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Review Article

METAL COMPLEXES: CURRENT TRENDS AND FUTURE POTENTIAL

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ABSTRACT

Metal ion plays important role in biology which has lead to the development of huge number of metal complexes with diverse therapeutic activity. The advances in the field of chemistry provide better opportunities to use metal complexes as therapeutic agents. Cisplatin, carboplatin and oxaliplatin are the well known metal-based drugs widely used in treatment of cancer. Besides these complexes other metal complexes have shown promising results in the treatment of diseases like diabetes, ulcer, rheumatoid arthritis, inflammatory and cardiovascular diseases etc. This review includes the application of some potential metal complexes in the treatment of various diseases/disorders to improve the therapeutic efficacy of the pharmaceuticals.

Key words: Metal complexes; Metallopharmaceuticals; Antibacterial activity.

INTRODUCTION

Medicinal applications of metals have played an important role in medicine since thousands of years. Many essential metal ions in our diets in varying quantities are essential, although its significance has been recently realized, which could probably be attributed our increased awareness of personnel and families' health.

Metal complexes or coordination complexes, is an atom or ion (usually metallic), bonded to a surrounding array of molecules or anions, which are in turn known as ligands or complexing agents. Virtually all compounds containing metals consist of coordination complexes.

Coordination first to the "coordinate covalent bonds" (dipolar bonds) between the ligands and central atom. Originally complex implied a reversible association of molecule, atoms or ions through such weak chemical bonds. As applied to coordination chemistry this meaning has evolved some metal complex are formed virtually irreversibly and many are bound together by bonds that are quiet strong.[1,2]

Metal complexes with labile ligands have long been known to undergo ligand-substitution reactions with biomolecular targets. Metal ions can bind to nitrogen, sulfur or selenium atoms of the histidine, cysteine, or selenocysteine residues in proteins leading to therapeutics effects.[3]

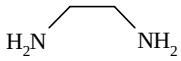
Metal complexes are so pervasive that the structure and reaction are described in many ways, some time confusingly. The atom within a ligand that is bonded to the central atom or ion is called the donor atom. A typical complex is bound to several donor atoms, which can be different or same.

Ligand based classification of metal complexes

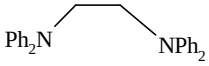
The majority of ligands are anions or neutral molecules that function as electron-pair donors (Lewis base)

Monodentate: Ligands that bind with a single donor atom to the metal are called monodentate ("one-toothed" ligands): -F, -Cl, -Br, -CN, NH_3, H_2O

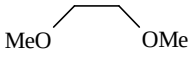
Bidentate or polydentate: Ligands with two or more heteroatoms are called bidentate or polydentate.



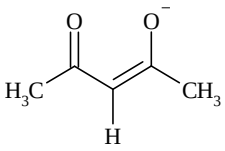
Ethylenediamine



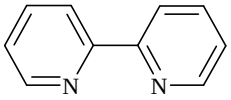
Bis(diphenylamino)ethane



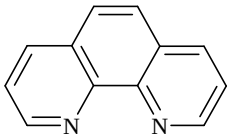
Glyme



Acetylacetone



2,2'-Bipyridine



1, 10-Pheanthroline

Metal complex provides better opportunities to use as therapeutic agents. The mode of action of metal complex on living organism is differing from non metals. It shows great diversity in action. The lipophilicity of the drug is increased through the formation of chelates and drug action is increased due to effective permeability of the drug into the site of action.

Metal complex in the body

Metal ions bound with ligands in some process, and to oxidize and reduce in biological systems. The important metal present in the body is iron which plays a central role in all living cells. Generally iron complexes are used in the transport of oxygen in the blood and tissues. The heme group is metal complex, with iron as central metal atom, which bind or release molecular oxygen.[4]

Metal complex in cancer treatment

Metal complexes have a higher position in medicinal chemistry. The therapeutic use of metal complexes in cancer and leukemia are reported from the sixteenth century. In 1960 an inorganic complex cisplatin was discovered, today more than 50 years, it is still one of the world's best selling anticancer drug. Metal complexes formed with other metals like copper, gold, gallium, germanium, tin, ruthenium, iridium was shown significant antitumor activity in animals.Formation of DNA adducts with cancer cell and results in the inhibition of DNA replication. In the treatment of ovarian cancer ruthenium compounds containing arylazopyridine ligands show cytotoxic activity. Now a day's metal complex in the form of nanoshells are used in the treatment of various types of cancer.[5]

Metal complex in neurological disorders

Metal complexes are also play a vital role in the treatment of various neurological disorders. Lithium on complex with drug molecules may cure many nerve disorders like Huntington's chorea, Parkinsonism, organic brain disorder, epilepsy and in paralysis etc. Other transition metals such as copper and zinc are involved as a transmitter in the neuronal signaling pathways.[6]

