Review Article

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Biological Importance of Schiff base Based Metal Complexes: A Brief Review

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Abstract

Schiff bases, generally synthesized by the condensation of aldehyde / ketone with primary amine, are imperative class of chelating ligands due to its coordination nature. In addition, Due to presence of imine group (-C=N), it shows various potential biological activities like antimicrobial, antifungal, antitumor, antiviral and anti-diabetic properties. Schiff base based metal complexes also exhibits potential applications in various fields such as magnetism, catalytic activity, sensing, biological activity, etc. Among the biological activity, till now Schiff base based metal complexes shows promising role as antibacterial, antifungal, antiviral, anticancer, antioxidant and anti-inflammatory agents. In this review we highlighted some Schiff base based metal complexes which attributed potential biological activity.

Key Words: Schiff Base; Metal-Schiff base Complex; Biological Activity

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1. Introduction

Metal ions play important role in living systems and among them crucially in humans like pernicious anaemia resulting from iron deficiency, growth retardation arising from insufficient dietary zinc, and heart disease in infants owing to copper deficiency. For these reasons, coordination complexes where artificial organic compounds acts as ligands, acts as either drugs or pro-drugs, become very attractive probes in medicinal chemistry in the past few decades. But, now a day's, bioinorganic chemist takes much attention on Schiff base based metal complexes due to potential biological activities like antimicrobial [1], antifungal [2], antitumor [3], antiviral [4] and anti-diabetic properties [5]. In addition, these compounds also exhibit potential free radical scavenging activities and hence, they may also use as anti-oxidant agents [6]. Therefore, different therapeutic applications of Schiff-base based transition metal complexes trigger scientists to explore the fundamental principles, which ultimately help to develop different structural and functional model systems [7].

Metal organic complexes are made by the combination of metal ions / metal and organic ligands. Upon the nature of coordination mode, organic ligands can be classified as chelating ligands and bridging ligands. Among various chelating ligands, Schiff bases are imperative class of chelating ligands to the scientist due to its coordination nature as well as its complexes exhibits wide range of applications in various fields like Anti-bacterial, Anti-fungal, Antiviral, Anti-cancer, Antioxidant, Anti-inflammatory,

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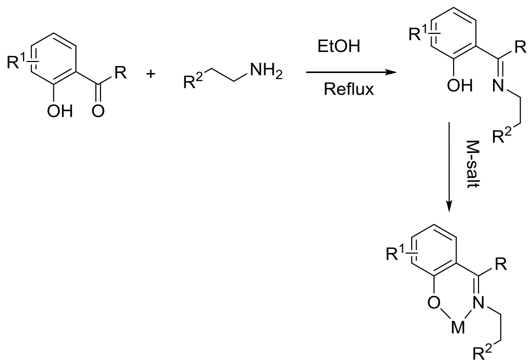
magnetism, luminescence, conductivity, sensing, catalytic, etc. [1-7].



Scheme 1. Direct synthesis procedure for the synthesis of Schiff base based metal complexes.

Schiff bases are generally synthesized by the condensation reaction of aldehyde / ketones with primary aliphatic / aromatic amines [8] and they are named according to the name of Hugo Schiff (1834-1915) [9]. They form a stable five / six member stable chelate ring when a functional group situated at the ortho position with respect to aldehyde / keto group. Schiff base based metal complexes are generally synthesized using the following procedure: (a) Direct synthesis: In this method, the Schiff base, which is previously synthesized allowed to react with metal ion in a suitable solvent, preferably in organic solvent due to prevent the hydrolysis of azomethine group of Schiff base, although there is a number of literature reported where the use of binary azeotropic mixture of water and an organic solvent has been reported (Scheme 1); and (b) In situ method: In this method the metal ion is added to the mixture of the aldehyde and amine. Though, it has been reported that the metal ion coordinates with one component and then reacts with other components, thus facilitating the reaction of complexation. In this review work, we mainly explored the biological importance of Schiff base based metal organic coordination compounds.

2. Biological importance of Schiff base based complexes

The development of bio-inorganic chemistry through applications of Schiff base based metal complexes becomes a promising area of research because of their various biological applications including antimicrobial, antioxidant, anti-proliferative, anti-inflammatory and anti-cancerous activities (Fig. 1).

