_2** affected PC-3, SKOV-3 and HeLa tumour cell lines. For PC-3, SKOV 3 and HeLa, the IC_{50} values for ligand were determined to be 1.0123 ± 0.05, 0.2163 ± 0.005 and 0.5877 ± 0.14 µg/mL, respectively. Among the synthesized complexes, **C_{10}** shows the highest anticancer activity against tumor cell lines PC-3, SKOV-3 and HeLa with IC_{50} values of 0.161, 0.063 and 0.087 µg/mL, respectively. Complex **C_9** shows lowest activity with IC_{50} values of 1.8287, 1.2502 and 3.8453 µg/mL, respectively against the corresponding cell lines. The IC_{50} values for the other complexes **C_4**, **C_5**, **C_6**, **C_7**, **C_8** and **C_{11}** were in the range of 0.1786-1.0607, 0.0615-0.8128 and 0.0719-1.534 µg/mL, respectively against tumor cell lines PC-3, SKOV-3 and HeLa (Table-2).

In continuation of their work, Aroua *et al.* [112] also reported the synthesis of new mononuclear octahedral complexes, $[Ni(L_3)(H_2O)_3Cl]$ (**C_{12}**), $[Fe(L_3)(H_2O)_2Cl_2]$ (**C_{13}**), $[Cu(HL_3)(H_2O)_2Cl_2]$ (**C_{14}**), $[Co(HL_3)(H_2O)_2Cl_2]$ (**C_{15}**), $[Mn(L_3)(H_2O)_3Cl]$ (**C_{18}**), $[Zn(L_3)(H_2O)_3Cl]$ (**C_{17}**) and $[Cr(L_3)(H_2O)_2Cl_2]$ (**C_{18}**) using hybrid urea Schiff base (**L_3**) in a L:M ratio of 1:1. A catalyst free condensation of *o*-phenylenediamine and naphthyl isocyanate in anhydrous dichloromethane was the first step in the ligand synthesis process. Following purification, the process produced the aminodiarylurea in a respectable yield of 90%. By refluxing 2-hydroxynaphthaldehyde into aminodiarylurea, the matching urea Schiff base (**L_3**) was prepared. The *in vitro* anticancer activities were conducted on ligand **L_3** and metal complexes **C_{12}**-**C_{18}**. The SBR test with six different concentrations of each compound was utilized to calculate IC_{50}. The cell lines tested were PC-3, SKOV-3 and HeLa. The results in Table-2 indicates that ligand **L_3** shows weak activity against three cancer cell lines. Complexes **C_{12}** and **C_{13}** show moderate activity against three cell lines PC-3, SKOV-3 and HeLa with IC_{50} values of 6.56 ± 0.56, 7.17 ± 1.89, 5.83 ± 2.00 and 5.05 ± 0.66, 9.32 ± 0.81, 5.44 ± 0.60 µg/mL, respectively. Complex **C_{15}** exhibits minimum activity against PC-3 and a moderate activity against HeLa. Complex **C_{18}** presents a moderate activity against PC-3 while the activity increases towards SKOV-3 and HeLa. Both complexes **C_{16}** and **C_{17}** show moderate activity against PC-3 and HeLa, they exhibit an excellent activity towards SKOV-3

TABLE-2
ANTICANCER ACTIVITY (IC_{50} VALUES) USING OVARIAN CANCER (SKOV-3), LIVER CANCER (HepG 2), BREAST CANCER (MCF-7), CERVICAL CANCER (HeLa), PROSTATE CANCER (PC-3) AND COLON CANCER (HcT 116) CELLS

Compound	SKOV-3	HepG 2	MCF-7	HeLa	PC-3	HcT 116	Unit	Ref.
L_1	–	5.7 ± 0.5	17.6 ± 1.5	–	–	10.2 ± 1.3	µg	[109]
C_1	–	46.1 ± 1.6	≥ 100	–	–	36.6 ± 2.6		
C_2	–	14.4 ± 0.5	19.5 ± 0.5	–	–	30.5 ± 1.6		
C_3	–	1.1 ± 0.2	6.7 ± 0.5	–	–	0.7 ± 0.1		
L_2	0.2163 ± 0.005	–	–	0.5877 ± 0.14	1.0123 ± 0.05	–	µg/mL	[111]
C_4	0.1997 ± 0.03	–	–	0.0719 ± 0.02	0.7262 ± 0.14	–		
C_5	0.0678 ± 0.03	–	–	0.7606 ± 0.05	0.7027 ± 0.25	–		
C_6	0.2189 ± 0.05	–	–	0.9254 ± 0.05	0.1786 ± 0.02	–		
C_7	0.8128 ± 0.20	–	–	1.5340 ± 0.30	0.3188 ± 0.02	–		
C_8	0.0615 ± 0.02	–	–	0.3921 ± 0.03	1.0607 ± 0.16	–		
C_9	1.2502 ± 0.20	–	–	3.8453 ± 0.32	1.8287 ± 0.10	–		
C_{10}	0.0630 ± 0.003	–	–	0.0872 ± 0.01	0.1612 ± 0.005	–		
C_{11}	0.1646 ± 0.04	–	–	1.3064 ± 0.46	0.4436 ± 0.07	–		
L_3	25.12 ± 1.91	–	–	23.32 ± 3.71	8.71 ± 0.50	–	µg/mL	[112]
C_{12}	7.17 ± 1.89	–	–	5.83 ± 2.00	6.56 ± 0.56	–		
C_{13}	9.32 ± 0.81	–	–	5.44 ± 0.60	5.05 ± 0.66	–		
C_{14}	0.12 ± 0.06	–	–	0.79 ± 0.23	0.71 ± 0.06	–		
C_{15}	0.73 ± 0.06	–	–	6.67 ± 0.80	18.89 ± 1.70	–		
C_{16}	0.84 ± 0.17	–	–	3.62 ± 1.48	4.98 ± 0.65	–		
C_{17}	1.82 ± 0.10	–	–	5.02 ± 0.75	3.16 ± 0.68	–		
C_{18}	0.95 ± 0.11	–	–	0.79 ± 0.06	7.05 ± 1.01	–		
C_{19}	–	–	–	38.73 ± 1.59	–	–	µM	[113]
C_{20}	–	–	–	17.94 ± 1.25	–	–		
C_{21}	–	–	–	10.54 ± 1.02	–	–		
C_{59}	–	–	22.19 ± 1.13	–	–	–	µM	[127]
C_{60}	–	–	14.58 ± 0.88	–	–	–		
C_{61}	–	–	16 ± 1.0	14 ± 0.8	–	–	µM	[128]
L_{28}	–	75 ± 0.02	70 ± 0.049	–	–	–	µM	[130]
L_{29}	–	52.0 ± 0.036	69.0 ± 0.22	–	–	–		
C_{68}	–	2.6 ± 0.031	3.0 ± 0.184	–	–	–		
C_{69}	–	21.0 ± 0.043	37.0 ± 0.062	–	–	–		
C_{70}	–	41.0 ± 0.101	37.0 ± 0.21	–	–	–		
C_{71}	–	29.0 ± 0.028	60.0 ± 0.061	–	–	–		

compared to the reference drug. Among the synthesized complexes, complex $\mathbf{C_{14}}$ exhibit the best results against three cell lines PC-3, SKOV-3 and HeLa with IC_{50} values of 0.71 ± 0.06, 0.12 ± 0.06 and 0.79 ± 0.23 μg/mL, respectively. All the urea based Schiff base complexes were used to evaluate the *in vivo* acute oral toxicity and the control group did not show any significant toxicity. The anticancer activity of the synthesized complexes was found to be significantly stronger than that of ligand $\mathbf{L_3}$ when compared to three cancer cells (PC3, SKOV3 and HeLa). This suggests that the addition of metal significantly improves the anticancer activity.