Metal complex in diabeties

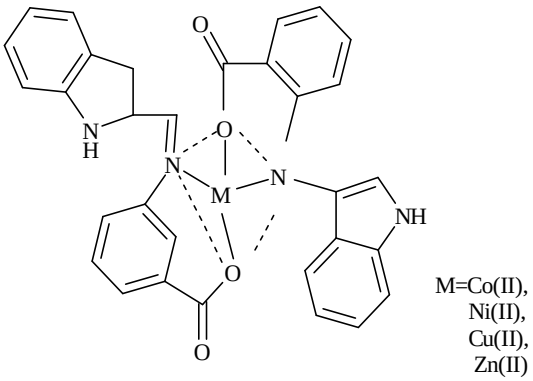
In diabetes intake of chromium metal complex shown considerable reduction in the glucose level. Insulinomimetic zinc complex with different coordination structures and with a blood glucose lowering effect to treat type 2 diabeties.[7]

Metal complexes in therapy

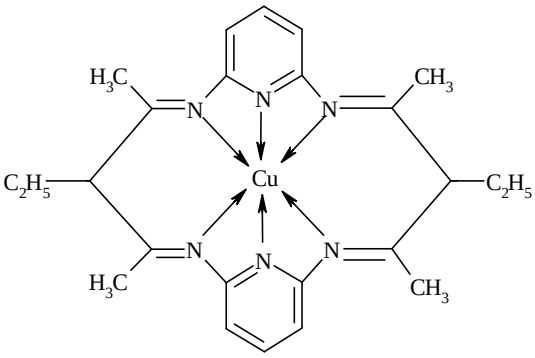
1. Metal complex with Schiff bases[8]

Metal complex	Activity
Schiff base-arsenic complex	Antifungal
Schiff base-antimony complex	Antifungal
Schiff base-bismuth complex	Antifungal
Schiff base-silver complex	Antiviral
Schiff base-cobalt complex	Dyes for giving color to leathers, food package and wool.

Nair MS were reported the Co(II), Ni(II), Cu(II) and Zn(II) complexes **(1)** of the Schiff base derived from indole-3-carboxaldehyde and m-aminobenzoic acid were synthesized and characterized by elemental analysis, molar conductance, IR, UV–Vis, magnetic moment. The antimicrobial activity of the synthesized ligand and its complexes were screened by disc diffusion method. The results show that the metal complexes were found to be more active than the ligand.[9]



Schiff-base metal complex (1)



Copper mixed ligand complex(2)

2. Copper complex with macrocyclic ligand

On the basis of molar conductance the complexes may be formatted as $[Cu(L)X_2]$ [X=Cl^-, Br^-,NO_3^-,$CH3COO^-$] **(2)** due to their nonelectrolytic nature in N,N'-dimethylformamide(DMF). All the complexes are of the high spin type and are six coordinated. The interaction of these complexes with calf thymus DNA has been explored by using absorption, emission, viscosity measurements, electrochemical studies and DNA cleavage.

Loesh *et al* were reported that spectroscopic studies together with viscosity experiments and electrochemical method supports that the complex binds to CT DNA by partial intercalation via its pyridine ring into the base pair of DNA. These observation suggest that the structure of the hexaaza macrocycle play an important role in the binding mode affinity.[10]

3. Metallobacitracin

Theeraphone *et al* reported that superoxide dismutase (SOD) activities of various metallobacitracin complexes and were evaluated using the riboflavin-methionine-nitro blue tetrazolium assay. The SOD activity of complex was found to be in the order of Mn(II) > Cu(II) > Co(II) > Ni(II). The effect of bacitracin and their complexation to metals on various microorganisms was assessed by antibiotic susceptibility testing.

Stability

Stability of Mn(II)-bacitracin in the presence of EDTA and BSA. Mn(II)-bacitracin at 1 mg/mL maintained its activity in the presence of EDTA up to 0.37

mg/mL while the BSA could not affect the SOD activity.

Biological activity

Mn(II)-bacitracin was found to exert greater inhibitory activity than the other metallobacitracins on S.*aureas* and *Enterococcus* spp.[11]

Test compound	Inhibition (%)
Mn(II)-bacitracin	48
Co(II)-bacitracin	31
Ni(II)-bacitracin	3.5
Cu(II)-bacitracin	47
Metal free bacitracin	0
Metal	0

4. Streptonigrin (SN)

Streptonigrin is a metal binding quinine containing antibiotic produced by *Streptomyces flocculus*. This antibiotic has been shown to inhibit several tumors and cancers. A recent study shows that SN also exhibit ionizing radiation like damage towards *Ataxis telangiectasia* heterozygote cells.

