Biological Applications of Schiff base Metal Complexes-A Review

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ABSTRACT: *Schiff bases synthesized from the condensation of an amino compound with carbonyl compounds and their complexes exhibit a wide range of biological activities including antifungal, antibacterial, antiviral, antitumor and anticancer properties. Over the recent few years, these complexes have gained much attention because of their unique biological properties. Many reports are published on their applications in biological activities of these compounds. Development of a new chemotherapeutic Schiff bases and their metal complexes is now attracting the attention of medicinal chemists. This review is nothing but a small attempt to show different examples of the most promising applied Schiff bases complexes in biological areas.*

Key Words: *Schiff base, Antifungal and antibacterial properties, Antiviral Activities, Anti-cancer agents.*

1. Introduction

Hugo Schiff reported the condensation of primary amines with carbonyls compounds in 1864 and the product was known as Schiff Bases [1]. Schiff Bases of aliphatic aldehyde are readily polymerized and therefore unstable in nature but their aromatic varieties are more stable due to conjugation system. Schiff base complexes have been the subject of studies since their discovery in the field of condensed matter physics, material chemistry as well as inorganic chemistry for their interesting magnetic properties [2]. When metal centers are present in an unsaturated coordination environment, some additional linkers can bridge the metal centers to form polynuclear complexes. Mainly to the inorganic chemists, the Schiff base compounds cantaining imine group(-RC=N-) [1] appear to be a point of interest as these are widely used in designing molecular ferromagnets, in catalysis, in biological modelling applications, as liquid crystals, as heterogeneous catalysts [3] and also in self assembling cluster complexes [4].

Schiff Bases derived from the condensation of a carbonyl compound and amino acids provides an amazing class of ligands that coordinate to metal ion by azomethine nitrogen. Presence of C=N linkage in ligand system is indispensable for biological activities. The lone pair residing on sp^2 hybridized nitrogen atom of the azomethine linkage carries an important role to show biological activities.

These classes of complexes have also received a great attention because of their active part in metalloenzymes and as biomimetic model compounds. They are very often found inside the natural proteins and enzymes. It has been seen that N atom has a significant role in the coordination of metals as the active site of numerous metallobiomolecules.

The transition metal complexes of ligands containing some hetero atoms, like oxygen, nitrogen and sulfur donors show the carcinostatic, antitumour, antiviral, antifungal and antibacterial activities [5]. The considerable interest in the chemistry of these complexes arises from these facts.

Therefore, the research field involving these types of metal complexes is very extensive and includes a number of interdisciplinary areas such as bioinorganic chemistry, catalysis, photochemistry and magneto chemistry. Again, with the developments in inorganic chemistry research people are having new ideas regarding versatile uses of metal complexes as therapeutic agents and as drugs for the treatment of several human diseases. Due to their potential applications in pharmaceuticals, antibacterial, antifungal, anticancer and anti-inflammatory actions synthesis of Schiff base metal complexes, particularly those of transition metal ions, with different molecular topologies and sets of donor atoms is becoming an emerging area of research.

Finally, the heterocyclic Schiff base ligands and their metal complexes have been the subject of extensive investigation because of their wide use in biological field [6].

The present paper reviews the uses of Schiff bases metal complexes in their antifungal, antibacterial, antiviral, antitumor and anticancer activities.

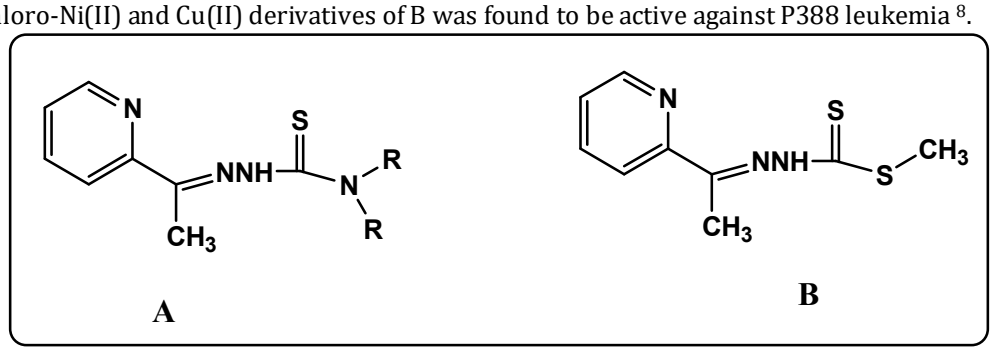
2. Biological importance of Schiff base complexes