Chang *et al.* [113] synthesized the mononuclear octahedral complex $[Mn(ONO\text{-}(S)L_4)_2]$ ($\mathbf{C_{19}}$), trinuclear complex $[Mn_3(S)\text{-}(ONO)L_5)_4(OAC)_4(H_2O)_2]$ ($\mathbf{C_{20}}$) and distorted square pyramidal tetranuclear complex $[Cu(ONO\text{-}(R)L_6)]_4{\cdot}2CH_3OH$, ($\mathbf{C_{21}}$), from ligands $\mathbf{L_4}$, $\mathbf{L_5}$ and $\mathbf{L_6}$, respectively. The ligands and their metal complexes were studied for their anticancer activity by employing the MTT method on A549, HeLa and MDA-MB-231 cell lines, with cisplatin serving as the positive control. The ligands failed to inhibit the growth of cancer cells in the experiment. All the complexes were more effective than cisplatin (reference drug) and showed some *in vitro* anticancer activity against three tumour cells. In case of HeLa cell line, complex $\mathbf{C_{20}}$ had a lower IC_{50} value (10.54 ± 1.02 μM) than complex $\mathbf{C_{19}}$ (38.73 ± 1.59 μM), while complex $\mathbf{C_{19}}$ (46.85 ± 1.67 μM) still had a moderate anticancer impact than complex $\mathbf{C_{20}}$ (18.42 ± 1.27 μM) against MDA-MB-231 tumour cells. Furthermore, compared to complexes $\mathbf{C_{19}}$ and $\mathbf{C_{20}}$ showed a more effective inhibitory effect. Among the synthesized complexes, $\mathbf{C_{21}}$ showed higher anticancer activity against MDA-MB-231 cell than the complexes $\mathbf{C_{19}}$ and $\mathbf{C_{20}}$.

Mandal *et al.* [114] synthesized $[Mn(L_7)(NCS)]$ ($\mathbf{C_{22}}$), $[Mn(L_8)(NCS)]$ ($\mathbf{C_{23}}$), $[Co(L_9)(NCS)]$ ($\mathbf{C_{24}}$) and $[Co(L_{10})(NCS)]\cdot0.5CH_3OH\cdot0.5H_2O$ ($\mathbf{C_{25}}$), all of which include thiocyanate as a common pseudohalide ion, are mononuclear octahedral Schiff base complexes. To synthesize the pentadentate Schiff base ligands $\mathbf{H_2L_7}$, $\mathbf{H_2L_8}$, $\mathbf{H_2L_9}$ and $\mathbf{H_2L_{10}}$ substituted salicylaldehydes were reacted with N-(3-aminopropyl)-N-methylpropane-1,3-diamine using condensation reaction. The metal complexes were synthesized by reacting metal(II) perchlorate (M = Mn or Co) with their corresponding Schiff bases in methanol solution containing thiocyanate. The growth inhibitory activity of the synthesized mteal complexes and a reference commercial antibiotic, gatifloxacin, were evaluated *in vitro* using the Kirby Bauer method with appropriate modifications. The bacteria tested were *S. aureus* MTCC 2940 and *B. subtilis* MTCC 441, two Gram-positive bacteria and *P. aeruginosa* MTCC 2453 and *E. coli* MTCC 739, two Gram-negative bacteria. According to the results, complexes $\mathbf{C_{22}}$ and $\mathbf{C_{23}}$ (IZD 8-14 mm) have poor antibacterial activity than complexes $\mathbf{C_{24}}$ and $\mathbf{C_{25}}$ (IZD 12-18 mm) against all bacterial strains. Schiff bases H_2L_7, H_2L_8, H_2L_9 and H_2L_{10} (IZD 6-12 mm) have a weak antibacterial effect even at large concentration, but their bactericidal ability is significantly amplified when they bind with metal ions (Table-1). It can be inferred from the *in vitro* antimicrobial assay that all the metal complexes exhibit dose-dependent, low-to-moderate antibacterial activity. At comparable concentrations, the bioactivities of the commercial antibiotics were higher than those of either of the metal complexes.

Awatade *et al.* [115] synthesized a new Schiff base ligand (*E*)-N′-(2-hydroxybenzylidene)-4-methoxybenzohydrazide (HBMB), $\mathbf{L_{11}}$ and its metal complexes $[Mn(L_{11})_2]$ ($\mathbf{C_{26}}$), $[Ni(L_{11})_2]$ ($\mathbf{C_{27}}$) and $[Cu(L_{11})_2]$ ($\mathbf{C_{28}}$). An exact molar ratio (1:1) of salicylaldehyde and 4-methoxy benzohydrazide was utilized in the condensation process to obtain ligand $\mathbf{L_{11}}$. The octahedral complexes were synthesized by reacting $MnCl_2{\cdot}2H_2O$, $NiCl_2{\cdot}6H_2O$ and $CuCl_2{\cdot}2H_2O$ with the corresponding Schiff base ligand $\mathbf{L_{11}}$ in ethanol at a ratio of 1:1. The Agar well-diffusion method was employed to evaluate the antibacterial activity of the ligand and its metal complex. It has been shown that the ligand exhibits reduced activity against some Gram-positive bacteria, Gram-negative bacteria and fungal strains. However, the metal complexes were susceptible against the tested organisms. A moderately active result was found against bacteria *S. aureus*, *E. coli* and fungal strains *A. niger* (IZ 10-20 mm) in case of complex $\mathbf{C_{26}}$. Complex $\mathbf{C_{27}}$ showed moderate activity against against bacterial strain *S. aureus* and fungal strains *A. niger* (IZ 10-20 mm) and strongly active against *E. coli* (IZ > 20 mm). Complex $\mathbf{C_{27}}$ exhibited highest antibacterial activity among all the tested compounds. The study found that in case of manganese complexes, having the biocompatibility and variable oxidation states of Mn, have better antibacterial activity than ligands. Microbial activities become more active in response to an increase in the concentration of the ligand and the metal complexes. Cancer cell lines MCF-7 and HT-29 were used to test the cytotoxicity of the synthesized compounds. Among the synthesized complexes, complex $\mathbf{C_{28}}$ exhibited most cytotoxic activity against the cancer cell lines with GI_{50} values of < 0.1 μM (MCF-7) and 35.0 μM (HT-29).

Jain *et al.* [116] reported the synthesis of 2-acetyl-5-methylsemicarbazone ligand $\mathbf{L_{12}}$ using condensation approach. The following octahedral complexes $[Mn(L_{12})_2]Cl_2$ ($\mathbf{C_{29}}$), $[Mn(L_{12})_2]\text{-}(OAC)_2$ ($\mathbf{C_{30}}$), $[Mn(L_{12})_2](NO_3)_2$ ($\mathbf{C_{31}}$), $[Mn(L_{12})_2]SO_4$ ($\mathbf{C_{32}}$), $[Co(L_{12})_2]Cl_2$ ($\mathbf{C_{33}}$), $[Co(L_{12})_2](OAC)_2$ ($\mathbf{C_{34}}$), $[Co(L_{12})_2](NO_3)_2$ ($\mathbf{C_{35}}$) and $[Co(L_{12})_2]SO_4$ ($\mathbf{C_{36}}$) were synthesized. The two fungus, *C. krusei* and *C. tropicalis* and two bacteria, *S. aureus* and *P. aeruginosa*, were tested *in vitro* biological activity. At 1000 ppm concentrations, the ligand and its metal complexes showed antifungal results against *C. krusei* strains with inhibition zone values of 18, 27, 27, 36, 38, 23, 23, 38 and 36 mm and against *C. tropicalis* strains 11, 34, 23, 43, 43, 27, 27, 43 and 34 mm, respectively. Compared to ligand, the complexes showed superior efficacy against bacteria and fungus (Table-1). Variations in the concentration of the synthesized compounds were found to influence biological activities.