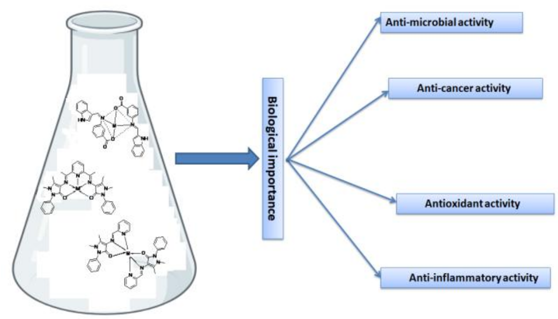
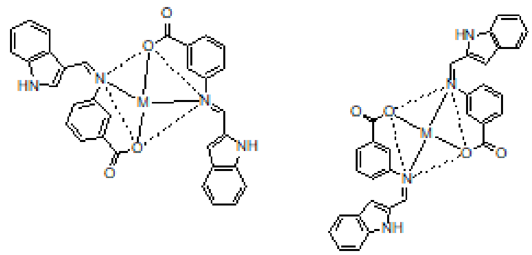


Fig. 1. Schematic representation of biological importance of Schiff base based metal complexes.

2.1. Anti-bacterial activity

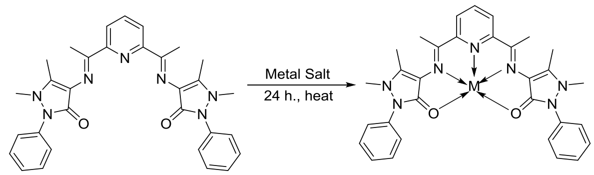
Synthesis of new antibacterial compounds becomes urgent in medical science due to multiple drug resistance properties of bacteria to different antibiotics. Mohamed *et al.* (2005) reported iron, cobalt and nickel complexes of general formulae $[M(HL1)_2](X)_n \cdot yH_2O$ [M = Fe(III); X = Cl, n = 3, y = 3; M = Co(II); X = Cl, n = 2, y = 1.5; M = Ni(II); X = Cl, n = 2, y = 1] (HL1 is a Schiff base derived from 2-thiophene carboxaldehyde and 2-aminobenzoic acid) and tested these complexes as well as Schiff base against bacterial species including *Escherichia coli*, *Pseudomonas* *aeruginosa*, *Staphylococcus pyogones* and noticed that metal complexes are more potent as compare to parent Schiff base ligand against bacterial species [10].



(a) (b)

Scheme 2. Proposed structure of Schiff base metal complexes (a) tetrahedral geometry for Co(II), Ni(II) and Zn(II) complexes and (b) square planar geometry for Cu(II) complex.

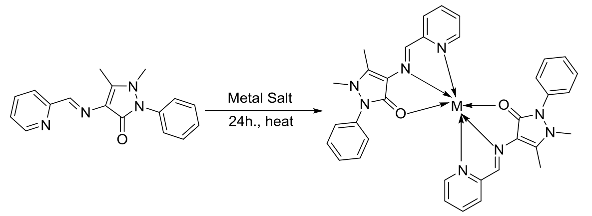
In another study, Mohamed *et al.* (2010) noticed bacterialcidal effect of metal complexes of Schiff base derived from condensation of sulphametrole and varelaldehyde against *E. coli* and *Staphylococcus aureus* and deduced that Schiff base and its metal complexes seem to be toxic against bacterial strains especially Gram-negative bacterium *E. coli* due to presence of lipophilic groups in order to enhance the membrane permeability of bacterium [11]. Gaballa *et al.* (2007) reported antibacterial activity of four Platinum(II) Schiff bases (synthesized by the condensation of salicylaldehyde and 2-furaldehyde with *O*- and *p*-phenylenediamine) complexes, $[Pt(L2)(H_2O)_2]Cl_2 \cdot nH_2O$ (where n = 0 for complexes **1**, **3**, **4**; n = 1 for complex **2**] against *E. coli*, *Bacillus subtilis*, *P. aeruginosa*, *Staphylococcus aureus* and noticed that the metal complexes are more potent antimicrobials than the corresponding Schiff base ligands against microorganisms [12].



