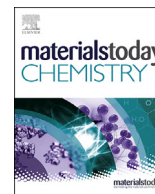




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Metal complexes driven from Schiff bases and semicarbazones for biomedical and allied applications: a review

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ARTICLE INFO

Article history:

Received 15 April 2019

Received in revised form

7 August 2019

Accepted 1 September 2019

Available online 18 November 2019

Keywords:

Schiff base

Semicarbazone

Metal complexes

Biological/biomedical activities

ABSTRACT

Schiff bases are versatile organic compounds which are widely used and synthesized by condensation reaction of different amino compound with aldehydes or ketones known as imine. Schiff base ligands are considered as privileged ligands as they are simply synthesized by condensation. They show broad range of application in medicine, pharmacy, coordination chemistry, biological activities, industries, food packages, dyes, and polymer and also used as an O₂ detector. Semicarbazone is an imine derivative which is derived from condensation of semicarbazide and suitable aldehyde and ketone. Imine ligand –containing transition metal complexes such as copper, zinc, and cadmium have shown to be excellent precursors for synthesis of metal or metal chalcogenide nanoparticles. In recent years, the researchers have attracted enormous attention toward Schiff bases, semicarbazones, thiosemicarbazones, and their metal complexes owing to numerous applications in pharmacology such as antiviral, antifungal, antimicrobial, antimalarial, antituberculosis, anticancer, anti-HIV, catalytic application in oxidation of organic compounds, and nanotechnology. In this review, we summarize the synthesis, structural, biological, and catalytic application of Schiff bases as well as their metal complexes.

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1. Introduction

Schiff base is known in the name of Hugo Schiff who first reported the reversible acid-catalyzed condensation reaction between primary amine with carbonyl compounds [1,2]. They are also known as imines with general structure R–CH=N–R', where R and R' is linear or cyclic alkyl and/or aryl group which may be differently substituted [3]. Schiff bases are an important class of ligands

for co-ordination chemistry, and they coordinate to metal ions via azomethine nitrogen [4]. Schiff base ligands have been extensively studied in the field of coordination chemistry mainly because of their facile syntheses, easy availability, and electronic properties. In recent times, Schiff base coordination chemistry has attracted much attention because of their significance in organic synthesis, analytical chemistry, refining of metals, metallurgy, electroplating, and photography [5–7]. Schiff bases have wide applications in dye

Abbreviations: CT DNA, Calf thymus deoxyribonucleic acid; DTBP, 2,6-di-tert-butylphenol; 35-DTBP, 3,5-di-tert-butylphenol; scCO₂, Super-critical carbon dioxide; DTBQ, 2,6-di-tert-butyl-4,4'-benzoquinone; TTBDQ, 3,5,3',5'-tetra-tert-butyl-4,4'-diphenylquinone; OLED, Organic light emitting diode; Phen, 1,10-phenanthroline; Bipy, 2,2'-bipyridine; BBPT, Biacetyl bis(4-phenyl-3-thiosemicarbazone); BGPT, Bipyridyl glyoxal bis(4-phenyl-3-thiosemicarbazone); BMTS, Biacetyl monothiosemicarbazone; PPTS, Picolinealdehyde-4-phenyl-3-thiosemicarbazone; NQTS, ortho-Naphthoquinone thiosemicarbazone; NQSC, Naphthoquinone semicarbazone; MCF-7, Michigan Cancer Foundation-7; SARS, Severe acute respiratory syndrome; M-IBDET, N-methylisatin-β-4',4'-diethylthiosemicarbazone; MLV, Moloney leukemia virus; SARS CoV, Severe Acute Respiratory Syndrome coronavirus; 3CL^{pro}, 3C-like protease; DAPY, 2,3-diamino-pyridine; PAS, p-amino salicylic acid; BCG, Bacillus calmette-guérine; HL-60, Human leukemia-60 cell line; VSV, vesicular stomatitis virus; HeLa, immortal cell lines; SB-HAG, Schiff bases of hydroxyamino guanidines; SSB-HAG, salicylaldehyde Schiff bases of HAG; MHV, Mouse hepatitis virus; TCID₅₀, Tissue culture Infective Dose; HepG2, Hepatic cellular carcinoma cells (Human liver cancer cell line); SK-OV-3 cells, Ovarian cancer cell line; SK-MEL-30, Human Melanoma Cell Line; MCF7 cells, Michigan Cancer Foundation-7 (breast cancer cell line); K B HCT-8, Human colon cancer cell line; MSOPD, N,N-bis(3-methylsalicylidene)-ortho-phenylenediamine; BBTSC, Benzoyloxybenzaldehyde thiosemicarbazone; ATT, 2-acetylthiophene thiosemicarbazone; BDT, Benzylthiosemicarbazone; 2,6-DAPBPTSC, 2,6-diacetylpyridine bis-4-phenyl-3-thiosemicarbazone; IgG, Immunoglobulin G; HEK-293, Human Embryonic Kidney cells; EAC, Enrichish Ascitices Cells; ATNR, Amine terminated liquid natural rubber.

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industry, catalysis, fungicidal, and agrochemical [8,9]. Several Schiff bases are reported to possess remarkable antibacterial, antifungal, and anticancer activities [10]. In such class of compounds, the C=N moiety is important for biological activity. Abdel-Rahman et al. [10] have reported number of transition metal complexes by using variety of Schiff base ligands and have studied their different biological activities such as antimicrobial, anticancer, antifungal, etc. For example, a number of Fe (II) complexes have designed and synthesized by using variety of Schiff bases ligands derived from 5-bromosalicylaldehyde (bs) and various α -amino acids such as L-alanine (ala), L-phenylalanine (phala), L-aspartic acid (aspa), L-histidine (his), and L-arginine (arg). These complexes were screened for their antibacterial and antifungal activity against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Bacillus cereus* and different antifungal cultures such as *Penicillium purpurogenium*, *Aspergillus flavus*, and *Trichothecium rosium*. It is found that Fe (II) complexes exhibited strong antibacterial and antifungal activity compared with the amino acids Schiff base ligands. Also, this complexes were tested for their interaction with calf thymus (CT) DNA by utilizing viscosity, UV-visible spectroscopy, and agarose gel electrophoresis measurements at pH = 7.2. The results revealed that the studied complexes showed different DNA binding constants that depend on the Schiff base ligands, and they strongly bind to CT DNA through intercalative mode [10b].

Several nanosized Fe(II), Cd(II), and Zn(II) complexes with Schiff base ligand 2-[(2-Hydroxy-3-methoxy-benzylidene)-amino]pyridin-3-ol obtained from 2-amino-3-hydroxy-pyridine and 3-methoxysalicylaldehyde have been prepared sonochemically, and all the compounds were investigated for their antimicrobial activity against some pathogens [10d]. It is found that ligand showed the less antimicrobial activity against the fungi and bacteria, whereas all the complexes exhibited more activity toward same fungi and bacteria. Some complexes showed great cytotoxic activity against colon carcinoma cells (HCT-116 cell line) and hepatic cellular carcinoma cells, (HepG-2). Metal Schiff base complexes are known since the mid-19th century. A large number of literature has highlighted their use as Schiff base ligands which are generally monodentate, bidentate, tridentate, tetradentate, etc. and depends on the presence of donor atoms. They have wide application in coordination chemistry as they are capable to form stable complexes with transition metals [11]. Owing to stability of Schiff base metal complexes as well as biological activity [12], electrochemistry [13] and potential applications in oxidation catalysis [14], researchers have focused significant attention to the chemistry of metal Schiff base complexes having nitrogen and other donor atoms [15] because of their vast applications in dyes, polymers, enzyme preparation as well as used as catalyst in different biological systems. Schiff bases are widely investigated owing to their selectivity, sensitivity, and synthetic flexibility to the central metal atom and the presence of azomethine group which brings in revealing the mechanism of transformation reaction biologically [16].

Some Cu (II), Co (II), and Ni (II) complexes have been reported by using Schiff base ligand derived from 2-amino-3-hydroxypyridine and 3-methoxysalicylaldehyde and were investigated for their *in vitro* antimicrobial activities against the numerous bacteria and fungi. Also, these complexes were tested for DNA binding, and it was found that these compounds could bind to DNA through intercalative mode. However, the cytotoxicity of these metal Schiff base complexes on different cell line such as human colon carcinoma cells, (HCT-116 cell line), as well as breast carcinoma cells, (MCF-7 cell line), illustrated effective cytotoxicity effect against the growth of carcinoma cells as compared with the clinically used vinblastine standard [16c]. Among most popular ones, the salen/salophen-based metal coordination complexes have found

immense applications in sensors, catalysis, biology, and material science. Many researchers have investigated a large number of Schiff base ligands as chelating compounds, e.g. metal chelates of copper, cobalt, etc. for a variety of interesting catalytic application. Co (II) salen complex of N,N-bis(3,5-di-*tert*-butyl-salicylidene)-1,2-cyclohexane diaminato) was used as catalyst in oxidation of 2,6-di-*tert*-butylphenol (DTBP) and 3,5-di-*tert*-butylphenol (35-DTBP) in super-critical carbon dioxide (scCO₂) [17].

The oxidation of DTBP resulted into 2,6-di-*tert*-butyl-4,4'-benzoquinone(DTBO) along with the side product of radical coupling, i.e. 3,5,3',5'-tetra-*tert*-butyl-4,4'-diphenoquinone (TTBDQ) (Scheme 1). The conversion and selectivity of catalyst were examined as a function of pressure, temperature, and concentration of catalyst.

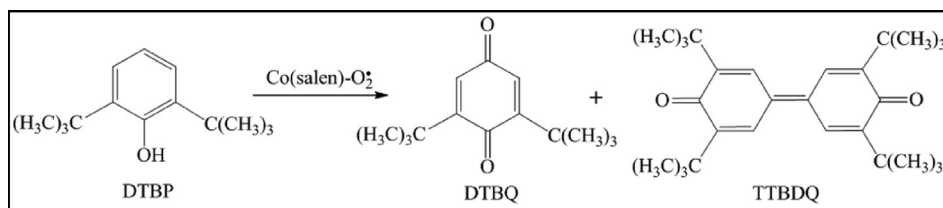
Number of transition and heavy metal ions complexes were synthesized by using novel salen-based Schiff base ligands (3–6) which were obtained from respective diamines (1 and 2) [18]. The Mn (III) complexes (7–10) (Scheme 2A) of these Schiff base ligands were chiral catalysts and are reported to be useful for asymmetric epoxidation of indene (Scheme 2B). Also some of the Mn (III) salen complexes were used to catalyze the asymmetric epoxidation of conjugated olefins, e.g. the Mn (II) complexes of bis(2-pyridinaldehyde)-ethylenediamine, bis(2-pyridin-aldehyde)propylenediamine ligands were used in epoxidation of olefins however reasonable epoxide selectivity was possible only in the presence of iodosobenzene (PhIO) as oxidant [19].

Recently, Che et al. [20] reported Pt (II) complexes with Schiff base ligands *N,N'*-bis(salicylidene)-1,2-ethylenediamine (**L1**), *N,N'*-bis(salicylidene)-1,3-propanediamine (**L2**), and *N,N'*-bis(salicylidene)-1,1,2,2-tetramethylethylenediamine (**L3**) and explained the utilization of vapor deposited Pt (II)-salen (**11**) triplet emitters as efficient electrophosphorescent dyes in multilayer organic light emitting diode (OLED) devices with a maximum luminous efficiency of 31 Cd A⁻¹. They observed that the performance of the OLEDs using the Schiff base dopant **L3** is significantly superior to the previously reported Pt (II) emitters.

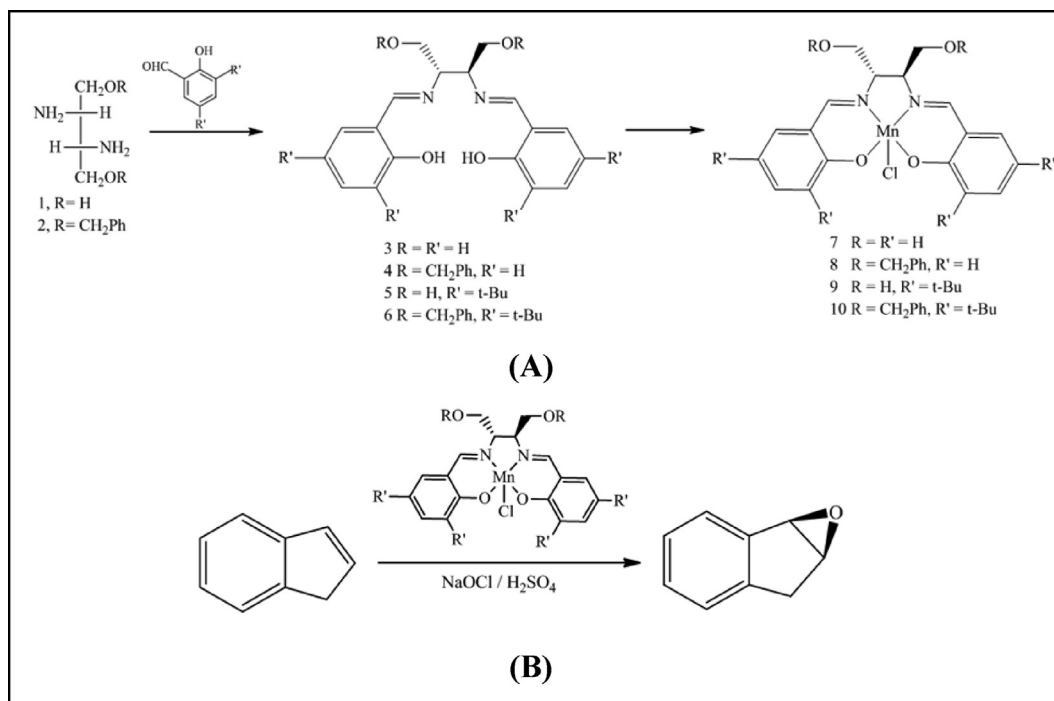
Most of the Schiff bases are synthesized by condensation of salicylaldehyde with aromatic amines as well as aliphatic amines. Several imines have been reported by Calvin and Bailes [21] by practicing condensation reaction of salicylaldehyde and substituted anilines and other aromatic amines. The spectroscopic analysis of such nitrogen-containing molecules revealed interesting electronic properties. It is reported that greater ligation with metal ions could be because of presence of a lone pair of electrons in these compounds. Large number of such azomethines and their complexes with a variety of transition metals has been documented as review articles in the recent past years [22,23]. Binuclear complexes have been synthesized from tridentate Schiff base ligands 2-[(Z)-[(2-hydroxyphenyl)imino]methyl]phenol (**12**) and 2-[(Z)-[(2-hydroxyethyl)imino]methyl]phenol (**13**), containing **ONO** and 2-[(Z)-(pyridin-2-ylimino) methyl]phenol (**14**) containing **ONN** or (2Z,4Z)-4-[(2-sulfanylphenyl)imino]pent-2-en-2-ol (**15**) containing **NSO** (Scheme 3) donor atoms. Such ligands are obtained from condensation of salicylaldehyde or acetylacetone with o-aminophenols, o-aminothiophenols, aminoalcohols, and aminothiols. IR spectroscopy suggested the involvement of imine nitrogen in coordination.