Action of metallo-SN: The interaction of metal-SN complexes with DNA has been proposed on the basis of some optical studies. A redox active metal ion such as Fe and Cu is required for this antibiotic to exhibit full antibiotic and anti-tumor activities. The redox active Fe and Cu complexes have been shown to accelerate SN-mediated DNA scission in the presence of NADH, (Nicotinamide adenine dinucleotide) thus enhance the anti-tumor activity of this antibiotic.[12-14]

Metal complexes of SN: Zn^{+2} binds SN to afford a few different complexes with different metal binding modes at various temperature, in which a 1:1 metal-drug complex is predominant complex. SN binds with several different paramagnetic metal ions including Co^{+2}, Fe^{+2} with large formation constant to form 1:1 metal-SN complexes.

5. Anthracyclines (AC)

Richardson *et al* reported the antineoplastic activity of AC antibiotic has been mainly attributed to their strong interaction with DNA in the target cells. The AC family membered possesss a quinine containing chromophore and aminoglycoside side chain.

Fe-AC complex

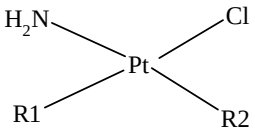
The binding of the Fe^{+3} with several other AC has been revisited.the result suggest that Fe^{+3} binds these drug to form 1:1 Fe-drug complexes with the metal bound at 11,12-β-ketophenolate site, and 2:1 Fe-drug complexes with the metal bound at both β-ketophenolate sites. The Fe^{+3} complexes of these drugs are very complicated systems since their spectra are dependent upon the preparation procedure, equilibrium time, metal-to-drug ratio, and drug concentration.[15]

6. Cisplastin

The antibiotic activity of the platinum complexes cisplatin, cis-$(pt^{II}(NH_3)_2CL_2)$ **(3)** and cis-$ptIVC_{l6}(NH_3)_2$ **(4)** were found serendipitously by Barnett Rosenberg.

Biological activity: Dramatic elongation of *E.Coli* during a study of the influence of the electric field of the bacterium by the use of a platinum electrode in a buffer solution containing NH_4Cl.

Cisplatin was soon found to be a potent anticancer drugs and is now a days one of the most prescribed anticancer drug which has been used for the treatment of several different cancers and tumors including head and neck tumor, breast and ovarian cancer.[16-17]



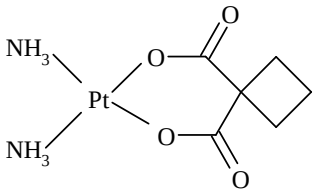
(3)

R1= NH_3
R2= Cl

Cisplastin

R1= Cl
R2= NH_3

Transplastin



Carboplatin(4)

7. Organometallic Complex

Farrall *et al* were reported organometallic compounds which was the characterized by the presence of direct metal-carbon bond. Of these, the metallocene compounds $M(CP_2CL_2)$ (CP=cyclopentadienyl; M=Ti, V, Nb, and Mo) show significant activity towards several experimental animal tumors and human tumors on nude mice. In addition to the metallocenes, there are non platinum metal complexes which have been extensively studied and tested for their anti-tumor activities. [18--19]

8. Mixed ligand metal complex

Ogunniran *et al* were reported mixed ligand metal complexes of ampicillin (AMP) and chloramphenicol(CHL) by using Ni(II) ,co(II) and Fe(III) metal chloride hexahydrate were reported. The complexes having the formula (ML^1L^2) (Cl)n gives antimicrobial activity.IR spectra suggested that both L^1 and L^2 coordinated to the metals ion in a terdentate manner with v(O-H), v(c=o) and v(N-H) as donor sites in the each of the ligands.

Biological activity: The synthesized complexes compares to their ligands, were also screened for their antibacterial activity against isolated strains of *Escherichia coli, staphylococcus aureas* and *klebsiella pneumonia* by using agar diffusion method.[20]

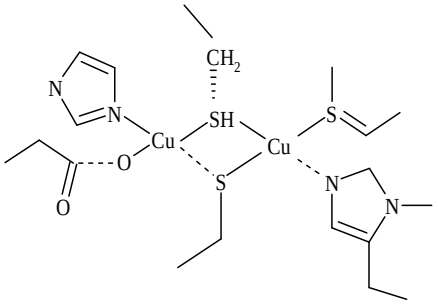
Ligand + metal salt	% yield
AMP + CHL + $NiCl_2$	59.3
AMP + CHL + $CoCl_2$	50.8
AMP + CHL + $FeCl_3$	56.4

9. Copper sulfur cluster:

The complex has a large hydrophilic region that protrudes into the intermembrane space and contains the binding site for cyt-C, the electrons are transferred to a copper sulfur cluster containing two Cu atoms called CuA. These two Cu atoms are linked by two sulfur atoms of cysteine side chains shown in **(5).**[21]

Biological activity

Biological activity of the ligand and its series of its metal complex were screened for antibacterial activity against *S.aureus* as gram-positive bacteria and *E.coli* as gram-negative and the fungi A. In fungal activity, the ligand showed activity against *Aspergillus fumigates* and metal complex show activity in following order Cu > Co > Ni > Mn. It is known that chelation tends to make the ligand to act as more powerful and potent bacterial agent.