Mamta *et al.* [117] synthesized and evaluated the biological activities of a new series of Schiff base macrocyclic ligands ($\mathbf{L_{13}}$-$\mathbf{L_{15}}$) and their bivalent manganese complexes, $[Mn(L_{13})\text{-}Cl_2]$ ($\mathbf{C_{37}}$), $[Mn(L_{14})Cl_2]$ ($\mathbf{C_{38}}$) and $[Mn(L_{15})Cl_2]$ ($\mathbf{C_{39}}$). The interaction of 1,2-diphenylethane-1,2-dione and *p*-phenylenediamine in methanol resulted in a dark yellowish green colour of ligand. To synthesize the macrocyclic ligands $\mathbf{L_{13}}$, $\mathbf{L_{14}}$ and $\mathbf{L_{15}}$, respectively, the equimolar methanolic solutions of ligand and ethanedioic acid/propanedioic acid/butanedioic acid were refluxed

with 1-2 drops of conc. HCl at 65 ºC with constant stirring for 7-8 h. The antibacterial activity of the synthetic compounds was tested against Gram-positive (*S. aureus* and *B. cereus*), Gram-negative (*E. coli* and *X. campestris*) bacterial and fungal (*C. albicans* and *F. oxysporum*) strains. The macrocyclic complex **C_{39}**, out of all the newly synthesized compounds, showed the strongest antibacterial activity against every single bacterial (*B. cereus,* MIC value: 4.0 µg/mL, *E. coli* and *X. campestris,* MIC value: 10.0 µg/mL) and fungus strain (*C. albicans*, MIC value: 10.0 µg/mL, *F. oxysporum*, MIC value: 3.0 µg/mL) with the exception of *S. aureus* (MIC value: 30.0 µg/mL) due to its small size. Because of its small size, it can easily penetrate the cell membrane and thus to inhibit the growth of antibacterial strains becomes easier. The virtual screening of *in vitro* antioxidant activity the synthesized Schiff base ligand, macrocyclic ligands (**L_{13}**-**L_{15}**) and their Mn(II) complexes (**C_{37}**-**C_{39}**) were also performed using the DPPH radical scavenging activity. The antioxidant activity of complex **C_{39}** was found to be excellent with inhibition IC_{50} value of 37.57 µg/mL. As particle size decreased, the biological activity increased [118]. With its diminutive size, complex **C_{39}** stands out among all the synthesized macrocyclic complexes. Based on the results, this complex outperforms other complexes in terms of antibacterial activity. Complex **C_{38}** exhibited effective bactericidal action against *S. aureus*, with a zone inhibition diameter of 20 mm at 100 ppm and 25 mm at 500 ppm, demonstrating its ability to readily cross cell membranes and limit microbial growth. According to the results of the antimicrobial screening, macrocyclic complexes exhibit a stronger inhibitory impact than macrocyclic ligands. The π-electrons shift across the entire chelate ring as a result of this, which makes the complex more lipophilic and enables the metal complexes to cross lipid membranes and block the metal-binding sites in microbial enzymes [119,120].

Al-Wasidi *et al.* [121] synthesized tetrahedral Schiff base complexes, $[Mn(L_{16})(H_2O)]\cdot 4H_2O$ (**C_{40}**), $[Cu(L_{16})(H_2O)]\cdot 4H_2O$, (**$C_{41}$**) and octahedral complexes, $[Fe(L_{16})(Cl)(H_2O)_2]\cdot 2H_2O$, (**$C_{42}$**), $[Co(L_{16})(H_2O)_3]\cdot 3H_2O$ (**C_{43}**), by reacting an equimolar combination of metal chlorides with a neutralized Schiff base (**L_{16}**) (pH = 7) in methanol. The Schiff base (**L_{16}**) was obtained when phthalic anhydride and thiosemicarbazide were condensed in acetic acid. A high inhibition zone of 7-10 mm diameter against bacterial strains *B. subtilis*, *S. pneumonia* and *E. coli*, a moderate inhibition zone of 4-6 mm diameter against bacterial strain *S. aureus* and a less inhibition zone value of 1-3 mm against bacterial strain *Pesudomonas* sp. for metal complex **C_{40}** was evaluated. Complex **C_{41}** showed a high inhibition zone of 7-10 mm diameter against *S. pneumonia* and *S. aureus* and a less inhibition zone value (1-3 mm) against *B. subtilis* and *Pesudomonas* sp. Complex **C_{42}** and **C_{43}** showing a low inhibition zone value (1-3 mm) against all the bacterial strains. **L_{16}** was found to have better activity against Gram-positive bacteria *S. aureas* in comparison to its metal complex due to the presence of hydroxyl group in the ligand. Furthermore, studies on the antifungal activity of the synthesized complexes revealed that complexes **C_{41}** and **C_{43}** showed a moderate inhibition zone of 4-6 mm diameter against *A. niger*, but all the complexes exhibited only a small inhibition zone of 1-3 mm diameter against *Penicillium* sp. Antimicrobial activities of Schiff base ligand and its complexes. Thus, the efficiency of antibacterial activity of the synthesized complexes against bacterial and fungal strains can be ordered as *B. subtilis* > *S. pneumonia* > *E. coli* > *S. aureas* > *Pesudomonas* sp.

Reshma *et al.* [122] also synthesized octahedral Schiff base complexes, $[Mn(L_{17})(H_2O)_2Cl]$ (**C_{44}**), $[Fe(L_{17})(H_2O)_2Cl]$, (**C_{45}**), $[Co(L_{17})(H_2O)_2Cl]$ (**C_{46}**), $[Ni(L_{17})(H_2O)_2Cl]$ (**C_{47}**), $[Cu(L_{17})$-$(H_2O)_2Cl]$ (**C_{48}**) and tetrahedral complex $[Zn(L_{17})Cl]$ (**C_{49}**), by reacting metal chlorides with **L_{17}**, a Schiff base in a methanolic solution. Condensation of equimolar amounts of imidazole-2-carboxaldehyde with L-histidine resuls in the formation of Schiff base **L_{17}**. When tested against several bacterial strains, ligand **L_{17}** and its metal complexes displayed inhibitory effects that ranged from moderate to strong. Among all the synthesized complexes, **C_{48}** showed maximum activity against all the tested species (*B. subtilis*, IZD value: 32 mm, *S. aureus*, IZD value: 31 mm, *E. coli,* IZD value: 33 mm, *A. niger,* IZD value: 34 mm and *C. albicans,* IZD value: 28 mm). Other complexes also exhibited moderate to strong activity against all the tested antibacterial and antifungal strains. In terms of activity against all species, the metal complexes generally outperform the Schiff base (Table-1).

Zhu [123] reported the synthesis of two novel octahedral manganese(III) complexes, $[MnL_{18}(EtOH)(Acac)]$ (**C_{50}**) and $[MnL_{19}(DMF)(Esal)]\cdot H_2O$ (**C_{51}**), where ligands **L_{18}** and **L_{19}** are the dianionic form of 2-[(2-hydroxyphenylimino)-methyl]-6-methoxyphenol and 4-chloro-2-[(3-ethoxy-2-hydroxybenzylidene)amino]phenol. The activity of the Schiff base H_2L_{18} against *S. aureus* (MIC 37.5 µg/mL) and *B. subtilis* (MIC 18.8 µg/mL) is mild, while no activity is observed against *E. coli* and *P. fluorescence*. While it has moderate activity against *S. aureus* (MIC 18.8 µg/mL) and *E. coli* (MIC 9.4 µg/mL), Schiff base ligand **L_{19}** demonstrates no action against *P. fluorescence*. However, **L_{19}** often possesses more potent actions compared to **L_{18}**. Although complex **C_{50}** is inactive against *P. fluorescence*, it is active against *B. subtilis* (MIC 4.7 µg/mL) and *S. aureus* (MIC 9.4 µg/mL). It is only weakly active against *E. coli*. When it comes to the bacterial species, complex **C_{51}** is highly effective against *E. coli*, *B. subtilis* and *S. aureus* (MIC 9.4, 1.2 and 4.7 µg/mL, respectively), but not found effective against *P. fluorescence*. Compared to complex **C_{50}**, complex **C_{51}** demonstrates greater activity, similar to the Schiff bases. One possible explanation is that both **L_{19}** and **C_{51}** contain halogen groups. In comparison to penicillin G, complex **C_{51}** complex clearly exhibits the superior efficacy against *S. aureus* and *B. subtilis*.