Similarly, Gao and Zheung [24] have synthesized some Schiff base ligands **16**, **17**, and **18** by condensation of 2-hydroxyacetophenone with different chiral diamines such as 1,2-diamino-cyclohexane, 1,2-diphenylethylenediamine, and 2,2'-diamino-1,1'-binaphthalene, respectively (Scheme 4), to study the steric, electronic, and geometric effect of a methyl (-CH₃) group on an azomethine carbon in asymmetric catalytic reaction.

Recently, More et al. [25] have described alkynyl functionalized salicylaldimine ligand 2-[(E)-[(4-trimethylsilylethynyl)phenyl]



Scheme 1. Typical aerobic oxidation of DTBP by Co(salen). DTBP, 2,6-di-*tert*-butylphenol.



Scheme 2. (A) Synthesis of derivatives of *D*-2,3-bis(arylideneamino)-1,4-butanediol (**3–6**) and their manganese complexes (**7–10**), and (B) the epoxidation of indene by using the Mn (III) complexes of *D*-2,3-bis(di-*t*-butyl-salicylideneamino)-1,4-butanediol.

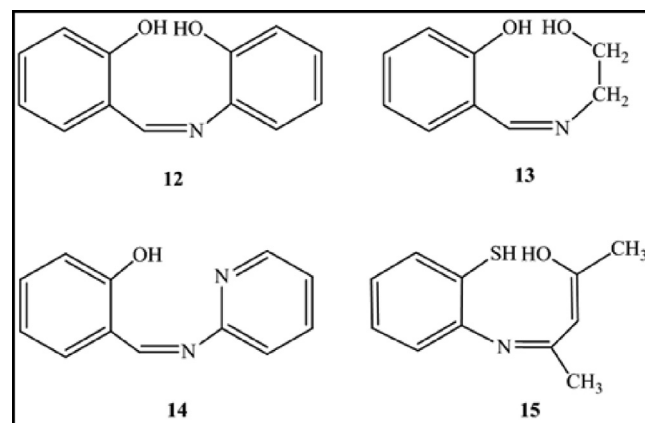
imino]methyl)-4-(4-nitrophenylethynyl)phenol (**19**) and its Zn (II) and Ni (II) complexes. It was reported that the emission properties of the complexes can be influenced by the π -conjugation, co-ligands (phen, bipy), and size of the counter anion (ClO_4^- , BF_4^- , and PF_6^-).

More et al. [26] also reported Ni (II) and Zn (II) salophen complexes as promising non-linear optical material because of the effect of π -conjugation in such luminescent complexes. (Scheme 5). A significant number of Schiff base metal complexes are reported as reasonably successful models of biological compounds [27].

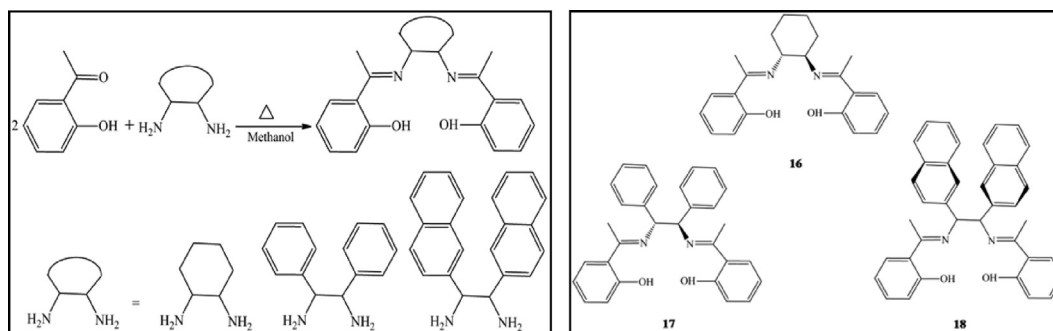
They have played vital role in the progress of modern coordination chemistry, and also in the improvement of inorganic biochemistry, catalysis as well as in useful materials due to optical and magnetic properties [28–30]. In recent years, the technology based on light emission or charge transport capacity is of specific interest for electronic devices such as solar cells and active components for image and data treatment storage [31]. Since the Schiff base and their metal complexes have different functional groups, they also play important role in the areas of stereochemistry, spectroscopy, and magnetic fields [32].

Similarly, Semicarbazone is an imine derivative, usually obtained by condensation of semicarbazide with suitable aldehyde or ketone. Semicarbazones have potentially wide range of biological applications, such as anticancer, antioxidant, antifungal,

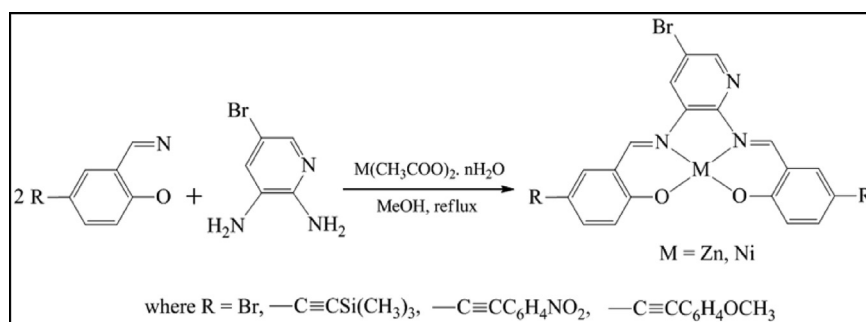
anticonvulsant, antiinflammatory, analgesic, and antibacterial agents [33]. Semicarbazone and its metal complexes play the significant role in an industrial, pharmaceutical, and agricultural chemistry. They are also used as polymers, dyes, and as catalysts in different biological systems, like Schiff base ligands. It is observed



Scheme 3. Schiff base ligands containing ONO, ONN, and NSO donor atoms.



Scheme 4. Schiff bases (16–18) from different chiral diamines.



Scheme 5. Synthesis of Ni (II) and Zn (II) salophen complexes.

that the metal complex can be more active than the free ligand. Transition metal complexes of semicarbazone have been widely studied because of their coordinating ability and analytical application [34].

A variety of structural and coordination aspects of semicarbazones and thiosemicarbazone metal complexes of different group element have been discussed by Casas et al. [35]. Large number of thiosemicarbazones is used for the detection and determination of different cations and anions. Spectrophotometry or extractive spectrophotometry are often employed for the quantitative determination of ions; in addition to these, some other techniques are also used such as gravimetry, titrimetry, and fluorimetry by Suvarapu et al. [36]. Asuero et al. [37] and Singh et al. [38] described application of thiosemicarbazone in inorganic analysis where they showed that biacetyl bis(4-phenyl-3-

thiosemicarbazone) (BBPT) as well as bipyridyl glyoxal bis(4-phenyl-3-thiosemicarbazone) (BGPT) can be employed in the spectrophotometric determination of copper, zinc, mercury, and palladium. Such studies explained that the complexing properties of BBPT and BGPT are much better than those exhibited by biacetyl monothiosemicarbazone (BMTS) and picolinealdehyde-4-phenyl-3-thiosemicarbazone (PPTS). Also, BBPT is recommended as a reagent for the extractive spectrophotometric determination of cadmium and bismuth. In addition to their interesting coordination chemistry, semicarbazone and thiosemicarbazones have attracted enormous attention because of their potentially useful biological activities [39]. There are several reports existing on biological activity of thiosemicarbazones and their transition metal complexes [40]. The mechanism of biological activity of thiosemicarbazones are because of their ability to inhibit the biosynthesis of DNA, probably by blocking the enzyme ribonucleotide diphosphate reductase; binding to the nitrogen bases of DNA, by hindering base replication; and by creating the lesions in DNA strands by oxidative rupture [41,42]. Zn (II) complexes of 2-acetylpyridine-4-phenyl semicarbazone have also been reported for their antimicrobial activity against various bacteria and fungi [43]. The synthesis of metal complexes of 1-vinyl-pyrrole-2-carbaldehyde semicarbazone and thiosemicarbazone and their importance in pharmaceutical as well as in medicinal field have been reported by Milkhaleva et al. [44]. *ortho*-Naphthoquinone thiosemicarbazone (NQTS) as well as naphthoquinone semicarbazone (NQSC) and their different Ni (II) complexes [45] were investigated for their *in vitro* anticancer activity in MCF-7 human breast cancer cells. It is observed that nickel complex with NQTS and NQSC is more active in the inhibitory action of MCF-7 cell proliferation than the free ligands. This exposed the remarkable anticancer properties of these compounds. Chandra and Tyagi [46] have reported the synthesis, electron paramagnetic resonance (EPR), and electronic spectral studies of Mn (II) and Cr (III) complexes of vanillin thiosemicarbazone and semicarbazone,

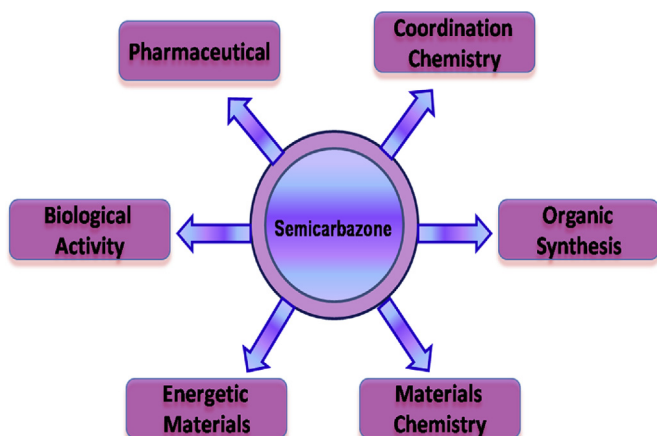
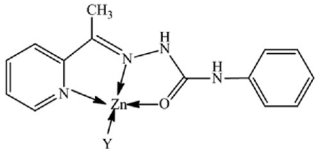
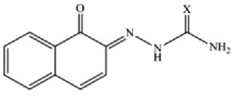
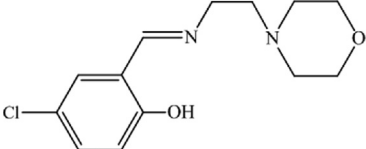
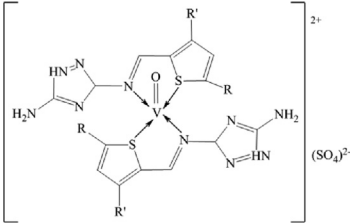
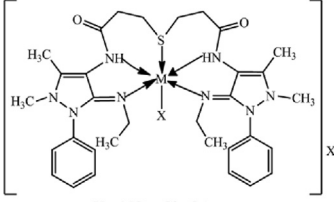
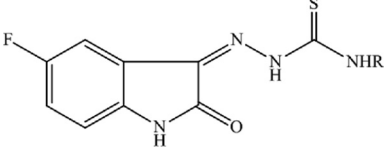
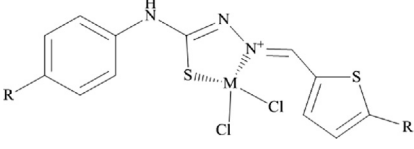
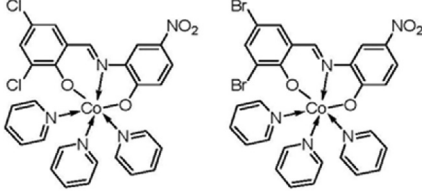
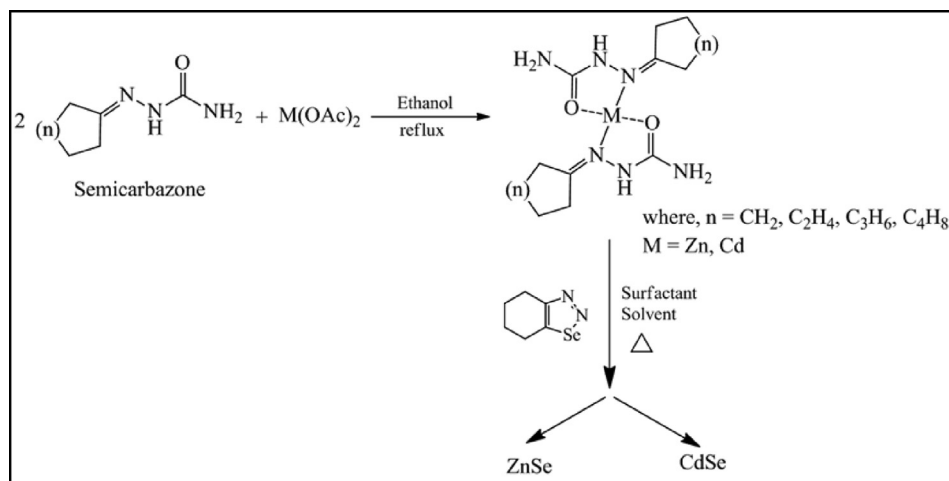


Table
Various semicarbazones, Schiff bases, and their biological applications

Structure	Biological application	Reference
 <p>Y = Thiophene/ Pyridine/ Picoline/ Aniline/ Ammonia</p>	Antimicrobial activity against <i>Staphylococcus aureus</i> , <i>Bacillus anthracis</i> , <i>Aspergillus niger</i> , and <i>Candida albicans</i>	[43] <i>Int. J. Scientific Technology Res.</i> , 3 (2014) 73–77.
 <p>X = O (NQSC); S (NQTS)</p>	Anticancer activity against MCF-7 breast cancer cell lines	[45] <i>J. Inorg. Biochem.</i> , 99 (2005) 1526–1531.
	Antibacterial activity against Gram +ve bacterial (<i>Bacillus subtilis</i> and <i>S. aureus</i>) and Gram –ve bacterial (<i>E. coli</i> and <i>P. fluorescence</i>)	[64] <i>J. Coord. Chem.</i> , 62 (2009) 3471–3477.
 <p>(SO₄)²⁻</p>	Antibacterial activity against Gram –ve bacterial strains (<i>E. coli</i> , <i>S. flexneri</i> , <i>P. aeruginosa</i>) and Gram +ve bacterial (<i>S. aureus</i> and <i>B. subtilis</i>)	[94] <i>J. Enz. Inhib. Med. Chem.</i> , 27 (2) (2012) 187–193.
 <p>X = NO₃⁻, Cl⁻, OAc⁻ M = Co(II), Cu(II), Ni(II)</p>	Antifungal activity against <i>Alternaria brassicae</i> , <i>Aspergillus niger</i> , and <i>Fusarium oxysporum</i>	[100] <i>Molecules</i> , 14 (2009) 174–190.
	Antiviral activity , Inhibits the replication of vesicular stomatitis virus and shows cytotoxicity in Vero clone CCL-81 cell lines	[119] <i>Monatsh Chem.</i> , 144 (2013) 1725
	Antiviral activity against DNA and RNA viruses e.g. human cytomegalovirus strains AD-169, cytostatic activity against human cervix carcinoma (HeLa) cells	[121] <i>Eur. J. Med. Chem.</i> , 46 (11) (2011) 5616–5624.
	Antitumor activity were tested for human cancer cell line (A-431, HT-144, and SK-MEL-30)	[129] <i>Brazilian J. Med. Bio. Res.</i> , 50 (7) (2017) 6390.