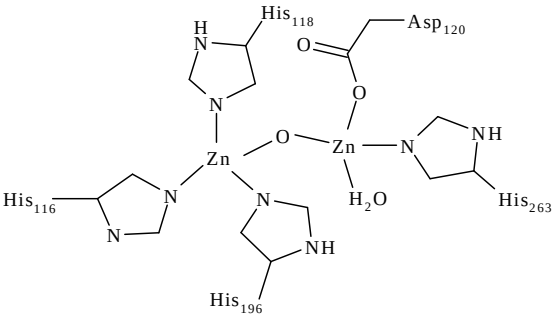
Sulphur Cluster Complex (5)

10. Metal complexes with antibiotics

a. β-lactum antibiotics:

Muthaiah Umayal *et al* they synthesized a few asymmetric phenolate-based ligands by sequential Mannich reaction and their corresponding zinc(II) complexes. Metallo-β-lactamases (mbl) **(6)** and phosphotriesterase (PTE) **(7)** are zinc(II) enzymes, which hydrolyze the β-lactam antibiotics and toxic

organophosphotriesters, respectively.These zinc(II) complexes were studied for their mbl and PTE activities. β -Lactam antibiotics are the most widely used class of antibiotics, and the bacterial enzymes that hydrolyze these antibiotics are known as β -lactamases. β-lactamases are classified into serine- β-lactamases (sbl) and metallo- β-lactamases (mbl). The serine β-lactamases possess an active site serine residue which is essential for its hydrolytic activity. Currently, the inhibitors namely clavulanic acid, sulbactam and tazobactam are known for sbl. However, bacteria have evolved the zinc(II) containing metallo β lactamases that are capable of hydrolyzing a variety of β-lactam antibiotics including the latest generation of cephalosporins and carbapenems (e.g. imipenem)[22,23]



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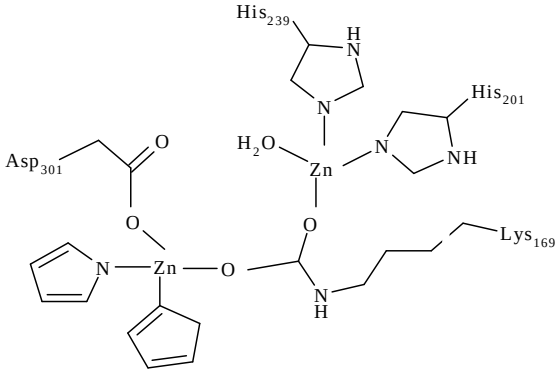
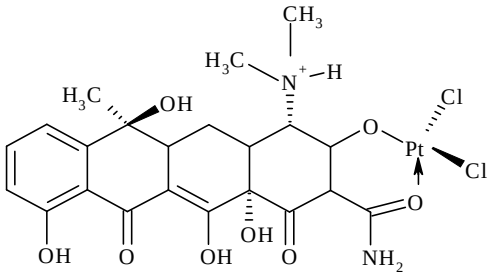


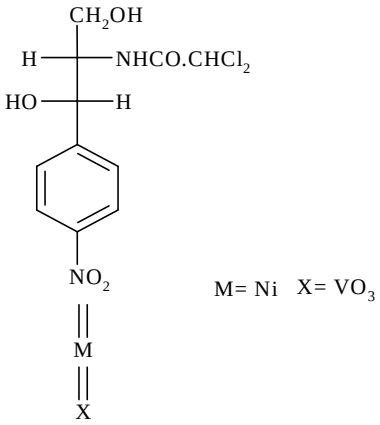
Zn(lactumase)complex(7)

b. Tetracycline

Chartone-Souza E *et al* were reported the synthesis of platinum (pt) complex with tetracycline. A tetracycline Pt(II) complex **(8)** turned out to be as efficient as the ligand alone against *Escherichia coli* bacterial strains. Moreover, these complex six times more potent against *Escherichia coli* than free tetracycline.[24]



Pt(tetracycline)complex (8)