Scheme 3. Proposed structure of bis(ethan-1-yl-1-ylidene)bis(azan-1-yl-1-ylidene)bis(1,5-dimethyl-2-phenyl- 1H-pyrazol-3(2H)-one) based Co(II), Cu(II), Ni(II), Mn(II) and Cr(III) complexes.

Nair *et al.* (2012) synthesized Schiff base (condensation product of indole-3-carboxaldehyde and m-aminobenzoic acid) based complexes of Co(II), Ni(II), Cu(II) and Zn(II) (Scheme 2) and tested the anti bacterial property of the Schiff bases as well as above mentioned complexes using disc diffusion assay method [13]. It was noticed that, Schiff base ligand was bacteriostatic against bacterial strains except *Proteus vulgaris* and *Klebsiella pneumoniae*. In addition, the Cu(II) and Ni(II) complex exhibited good bactericidal potential against all the tested bacterial strains whereas Co(II) complex found to be more effective against *P. aeruginosa* and *E. coli*, respectively. However, Zn(II) complex produced moderate zone of inhibition against *K. pneumoniae*, *P. vulgaris* and *S. aureus* in disc diffusion plate. Such antibacterial effect could be associated with permeability of metal ions through cell and tissues of different bacteria [13]. Ipsir *et al.* (2008) studied in vitro antibacterial activity of Co(II), Cu(II), Ni(II), Mn(II) and Cr(III) based complexes of Schiff bases including bis(ethan-1-yl-1-ylidene)bis(azan-1-yl-1-ylidene)bis(1,5-dimethyl-2-phenyl- 1H-pyrazol-3(2H)-one) (Scheme 3) and (E)-1,5-dimethyl-2-phenyl-4-(1-(pyridin-2-yl)ethylideneamino)- 1Hpyrazol-3(2H)-one (Scheme 4) against *E. coli, S. aureus, K. pneumoniae, Mycobacterium smegmatis, P.*

aeruginosa and *Enterobacter cloacae* [14]. Shaker *et al.* (2013) reported potential antibacterial activity of Fe(II) based complexes of Schiff base derived from the condensation of amino acids and sodium-2-hydroxybenzaldehyde-5-sulfonate against *Bacillus cereus, P. aeruginosa* and *Micrococcus* sp [15]. Kaya *et al.*(2008) noticed potential antibacterial activity of two different metal complexes $[Co(HL4)(L4)(Ac)_2]\cdot 4H_2O$ and $[Ni_2(L4)_2(Ac)_2]\cdot 4H_2O$ [HL4 = 3-(4'-aminobiphenyl-4-ylimino)-butan-2-one oxime, Ac = CH_3COO^-] against *B. subtilis* and *S. aureus,* however no activity was noticed against Gram-negative bacteria *E. coli* and *Enterobacter fecalis* [16]. Raman *et al.* (2002) studied antibacterial properties of Schiff bases l-phenyl-2,3-dimethyl-4(4-iminopentan-2-one) pyrazol-5-iminophenol and 1-pheny-l-2,3-dimethyl-4(4-iminopentan-2-one)pyrazol-5-imino thiophenol and their Cu(II), Ni(II), Zn(II), Co(II) and VO(II) based complexes against *B. subtilis, Salmonella typhi, S. aureus, Pseudomonous aeruginosa* [17]. Series of Fe(II) complexes based on Schiff bases amino acids ligands have been synthesized and screened for antibacterial activity against *E. coli, P. aeruginosa* and *B. cereus* [18]. Chaudhury and Mishra (2017) reported that Schiff base (condensation product of amoxicillin trihydrate and nicotinaldehyde) based Co(II), Ni(II), Cu(II) and Zn(II) complexes exhibited higher antibacterial activity when compared to that of amoxicillin and control drug amikacin [19].



Scheme 4. Proposed structure of (E)-1,5-dimethyl-2-phenyl-4-(1-(pyridin-2-yl)ethylideneamino)- 1Hpyrazol-3(2H)-one based Co(II), Cu(II), Ni(II), Mn(II) and Cr(III) complexes.