The advances in the field of bio-inorganic chemistry increases the interest in Schiff base complexes, keeping the idea in mind that many of these complexes may serve as models for biologically important species. Thus, we report them in the following:

2.1. Antifungal and antibacterial properties:

Some complexes involving copper(II) have been thoroughly studied for their antifungal and antibacterial properties. Their antifungal properties have been evaluated against the three phytopathogenic fungi, *A. solani, F. equisetti and M. phaseolina.* Again their antibacterial properties have also been tested, against the two pathogenic bacteria, *E. coli* and *S. aureus.* M.E. Hossain et al. reported a detail test results on the basis of their study. From their study it has been verified that these copper(II) complexes are generally less fungitoxic towards *A. solani, F. equisetti and M. phaseolina than* either the free ligands or the commercially available antifungal agent nystatin. Again copper (II) complexes of benzoylpyridine Schiff base ligands are found to be sufficient active towards the organism *F. equisetti*. Investigation shows that the given complexes are active against the organism *S. aureus,* but the presence of *E. coli* remains undisturbed [7].

A series of 2-acetylpyridine thiosemicarbazone (A) derivatives were found to have significant antimalarial activities. The presence of a 2-pyridylalkylidene moiety and a thiocarbonyl or selenocarbonyl group (in contrast to a carbonyl group) plays an essential role to show antimalarial activity. Again the presence of certain bulky groups at position N of the thiosemicarbazone moiety increases antimalarial activity. Intensive study revealed that these thiosemicarbazide ligands become more active when they are associated with a metal ion. Saryan et al. reported that iron complexes of some α- N-heterocyclic thiosemicarbazones acts as more active inhibitors of ribonucleotide reductase or in the intensification of antitumor activities than the free ligands. In this context it is worth mentioning that Das and Livingstone reported the antitumor properties a number of transition-metal complexes of methyl 3- [1- (2-pyridyl)ethylidene] carbodithioate (B).The chloro-Ni(II) and Cu(II) derivatives of B was found to be active against P388 leukemia [8].



It is well known that some drugs have higher activity when administered as metal complexes than as free ligands. Ramesh and Sivagamasundari reported a group of hexa-coordinated ruthenium(II) complexes which showed a reasonable amount of antifungal activity [5].

These Schiff base ligands and their ruthenium chelates were studied in vitro in order to explain their antifungal activities against *Aspergillus flavus* at four different concentrations. The results reiterated the same fact that the ruthenium chelates are more toxic compared to their parent ligands against the same microorganisms under identical experimental conditions. With the increase in concentration the toxicity of ruthenium chelates increases. A probable explanation of this greater toxicity of the metal chelates over their corresponding free ligands may be considered in light of Tweedy's chelation theory [9]. As a result of chelation, the polarity of the metal ion decreases since the positive charge of the metal ion is shared by the ligands and the π-electron gets delocalised over the whole chelate ring. And this will increase lipophilic character of the central metal atom, which then allows its greater permiability through the lipid layers of cell membrane. Thus the lipophilicity is an important factor that controls the antimicrobial activity. In addition to that, the presence of the azomethine (> C=N) group can form a hydrogen bond with the active centers of cell constituents, which interferes the normal cell processes [10].

Mohamed et al. reported [11] that Schiff base metal complexes derived from 2-thiophene carboxaldehyde and 2-aminobenzoic acid and Fe(III) or Co(II) or Ni(II) or UO_2(II) showed an excellent antibacterial activity against *Escherichia coli, Pseudomonas aeruginosa and Staphylococcus pyogenes*. Fe(III), Cu(II), Zn(II) and UO_2(II) complexes can inhibit the growth of *E. coli*. Thus, these complexes could be applied fairly to prevent some common diseases caused by *E. coli*. Again the growth of Gram-positive bacterial strains (*Staphylococcus pyogenes* and *P. aeruginosa*) could be inhibited by using Fe(III), Co(II), Cu(II), Zn(II) and UO_2(II) Schiff base complexes.