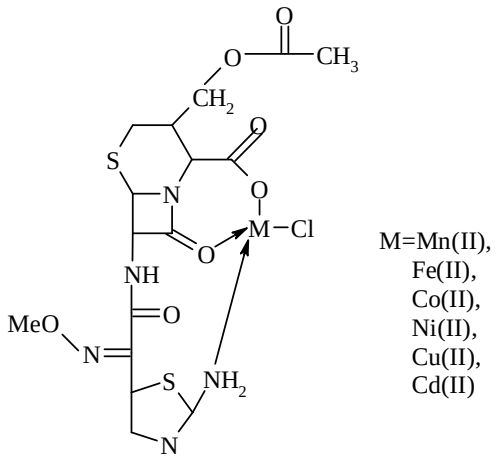
M(Chloramphenicol) Complex (9)

c. Chloramphenicol

Pranay Guru carried out the synthesis on the metal vanadate with organic ligand, the synthesis scheme describes Nickel(II) with Chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$) in the presence of vanadate. The complex **(9)** has been synthesized and characterized using analytical and spectral methods like infrared, TGA, XRD.[25]

d. Cephalosporin

R. Anacona *et al* reported the synthesis and antibacterial activity of cephalexin. Different metal bind with cefotaxime and shows antibiotic activity which shows in **(10).** Metal like Mn(II) , Fe(II), Co(II), Ni(II), Cu(II), Cd(II). The anti-bacterial study of Cu(II)-cefalexin and Zn(II)-cefalexin complexes demonstrated that the complexation of cefalexin with these metals enhances its activity significantly compared to cefalexin alone. The complex [Cu(cefotaxime)Cl] was found to have higher activity than that of cefotaxime against the bacterial strains studied under the test conditions, showing that it has a good activity as bactericide.[26,27,28]



M(Cefatoxime)complex(10)

e. Aminoglycoside

Aminoglycoside have been determined to bind Cu^{+2} ,including lincomycin, kanamycin, Genticin, tobramycin. These complex exhibit oxidative activity.[29-32]

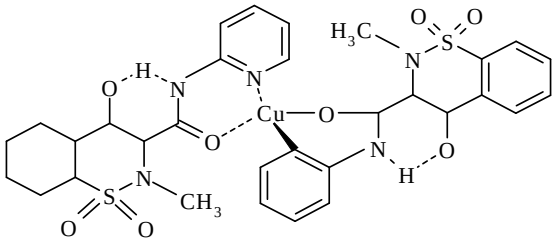
11. Cu(II) Complex with salsalate (SAS)

Underhill *et al* were reported that $Cu(SAS)_2.H_2O$ for the antiinflamatory superoxide dismutase activity compared with the parent drug molecule in the nitroblue tetrazolium assay. The mechanism believed to be operating in both Cu-Zn superoxide dismutase and Cu(II) complexes involvs the initial binding of superoxide to be axial Cu(II) site, with subsequent redox cycling of the Cu(II) ion . The rate of the exchange of axially coordinated water and steric hindrance to the approach of the superoxide ion are believed to account for the variation in O_2^- activity of Cu(II) complexes.[33]

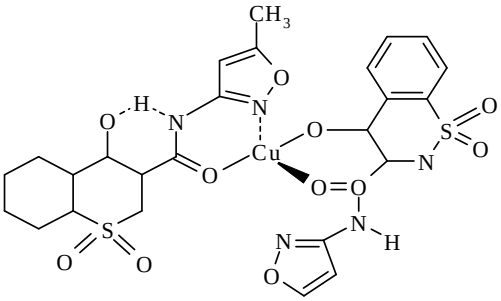
Copper(Cu) complex with suprofen(SUP**):** Underhill had reported that Cu(II) complex of $Cu(SUP)_2.H_2O$ for the antiinflammatory drug suprofen. The Cu(II) complex exhibits an increased superoxide dismutase activity compared with the parent drug molecule in the nitroblue tetrazolium assay. The Cu(II) complex exhibit a slight increase in superoxide dismutase activity compared to the parent drug molecules and supports earlier findings that O_2^- scavenging is not restricted to the metalloprotein SOD but exhibited by a number of low molecular mass copper(II) compounds.[34]

Copper(Cu) complex with piroxicam and isoxicam: Cini *et al* had reported that basic study of loading and release capacity for active drugs from the oxicam family were performed on poly(N-acryloyl-l-phenylalanine-co-N-isopropylacrylamide) **(11)** and poly(N-methacryloyl-l-histidine-co-N-isopropylacrylamide) **(12)** cross linked with N,N'-ethylene-bis-acrylamide(EBA)swellable hydrogels, CP_2 and CMH_2 respectively. Owing to the low solubility of the oxicam and $Cu(Oxicam\text{-}H)_2$ species in aqueus media, swelling, loading and release measurement were performed first in DMSO, an efficient solvent for these molecule as well as for their Cu complex, and a chemical that widely administered to the animals and to the humans. The analysis of the data shows that CMH_2 hydrogel is able to carry and deliver a larger amount of metal complex when compared to CP_2; furthermore the release kinetic from CMH_2 is slower than the from CP_2.These facts are

in agreement with an higher affinity of Cu-HPIR species for CMH_2 than for CP_2.[35-36]



Cu(HPIR)$_2$DM complex(11)