2.2. Antifungal activity

Neelakantan *et al.* (2008) reported fungicidal properties of Schiff base derived from o-phthalaldehyde and amino acids including glycine L-alanine, L-phenylalanine and their transition metal complexes of Cu(II), Co(II), Ni(II) and Mn(II) (Fig. 2) against *Candida sp*, *Aspergillus sp* and *Mucor sp*. In addition, it was also revealed that Cu(II) and Ni(II) complexes exhibited strong inhibition against all the fungi as compared with that of Co(II) and Mn(II) complexes [20]. Schiff base ligands derived from benzofuran-2-carbohydrazide and 3,4,5-trimethoxybenzaldehyde with ortho-phenylenediamine and its Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) complexes have been tested for antifungal activity [21]. Moreover, Cu(II), Fe(II) and Mn(II) based complexes based on Schiff base prepared from N-(2-hydroxybenzylidene)-3- (benzylideneamino) benzenesulfonamide produced significant antifungal activity against *Mucor inducus* and *Aspergillus fumigatus* [22]. Rehman *et al.* (2004) noticed antifungal activity of Schiff base ligands and Sn(IV) complexes have been screened against some plant pathogens including *Colletotrichum glocosporiodes*, *Alternaria brassicicola*, *A.*

brassicae, and *Helminthosporium graminium* [23]. Antifungal potenntial of ligands derived from diethyl phthalate with Schiff bases derived from o-phenylenediamine and Knoevenagel condensed b-ketoanilides and its Cu(II) complex were tested against *Rhizopus stolonifer, Rhizoctonia bataicola, A. niger, A. flavus* and *C. albicans*. In addition it was noticed that Cu(II) complexes produced stronger antifungal properties than free ligands [24]. Prashanthi *et al.* (2008) reported antifungal activity of 3-(2-hydroxy-3-ethoxybenzylideneamino)-5-methylisoxazole and 3-(2-hydroxy-5-nitroben-zylidene amino)-5-methylisoxazole based Cu(II), Ni(II) and Co(II) complexes against *Aspergillus niger* and *Rhizoctonia solani* and deduced that the metal complexes found to be more potential inhibitor against fungal growth when compared with that of parent Schiff base [25].

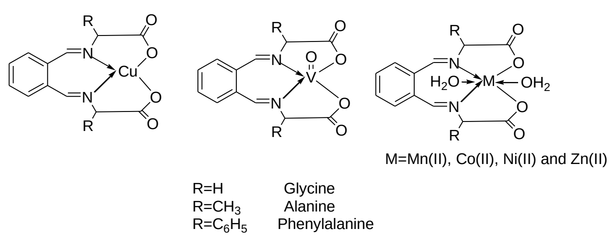


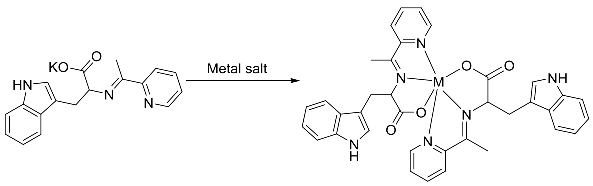
Fig. 2. Structure of the Schiff base metal complexes.

2.3. Antiviral Activity

Application of Schiff base as well as metal complexes as potent antiviral agents becomes a promising area in biomedical research due to unavailability of potent antiviral compounds. Schiff bases of isatin exhibits a wide range of biological activity including antibacterial, anticonvulsant, anti-HIV, antifungal and antiviral activity [26]. Epstein *et al.* (2006) reported a series of Co(III) complexes to prevent virus entry by inhibiting membrane fusion [27]. Chen *et al.* (2005) noticed that Schiff base ligands of isatin have antiviral properties against Moloney leukemia virus, vaccinia, rhino virus and SARS virus [28]. Moreover, Schiff base 2-(3-allyl-2-hydroxybenzylidene)-N-hydroxyhydrazinecarboximidamide was found to be effective against mouse hepatitis virus (MHV) [29]. Jarrahpour *et al.* (2007) reported some Schiff base based Co(III) complexes as potent antibacterial or antiviral compounds [30]. Kumar *et al.* (2010) synthesized a series of Schiff base based on 3-(benzylideneamino)-2-phenylquinazoline-4(3H)-one and investigated antiviral activity against herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), vaccinia virus, vesicular stomatitis virus, herpes simplex virus-1 TK- KOS ACVr, para influenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus, feline corona virus (FIPV), feline herpes virus, respiratory syncytial virus and influenza A H1N1 subtype, influenza A H3N2 subtype, influenza B [31].