In the year 2007, Gaballa et al. reported that Platinum(II) Schiff bases complexes containing of salicylaldehyde and 2-furaldehyde with *o*- and *p*-phenylenediamine have antibacterial properties against *E. coli*, *Bacillus subtilis*, *P. aeruginosa*, *Staphylococcus aureus*. Here also the same observation arises that the Platinum(II) complexes are more active antimicrobials than the precursor Schiff base ligands against one or more microorganisms [12].

In this context, it has been reported that some novel Schiff base metal complexes of sulphametrole and varelaldehyde have excellent antimicrobial behaviour against bacterial E. coli(Gram-negative bacteria) and S. aureus(Gram-positive bacteria). The reason of their greater toxicity may be due to the sulphonic OH, OCH_3, S and CH_3CH_2CH groups, which might interact with the double membrane. 2-Aminomethylthiophenyl-4-bromosalicylaldehyde Schiff base and its metal complexes have been reported for their antimicrobial activities [11].

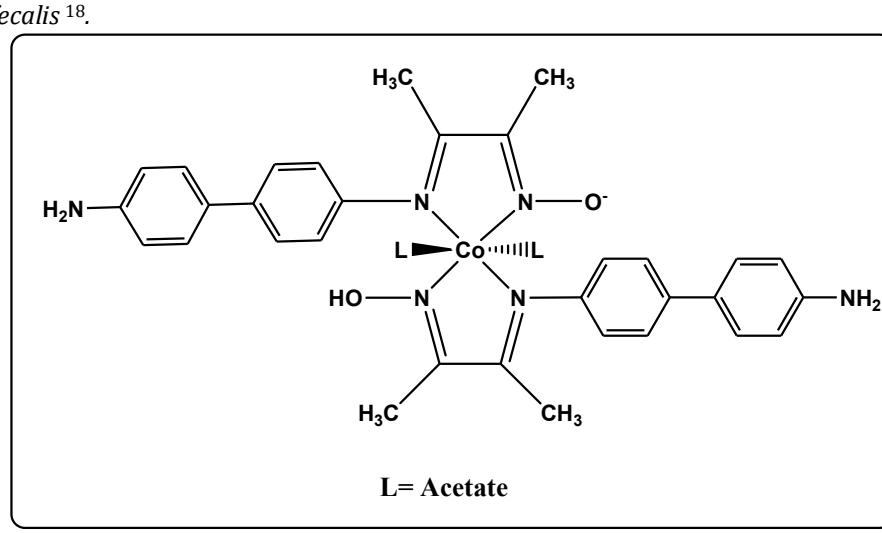
In conclusion, it can be said that antibacterial activity of the compounds is related to cell wall structure of the bacteria. Some antibiotics inhibit a step in the synthesis of peptidoglycan, a polymer consisting of sugar and amino acids that forms the cell wall outside the plasma membrane of bacteria [13].

Nair et al., examined the antibacterial activity of some Schiff base complexes of Co(II), Ni(II), Cu(II) and Zn(II) incorporating indole-3-carboxaldehyde and m-aminobenzoic acid by disc diffusion method [14]. He explained that the activity of the metal complexes depends on the effect of metal ions on the normal cell membrane. Metal ions when chelated by some chelating ligands bear polar and nonpolar properties together. And this dual nature increases the permiability of metal ions to the cells and tissues of different bacteria. Nair et al reported that Cu(II) and Co(II) is more active than Ni(II) and Zn(II) in their antibacterial activities.

Shaker et al. synthesized a series of Fe(II) Schiff base complex of a ligand derived from the condensation of amino acid and sodium 2- hydroxybenzaldehyde-5-sulfonate. The complexes were characterized by elemental, electronic, IR spectral analyses and conductance measurements. Their antibacterial activities were tested against *Bacillus cereus, P. aeruginosa* and Micrococcus bacteria [15-17].

Literature survey reveals that cobalt complexes demand a great attention due to their amazing antibacterial properties. In this regard, Co(II) complexes, owing to their aqueous stability, availability, and simplicity of synthesis, are more studied than Co(III) complexes. Co(III) ion can be stabilized in presence of some polydentate ligands with N, O and S donor atoms and in aqueous phase. In presence of NH_3 as a ligand Co(III) shows kinetic inertness in water.