Scheme 6. Synthesis of metal complexes of semicarbazones and their respective selenides.

and they observed octahedral geometry for these complexes. Several novel semicarbazones and their Zn (II) and Cd (II) complexes (Scheme 6) were reported by Jadhav et al. [47] for their use as precursor for the synthesis of nanostructured metal selenides with particle diameter typically below 5–10 nm. Such precursors gave new dimension to their utility and possibly allowed their entry in the field of nanotechnology.

In recent years, sulfur-containing ligands such as thiosemicarbazones and dithiocarbamates and their transition metal complexes have attracted enormous attention because of their pharmacological properties such as antibacterial, antifungal, antiviral, and antitumor activities [48,49] e.g. Cory et al. [50] have studied and reported that 3-aminopyridine-2-carboxaldehyde thiosemicarbazone and 3-amino-4-methylpyridine-2-carboxaldehyde thiosemicarbazone were most active with respect to inhibition of cell growth and ribonucleotide reductase activity as compared with 5-aminopyridine-2-carboxaldehyde thiosemicarbazone and 4-methyl-5-aminopyridine-2-carboxaldehyde thiosemicarbazone.

Liberta and West [51] have described that the heterocyclic thiosemicarbazones containing hydrogen and either an alkyl or aryl group attached at ^4N are moderately inactive antifungal agents. Fungal growth inhibition resulted for the uncomplexed thiosemicarbazones and its Cu (II) and Ni (II) complexes against *Aspergillus niger* showed that the thiosemicarbazones exhibit higher antifungal activity against *A. niger* as compared with their Cu (II) and Ni (II) complexes, which showed less or no activity toward *A. niger*. Each compound showed activity above the minimal concentration, i.e. $200 \mu\text{g ml}^{-1}$.

2. Synthesis

2.1. Preparation of Schiff base

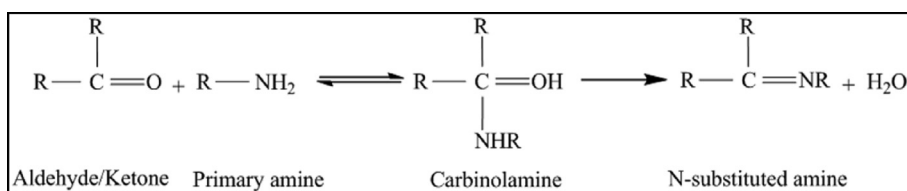
There are various reaction pathways to synthesize Schiff base(s). An acid catalyzed condensation reaction of primary amine with an

aldehyde or ketone under refluxing condition is the most commonly used method, e.g. mineral acids are often employed as catalysts (Scheme 7). In this reaction, the nucleophilic nitrogen atom of amine attacks on the carbonyl carbon results into an unstable intermediate, i.e. carbinolamine. Owing to the elimination of one molecule of water, a C=N bond is formed, and the product is known as imine. In general, reactivity of aldehyde is more than ketone in the formation of Schiff base as the reaction center of aldehyde is sterically less hindered as compared with the ketone. The condensation reaction is affected by the pH of the solution and the steric as well as electronic effect of an amine and carbonyl compounds. Because the dehydration of the carbinolamine is the rate-determining step of Schiff base formation, such reactions are catalyzed by acids. One should also note that the higher concentration of acid will protonate the amine and restricting its functionality as a nucleophile, thus suppressing formation carbinolamine. Therefore, syntheses of many Schiff bases are carried out at mild acidic pH. Similarly, in basic conditions, the reaction is hindered because of non-availability of protons to catalyze the elimination of the carbinolamine hydroxyl group.

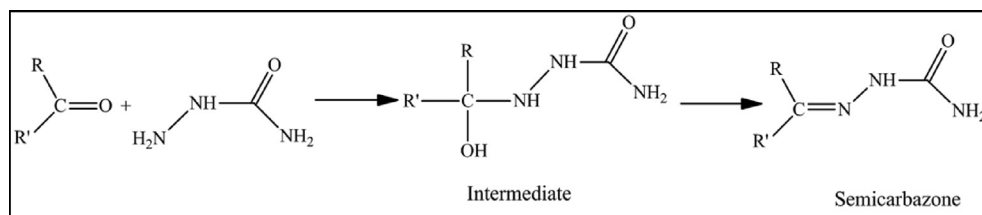
2.2. Preparation of semicarbazone

Different types of semicarbazone (Scheme 8) derivatives could be synthesized by adding stoichiometric quantity of suitable aldehyde or ketone with respective semicarbazide in presence of sodium acetate [52]. Sometimes hydrochloric acid must be added in the reaction mixture. Usually ketones require the elevated temperature than aldehydes for reaction completion. The ammonia-related compounds such as semicarbazide is added to the carbonyl group, and it results into the formation of semicarbazone. Such transformation of carbonyl compounds such as aldehydes and ketones into imine derivatives is an exothermic and pH dependent reaction.

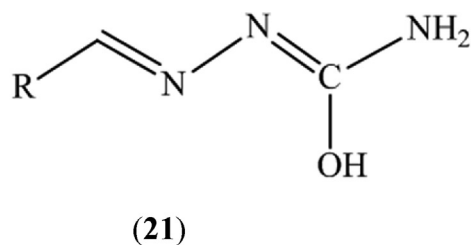
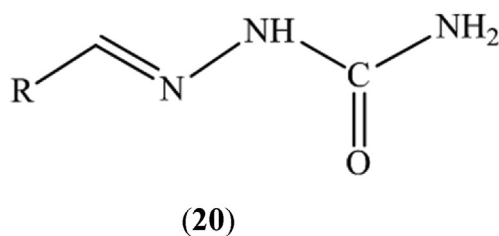
There is possibility that they exist in tautomeric keto (**20**) and enol (**21**) forms in metal complexes. In keto form, semicarbazone



Scheme 7. General reaction for synthesis of Schiff bases.



Scheme 8. General reaction mechanism of semicarbazone synthesis.



acts as neutral bidentate ligand as they coordinate to metal ion through imine nitrogen and carbonyl oxygen; while in enol form, it can deprotonate and emerges to serve as a mono anionic bidentate ligand in metal complexes.

The ligand may coordinate through N (NH) and O (C=O) groups as bidentate. Though if there could be some additional coordination position in the semicarbazone, it may act as tridentate ligand, i.e. NNO type. Thus, there are high coordination probabilities that the ligand may show through the keto-enol transformation.

3. Applications

Schiff bases, semicarbazones, thiosemicarbazones, and their metal complexes are extensively studied owing to their wide range of applications in biological activity such as antifungal, antitumor, antibacterial, anticancer, etc.; in pharmaceuticals; and as catalyst [53]. They are also used in dyes [54], polymers, [54] as well as they are applied in nanotechnology [55], laser [56], transistor [57], in defense as gas generating agents [58], and pyrotechnic mixtures [59]. Imine derivatives are employed in optical computers, to measure and to control the intensity of the radiation, in molecular memory storage, and in imaging systems, as organic material in reversible optical memories also in biological systems used as photo-detectors (Fig. 1).

3.1. Biological activity for biomedical field

Majority of Schiff bases are useful as antibacterial and antifungal agents. An azomethine (imine) group $-N=CH-$, in Schiff base helps to explain the mechanism of *trans*-amination as well as racemization reaction in biological system. Metal-Schiff base complexes have been widely studied for their application as antitumor, antibacterial, antifungal, and herbicidal agents [60,61] as is depicted in Fig. 2 below.

Schiff base ligands, 4-[(4-bromo-phenylimino)-methyl]-benzene-1,2,3-triol (**22**), 4-[(3,5-di-tert-butyl-4-hydroxy-phenylimino)-methyl]-benzene-1,2,3-triol (**23**), 3-(p-tolylimino-methyl)-benzene-1,2-diol (**24**), 3-[(4-bromo-phenylimino)-methyl]-benzene-1,2-diol (**25**), and 4-[(3,5-di-tert-butyl-4-hydroxy-phenylimino)-methyl]-benzene-1,3-diol (**26**), and their Cd (II) and Cu (II) complexes have been reported by Golcu et al. [62] where, ligands and their metal complexes were studied for *in vitro* antibacterial

and antifungal activities against *Bacillus megaterium* and *Candida tropicalis*. All the ligands and their Cu (II) and Cd (II) complexes were found to be highly active against the bacterium *B. megaterium*. Authors reported that Cu (II) complex with ligand (**23**) showed higher activity against *C. tropicalis* than the complex with ligand (**22**).

3.1.1. Antimicrobial activity

Ispir et al. [63] described the Schiff bases of 2,6-diacetylpyridine and 2-pyridine carboxaldehyde with 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one[4,4'-(1E,1'E)-(1,1'-(pyridine-2,6-diyl)bis(ethan-1-yl-1-ylidene))bis(azan-1-yl-1-ylidene)bis(1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)one) (**27**), and (E)-1,5-dimethyl-2-phenyl-4-(1-(pyridin-2-yl)ethylideneamino)-1H-pyrazol-3(2H)one (**28**) and their Co (II), Cu (II), Ni (II), Mn (II) and Cr (III) complexes (**29–38**) (Scheme 9) exhibit antibacterial and antifungal activities against *E. coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycobacterium smegmatis*, *P. aeruginosa*, *Enterobacter cloacae*, and *Micrococcus luteus*.

The Schiff base 4-chloro-2-(2-morpholinoethylimino)methylphenolatomethanolchloro (**39**) and its Zn (II) complex also was reported to be antibacterial in nature against Gram +ve bacterial strains (*Bacillus subtilis* and *S. aureus*) and Gram –ve bacterial strains (*E. coli* and *Pseudomonas fluorescence*) [64]. It was stated that the ligands showed greater activity against some of the Gram-

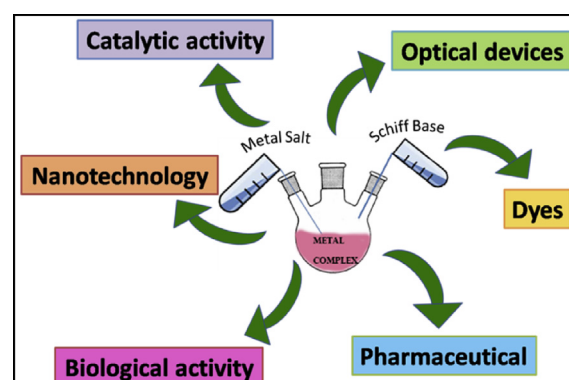


Fig. 1. Schematic presentation of application of complexes of imine derivatives.

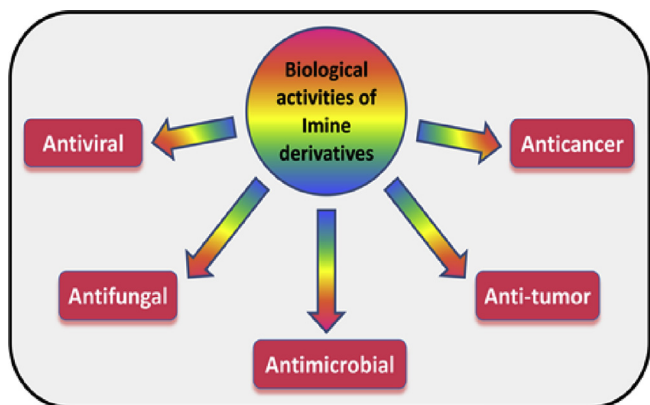


Fig. 2. Biological applications of imine derivatives.

negative bacterial strains. Cu (II), Co (II), and Mn (II) salicylidene complexes were reported for good antimicrobial activity toward all the gram +ve and gram -ve bacteria, and it was reported that metal-ligand complexes have higher antibacterial activity than the free ligands [65]. It is also highlighted that the complexes containing nitro group showed better activity than the complexes with chloro and bromo group [66]. Pandeya et al. [67] have reported the Schiff base of substituted Isatin with 4-(4'-chlorophenyl)-6-(4''-methylphenyl)-2-aminopyrimidine (e.g. 3-[4'(4''-chloro phenyl)-6'-(4'''-methylphenyl)pyrimidin-2'-yl]iminoisatin) and its Mannich base derivatives (Scheme 10). These compounds were tested for *in vitro* antibacterial activity and observed that all compounds are more active against *Salmonella typhimurium*, *S. aureus*, *Enterococcus faecalis*, *P. aeruginosa*, *K. pneumoniae*, *Staphylococcus albus*, *Aeromonas hydrophila*, *Vibrio cholerae*-01, *B. subtilis*, and *Providencia rettgeri*. All compounds were tested for their inhibitory effect of the replication of HIV-1 in human MT-4 cells.

Schiff base obtained from 2-aminophenol or 2-aminothiophenol with 1-phenyl-2,3-dimethyl-4(4-iminopentan-2-one)-pyrazol-5-one, [1-phenyl-2,3-dimethyl-4(4-iminopentan-2-one) pyrazol-5-iminophenol (40), and 1-phenyl-2,3-dimethyl-4(4-iminopentan-2-one)pyrazol-5-imino thiophenol (41)] and their neutral tetradentate transition metal [Cu (II), Ni (II), Zn (II), Co (II) and VO (II)] complexes showed antimicrobial activity against *Bacillus subtilis*, *Salmonella typhi*, *S. aureus*, *Pseudomonas aeruginosa*, *Aspergillus niger*, etc. It is observed that compared with free ligands, metal complexes have higher antimicrobial activity [68].