2.4. Anti-cancer activity

Cancer is a devastating disease that badly affects a large portion of the world population every year and the foremost health problem of global concern. Cancer is a class of diseases characterized by uncontrolled cell division, invasion and subsequent metastasis [32]. Presently, surgery and chemotherapy techniques are adopted for cancer treatment. However, several side effects are associated with presently used chemotherapeutic drugs. Hence, it becomes a thrust area for the scientists to develop potent chemotherapeutic compound having limited side effects in cancer treatment. Various Schiff bases derivatives have been found to be associated with anticancerous properties.

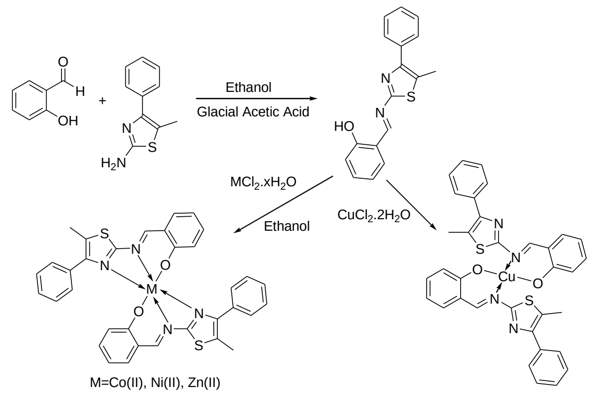


Scheme 5. The general synthesis reaction of the three complexes (M=Cu, Zn, Cd).

Dongfang *et al.* (2008) reported a branch of Schiff base based rare earth ion complexes having anti-proliferative activity against K562 tumour cell [33]. Zhang et al. (2012) noticed that Schiff base (condensation product of 2-acetylpyridine and L-tryptophan) based Cu(II), Zn(II) and Cd(II) complex (Scheme 5) exhibited significant anticancer activity on MDA-MB-231 breast cancer cells [34]. In addition, it was also revealed that among three complexes Cd(II) complex displayed highest anti-proliferative activity as well as inhibition of proteasomal chymotrypsin like activity and induction of apoptosis [34]. Mokhles M. Abd-Elzaher *et al.* (2016) studied anticancerous property of Schiff base based metal complexes (Scheme 6) where Schiff base is made of the condensation of salicyaldehyde with 2-amino-4- phenyl-5-methyl thiazole against different human cancer cell lines including MCF-7, HepG2, A549 and HCT116 in comparison with the effect of doxorubicin as a reference compound [35]. Yang *et al.* (2000) reported anti-tumor activity of lanthanide compounds against leukemia cells (L1210) [36]. Hajrezaie *et al.* (2014) investigated on *in vitro* anticancer activity of platinum (II) complexes of reduced amino acid Schiff bases against HL-60, KB, BGC-823 and Bel-7402 cell lines [37]. Antiproliferative effect of a Schiff base complex Cu(BrHAP)2 on HT-29 colon cancer cells has been studied by Li et al. (2013) [38]. Ahamad *et al.* (2020) studied anticancer properties, apoptosis and catecholase mimic activity of dinuclear cobalt(II) and copper(II) complexes of Schiff bases [39]. Schiff base 1-((2-aminophenylimino)methyl) naphthalen-2-ol and its Cu(II), Co(II), Ni(II) and Zn(II) complexes were tested against colon carcinoma HCT-116cell lines [40]. Significant anticancer effects against human cancer cell lines (Hep-G2, MG-63 and MCF-7) were observed through application of Schiff bases of 4-amino-1,2-naphthoquinone, 4-(3,4,5-trimethoxybenzylidene amino) naphthalene-1,2-dione and 4-(4-hydroxy-3-methoxybenzylidene amino)naphthalene-1,2-dione [41].