Co(III) complex of a new hybrid amine-imine-oxime ligand derived from the condensation reaction of diacetylmonoxime with benzidine was reported to have antibacterial activity against *Bacillius subtilis*. But it has no activity against *Staphylococcus aureus* or the Gram-negative bacteria *Escherichia coli* and *Enterobacter fecalis* [18].



N. K. Chaudhary and P. Mishra reported an important observation [19]. They synthesized Schiff base ligands by the condensation of amoxicillin trihydrate and nicotinaldehyde and used Co^{+2}, Ni^{+2}, Cu^{+2}, and Zn^{+2} as central metal ions. The metal complexes were tasted in vitro for antibacterial assay. It was found that the new complexes were more powerful than amoxicillin and control drug amikacin. The complexes were shown to have high activity against all the bacterial pathogens at their higher concentration. The reason behind their

greater activity is chelation. Schiff base with metal ions that provide stability and more succeptibility against the bacterial pathogens. The structural components containing additional C=N bond with N, O donor atom coordinate the metal ion and as a result polarity of the complex decreases. This allows their efficient permeation through the lipid layer of bacterial organism and destroys their activity.

2.2. Antiviral Activities

Isatin has been known since long for its biological activity in mammals. Schiff bases and Mannich bases of isatin show a wide range of pharmacological properties including antibacterial, anticonvulsant, anti-HIV, antifungal and antiviral activity [20]. In 2007, A. Jarrahpour et.al. reported a group of Schiff bases of isatin and 5-flouroisatin about their antiviral activities [21].

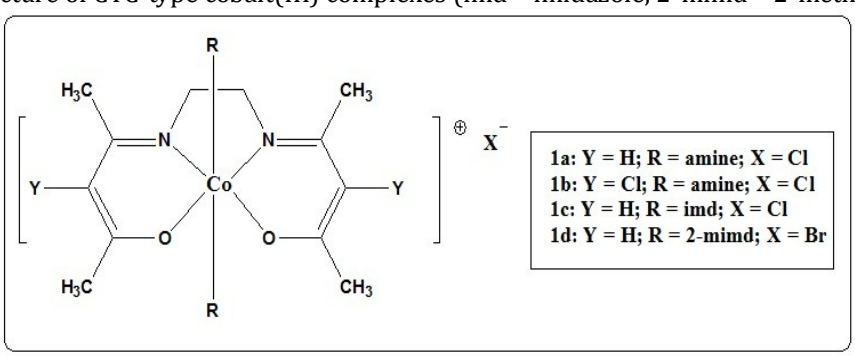
Generally, cobalt(III) ion is not stable in aqueous solution. It can be stabilized in aqueous solution in presence of chelating N,O donor ligand atmosphere. This cobalt(III) complexes of such ligands found to be important due to their antibacterial or antiviral activities. In 1998, Epstein and coworkers reported a series of Co(III) complexes (**1d**) containing N, O donor ligands of the following type for their use in the treatment of blindness in industrial nations, known as epithelial herpetic keratitis [22].

Initially, the drug was applied upon a rabbit eye model infected with Herpes Simplex Virus Type 1 (HSV-1) and found to be active inhibitor of HSV-1 replication in vitro. There are some evidences that these series of complexes prevent virus entry by inhibiting membrane fusion. The complex **1d** inhibited plaque formation by vesicular stomatitis virus VSV and VZV (varicella-zoster virus) [23].

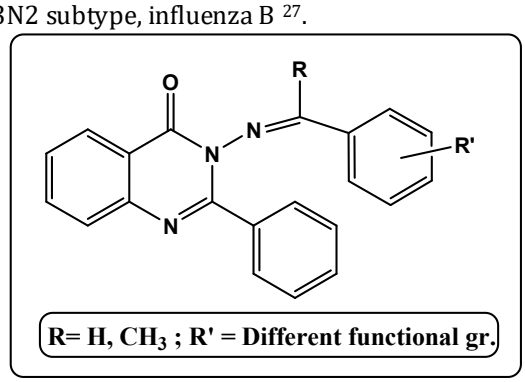
The activity of CTC-96 (1d) against adenovirus in cell culture model and adenovirus kerato conjunctivitis in a rabbit model was reported [24] by Epstein in 2006. Böttcher et al. synthesized a drug and it is commercially known as Doxovir™ by the Redox Pharmaceutical Corporation [25].