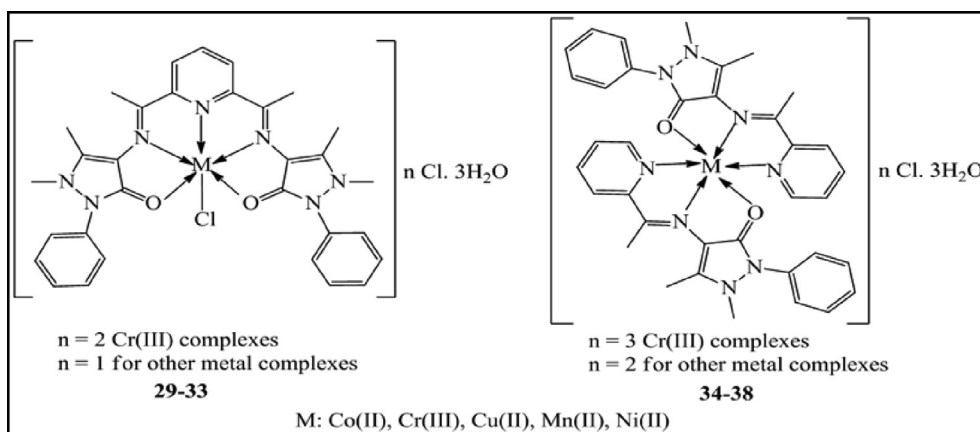
Schiff bases derived from thiophene carboxaldehyde and aminobenzoic acid [69], furaldehyde [70], benzimidazole [71], thiazole [72,73], furfuraldiamine [74], pyridine and benzyldithiocarbazate [75], pyrazolone [76,77], glucosamine [78], hydrazide [79], p-fluoro benzaldehyde [80], p-anisidine [81], thiosemicabazones [82], and imidazolinones [83] show antibacterial activity.

Desai et al. [82] have been reported some oxime, semicarbazone, and thiosemicabazones by using 2,4-dihydroxyacetophenone, 2,4-dihydroxy-5-nitroacetophenone, and 2,4-dihydroxy-5-bromo-acetophenone and were evaluated for their inhibitory effect against *S. aureus* and *E. coli* by agar diffusion technique. All the compounds exhibited great activity against Gram -ve bacteria, i.e. *E. coli* and poor activity against Gram +ve bacteria, i.e. *S. aureus*.

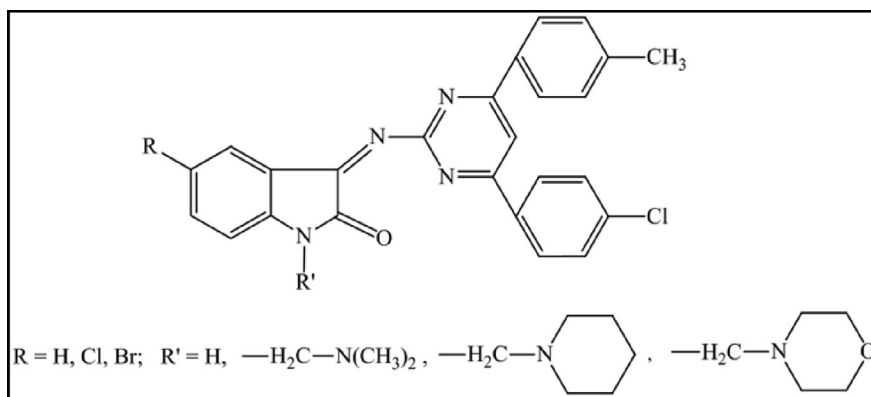
Mohmed et al. [84] have reported some Fe (III), Cu (II), Zn (II), and UO₂ (II) complexes of Schiff base obtained from 2-thiophene carboxaldehyde and 2-aminobenzoic acid and were tested for their antibacterial activity against bacterial species, *E. coli*, *P. aeruginosa*, *Streptococcus pyogenes*, and fungi (*Candida*). It is found that metal complexes are more effective against some bacterial species (Gram-positive and Gram-negative bacteria) as compared with the parent Schiff base ligand. It is also reported that Fe (III), Cu (II), Zn (II), and UO₂ (II) complexes inhibited the growth of *E. coli* and could be employed in the treatment of common diseases such as septicemia, gastroenteritis, and urinary tract infections caused by *E. coli*. A series of Cu (II), Zn (II), and Ni (II) complexes of Schiff base ligands DAPY-{SalH} 42, DAPY-{SalH}2 43, DAPY-{4-OHBenz} 44 and DAPY-{4-NO₂Benz} 45 were synthesized from 2,3-diaminopyridine (DAPY) and different aldehydes; salicylaldehyde (SalH), 4-hydroxy-benzaldehyde (4-OHBenz) and 4-nitro-benzaldehyde(4-NO₂Benz) have been reported by Jeewoth et al. [85].

2,3-diamino-pyridine is significantly does not show activity against *P. aeruginosa*, *S. typhi*, *E. coli*, and *S. aureus*, but its Schiff base ligands have been found more effectual against these bacteria. The Cu (II) and Zn (II) complexes of the Schiff base DAPY-{4-NO₂Benz} show antibacterial activities against *P. aeruginosa* and *S. typhi*. The proposed structures of metal complexes are shown in (Scheme 11).

Khanna et al. [86] have synthesized a number semicarbazone and their corresponding heterocyclic organoselenium compounds such as cycloalkeno-1,2,3-selenadiazoles (cyclopenteno, cyclohexeno, cyclohepteno, and cycloocteno-1,2,3-selenadiazoles), at room temperature by applying solventless conditions. The synthesized semicarbazones and their 1,2,3-selenadiazoles were tested for their antimicrobial activity against different pathogenic bacteria. It was observed that selenadiazoles exhibited enhanced



Scheme 9. The proposed structure of metal complexes with 27 and 28.



Scheme 10. Proposed structure of Isatin derivatives.

antimicrobial activity against *E. coli*, *S. aureus*, *S. typhi*, and *P. aeruginosa* as compared with their respective semicarbazones. Among these all selenadiazoles, cyclopenteno-1,2,3-selenadiazole exhibited very good inhibition against highly resistant *P. aeruginosa*.

Schiff base ligands containing p-amino salicylic acid improve the antimycobacterial activity against *Mycobacterium* and *M. Lovis BCG*. Patole et al. [87] have been described some new multifunctional conjugates (**46–51**) of p-amino salicylic acid (PAS) (Scheme 12) capable of metal chelation along with the results on the evaluation of their antimycobacterial activity against *M. smegmatis* and *Mycobacterium bovis* (BCG). Hydroxyl-rich side chains in ligands exhibit increased antimycobacterial activity against *M. smegmatis* and *M. bovis* BCG. Schiff base of cyclobutane and thiozole ring show antimicrobial activity. Some Cu (II), Ni (II)—Schiff base complexes exhibit antibacterial activity against *Colibacillus* and *P. aeruginosa* [88].

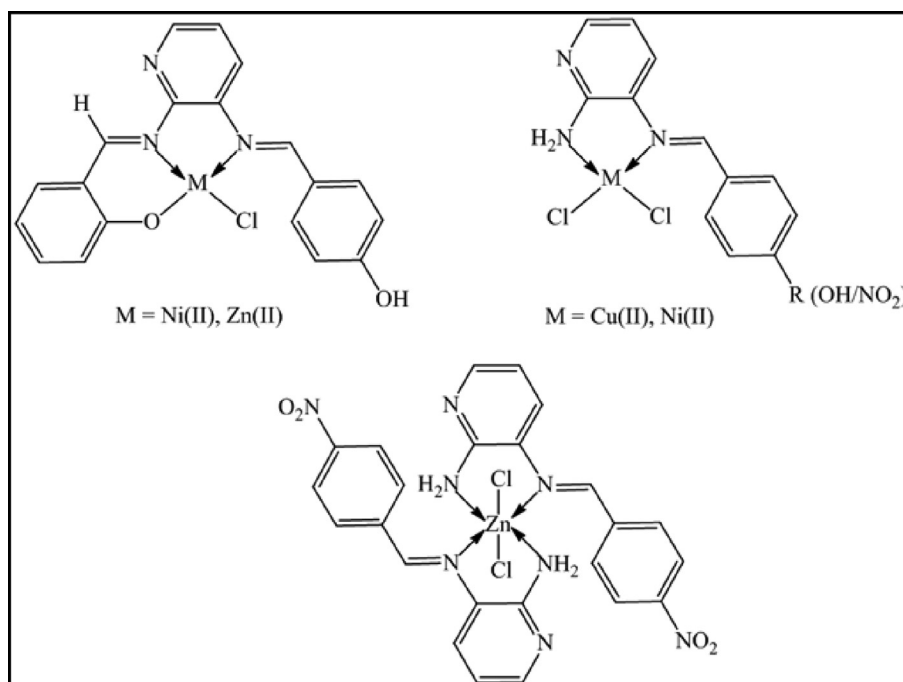
Schiff base (Scheme 13) derived from glycyglycine respectively with imidazole-2-carboxaldehyde (**52**) and indole-3-carboxaldehyde (**53**) and their Zn (II) complexes were biologically

tested against *S. aureus*, *E. coli*, *K. pneumoniae*, *Proteus vulgaris*, and *P. aeruginosa* by the disc-diffusion method. As comparative study of inhibition value, the complexes show higher antimicrobial activity than the free ligands [89].

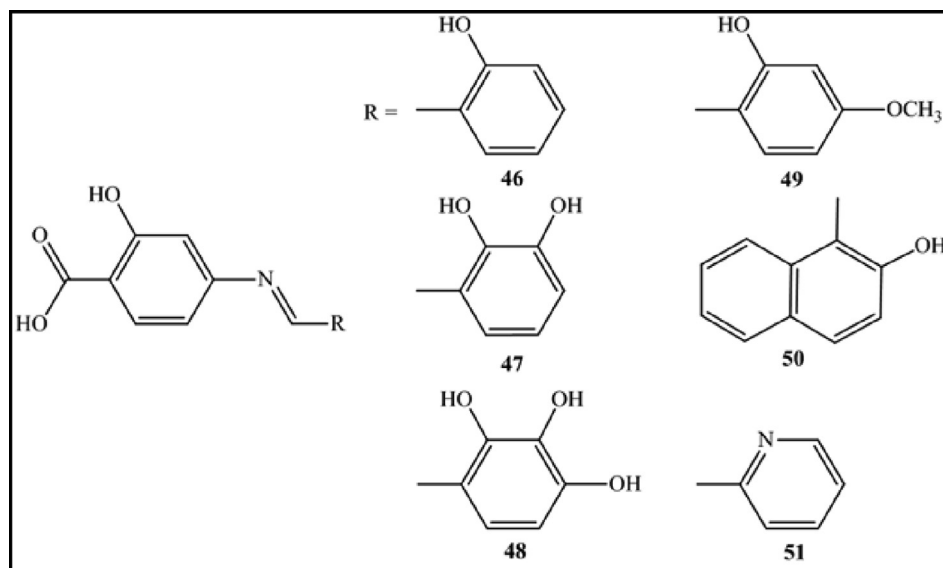
Wadher et al. [90] have reported a series of Schiff base and 2-azetidinones of 4,4'-diamino-diphenylsulphone. The Schiff base synthesized by condensation of 4,4'-diamino-diphenylsulphone with various aromatic or heterocyclic aldehyde in ethanol to yield the Schiff base (**54–58**) (Scheme 14). All the compounds were screened for their *in vitro* activity toward a number of bacteria. Compound **56** [4,4'-bis(4-fluorobenzylidene-amine)diphenylsulphone] and **58** [4,4'-bis(4-methoxy-benzylideneamine)diphenylsulphone] exhibited effective antibacterial activity.

By using 5-bromo salicylaldehyde and 4-substituted amines a novel Schiff base ligands and its Co (II), Cu (II), and Ni (II) complexes have been synthesized, and their antimicrobial properties have been investigated [91].

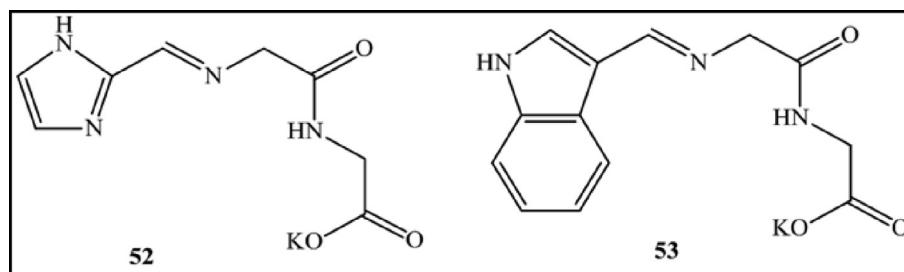
Azam et al. [92] have reported a series of Schiff base ligands (Scheme 15A) of naphtha-[1,2-d] thiazol-2-amine with the



Scheme 11. Proposed structure of Cu (II), Ni (II), and Zn (II) Schiff base complexes.



Scheme 12. Schiff base ligands (46–51) of PAS.



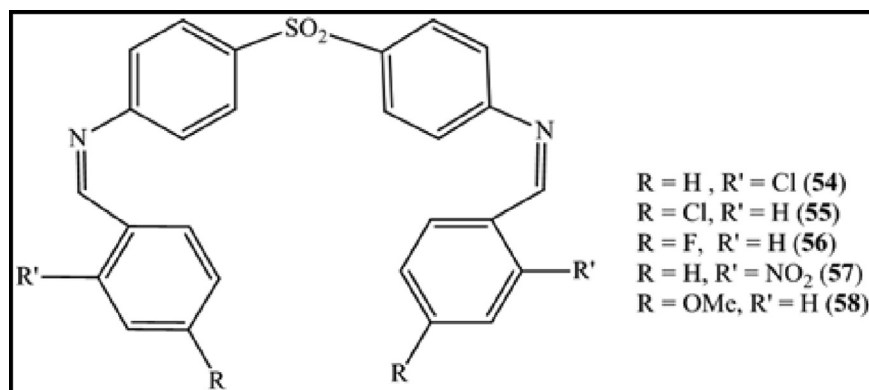
Scheme 13. Schiff base obtained from glycylglycine.

substituted aldehydes (**59–72**) and the Cu (II), Co (II), Ni (II) complexes (Scheme 15B) of 2-(2'-hydroxy)benzylidene-amino-naphthathiazole (**64**).