2.5. Antioxidant activity

Free radicals are produced during normal cellular functions in the body and associated with several human disorders through oxidative damage. Antioxidants play a pivotal role in protection of the human body against oxidative damage caused by reactive oxygen species. Synthesis of metal based antioxidants has gained much attention in order to identify compounds with high free radical scavenging capacity. In addition, synthetic antioxidants are found to more promising due to effectiveness in scavenging activity as well as cheaper rate when compared to natural antioxidants. Schiff bases of chitosan and carboxymethyl chitosan were synthesized and it was noticed that scavenging activity of the compounds against superoxide and hydroxyl radical triggered with gradual increase of the Schiff base concentration [42]. Wang *et al.* (2007) noticed binding affinity of Schiff base of Glutamic acid and salicylaldehyde and Cu(II), Co(II), Ni(II) and Zn(II) complexes toward bovine serum albumin (BSA) and reported that antioxidant activity of BSA found to be increase more than 10 times after binding with the Schiff base based metal complexes [43]. Li and Liu (2011) studied antioxidant capacities of some ferrocenyl Schiff bases such as o-(1-ferrocenylethylideneamino)phenol (OFP), m-(1-ferrocenylethylideneamino)phenol (MFP),and p-(1-ferrocenylethylideneamino)phenol (PFP) and reported that OFP, MFP and PFP have almost similar activities in trapping 2,2'-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonate)cationic radical ($ABTS^{\cdot+}$), respectively [44]. Jiang *et al.* (2020) investigated interaction between human serum albumin (HSA) and copper(II) complexes of Schiff bases derived from benzohydrazide with 5- fluoro-2-hydroxybenzaldehyde, 5-chloro-2-hydroxybenzaldehyde and 5-bromo-2-hydroxybenzaldehyde [45]. The interaction between bovine serum albumin (BSA) and cobalt(II) as well as zinc(II) complexes of N-2-hydroxyacetophenon-N0-2-hydroxy naphthaldehyde-1,2 phenylenediimine was studied by Sedighipoor *et al.* (2018) [46]. Antioxidant activity of 4,8-dimethyl-2-(salicylidenethiosemicarbozone) quinoline and its Ni(II) and Co(II) complexes were studied using DPPH by Priyadarshini et al. (2016) and it was revealed that Ni(II) complex produced good scavenging activity against DPPH whereas Co(II) complex exhibited moderate activity when compared to that of ligand [47].



Scheme 6. Preparation of the ligand and its complexes.

2.6. Anti-inflammatory activity

Several Schiff base complexes were screened for anti-inflammatory, analgesic and antipyretic activities. Pontiki *et al.* (2008) reported anti-inflammatory activity of Schiff mono-base of dipropylenetriamine with 2-thiophene-carboxaldehyde against carrageenin-induced rat paw oedema [48]. Dose dependent inhibition of the paw oedema in mice using Schiff base derivatives of 4-aminophenazone (5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one) with different aldehydes was studied by Murtaza *et al.* (2017) [49]. Nirmal *et al.* (2010) reported a series of novel 3-(4-(benzylideneamino) phenylimino) 4-fluoroindolin-2-one derivatives for significant analgesic, anti-inflammatory activities when compared with that of standard diclofenac sodium. In addition, it is Interesting to note that the test compounds exhibited mild ulcerogenic side effect in comparison with aspirin [50]. Alam *et al.* (2012) investigated that Schiff base derived from 4-aminoantipyrine (4-amino-1,5-dimethyl-2-phenylpyrazole-3-one) and benzaldehydewhich produced promising anti-inflammatory activity and it was inferred that such compounds could be used in the treatment of inflammatory disorders [51].

3. Concluding remarks

Schiff bases present a very important class of organic compounds due to their ability to form complexes with transition metal ions and of their pharmacological properties. The complexes have been of much interest over the last years, largely because of their various applications in biological processes as well as their catalytic activity. In this review, we mainly focused on the biological activity of various Schiff base based metal organic complexes. Among the biological activity, here we discuss about the Anti-bacterial, Antifungal, Antiviral, Anti-cancer, Antioxidant and Anti-inflammatory activity of various Schiff base based metal organic complexes.

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