These Co(III) Schiff base complexes have a capacity to inhibit Sp1, a DNA binding zinc finger protein and used in the treatment of human immunodeficiency virus type 1 (HIV-1) [26].

Figure 1. Structure of CTC-type cobalt(III) complexes (imd = imidazole, 2-mimd = 2-methylimidazole).



K.S. Kumar et al. synthesized a group of Schiff Base compound based on 3-(benzylideneamino)-2-phenylquinazoline-4(3H)-one and presented a detail report of anti viral activity of these compounds 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 [27].



2.3. Anti-cancer activities

Cancer is a group of diseases that involves abnormal cell growth with the potential to attack or spread to other parts of the body. It appears as a serious public health problem throughout the world as the most

feared diagnosis. Currently, Chemotherapy is the main approach for both localized and metastasized cancer. But all these curative effects of the existing chemotherapeutic drugs have serious side effects. In this regard, many researches continue to develop more effective drugs for treating patients with cancer over the last five decades.

In the last few years, the organic compounds containing Schiff bases as main part of their structures have achieved much attention because of their anticancer properties. Especially metal complexes of Schiff base ligands draw attentions of chemists as these are used as potent drugs or diagnostic agents. Metal complexes can offer unique mechanisms of drug action because of wide range of co-ordination numbers, geometries and kinetic properties, which are not possible with pure organic molecules. Rosenberg and co-workers [28] invented Cisplatin which is one of the best-selling anti-cancer drugs throughout the world. After that many reports were published, till date, where the metal complexes of Schiff bases have been used as anti-cancer agents.

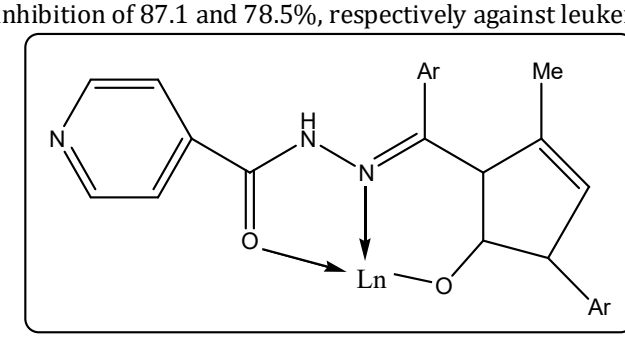
Mokhles M. Abd-Elzaher et.al. reported some metal complexes of the Schiff base of salicyaldehyde with 2-amino-4- phenyl-5-methyl thiazole. The complexes were studied against different human tumor cell lines: breast cancer MCF-7, liver cancer HepG2, lung carcinoma A549 and colorectal cancer HCT116 in comparison with the activity of doxorubicin as a reference drug. The study showed that ZnII complex showed potent inhibition against human TRK in the four cell lines (HepG2, MCF7, A549, HCT116) by the ratio 80, 70, 61 and 64% respectively as compared to the inhibition in the untreated cells [29].

Another report was published by K. Subin Kuamr in the year 2017 where a series of metal complexes of Schiff base derived from Vanillin and acetoacetanilide with ethylenediamine were tested its cytotoxic activities and found that the copper complex to be higher Inhibitory Concentration (IC50) value around 49 µ/ml. Daltons Lymphoma Ascites cell induced solid tumour model and Ehrliche`s Ascites Carcinoma cell induced ascites tumour model were mainly used for antitumor studies [30].

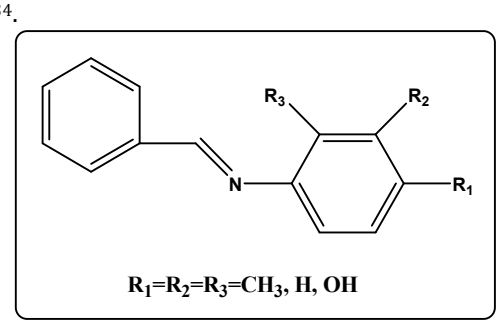
Five ternary complexes of the rare earth ions with o-phenanthroline and Schiff base salicylaldehyde L-phenylalanine were used to test the anticancer effect of the complexes with K562 tumour cell. The complexes could inhibit K562 tumour cell's growth, generation, and induce apoptosis. This inhibition can be accelerated by increasing the dosage [31].