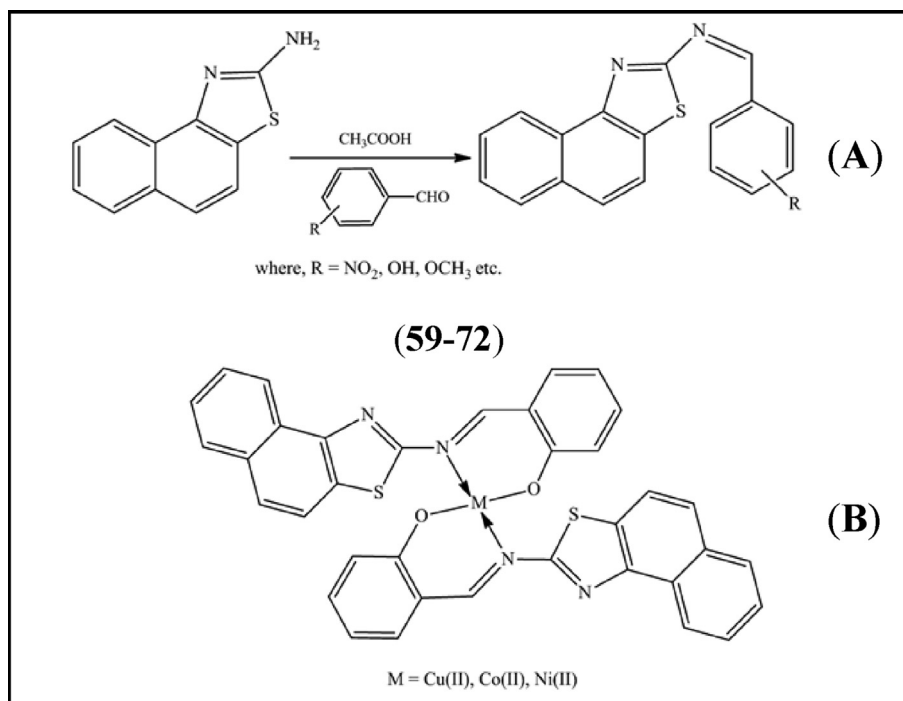
All ligands and these metal complexes were investigated for their antimicrobial activity against Gram +ve and Gram –ve bacteria by measuring the zone of inhibition in mm. It is observed that the Cu (II) complex with 2-(2'-hydroxy)benzylidene-amino-naphthathiazole acts as potential antimicrobial agent as well as the ligands containing nitro, halogen, hydroxyl, methoxy, etc. exhibited good inhibitory activity.

The antimicrobial activity of Schiff base methyl-2-pyridyl ketone semicarbazone (**73**) and its Cu (II) complexes have been synthesized by Shaabani et al. [93] and have been investigated against the bacteria *B. subtilis*, *S. aureus*, *E. coli*, and *Erwinia carotovora* and fungals *Candida kefyr*, *Candida krusei*, and *A. niger*. The ligand **73** shows poor biological activity as compared with the thiosemicarbazone which contains sulfur instead of oxygen atom. Cu (II) complexes showed enhanced antimicrobial activity than the parent ligand.

Chohan and Sumrra [94] have reported a new series of biologically active thienyl-derived triazole Schiff bases and their VO (IV)



Scheme 14. Proposed structure of Schiff base (54–58).



Scheme 15. (A) Schiff base of naphtho[1,2-d]thiazol-2-amine, (B) its Cu (II), Co (II), Ni (II) complexes.

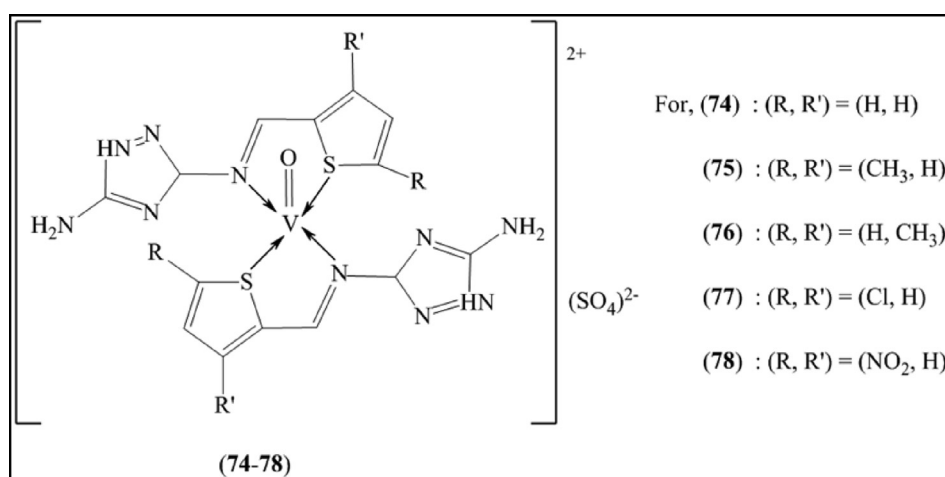
(74–78) complexes (Scheme 16). All the ligands and their VO (IV) complexes were tested *in vitro* antimicrobial activity against Gram-negative bacterial strains (*E. coli*, *Shigella flexneri*, *P. aeruginosa*, *Salmonella enterica serover typhi*) as well as Gram-positive bacterial strains (*S. aureus* and *B. subtilis*). It was reported that because of the presence of chloro and nitro group in the VO (IV) complexes, (77) and (78) were found to be the most active antimicrobial agent against Gram-positive and Gram-negative bacterial strains. Among these compounds, the compound (78) showed highest inhibition against *B. subtilis* bacterial strain (3.891×10^{-8} M).

3.1.2. Antifungal activity

Fungi are the heterotrophic eukaryotic organisms which can grow on any surface. In recent years, there was a significant increase in the occurrence of general fungal infections [95]. Generally fungal infections are bounded to the surface tissues and

moderately easy to cure. So it is necessary to explore and develop more effective antifungal agents. The fungicidal activity toward *Curvularia* enhanced with the presence of methoxy, halogen, and naphthyl groups in the ligands. Sulfur-containing Schiff bases derived from thiazole and benzothiazole derivatives possess effectual antifungal activity [96,97].

Pahontu et al. [96] have reported the 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone-4-ethyl-thiosemicarbazone (79) (Scheme 17) and its Cu (II), V (V), and Ni (II) complexes such as [Cu(L)(Cl)].C₂H₅OH (80), [Cu(L)₂].H₂O (81), [Cu(L)(Br)].H₂O · CH₃OH (82), [Cu(L)(NO₃)].2C₂H₅OH (83), [VO₂(L)].2H₂O (84), and [Ni(L)₂].H₂O (85) were tested *in vitro* for their antibacterial activity against *E. coli*, *Salmonella abony*, *S. aureus*, *Bacillus cereus* and the antifungal activity against *C. albicans* strains. The metal complexes exhibited higher activity than that of free ligand. The effect on the proliferation of HL-60 cells was tested by the free ligand and its metal



Scheme 16. VO (IV) complexes (74–78).

complexes. The antimycotic property of the copper complexes **80**, **81**, **82**, and **83** was studied, and they showed that bacteriostatic and bactericidal activity toward *Candida* fungi in a concentration range of 1.5–4.0 lg/ml. Copper complexes were compared with the nystatin, a compound employed in medicine for mycoses treatment and found that copper complexes have 20–25 times higher antimycotic activity against *Candida* fungi than nystatin. Semicarbazones (**86**, **88**) and thiosemicarbazones (**87**, **89**) and its Ni (II) complexes exhibited antifungal activities toward many pathogenic fungi. Some of the Ni (II) complexes show reasonable activity against the pathogenic fungi, but they were found to be much lower than those of standard fungicide Nistatin [98] (Scheme 18).

The synthesis and antifungal activity of some Schiff base ligands and its Sn (IV) complexes against some plant pathogenic fungi has been investigated and reported by Rehman et al. [99]. The various concentrations (50, 100, 250, and 500 ppm) of the ligands and its Sn (IV) complexes were employed to investigate the germination effect of *Colletotrichum gloeosporioides*, *Alternaria brassicicola*, *Alternaria brassicae*, *C. capsici*, and *Helminthosporium graminum* by using the hanging drop method. It is observed that all the

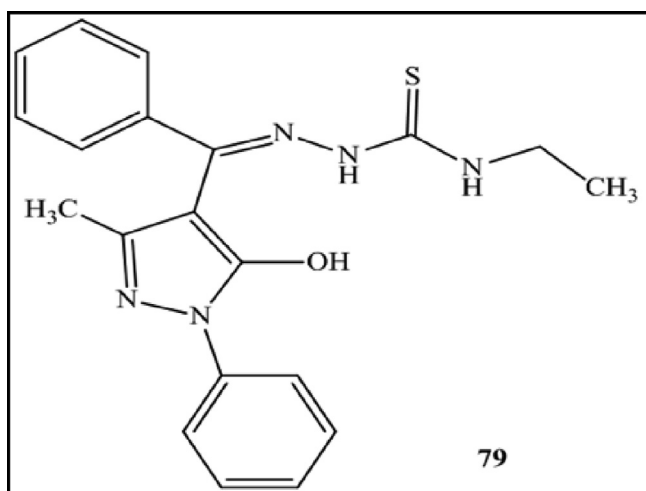
compounds have outstanding fungicidal activity. The toxicity is enhanced with the increase in concentration of compounds.

Chandra et al. [100] have reported the synthesis and characterization of Schiff base ligand 3,3'-thiodipropionic acid-bis(4-amino-5-ethylimino-2,3-dimethyl-1-phenyl-3-pyrazoline (**90**) and its Co (II), Ni (II) and Cu (II) complexes (**a** and **b**) (Scheme 19). All the compounds were screened for their antifungal activity against *A. brassicae*, *A. niger* and *Fusarium oxysporum*, and it is found that all the synthesized complexes exhibit enhanced activity as compared with that of free ligands. Schiff base synthesized from furan or furylglyoxal with different amines exhibit antifungal activity against *H. gramineum*, *Syncephalostrum racemosus*, and *Colletotrichum capsici* [101].

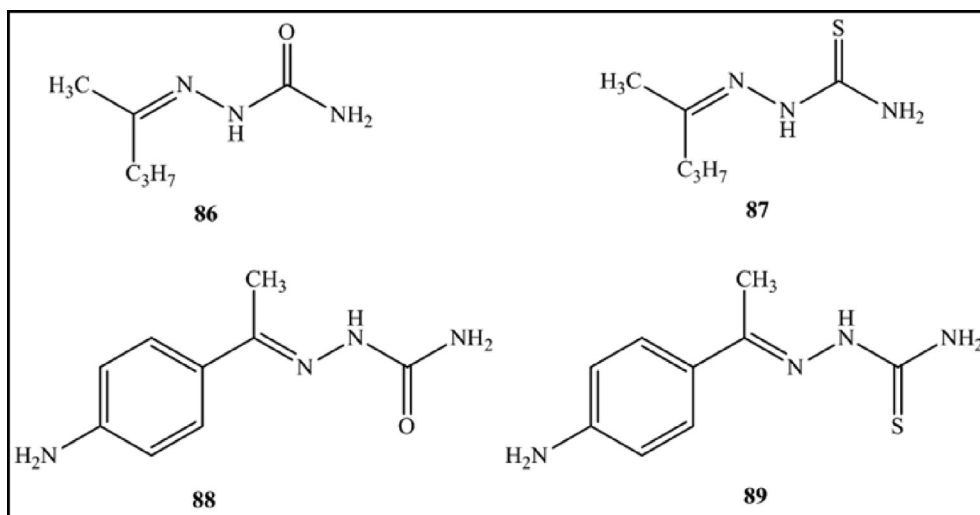
Raman et al. [102] have been synthesized macrocyclic ligands by the condensation reaction of diethyl phthalate with Schiff bases obtained from *o*-phenylenediamine and Knoevenagel condensed β -ketoanilides and its Cu (II) complexes. These complexes were investigated the *in vitro* antifungal activities against fungi such as *Rhizopus stolonifer*, *Rhizoctonia bataicola*, *A. niger*, *A. flavus*, and *C. albicans*.

It is observed that all the Cu (II) complexes exhibited stronger antifungal activities than free ligands. Some Schiff bases of furfuralidene nictoinamide [103] exhibits antifungal activity against *A. niger*, *Alternaria solani*, and *C. capsici* whereas Schiff base of quinazolinones [104] exhibit antifungal activity against *C. albicans*, *Trichophyton rubrum*, *mentagrophytes*, *A. niger*, and *Micosporum gypseum*. Schiff base derived from 3-substituted phenyl-4-amino-5-hydrazino-1,2,4-triazole with benzaldehyde, 2-hydroxyacetophenone or indoline-2,3-dione and its Zn (II) complexes have been reported by Singh et al. [105]. All the Schiff base ligands and their Zn (II) complexes were studied for their antifungal activities against *Colletotrichum falcatum*, *Aspergillus niger*, *F. oxysporum*, and *Carvularia pallescens*. VO (IV) complexes of triazole, Ru (II) complexes with salicylaldimine, Cu (II) complexes with benzoylpyridine, and Tl (I) complexes of benzothiazolines show antifungal activity [106].

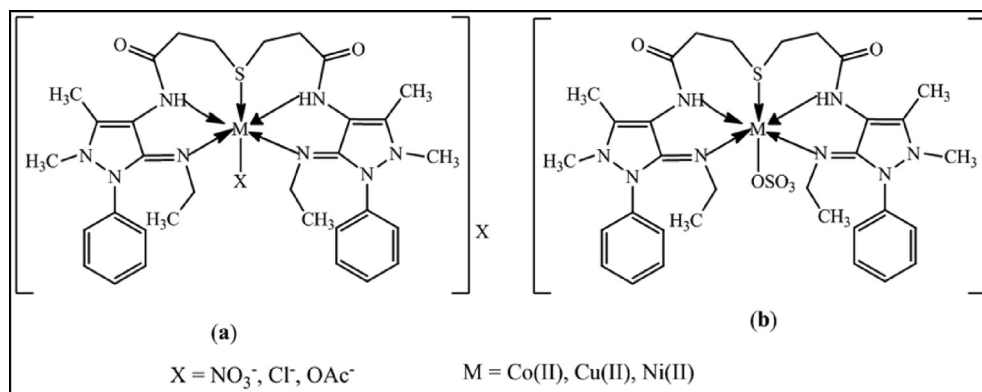
Schiff base derived from condensation of 3-methyl- or 3-ethyl-4-amino-5-thiolato-1,2,4-triazole with benzaldehyde, 2-chlorobenzaldehyde, 4-methoxybenzaldehyde or acetophenone and salicylaldehyde or *o*-hydroxyacetophenone and its VO (IV) complexes of the types [VOL₂.(H₂O)], [VOL'₂.(H₂O)], and [VOL''.(H₂O)₂] have been reported by Yadav et al. [107]. The fungicidal activities of these complexes were evaluated in dimethyl



Scheme 17. Structure of 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone-4-ethylthiosemicarbazone.



Scheme 18. Structure of semicarbazones and thiosemicarbazones (**86**–**89**).