Bin-Selim *et al.* [124] synthesized two novel Schiff base tetradentate ligands **L_{20}** and **L_{21}** by condensing 4-hydroxy-3-methoxy-5-((2-nitrophenyl)diazenyl)benzaldehyde with 1,2-diaminoethane and 1,2-diaminobenzene, respectively. The antibacterial activities of ligands **L_{20}** and **L_{21}** as well as their Schiff base Mn(II) complexes **C_{52}** and **C_{53}**, were evaluated against *S. aureus*, *E. coli* and *P. mirabilis* using Nutrient agar slopes method. At room temperature, ligand **L_{21}**, complexes **C_{52}** and **C_{53}** exhibited the antibacterial action against the Gram-negative *P. mirabilis*, but no such effect was observed against

S. aureus or *E. coli* (IZ < 7 mm). All the studied bacteria, including *S. aureus*, *E. coli* and *P. mirabilis*, were rendered inactive at a concentration of 0.125 mM of complex **C$_{53}$**. In comparison to complexes **C$_{52}$** and **C$_{53}$**, ligand **L$_{21}$** has a potent antibacterial action against *P. mirabilis* at doses of 0.125 and 0.25 mM with (IZ 13-19 mm).

Qian *et al.* [125] also reported the synthesis of two mononuclear octahedral Mn(III) complexes, [MnL$_{22}$(N$_3$)(OH$_2$)] (**C$_{54}$**) and [MnL$_{23}$L′] (**C$_{55}$**) where **L$_{22}$** and **L$_{23}$** are the dianionic forms of *N,N′-bis*(3-ethoxysalicylidene)-1,2-ethanediamine (H$_2$L$_{22}$) and *N,N′-bis*(3,5-dichlorosalicylidene)-1,4-butanediamine (H$_2$L$_{23}$), respectively and L′ is the deprotonated form of 2,4-dichloro-6-(dimethoxymethyl)phenol (HL′), have been synthesized. Three strains of Gram-positive bacteria (*B. subtilis*, *S. aureus* and *St. faecalis*) and three strains of Gram-negative bacteria (*E. coli*, *P. aeruginosa* and *E. cloacae*) were used to screen the antibacterial activities of the complexes and free Schiff bases using MTT techniques. The antimicrobial activity of complex **C$_{54}$** is moderate against *P. aeruginosa* (MIC 25 µg/mL) and *B. subtilis* (MIC 25 µg/mL) and non-existent against *St. faecalis*, *E. coli* and *E. cloacae*. Complex **C$_{55}$** is very active against some bacteria including *B. subtilis*, *S. aureus*, *P. aeruginosa* and *E. coli* (MIC 1.56, 0.78, 3.12 and 6.25 µg/mL) and moderately active against two other bacteria *St. faecalis* (MIC > 50 µg/mL), *E. cloacae* (MIC > 50 µg/mL). While ligand H$_2$L$_{22}$ demonstrates medium activity against *S. aureus*, but it does not exhibit any action against the other strains of bacteria. In terms of bacterial activity, H$_2$L$_{23}$ is effective against *S. aureus* (MIC 6.25 µg/mL), moderately effective against *B. subtilis*, *P. aeruginosa* and *E. coli* and completely inactive against other strains. Complex **C$_{55}$** has higher activity compared to complex **C$_{54}$**. The biological potential of these complexes is generally higher when halides are present.

Kongot *et al.* [126] synthesized the octahedral complex, [Mn(L$_{24}$)(H$_2$O)$_2$] (**C$_{56}$**) and tetrahedral complexes [Ni(L$_{24}$)] (**C$_{57}$**) and [Cu(L$_{24}$)] (**C$_{58}$**), by employing a Schiff base ligand (**L$_{24}$**) synthesized from an azo aldehyde and *s*-benzyldithiocarbazate. For *C. albicans*, the inhibition of fungal growth was assessed at 530 nm, while for *C. neoformans*, it was determined by comparing the absorbance at 570 nm and 600 nm. The primary screening revealed that manganese complex inhibited the development of *C. neoformans*, a fungal species, by approximately 93%. This compound can now be considered for use in future dose-response experiments and *in vivo* trials. Other bacterial and fungal species that were tested showed no appreciable action against complexes **C$_{56}$** and **C$_{58}$**. The complex **C$_{57}$** showed remarkable anti fungal activity against fungal strain *C. albicans* with an inhibition value of 87%. The antifungal activity of ligand was also tested and found to have no strong effect on the tested fungus species. The glucose absorption potential of the novel manganese(II) complex was examined in order to determine its antidiabetic medication potency. The studies were conducted using immortalized human liver cancer cells, HepG2, as the control cells. These cells were engineered to have low glucose uptake potency or insulin resistance for the purpose of the experiment. The absorption of 2-NBDG by these cells varied when exposed to varying amounts of Mn(II) complex. It is remarkable that the activity was also found to be comparable to that of metformin, the main type II antidiabetic medicine, which is 85.73% effective. The spectroscopic studies also showed the strong binding and interaction of Mn(II) complex with the serum protein BSA under physiological pH conditions. This suggests that the biocompatible and widely available serum proteins can facilitate the transport of potent antifungal and antidiabetic drug candidate through biological fluids and membranes.

Keypour *et al.* [127] synthesized novel octahedral macrocyclic Schiff base complexes, [Mn(L$_{25}$)(H$_2$O)$_2$](ClO$_4$)$_2$ (**C$_{59}$**) and [Zn(L$_{25}$)(H$_2$O)$_2$](ClO$_4$)$_2$ (**C$_{60}$**), which were prepared using Mn(II) or Zn(II) templated [1+1] cyclocondensation of phthaldehyde and an asymmetrical diamine, 2-((4-(2-((2-aminobenzyl)-amino)ethyl)piperazine-1-yl)methyl)aniline. The MCF-7 breast cancer cell line, the A549 lung cancer cell line and the AGS stomach adenocarcinoma cell line were used to assess the cytotoxicity of the synthesized compounds using MTT assay. The result of the studies reveals that the complex, complex **C$_{59}$** shows a moderate cytotoxic effect against the tested cell lines with IC$_{50}$ values of 22.19 ± 1.13, 47.94 ± 2.23 and 59.73 ± 2.48 µM, respectively. Complex **C$_{60}$** showed better cytotoxic effect against the tested cell lines with IC$_{50}$ values of 14.58 ± 0.88, 28.5 ± 1.4 and 32.78 ± 1.73 µM, respectively. The study also revealed that the antioxidant property of complex **C$_{60}$** is better than that of complex **C$_{59}$**.