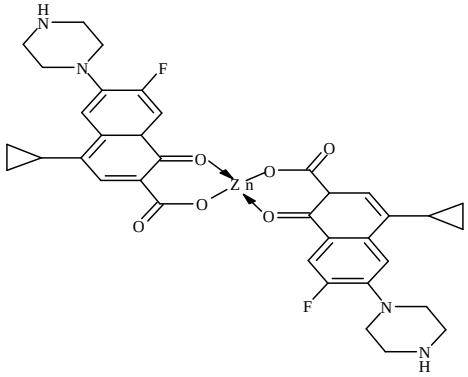
Cu(HISO$_2$)complex(12)

12. Metal interacts with quinolone drug

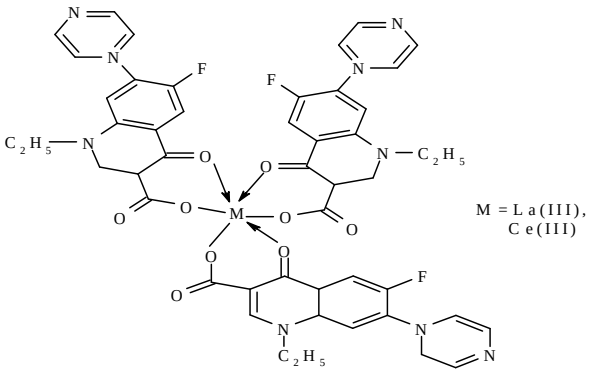
Norfloxacin and Ciprofloxacin with magnesium(Mg(II)), calcium(Ca(II)), and barium(Ba(II)) increase antibacterial activity and decrease toxicity.[37]

Iztok Turel *et al* reported the complexation of Zn(II) ions with quinolone in aqueous solution depending mainly upon pH. To investigate the pH dependence of the complexation between Zn(II) and the quinolone derivative ciprofloxacin (cfH), UV-Vis spectroscopy was used. The crystal structure of the compound $[C_{17}H_{19}N_3O_3F]_2[ZnCl_4].2H_2O$ **(13)** was determined by X-ray diffraction. These complexes was characterized by elemental analysis, mass spectrometry, TG analysis and IR spectroscopy.[38]

Moamen S. Refat *et al* reported the interaction between norfloxacin (norH) and two lanthanide (lanthanum(III) and cerium(III)) metal ions **(14)**, which prepared in normal and nano-features. La(III) and Ce(III) complexes were synthesized with chemical formulas $[La(nor)_3]3H_2O$ and $[Ce(nor)_3]2H_2O$. Lanthanum and cerium(III) ions coordinated toward norH with a hexadentate geometry. The norH acts as deprotonated bidentate ligand through the oxygen atom of carbonyl group and the oxygen atom of carboxylic group. The highest antibacterial and antifungal activities data of the nano-particles complexes were observed with more potent than the free norH and normal lanthanide complexes.[39]



Zn(Ciprofloxacin)$_2$.2H$_2$O complex(13)



M (Norfloxacin)$_3$.3H$_2$O complex (14)

13. DNA binding metalloantibiotic bleomycin(BLM)

Bleomycin was first isolated as a Cu^{+2} containing glucooligopeptide antibiotic from the culture medium of *streptomyces verticullus*, and was later found to be also an antiviral agent.In the presence of the reducing agents,the metal ion in Fe^{+2} or Co^{+2}-BLM binds dioxygen and converts into an "activated form" HOO-M^{III}-BLM via an superoxide-M^{III}-BLM intermediate. Several study indicate that Fe^{+2}-BLM can also bind and cleave RNA molecules, including tRNA and its precursors and rRNA. It has also been known to be an excellent ligand for binding with several different metal including Mn^{+2}, Fe^{+2}, Co^{+2}, Ni^{+2}, Zn^{+2}, Cd^{+2}, Ga^{+2}, Ru^{+2}.

The diamagnetic Zn^{+2}-BLM complex of BLM has been utilized as a structural model for the paramagnetic Fe^{+2}-BLM complex owing to the difficulty in the high resolution NMR studies.[40-42]

The Co^{+2} in Co^{+2}-BLM can form an activated "green species" HOO-Co^{+3}-BLM upon treatment with peroxide.[43-48]

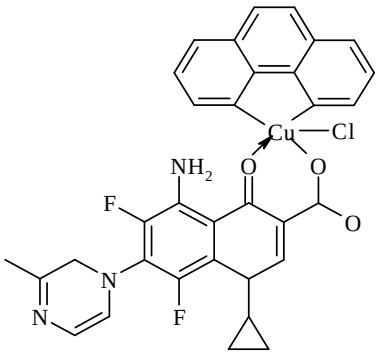
14. Aureolic acid

It contain metal binding beta-ketophenol chromophore, highly functionalized aliphatic side chain and a disaccharide and trisaccharide chains important for DNA binding and inhibition of DNA transcription. Divalent metal ion such as Mg^{+2}, Co^{+2}, Zn^{+2}, Mn^{+2} is required for aureolic acid to bind to a double helical DNA to form $drug_2$–metal-$(DNA)_2$ ternary complex.[49-51]