Scheme 19. Structure of complex (a) $[\text{M(L)X}]\text{X}$ and (b) $[\text{M(L)SO}_4]$, where L = ligand **90**.

formamide (DMF) against *A. niger* and *Hirschmanniella oryzae* by the agar plate technique at concentrations of 10, 100, and 1000 ppm. Ramesh et al. [108] reported numerous new hexacoordinated Ru (II) complexes with monobasic bidentate Schiff base (L) such as salicylaldehydemethylamine (HSalmet) (**91**), salicylaldehyde-cyclohexylamine (HSalchx) (**92**), and salicylaldehyde-2-aminopyridine (HSalampy) (**93**) of the type $[\text{Ru}(\text{CS})(\text{Cl})(\text{Py})(\text{PPh}_3)(\text{L})]$, $[\text{Ru}(\text{CS})(\text{Cl})(\text{Bipy})(\text{L})]$ and $[\text{Ru}(\text{Cl})(\text{Phen})(\text{PPh}_3)(\text{L})]$, (where Py = pyridine, Bipy = 2,2'-bipyridyl, Phen = 1,10-phenanthroline (Scheme 20).

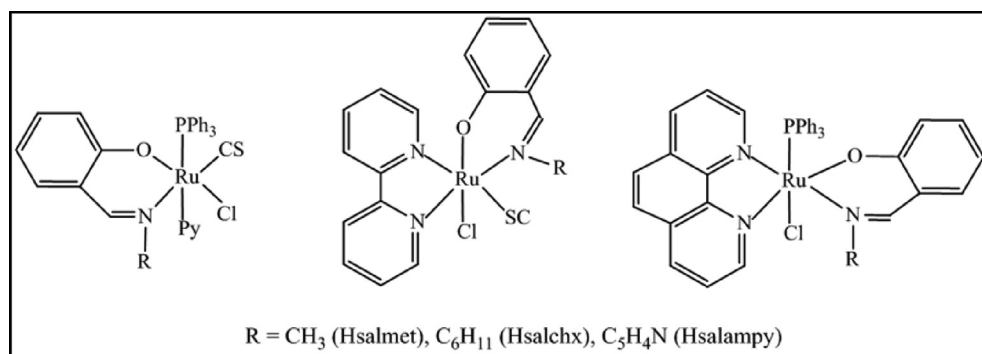
To evaluate their antifungal activity against *A. flavus*, these ligands and their ruthenium complexes were tested *in vitro* at four different concentrations. It is observed that the ruthenium complexes were more toxic against the *A. flavus* as compared with their parent ligands. The toxicity of these complexes increased on increasing the concentration.

3.1.3. Antiviral activity

Nowadays, our society is facing one of the main health disorder apoptosis obstructions, i.e. cancer [109]. For the treatment of cancer, chemotherapy is not effective. Hence, it has great importance to discover some novel and effective anticancer medicine [110]. Platinum-based complexes like *cis*-platin have been used as anticancer agent in chemotherapy [111,112]. In recent years, researchers have attracted enormous attention to develop non-platinum metal-based complexes as anticancer agents. Isatin derivatives show noticeable antiviral activity in the treatment of HIV. Either HIV-1 infected or mock-infected MT-4 cells in human were incubated with different concentration of Isatin derivatives (shown in Scheme 10), and the number of viable cells was determined by 3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) method after virus infection. At the concentration below its

threshold toxicity, none of the Isatin derivatives displayed noticeable anti-HIV activity [113]. In addition to this, Isatin Schiff base ligands have been widely reported antiviral activities against Moloney leukemia virus [114], vaccinia [115], rhino virus [116], and SARS virus [117]. Ronen et al. have been described the mode of inhibition of N-methylisatin- β -4',4'-diethylthiosemicarbazone (M-IBDET) on Moloney leukemia virus (MLV) production. They proposed that the inhibition of MLV by M-IBDET engaged a block in the translation of viral RNA rather than interference with viral RNA transcription [114]. Similarly, inhibition activities of Isatin derivatives derived from Isatin, sodium hydride, and different bromide compounds against a new viral uncharacteristic pneumonia, i.e. severe acute respiratory syndrome coronavirus (SARS CoV) were also studied by Chen et al. [117]. They concluded that the N-substituted Isatin derivatives showed the inhibition activity against SARS CoV 3C-like protease (3CL^{pro}) in minimum micromolar range such as 0.95–17.50 μM . The inhibition properties were evaluated by fluorescence resonance energy transfer (FRET) as well as confirmed through high performance liquid chromatography (HPLC) analysis. Among these all derivatives, compound **94** (Scheme 21A) was found the more potent and selective inhibitor for the SARS CoV 3CL^{pro}.

An Isatin-thiosemicarbazone (methisazone) plays a vital role as a prophylactic agent against several viral diseases [118]. Some 5-fluoroisatin derivatives have been prepared and screened for antiviral activity, the replication of vesicular stomatitis virus (VSV), as well as cytotoxicity evaluation in Vero clone CCL-81 cell lines by Abbas et al. [119]. Among these all compounds, N1-(5-fluoro-2-oxoindolin-3-ylidene)-N4-(*p*-fluoro-(or *p*-dimethylamino)benzylidene) thiocarbohydrazide and N-allyl (or *n*-butyl)-2-(5-fluoro-2-oxoindolin-3-ylidene)hydrazine carbo-thioamide as well as **95a-f** (Scheme 21B) showed good inhibitory activity as antiviral agents.



Scheme 20. Structure of ruthenium complexes.

Schiff bases of oximes, hydrazone, semicarbazones, and thiosemicarbazones derived from 5-acyl-1,2,4-triazines (**96a-c**) have been reported by Mojzych et al. [120] to investigate their biological activities. Among those, few compounds showed considerable antiviral activities. It is observed that 5-acyl-3-methylsulfamyl-1,2,4-triazine **96a** and its derivatives (**97a-b**) (Scheme 22) showed potential antiviral activity against Coxsackie Virus B4 in Vero cell culture as well as in HeLa cell culture with the EC₅₀ value of 20 and 45 µg/mL, respectively.

Many traditional as well as novel Pt (II) (**98–102**) and Pd (II) (**103–107**) complexes (Scheme 23) of thiosemicarbazones derived from 5-substitutedthiophene-2-carboxaldehydes have been documented along with their antiviral and cytotoxic activities by researchers where they reported that the platinum complexes or free ligands were more cytostatic than the corresponding palladium complexes [121].

Variety of polyphenol derivatives are biologically important Schiff bases, and they offer great scope in pharmaceutical chemistry, e.g. Gossypol derivatives exhibit high antiviral activities. Owing to its much lower toxicity, Gossypol derivatives often used in medical therapy [122,123]. Schiff base Ag (I) complexes with glycine salicylaldehyde showed effective results against *Cucumber mosaic virus* [124]. Ni (II), Pd (II), and Pt (II) complexes with semicarbazone (**108**) and thiosemicarbazone (**109**) of *p*-tolu-aldehyde have been reported by Chandra and Tyagi [125]. They have investigated their antifungal activities against the fungal species *Alternaria alternata*, *A. niger*, and *Fusarium odum* by using food poison technique on potato dextrose agar medium. The fungicidal screening of these compounds showed that the metal chelates possess a great antifungal activity compared with the parent ligands. This result is attributed because of the increase in delocalization of π -electrons upon chelation which improved the penetration of the metal complexes to the lipid membrane, and the metal binding sites are blocked in the enzymes of microorganisms.

Schiff base derived from salicylaldehyde and 1-amino-3-hydroxyguanidine tosylate is good compound for planning the new antiviral agents. Wang et al. [126] have modified some structural features of Schiff bases of hydroxyamino guanidines (SB-HAG)

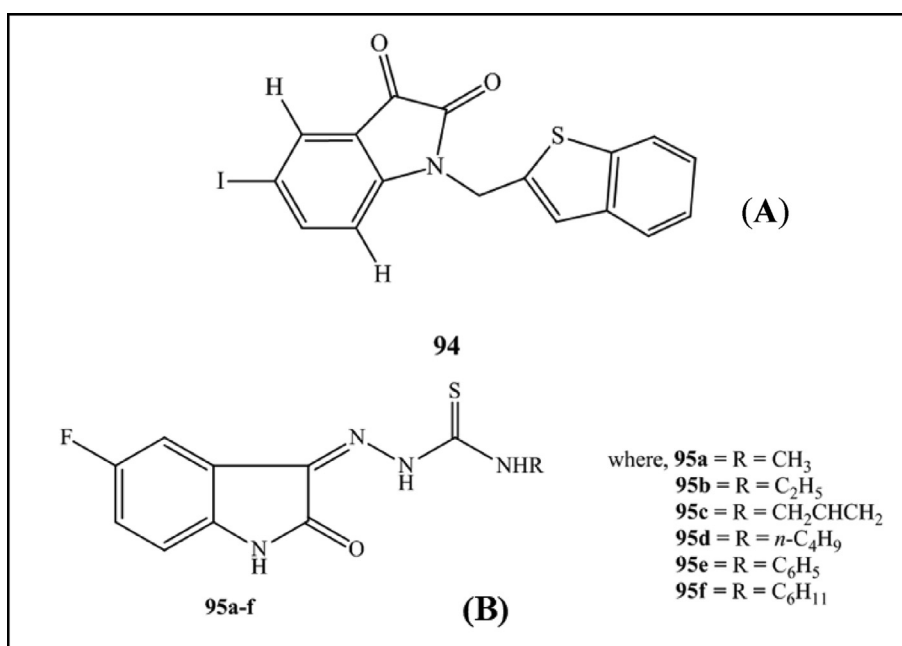
led to formation of new substituted salicylaldehyde Schiff bases of HAG (SSB-HAG) derivatives and three other SB-HAG derivatives. All these compounds were studied for the first time against infection by a coronavirus, mouse hepatitis virus (MHV). When the TCID₅₀ values are compared, it was found that [1-[(3'-allyl-2'-hydroxybenzylidene)amino]-3-hydroxyguanidine] was the most active compound against the growth of MHV about 376 times more active than hydroxyguanidine and about 564 times more effective than hydroxyaminoguanidines (HAG).

3.1.4. Antitumor activity

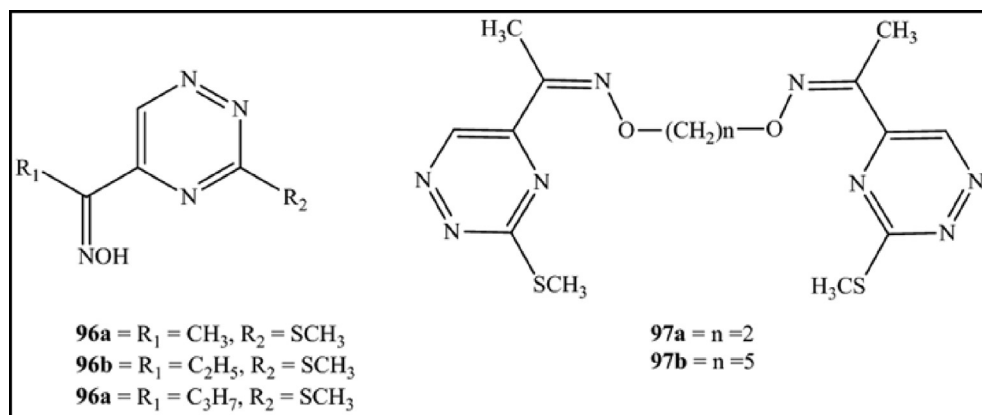
Hodnett et al. [127] have investigated the probable antitumor action of numerous synthetic and semisynthetic compounds. Schiff base obtained from 2-thiophene-carboxaldehyde and 2-amino-benzoic acid and its metal complexes have been developed a new line for search to new antitumor activity. A large number of transition metal including Zn (II), Ni (II), and Co (II) has been reported with high antitumor activities. Qin et al. [128] have reported new Co (II), Ni (II), and Zn (II) complexes of oxoaporphine (Scheme 24) and their *in vitro* and *in vivo* antitumor activities. These complexes possess higher cytotoxicity against some selected human tumor cells particularly the HepG2, T-24, and SK-OV-3 cells.

Xiao et al. [129] have reported Co (II) complexes with the two flexible Schiff base ligands of type Py₃CoL₁ (**113**) and Py₃CoL₂ (**114**) (where, Py = Pyridine, L₁ = 3,5-ClC₆H₂(O)C≡N C₆H₃(O)-4-NO₂, L₂ = 3,5-Br C₆H₂(O)C≡NC₆H₃(O)-4-NO₂) (Scheme 25), and their antitumor activity were tested for human cancer cell line (A-431, HT-144, and SK-MEL-30). They found that Co (II) complexes showed better antitumor activity than the free ligands.

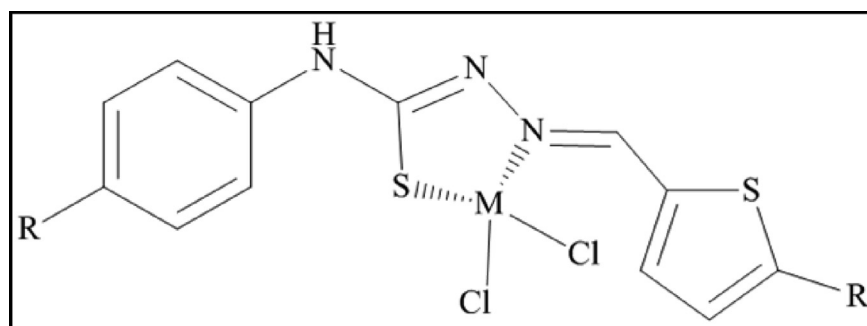
The biological activities of Cu (II), Ni (II), Ga (III), or V (V) complexes of salicylaldehyde semicarbazone (SSC) and 5-bromosalicylaldehyde semicarbazone (Br-SSC) have been already proved and characterized in solid phase or in solution of organic solvents by Enyedy et al. A series of Ga (III) complexes with SSC and its derivatives was investigated on various human tumor cell lines (ovarian, breast, prostate), and it showed higher activity than that of ligands. Some Ga (III) complex derived from Br-SSC exhibited significant activity against *cis*-platin sensitive ovarian cells [60,



Scheme 21. Structure of Isatin derivative **94** (A), some derivatives of 5-fluoroisatin (B).



Scheme 22. Structure of substituted 5-acyl-1,2,4-triazine (**96a-c**) and derivatives of 5-acyl-3-methylsulfamyl-1,2,4-triazine (**97a-b**).