Zhang et al. reported that three metal complexes (Cu^{2+}, Zn^{2+}, Cd^{2+}) of a ligand derived from 2-acetylpyridine and L-tryptophan have anticancer activities on MDA-MB-231 breast cancer cells [32].

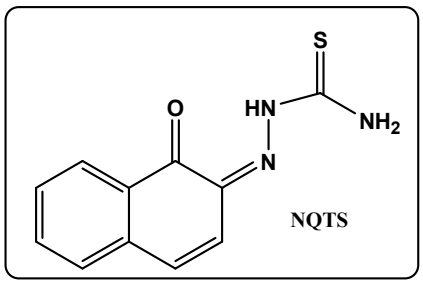
A series of compound was reported by Yang *et al.* with general formula $Ln(HL)_3 \cdot 3.5H_2O$ (where Ln (III) = La, Eu, Gd, Tb, Dy, Ho and Er) [33]. Among them, the complexes of La and Eu are most potential in anti-tumor activity with percentage inhibition of 87.1 and 78.5%, respectively against leukemia cells (L1210).



Garcıa-Friaza *et al.* reported some Pd(II) and Pt(II) complexes with the following Schiff bases and studied anti-tumor activities, changing the substituents on the pyridyl and toluene rings. All the complexes possess potential anti-cancer activities [34].

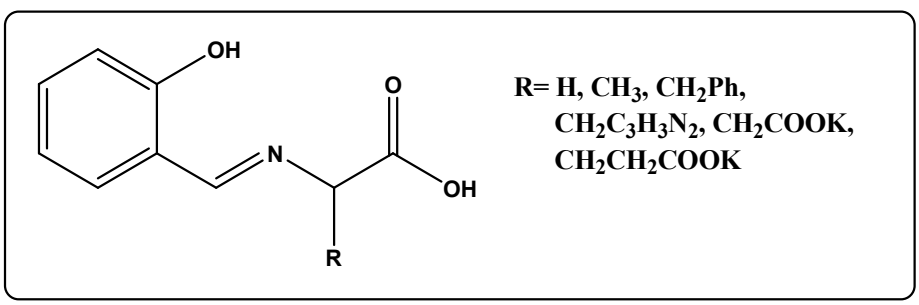


Afrasiabi *et al.* reported some Cu (II), Ni (II), Pd (II) and Pt (II) complexes of *ortho*-naphthaquinone thiosemicarbazone (NQTS) and evaluated their *in vitro* anti-cancer activities against MCF7 human breast cancer cell lines [39]. Among the complexes, the complexes of Ni (II) were tested to be most potent IC50 value of 2.25 μM [35].