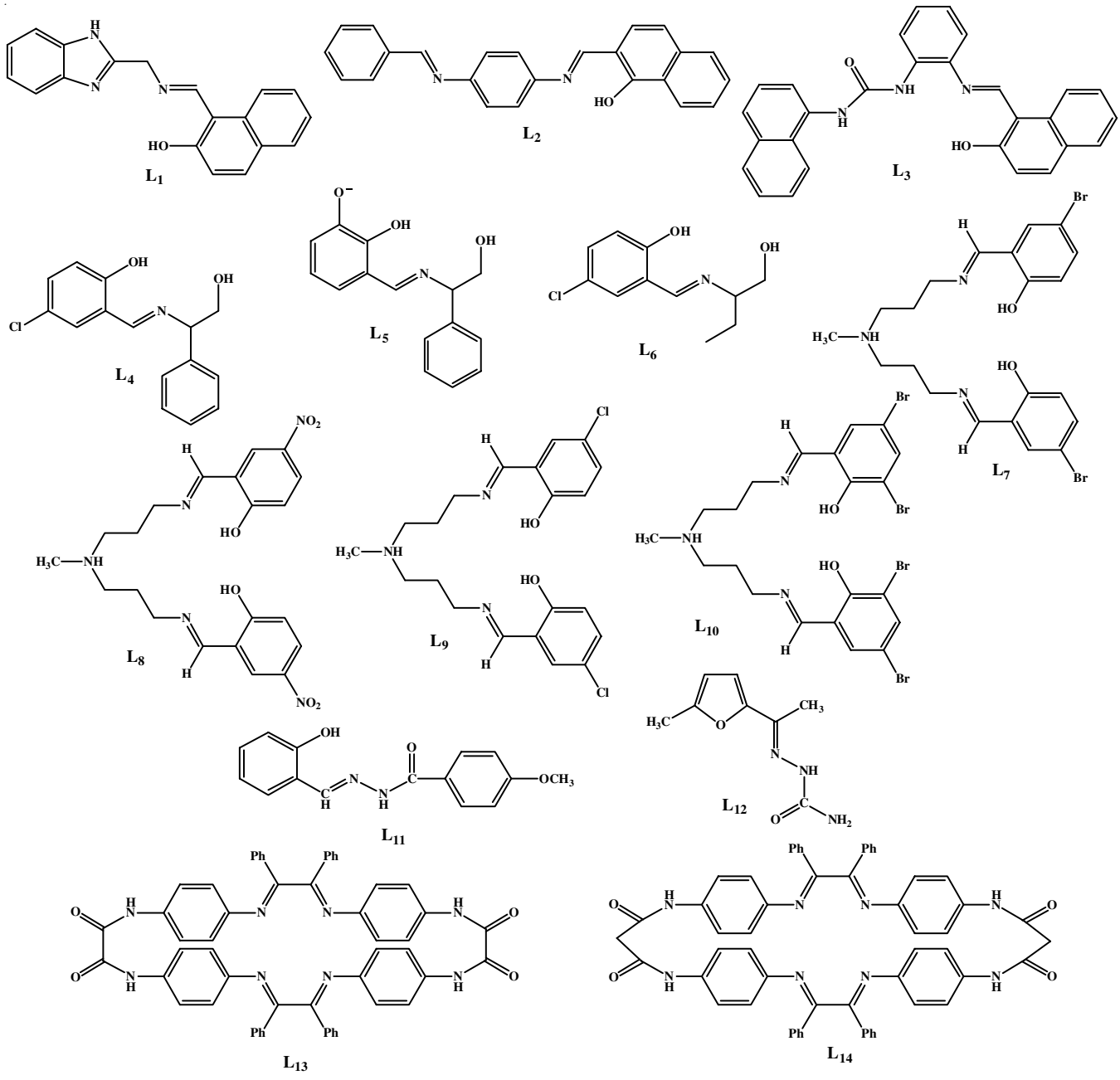
Rajakkani *et al.* [128] synthesized stable mononuclear metal(II) tetrahedral complexes, [Cu(L$_{26}$)]Cl$_2$ (**C$_{61}$**), [Ni(L$_{26}$)]-Cl$_2$ (**C$_{62}$**) and [Zn(L$_{26}$)]Cl$_2$ (**C$_{63}$**), with an unsymmetrical 13-membered Knoevenagel macrocyclic Schiff base ligand (**L$_{26}$**). The antimicrobial activity was assessed against two Gram-positive bacteria (*S. aureus, B. subtilis*) and three Gram-negative bacteria (*E. coli*, *K. pneumoniae*, *S. typhi*) compared to standard kanamycin and fungal strains (*A. niger*, *F. solani*, *A. flavus*, *R. bataticola*, *C. albicans*) compared to standard fluconazole by using well-dilution method. Complex **C$_{61}$** demonstrating higher activity among the synthesized complexes against bacterial strains with MIC values of 1.4, 1.2, 1.8, 2.2 and 2.0 µM, respectively and against fungal strains with MIC values of 1.2, 1.5, 1.2, 1.8 and 1.8 µM, respectively. Additionally, the anticancer activity of the synthesized complexes was assessed against breast (MCF-7), cervical (HeLa) and epithelioma (Hep-2) cancer cell lines using the MTT assay method. Complex **C$_{61}$** exhibited promising anticancer activity against cancer cell lines compared to cisplatin with IC$_{50}$ values of 16 ± 1.0, 14 ± 0.8 and 16 ± 1.0 µM, respectively.

Al-Fakeh *et al.* [129] reported a novel class of biologically active octahedral complexes, [Mn(L$_{27}$)(ADMPY)(H$_2$O)-Cl$_2$] (**C$_{64}$**), [Co(L$_{27}$)(ADMPY)(H$_2$O)Cl$_2$]·H$_2$O (**C$_{65}$**), [Cu(L$_{27}$)-(ADMPY)(H$_2$O)Cl$_2$] (**C$_{66}$**) and [Cr(L$_{27}$)(ADMPY)(H$_2$O)Cl$_2$]·H$_2$O (**C$_{67}$**) by reacting metal chlorides with 2-amino-4,6-dimethylpyrimidine (ADMPY) and Schiff's base (**L$_{27}$**), which is obained by the condensation reaction of benzaldehyde with *p*-phenylenediamine and 2-hydroxy-1-naphthaldehyde. The Schiff base and the metal complexes were tested for their cytotoxic activities against two different cancer cells *in vitro*. To determine the cytotoxic activity, A-549 and MRC-5 cells were exposed to

solutions having concentrations ranging from 0 to 500 µg/mL. Complex **C_{64}** exhibited substantial cytotoxicity against A-549 cancer cells (IC_{50} value: 201.86 µg/µL) and MRC-5 cancer cells (CC_{50} value: 233.01 µg/µL). When tested against *A. fumigates*, *C. albicans*, *C. neoformas* and *S. racemosum*, the metal complexes exhibited the minimal antifungal activity. Both the free ligand and its metal complex were tested for their antibacterial effectiveness against *S. aureus*, *B. subtilis*, *E. coli* and *P. vulgaris*, among other bacterial strains.

Abdel-Rahman *et al.* [130] also synthesized four octahedral complexes, $[Mn(L_{29})(H_2O)_3Cl]$ (**C_{68}**), $[Cr(L_{28})(H_2O)_2Cl_2]$ (**C_{69}**), $[Cr(L_{29})(H_2O)_2Cl_2]$ (**C_{70}**) and $[Fe(L_{28})(H_2O)_2Cl_2]$ (**C_{71}**) with the Schiff base ligand namely, 4-bromo-2-[(*E*)-{[4-(2-hydroxyethyl)phenyl]imino}methyl]phenol (**L_{28}**) and 2-[(*E*)-{[4-(2-hydroxyethyl) phenyl]imino}methyl]-4-methoxy phenol (**L_{29}**). The ligands and its metal complexes were tested for *in vitro* cytotoxicity using the MTT assay on two human cancer cell lines: HepG2 (liver carcinoma) and MCF-7 (breast cancer). Complex **C_{68}** showed more action than the free ligand. In comparison to the conventional drug cisplatin (4.0 µg/mL), complex **C_{68}** exhibited more activity against Hep-G2 with an IC_{50} value of 2.6 ± 0.11 µg/mL and against MCF-7 with a IC_{50} value of 3.0 ± 0.2 µg/mL when compared to the other synthesized complexes. The antibacterial activity of the ligands and its metal complexes was evaluated against *S. aureus*, *E. coli*, *B. subtilis* and *P. vulgaris* at different dosages. The antibacterial activity of ligand **L_{28}** and its complexes (**C_{69}** and **C_{71}**) were in the order **$C_{69} > C_{71} > L_{28}$**, where as for ligand **L_{29}** and its metal complexes **C_{68}** and **C_{70}** were as **$C_{68} > C_{70} > L_{29}$**.