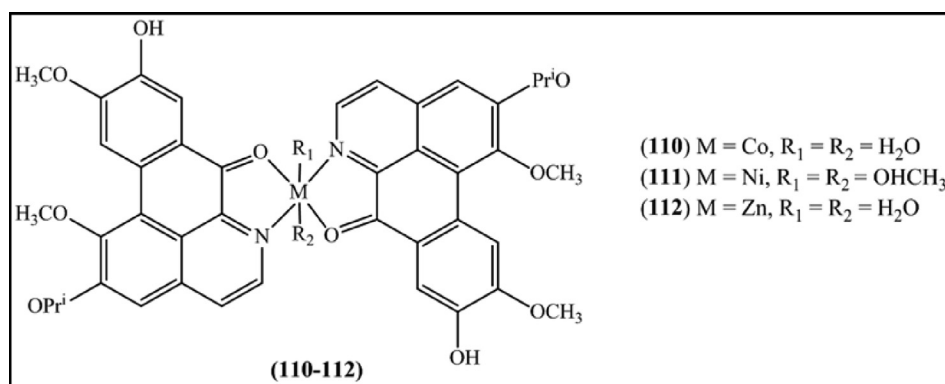


Scheme 23. Structure of Pt (II) (**98–102**) and Pd (II) (**103–107**) complexes.

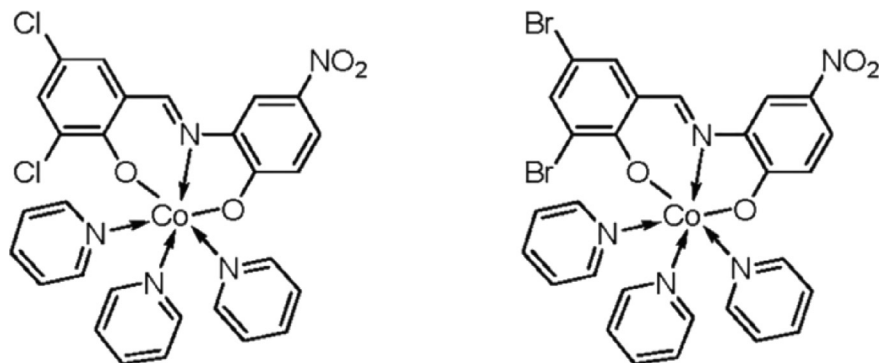
130–134]. Gambino et al. [130] have reported the bioactive gallium complexes with tridentate substituted salicylaldehyde semicarbazone of the type $[\text{Ga}^{\text{III}}(\text{L}-\text{H})_2](\text{NO}_3)$ (**115–119**) (Scheme 26) and have investigated for their antitumor activity. They have observed that Ga (III) complex with 5-bromosalicylaldehyde semicarbazone (**116**) as well as 5-bromo-2-hydroxy-3-methoxybenzaldehyde semicarbazone (**119**) showed higher activity against *cis*-platin sensitive A2780 ovarian cells; also complex **116** has shown moderate cytotoxicity against breast (MCF7) prostate (PC3) cells.

A series of thiosemicarbazones derived from 3-acylpyridazines, 4-acetyl-pyrimidines and 2-acetyl-pyrazines have reported by Easmon et al. [135] as potential antitumor agents. Thomas et al.

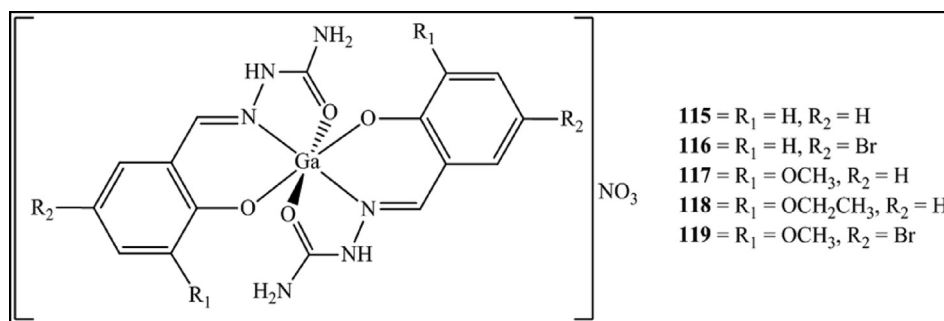
[136] have reported the antitumor activities of Mn (II), Ni (II), and Cu (II) complexes of anthracene-9-carboxyldehyde thiosemicarbazone as well as cytotoxic activity of phenylglyoxal bis(-thiosemicarbazone) against Ehrlich ascites carcinoma cells. Some mixed ligands V (IV) complexes with Schiff base and thiosemicarbazones were synthesized, and its antitumor activity has been reported by Lewis et al. [137]. Schiff base obtained from salicylaldehyde, 2,4 dihydroxy-benzaldehyde, glycine, and L-alanine and their Cu (II), Ni (II), Zn (II), and Co (III) complexes show antitumor activity, and their order of reactivity with metal complex is $\text{Ni} > \text{Cu} > \text{Zn} > \text{Co}$ [138]. Some Mn (II), Co (II), and Zn (II) complexes were synthesized, and their antitumor activity was determined by Li et al. [139]. Schiff base and its diorgano-Sn (IV) complexes exhibit



Scheme 24. Structure of Co (II), Ni (II) and Zn (II) complexes of oxoaporphine.



Scheme 25. Schematic representation of complexes Py_3CoL_1 (**113**) and Py_3CoL_2 (**114**).



Scheme 26. Typical structure of Ga (III) salicylaldehyde semicarbazone complexes.

antitumor activities *in vitro* and inhibit interaction to KB HCT-8 and BEL-7402 tumor cell lines [140].

3.1.5. Scope of Schiff bases and their complexes for nanobiotechnology

Metal complexes containing the elements from group II (e.g. Zn, Cd, Hg) and group VI (e.g. S, Se, Te) of the periodic table can be considered as plausible precursors for synthesis of semiconductor nanoparticles and as well as quantum dots which have broad range of application in modern day technology development [141]. In recent years, researchers have focused on the functionalized nanoparticles and its numerous biological and biomedical applications such as fluorescent tags for detection of lymph node prostate cancer, *in vivo* fluorescent probes, delivery of drugs and images, etc. Some of these nanomaterials also show potential applications in nanolasers and photovoltaics [142–146]. From several decades, in the biomedical field, researchers have been exploring light emitting nanocrystals (about 2–10 nm) commonly known as semiconductor Quantum dots (QDs) by virtue of their tunable optical properties as fluorescent probes particularly in cellular imaging. CdSe, ZnS, and CdS are most commonly used QDs because of their exceptional characteristics such as enhanced brightness, better photostability, tunable emission spectra, and simultaneous excitation of multiple fluorescence colors as compared with the conventional fluorescent proteins and organic dyes. Xing et al. [144] have discussed the optical properties of QDs along with their *in vitro* diagnostic applications as well as *in vivo* imaging applications, also the formation of self-illuminating QDs and its *in vivo* sensing, imaging applications. Wu et al. [146a] have reported the semiconductor quantum dots-based fluorescent labels could be very effective for cellular imaging by linking to immunoglobulin G (IgG) as well as streptavidin for labeling the breast cancer marker Her2 to detect nuclear antigens inside the nucleus and to stain actin

along with microtubule fibers in the cytoplasm. They have been noticed that the labeling signals shown by these QDs are more particular for the proposed objects and are considerably more photostable as compared with organic dyes. Khanna et al. [146b] have studies a series of quantum dots for cytotoxic effect various cells, e.g. human embryonic kidney cells (HEK-293), breast cancer cells (MCF-7), and Enrichlish ascitices cells. 65% biotoxicity was observed in MCF-7 for the CdS/CdSe core-shell QDs.

Semicarbazone are used as typical starting compounds for synthesis of 1,2,3-Selenadiazole which exhibit interesting reactivity by virtue of their thermal or photochemical decomposition thus liberating either reactive free selenium or convert into respective 1,4-diselenines [147]. Owing to these properties, 1,2,3-selenadiazole acts as vital precursor in material chemistry including nanotechnology as well as in ligand chemistry [148–152]. Reaction of 1,2,3-selenadiazoles with organotransition-metal complexes yielded respective diselenolenes. Morley et al. [149] have employed 1,2,3-selenadiazoles for the synthesis of cyclopentadienylcobalt and pentamethylcyclopentadienylcobalt diselenolenes by the formation of selenaketocarbene as intermediate through the elimination of dinitrogen from 1,2,3-selenadiazole. Such transition-metal dithiolenes or diselenolenes attracted enormous early attention because of their electrochemical and optical properties. It was reported that transition metal bis(dithiolenes) have been applied for the making of molecular superconductors, in mode locking and passive Q-switch applications. Considerable attention has been paid in the study of II-VI semiconductors such as CdSe, because by changing the particle size, its band gap can be adjusted across the visible region. In addition to this, CdSe shows different applications such as laser diodes, blue light emitting diodes, solar cells, and biological labeling [151]. Khanna et al. [152] have used selenadiazoles as selenium source for the synthesis of range of metal selenides including CdSe, ZnSe QDs as well as ZnSe/

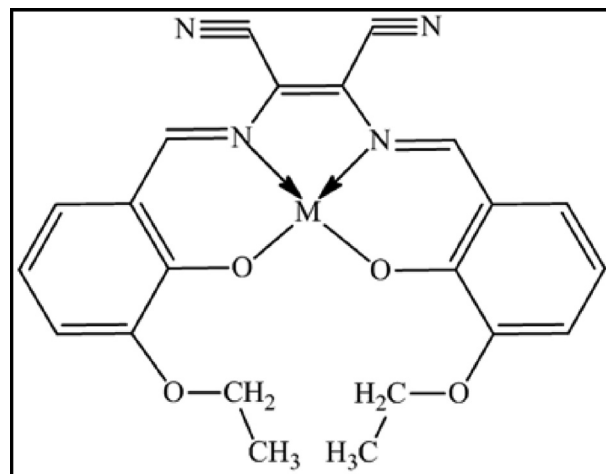
CdSe core shell quantum dots to promote plausibly less toxic and an eco-friendly synthetic method for development of QDs. Jadhav et al. [153,153a] have reported the solventless method for the preparation of heterocyclic organoselenium compounds, i.e. cycloalkano-1,2,3-selenadiazole by using their respective cycloalkane semicarbazones. The heterocyclic compounds containing nitrogen and selenium atom like 1,2,3-selenadiazoles have been used as vital precursors for the material chemistry including nanotechnology as they shows thermal and photochemical decomposition during the dimer formation or formation of acyclic or new heterocyclic compounds.

Overall, synthesis of CdSe quantum dots and magic-sized nanocrystals from such precursor have been reported by Jadhav et al. [153b,c] thermal and microwave method. It has been observed by the authors that these reactions can produce particles of 2–5 nm dimensions with useful optical properties (Fig. 3).

Owing to characteristic physical and chemical properties such as facile surface modification, stable optical property, and well defined structure; a particular gold nanoclusters and gold nanomaterials with specific size have attracted the attention of many researchers [154,154a–d]. Gold imine complexes may further boost this prospect and may offer a new precursor for synthesis of optically tuned gold nanoparticles [154e,f]. It is reported that gold nanoclusters with various functional groups show excellent photostability, compatibility, and greater solubility in water so they can be employed as biosensors and can also be good candidate as fluorescent nanoprobe for biomedical applications in bioimaging, tumor therapy, and high sensitivity detection [155,155a–c].

Azam et al. [156] have reported the hydrothermal reduction method for the synthesis of pure face-centered cubic Ni and Cu nanoparticles by using Cu (II) and Ni (II) complexes (120 and 121) (Scheme 27) of N2O2 donor tetradentate Schiff base ligand derived from 3-ethoxy-salicylaldehyde and 2,3-diamino but-2-ene dinitrile. They have tested *in vitro* cytotoxicity of the Schiff base ligand and its Cu (II) and Ni (II) complexes against human carcinoma cell lines (HeLa and MCF-7) as well as Cu NPs were studied for their antibacterial activity. It is reported that Cu (II) complexes better activity against HeLa and MCF-7 cell line than the Ni (II) complex. Also it is reported that Cu nanoparticles are better antibacterial agent against *E. coli*. The catalytic activity of the synthesized Ni nanoparticles is reported to be slightly higher toward hydrogenation of nitrobenzene to aniline compared with the commercial Raney Ni.

Owing to the promising application of Ni and Zn NPs as catalysts, capacitor and magnetic materials such metal complexes have become highly attractive to researchers specially magnetic transition metal-based materials as they are used as high density magnetic recording media [157–159]. For example some Ni NPs are



Scheme 27. Structure of metal complex with 2,3-bis-[(3-ethoxy-2-hydroxybenzylidene) amino]but-2-enedinitrile (where, M = Cu (120), Ni (121)).

considered as anode materials for rechargeable batteries, ethanol fuel cell, and a fine substitute for a noble metal used in the internal electrodes of multilayer ceramic capacitors [160]. Nickel, cobalt, cadmium, and copper complexes with carbohydrazide have been attracted more attention because of its variety of applications in defense. It is documented that they are used as primary explosives [161–163], burning rate modifiers [57], and also in gas generating agents, [164–166]. Such types of compounds are used in Pyrotechnics as they possibly act as flame colorants. Copper complexes with carbohydrazide are used in pyrotechnics as an alternative for barium compounds which are normally toxic in nature, to produce flame in blue and green colors. Bushuyev et al. [58] have reported the energetic compounds of type $[CuX_2(C_7H_{14}N_4O)_2 \cdot H_2O]$; where $X = ClO_4^-; NO_3^-$ (122–124) and were tested for drop hammer, electric spark tests, and burn test as they are energetic in nature. It is reported that 122 and 123 (Scheme 28) were highly combustible and can be employed in pyrotechnics as the complex 122 generate blue flame and 123 generated bright green flame on ignition.