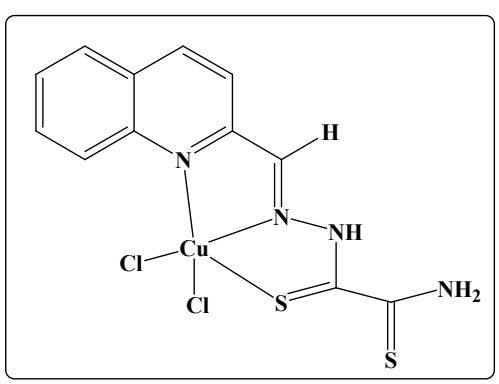


NQTS

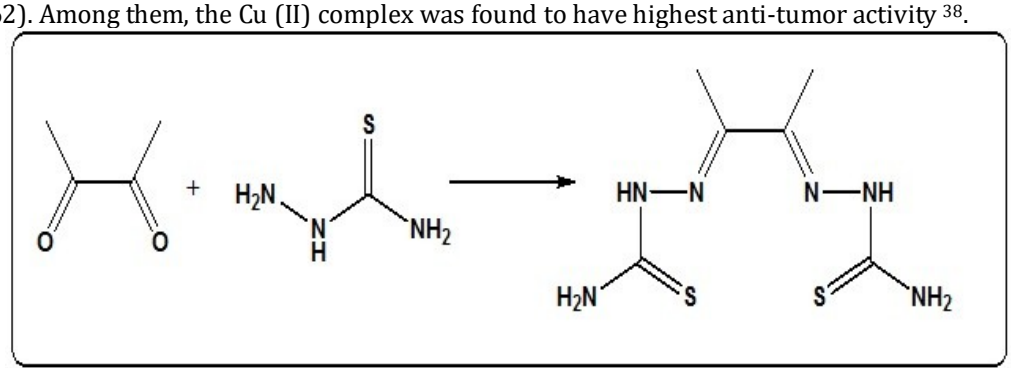
A series of Cu^{2+}-salicylidene-amino acid Schiff bases-Phen(Bipy) ternary complexes of the following Schiff base ligand were reported by Wang *et al.* All the compounds showed fair anticancer activities [36].



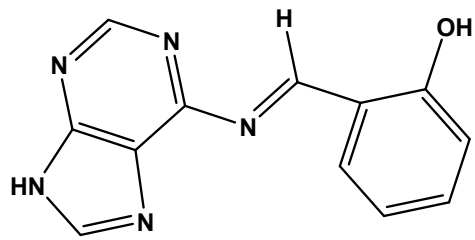
The following Cu(II)-complex, synthesized by Adsule *et al.,* is important for its anti-proliferative activity against PC-3 and LNCaP prostate cancer cell lines [37].



Zhong *et al.* reported some mononuclear complexes of Cu (II), Mn (II), Co (II), Ni (II) with *bis*- Schiff base ligand derived from 2,3-butanedione and thiosemicarbazide about their synthesis and anti-cancer activities. The cytotoxicity assay was done against five different kinds of cells lines (HL-60, Spca-1, Tb, MGC, K562). Among them, the Cu (II) complex was found to have highest anti-tumor activity [38].

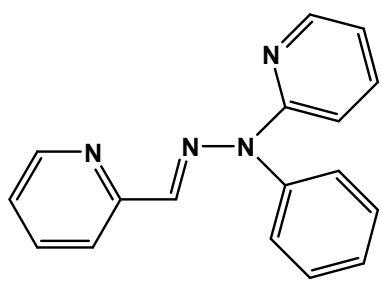


Rehman *et al. reported some heterocyclic* diorganotin (IV) complexes of the ligand 2-[(9H-Purin-6-ylimino)-methyl]-phenol. The complexes were studied to have promising anti-tumor activity [39].



2-[(9*H*-Purin-6-ylimino)-methyl]-phenol

Chakraborty *et al.* synthesized some Schiff base copper complexes of a tridentate ligand containing two pyridine and one imine nitrogen donor atom and the complexes possess anticancer activities. The IC50 values of this complex was found to be 4.29 ± 0.42, 6.34 ± 0.58 and 5.32 ± 0.38 μM against MCF7, PC3 and HEK 293 cell lines, respectively [40].



N-Phenyl-*N*-pyridin-2-yl-*N*'-pyridin-2-ylmethylene-hydrazine

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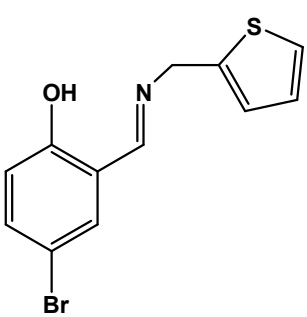
EI-Sherif *et al.* reported the cytotoxic activities of some metal complexes of the following Schiff base ligand. Cytotoxic studies were done against colon carcinoma (HCT116) and larynx carcinoma (HEP2) cells. Complexes of Cu and Zn showed potential activities against larynx cancer cells with IC50 values of 0.47 and 0.60 μg/mL, respectively [41-43].



4-Bromo-2-[(thiophen-2-ylmethylimino)-methyl]-phenol

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 and potential applications in designing new therapeutic agents. But still it needs to explore the biological

applications of these transition metal complexes, already synthesized and to synthesize new complexes with more properties accordingly.

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