The structures of the studied Schiff base ligands and their corresponding metal complexes are shown in Figs. 2 and 3, respectively.



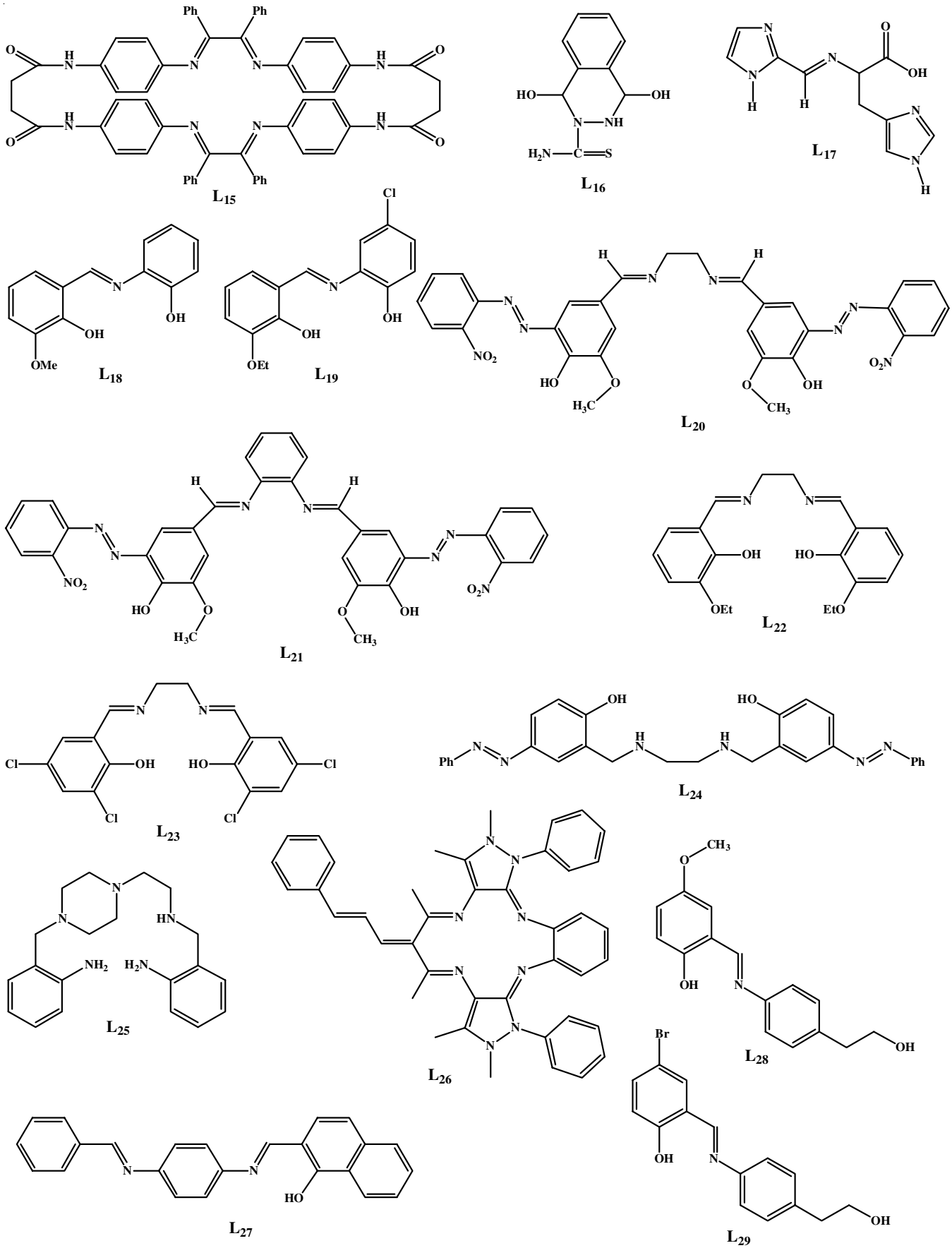
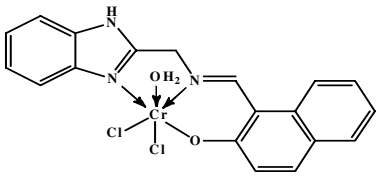
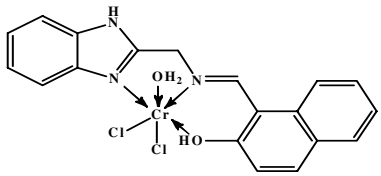


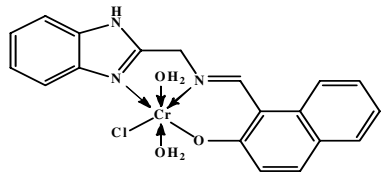
Fig. 2. Structures of the Schiff base ligands from L_1 to L_{29}