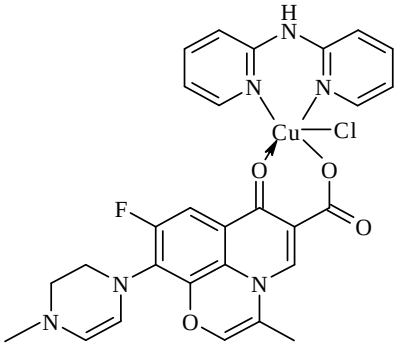
15. Metal interacts with quinolone and N-N- donor

Metal like CO, Ni, Cu interact with quinolones (ciprofloxacin, norfloxacin, pefloxacin) and N-N-donor like 2,2'-bipyridine ternary complex observed by means of electroscopy ionization and laser desorption mass spectroscopy. These complex inhibit DNA gyrase and gives antibacterial activity. [52]

Efthimiadou *et al* copper(II) complexes **(15)** of the third-generation quinolone antibacterial drug sparfloxacin in the presence of a nitrogen donor heterocyclic ligand 2,2'-bipyridine, 1,10-phenanthroline or 2,2'-dipyridylamine have been prepared and characterized physicochemically and spectroscopically.[53]



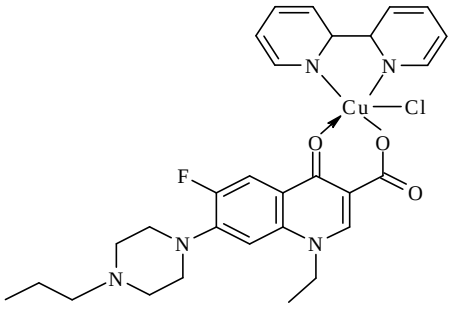
Cu(Sparfloxacin)(1,10-phenanthroline)comple(15)



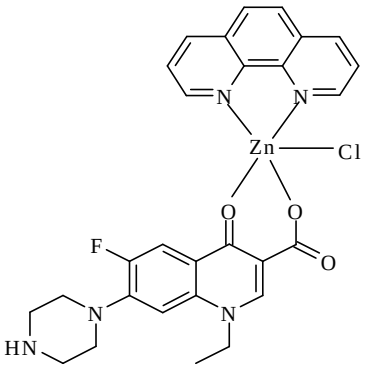
Cu(Levo)(bpd)complex(16)

Patel *et al* studied the drug based copper (II) complexes **(16)** with levofloxacin in presence of 2,2'-bipyridylamine(bpd). It shows antibacterial activity.[54]

George Psomas *et al* observed the synthesis of copper(II) complex **(17)** with the quinolone antibacterial drug N-propyl-norfloxacin and 2,2'-bipyridine. The antimicrobial activity of the complex has been tested on different microorganism.[55]



Cu(N-propyl norfloxacin)(2,2'-bipyridine)cl complex(17)



Zn(norfloxacin)(1,10-phen) Complex (18)

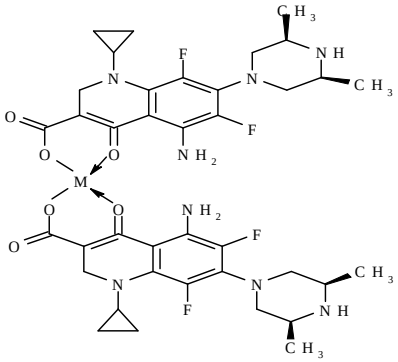
Our research group had synthesized zinc metal complexes with fluoroquinolone antibacterial drugs like Sparfloxacin, Ofloxacin, Levofloxacin, Pefloxacin, Norfloxacin and Gatifloxacin in the presence of a nitrogen donor heterocyclic ligand 1,10-phenanthroline. The antimicrobial activity of the complexes had been tested on two different microorganisms and the results shown a diverse biological activity in comparison to the free fluoroquinolone. The mixed fluoroquinolone and N-donor ligands zinc complexes were found among the most active ones against *E. coli* compared to *S. aureus*. Especially, the zinc-norfloxacin-N-donor complex (**18**) was found the most active one against *E. coli* and *S. aureus* when compared to other corresponding zinc–quinolone complexes.

16. Sparfloxacin metal complex

Nadia *et al* were reported that Sparfloxacin forms metal complex with Cu(II), Co(II), Ni(II), Mn(II), Cr(III), Fe(III) **(19)** All complexes were of the high-spin type and found to have six-coordinate octahedral geometry except the Cu(II) complexes which were four coordinate, square planner and U- and La-atoms in the uranyl and lanthanide have a pentagonal bipyramidal coordination sphere.