Similarly, some other transition metal complexes Co, Ni, and Zn of carbohydrazide with perchlorate salt were investigated by Talawar et al. [162] where they reported that Co and Ni complexes were superior detonants as compared with lead azide and mercuric fulminate in terms of low vulnerability. They were used in detonators because of their ecofriendly and chemically compatible primary explosive nature. Sonawane et al. [57] have reported the copper, nickel, and cobalt carbohydrazide nitrate complexes and studied their burning rate for propellant composition. It is reported

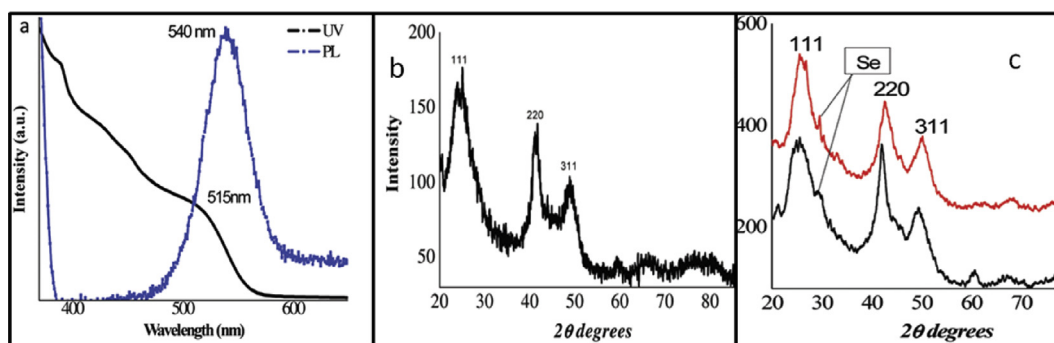


Fig. 3. (a) UV-Visible/Photoluminescence and (b) X-ray diffraction as reproduced from ref (A. A. Jadhav, P. V. More, P. K. Khanna, *New J. Chem.*, 2017, 41, 7438) and (c) reproduced from ref (A. A. Jadhav, P. K. Khanna, *New J. Chem.*, 2017, 41, 14713).

that there is great enhancement of burning rate by incorporation of nickel complex in the order of 27–72% in the pressure range of 1.9–8.8 MPa, whereas addition of Cobalt complex resulted in the enhancement of burning rate of the order of 9–19% in same pressure range. Some Schiff bases possess simple harmonic generation activity [167]. Zn (II) complexes with Schiff base as chelating ligand has been reported that they can be used as an effective emitting layer [168]. The Schiff base derived from tetradentate precursor 1-phenyl-butane-1,3-dione mono-S-methylisothio-semicarbazone with *o*-hydroxy-benzaldehyde or its 5-phenylazo derivatives and its metal complexes exhibited non-linear optical (NLO) properties.

A comparison between the phenylazo-substituted Schiff base ligand with its different metal complexes indicated that the NLO response strongly depends upon the electronic configuration of the metal center [169]. It has been reported that Zn (II) complexes with benzothiazoles [170] and Zn (II) and Cd (II) complexes with N₂S₂ donor Schiff base ligands can be used as precursors for tuning of the emission wavelength [171].

3.2. Miscellaneous applications

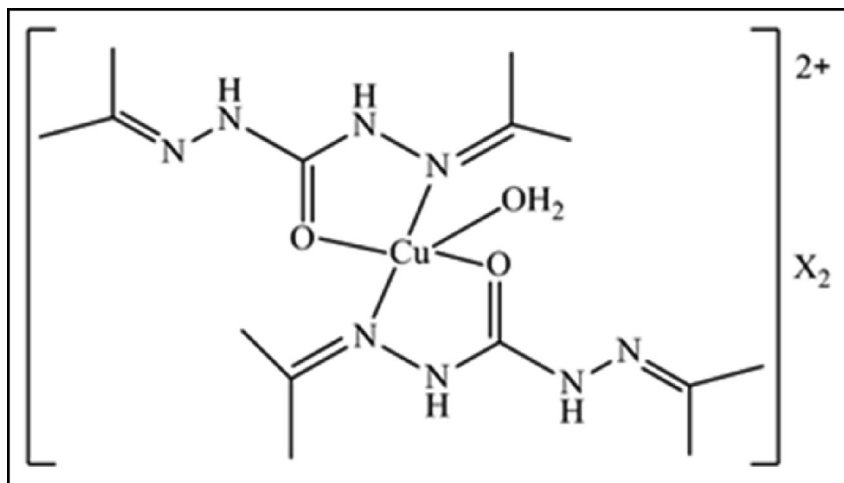
Schiff bases are potential candidates as catalysts for a variety of organic and inorganic transformations. A few examples are described here in brief, e.g. Li et al. [172] have reported asymmetric cyclopropanation of styrene by using Cu (II) complexes with Schiff base of chiral amino alcohol like (S)-2-amino-1,1-di(3,5-di-*t*-butylphenyl)propanol and substituted salicylaldehyde as catalyst. It is reported that these Cu (II) complexes of chiral amino alcohol are effective for the asymmetric cyclopropanation of styrene. It has been reported [173] that many of the Cu (I) complexes having mixed ligands including the with Schiff base [2-methoxy-(5-trifluoromethylphenyl)-pyridine-2-yl-methylene-amine] and PPh₃/dppe shows great catalytic activity for the amination of iodobenzene.

A series of Cu (I) complexes (**125–128**) attributing N-(2-pyridylmethylene)-1,5-dimethyl-2-pyrazole-3-(2H)-one and triphenylphosphine have been reported and tested for efficient catalytic activity (Scheme 29), and it is reported that these complexes act as effective catalyst in the Sonogashira cross-coupling reaction of phenylacetylene with aryl halides [174]. Many Cu (II) Schiff base complexes have also been used as catalyst for oxidation with specific focus on the DNA-binding and DNA-cleaving properties and mimic of galactose oxidase [175,176].

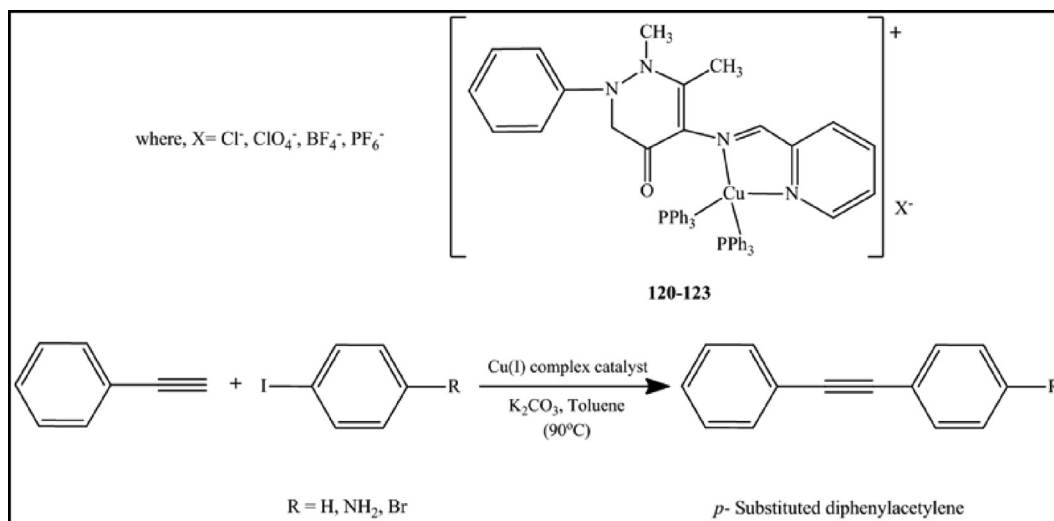
Similarly other metal complexes also are reported for various catalytic activities. Aromatic Schiff base and their Co (II), Fe (III), and Ru (II) complexes are employed in oxidation of cyclohexane in presence of hydrogen peroxide into cyclohexanol and cyclohexanone [177,178]. These metal Schiff base complexes are also used to catalyze reaction on hydrolysis [179], carbonylation [180], decomposition, and electroreduction. It is observed that Co (II) Schiff base complexes show high catalytic activity in alkane oxidation reaction as compared with Fe (III) complexes [181]. Fe (III) Schiff base complex shows catalytic activity toward electroreduction of oxygen [182]. Some Cr (III) salen complexes are renowned catalyst for homogeneous as well as heterogeneous reaction [183]. A number of Schiff base complexes exhibit important applications in reduction of alkylation of allylic substrates and ketones to alcohols [184]. The complexes of Fe, Co, Ni, and Zn with Schiff bases play the significant role in the oligomerization of ethylene [185]. The metal salen complexes were used as catalyst efficiently in Michael addition reaction [186].

Some metal complexes exhibit catalytic activity on oxidation of ascorbic acid and decomposition of hydrogen peroxide [187]. The heteroannulation reaction by using the Schiff base metal complexes as catalyst has been an area of current research [188]. Usually the ring opening of large cycloalkane is a very difficult process, but in this reaction, Co (II) and Cr (III) Schiff base complexes were effective with considerable enantioselectivity [189,190]. Schiff bases act as an electrical conductor and having various applications as they are used as catalysts in photoelectrochemical processes, microelectronic equipment and electrode materials, organic batteries, or electrochromic display device [48].

N,N-bis(3-methylsalicylidene)-*ortho*-phenylenediamine (MSOPD) acts as a chromogenic reagent for the spectrophotometric determination of Nickel in some food and other natural samples [191]. Schiff base derived from salicylaldehyde and diamine, and its cobalt complexes have been shown to be light resistance as well as have storage ability and such complexes do not degrade even in acidic gases (CO₂) [192]. Metal complexes containing azo groups are used for dyeing cellulose polyester textiles [193], e.g. chromium azomethine complexes and un-symmetrical chromium complexes act as dyes, and they give fast color to wools, leathers, food packages, etc [194,195]. There are reports that some thio and phenylthiosemicarbazones can be used as analytical reagents for the detection of variety of metal ions in different environmental samples, such as water, soil, human blood, leafy vegetables, medicinal leaves, etc., as well as in pharmaceutical samples. Narayan et al.



Scheme 28. Structure of [CuX₂(C₇H₁₄N₄O)₂·H₂O] where, X = ClO₄⁻ (**122**), NO₃⁻ (**123**).

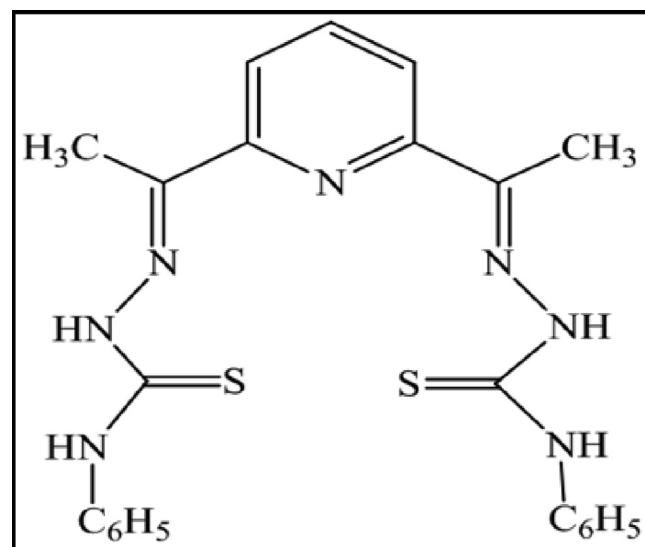


Scheme 29. Sonogashira coupling reaction of phenylacetylene with aryl halides catalyzed by Cu(I) complexes (125–128).

[196] have used benzyloxybenzaldehydethio-semicarbazone (BBTSC) as a complexing agent for the selective and sensitive determination of Cu (II) in food and water samples. It was reported that BBTSC is the best reagent for the extractive spectrophotometric determination of Cu (II) as compared with other spectrophotometric techniques reported earlier. Similarly, Rao et al. [197] have reported 2-acetylthiophene thiosemicarbazone (ATT) which act as a ligand for the spectrophotometric determination of Cu (II) from edible oils and alloys. Extractive spectrophotometric method has been reported based on benzyldithiosemicarbazone (BDT) for determination of micro amounts of Ni (II) in nichrome wire and chromium steel owing to formation of yellowish-orange complex with Ni (II) salt at pH 9 [198]. Similarly, Reddy et al. [199] have studied 2,6-diacetylpyridine bis-4-phenyl-3-thiosemicarbazone (2,6-DAPBPTSC) (129) (Scheme 30) for the extractive spectrophotometric determination of Co (II) in vegetable, water, soil and standard alloy samples. 2,6-DAPBPTSC forms reddish brown complex with Co (II) which is easily extracted into isoamylalcohol.

Imine derivatives can be exerted to obtain conductive polymers. Tridentate Schiff base and their organo-cobalt complexes act as initiator of emulsion polymerization and co-polymerization of diene and vinyl monomers [200]. The amine terminated liquid natural rubber (ATNR) is synthesized when photochemical degradation of natural rubber is carried out in solution in presence of ethylenediamine. The poly Schiff base derived by the reaction of ATNR with glyoxal, improves aging resistance as they act as metal deactivator [201]. Transition metal complexes with 1, 10-phenanthroline and 2, 2-bipyridine are used in petroleum refining [202]. The chemistry of primary amines, thiols induced the separation of mammalian sperm head, and the similar action by pyridoxal shows that head and tail of sperm are connected by Schiff base which is formed between proteins inside the nuclear membrane [203]. Popova and Berova [204] have reported that copper is good for liver function as well as its level in blood and urine has influence in pregnancy disorders, nephritis hepatitis, leprosy, anemia, and leukemia in children. The effect of Cu (II) and Zn (II) complex with Schiff base, N-salicylaldehyde amino glucose inhibit synthesis of O₂ noticeably [205].

Macrocyclic Schiff bases of dithiocarbazic acid have several essential biological functions such as transport of oxygen in mammalian and other respiratory systems and photosynthesis [206]. Cu (II) and Fe (II) forms chelates with amido Schiff bases



Scheme 30. Structure of 2,6-diacetylpyridine bis-4-phenyl-3-thiosemicarbazone (129).

which acts as a thrombin inhibitor [207]. Transition metal (Mn (II), Ni (II), Cu (II), and Zn (II)) complexes with tetradentate Schiff base ligands exhibit miscellaneous effect on membrane in amylase productions. Mn (II) and Zn (II) complexes stimulated amylase transportation through membrane, while Ni (II) and Cu (II) complexes inhibited it.

4. Summary

Schiff bases have been reported for a long time and their applications have been mainly limited to chemistry of pharmaceutical importance (biological importance) and catalysis. In recent years, the scope of such compounds has broadened, and their new synthetic methodology has been evolved that are based on normal chemical reactions as well as by solid state reaction. There are also some reports on use of other source of energy during their synthesis. Recent literature also highlights the modern day application that has extended to materials chemistry as well as into nanotechnology. Schiff bases and semicarbazones offer a variety in their

coordination of vast majority of transition metals and therefore offer great potential as precursors for new generation nano-materials of respective metal or their compound semiconductors. Imine ligands such as Schiff base, semicarbazones, and their derivatives have therefore been widely explored for catalytic, pharmacological, industrial, etc. applications. Schiff base ligands are considered as interesting ligand because of the ease of preparation with versatility and variable denticity. Nowadays, Schiff base and their metal complexes are fascinating research topic that continuously provides us with new information about newly synthesized compounds. In this review, the biological, catalytic activity along with some miscellaneous applications of imine ligands and its metal complexes have been summarized taking the scope into materials chemistry directly or indirectly.

Acknowledgment

The authors thank Vice Chancellor, DIAT (DU), Pune, for the support. Authors are thankful to the CSIR for the research grant through project No. 09/992 (004)/2018-EMR-I. PKK is thankful to RSC, UK for provision as per their copyright instruction for reproducing the Fig. 3a–c. PKK thanks SPARC MHRD, Govt of India for support (grant no. SPARC/2018–2019/P573/SL).

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