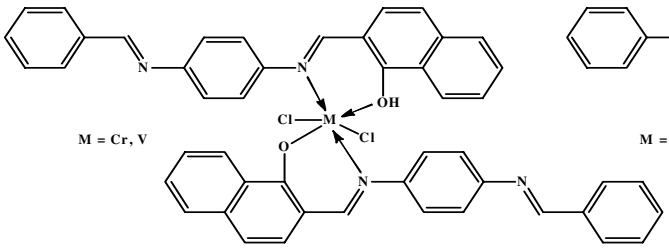
C_1



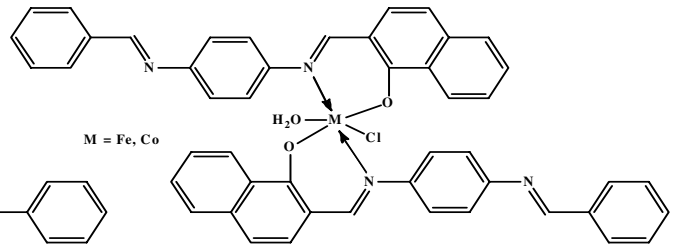
C_2



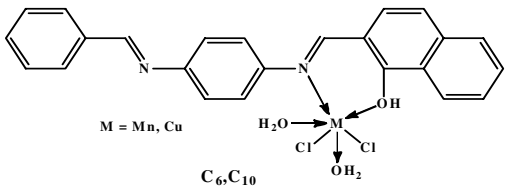
C_3



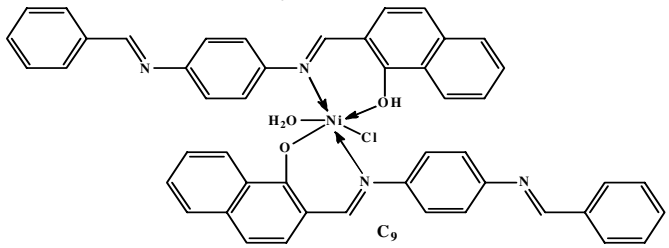
C_4,C_5



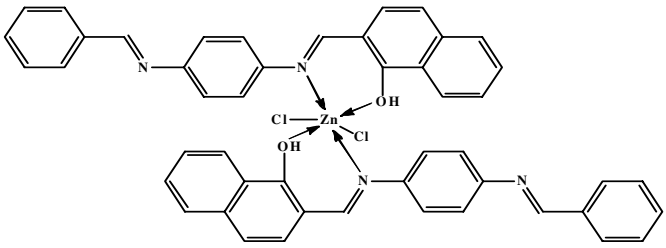
C_7,C_8



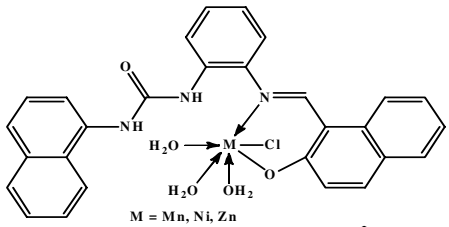
C_6,C_{10}



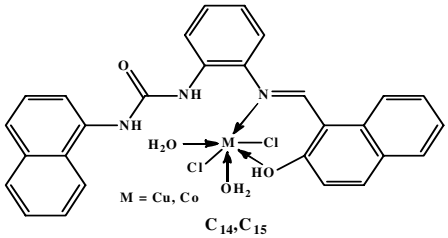
C_9



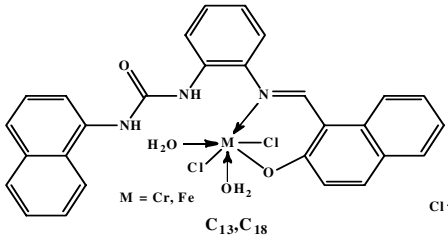
C_{11}



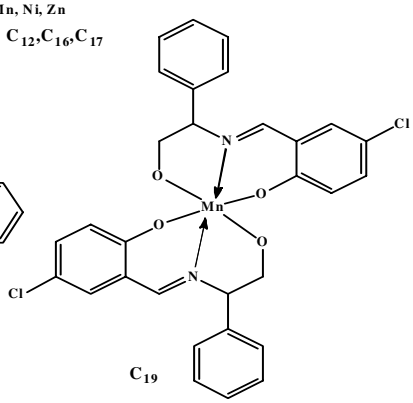
C_{12},C_{16},C_{17}



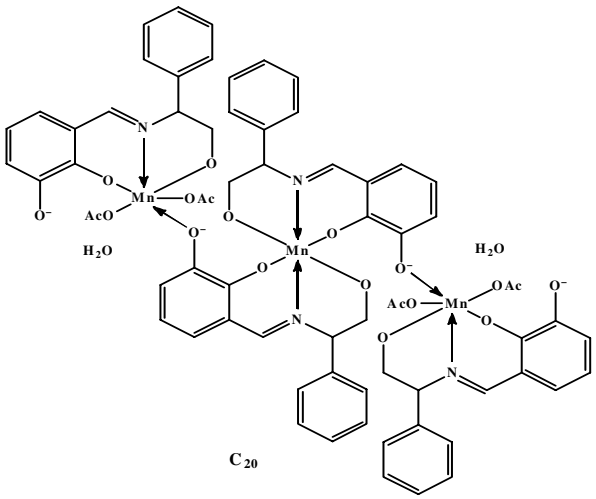
C_{14},C_{15}



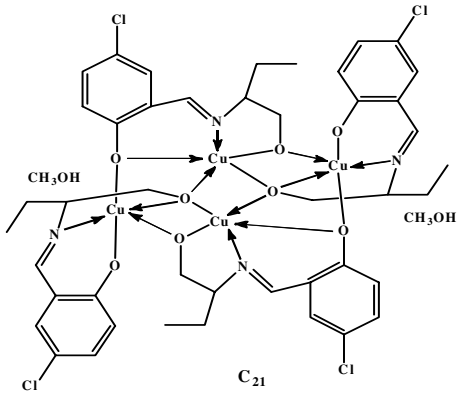
C_{13},C_{18}



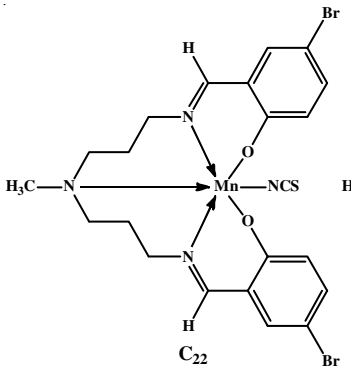
C_{19}



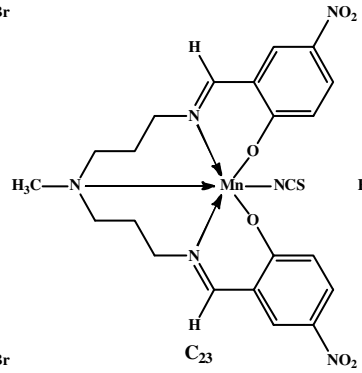
C_{20}



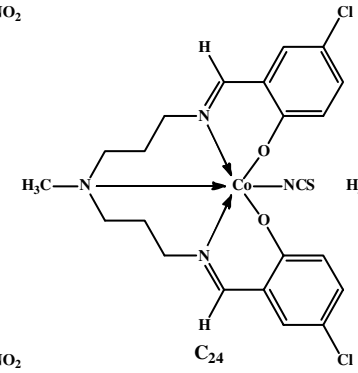
C_{21}



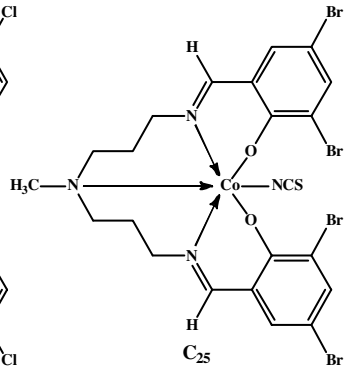
C_{22}



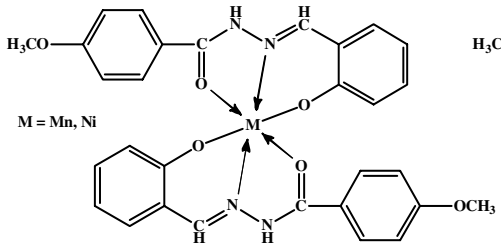
C_{23}



C_{24}

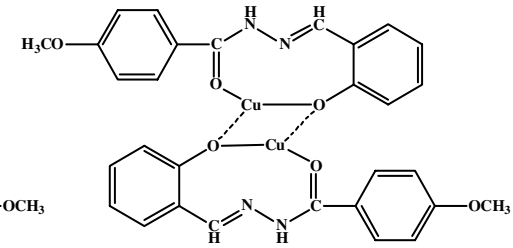


C_{25}

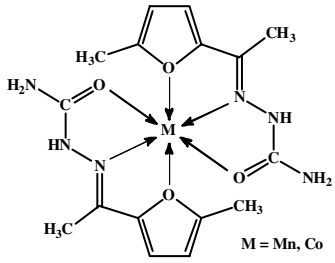


M = Mn, Ni

C_{26},C_{27}

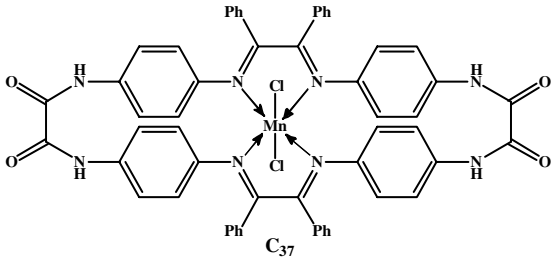


C_{28}

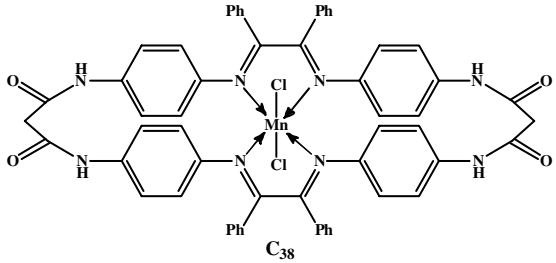


M = Mn, Co

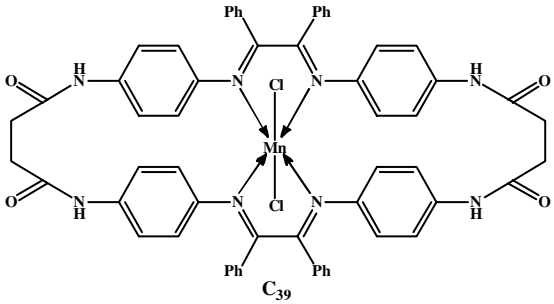
C_{29}–C_{36}



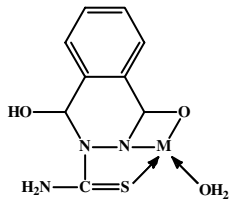
C_{37}



C_{38}

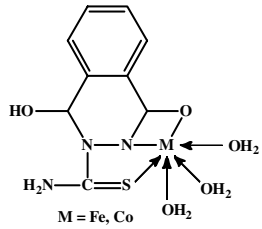


C_{39}



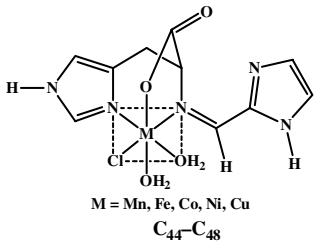
M = Mn, Cu

C_{40},C_{41}



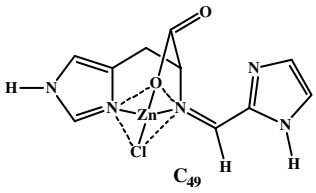
M = Fe, Co

C_{42},C_{43}

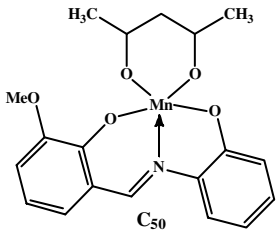


M = Mn, Fe, Co, Ni, Cu