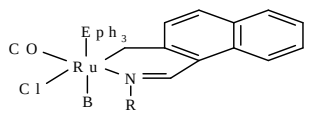
Biological activity

The antimicrobial activity of these complexes has been screened against two gram-positive and two gram-negative bacteria. Antifungal activity against two different fungai has been evaluated and compared with reference drug sparfloxacin. All the binary and ternary complexes showed potential antimicrobial activity higher than the recommended standard agents. [56]



M = Cu(II), Co(II), Ni(II), Mn(II), Cr(III), Fe(III)

M (Sparfloxacin)$_2$ complex(19)



E = P, B = PPh$_3$

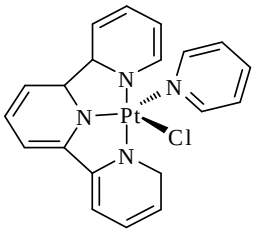
Ru.Hcl(CO)(EPh$_3$)$_2$(B)complex(20)

17. Ru(II) carbonyl Schiff base complex

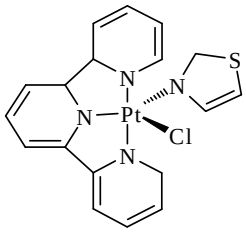
Sivagamasundari *et al* were reported that the reaction of the chelating ligand with $[RuHCl(CO)(EPh_3)_2(B)]$ (where E=P;B=PPh_3,py or pip) **(20)** in benzene afforded new stable ruthenium(II)carbonyl complexes. The luminescence efficiency of the ruthenium(II) complexes was explained based on the ligand environment around the metal ion. These compound catalyze oxidation of the primary and secondary alcohol into their corresponding carbonyl compounds in the presence of N-methylmorpholine-N-oxide(NMO)as the source of oxygen.[57]

18. Platinum(II) complex with five membered heterocycles

Platinum forms complex with the heterocycles like oxazoles, isoxazoles, imidazole, pyrazoles, Pyridine **(21)** and thiazole **(22)**. These are the ambidentate ligands and it is necessary to ascertain the site of binding to Pt(II) in its complexes,but there is considerable evidence to indicate bonding through nitrogen of which are probabaly important. Thiazole and oxazole bind to the analogues soft d8 Au(III)through nitrogen. Thiazoles ligands binds to the platinum through nitrogen atom. Bruno *et al* reported that the lability of the five membered N-donor heterocycles have considerably lower than that of pyridines, strongly suggesting that, in addition to possible but unlikely solvation effects, the Pt-N bond in case of the five membered N-donor may be rainforced by π bonding. It seems reasonable to conclude that the π system of five membered N-donors can interact in the ground state with the filled d-orbital of Pt(II) better than pyridine.[58]



Pt(Pyridine)4.cl complex(21)



Pt(thiazole)complex(22)

19. Heterocyclic Zn(II)-Metal complex

Ag(I)-Metal complex: In the dimeric Ag(I)complex each metal is coordinated to the imine nitrogen of the two (Z)-3-(1H-imidazol-1-yl)-2-phenylpropenenitrile (imppn) ligands in an almost linear fashion and the two $[Ag(imppn)_2]^+$units are linked by an Ag-Ag bond, supported by two trans bridging bidentate percholate groups and by π-π interaction between the ligands.

In vitro test on the ability of the compounds to inhibit the growth of the pathogenic yeast *candida albicans* showed that imppn and its metal complexes were markedly less effective than prescription drug, ketoconazole.[59]

20. Other Metal organic complex

Florence *et al* were reported that Cu complex of N1-(4-methyl-2-pyridyl)-2,3,6-trimethoxybenzamide interact with the active site of the enzyme leading to competitive inhibition. On the other hand, N_2-pyridine-amide ligands and oxazinane carboxamide ligand were found to be poor chelators of the cupric ion under the enzymatic assay conditions. In these cases, the observed inhibition was attributed to released cupric ions which react with cysteine residues on the surface of the protease.while unchelated metal cations are not likely to be useful agents, metal chelates should be considered as promising lead compounds for the development of the drugs. This approach can be successfully

used to inhibit the protease of the human immunodeficiency virus (type I).[60]

CONCLUSION

In this review, an overview of the metal complexes which have shown promising results had been discussed. Metal complexes offer a platform for the design of novel therapeutic compounds. Activity of the compound can be increased by the formation of complex with different metal ion. It seems that opportunities exist to develop metal and metal based drug candidates in the discovery and development of novel therapeutic agents. The encouraging results of preclinical and clinical studies with metal compounds form the basis for further investigations towards the development of metal complexes for better therapeutic profile. Although, metal complexes have some side effects, they are successfully being used in cancer therapy and several other therapies. Therefore there is a need for new approaches that are required to circumvent these drawbacks and pave a way for potent drug therapies.

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