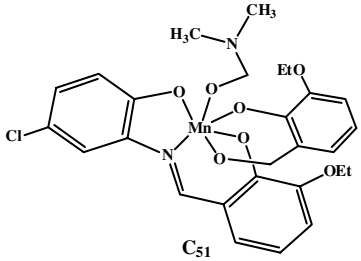
C_{44}–C_{48}



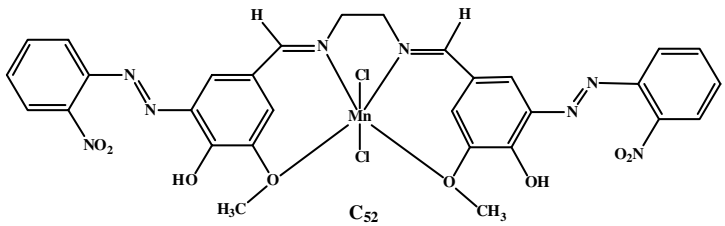
C_{49}



C_{50}



C_{51}



C_{52}

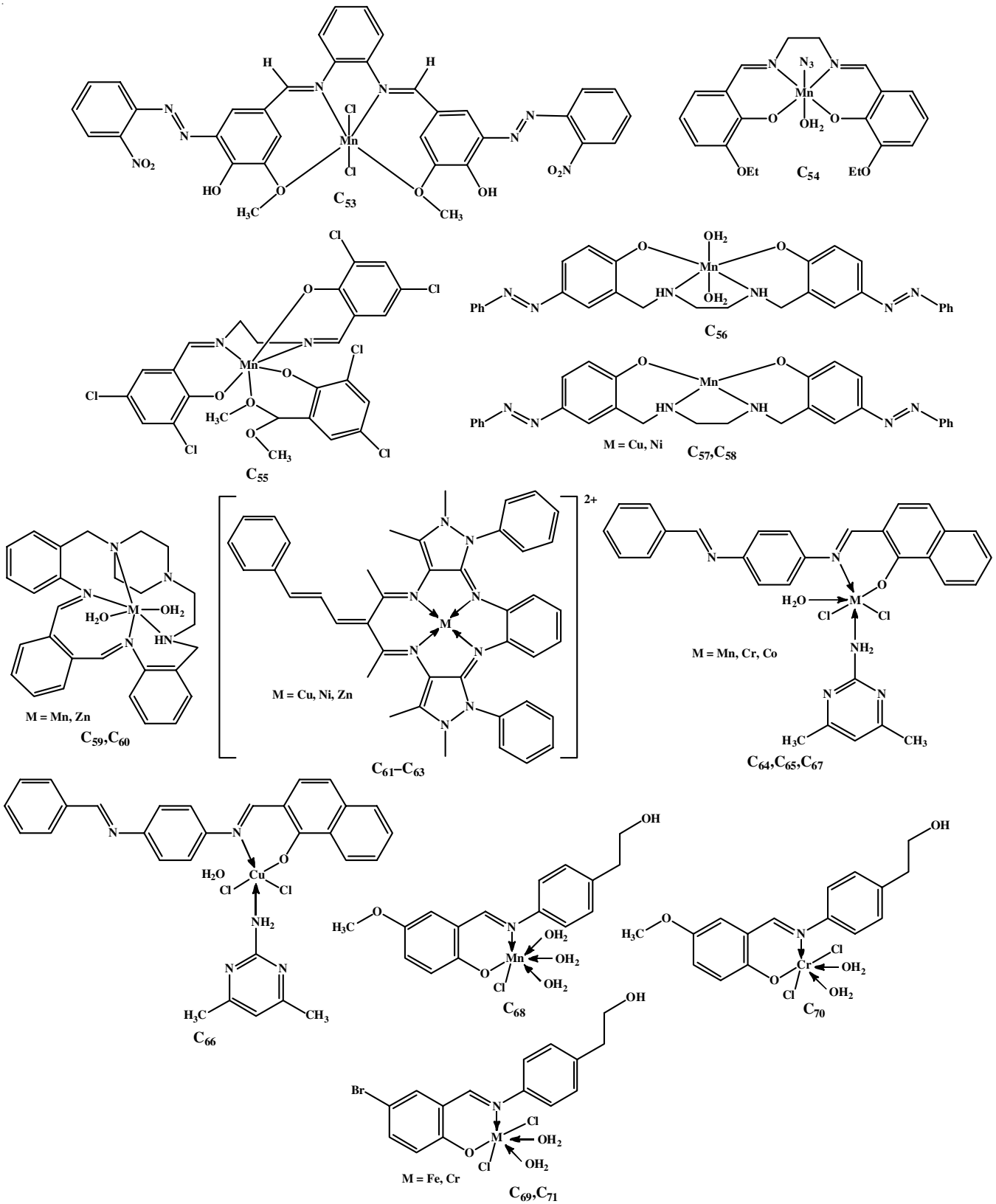


Fig. 3. Structures of the Schiff base metal complexes from C_1 to C_{71}

Conclusion

Schiff bases and their metal complexes are one of the most important class of organometallic compounds due to their ability to form complexes with transition metal ions and their pharmacological properties. Schiff base ligands are considered interesting ligands due to their ease of formation, diversity and different denticity. Transition metal complexes containing Schiff bases have attracted great attention in the last few years, especially

due to their many applications in biological processes and their potential use in the production of updated drugs. However, there is still a need to investigate the biological properties of transition metal complexes and to make new complexes with various properties. The review article covers various antimicrobial and anticancer applications of Schiff bases and their transition metal complexes. Several types of antibiotics and anticancer drugs are currently used in treatment, but the development of antimicrobial resistance and tumor resistance requires the development of new effective antibiotics and anticancer drugs.

CONFLICT OF INTEREST

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

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