International Journal of Scientific Research in Science and Technology
Available online at : www.ijsrst.com
OPEN ACCESS
Print ISSN: 2395-6011 | Online ISSN: 2395-602X
doi : https://doi.org/10.32628/IJSRST

Anti-Microbial and Anti-Fungal Activity Some Drug Metal Coordination Complexes: A Review

Mukesh S. Kadam[1*], Dr. B.C. Khade[2]

[1]Department of Chemistry, Loknete Gopinathji Munde Arts, Commerce and Science College, Mandangad, Ratnagiri- 415203, Maharashtra, India

[2]Department of Chemistry, DSM College, Parbhani, Maharashtra, India

ARTICLEINFO

Article History :

Published : 07 Dec 2024

Publication Issue :
Volume 11, Issue 23
Nov-Dec-2024
Page Number :
202-208

ABSTRACT

Drug and Schiff's base metal coordination complexes has gained a great interest of the inorganic chemists as well as researchers. A literature survey has revealed that transition series of metalion with ligand like Schiff's basesor drug have the ability to form a coordinate bond. The synthesized metal complex was evaluated for in vitro antibacterial activity against various the bacterial strains (Plasmodium falciparum, Pseudomonas aeruginosa, E. coli, Streptococcus, Bacillus, Staphylococcus aureus) and anti-fungal activity against fungus (Aspergillus niger and Candida). For this reason, we have to focus on design and development of novel antimicrobial drugs in order to control infections and diseases. Metal complexes usually contain a variety of structural and electronic features which can be exploited in designing of drugs. These properties allow the fine-tuning of chemical reactivity, including the rates of ligand exchange, the strength of metal–ligand bonds, metal- and ligand- based redox potentials, ligand conformations, and outer-sphere interactions. These review works depict the current studies on the antimicrobial activities of transition metal complexes with N, O donor chelating agent.The metal drug complex shows potent antibacterial as well as antifungal activity comparatively commercial drug which available in market.

Keywords: Metal complexes, Schiff's bases, Anti-microbial, Anti-fungal.

Introduction

Organo-metallic compounds have been used in medicine for centuries. Metal complexes playessential role in pharmaceutical industry and in agriculture. The metallo-elements present intrace quantities play vital roles at the molecular level in living system. The transition metal ionsare responsible for proper functioning of different

enzymes. The activity of biometals is attainedthrough the formation of complexes with different bioligands and the mode of biological actionfor complexes depends upon the thermodynamic and kinetic properties

Hospitalized patients suffering from critical conditions such as kidney, heart transplantation or failure, diabetes, hypertension, anemia, pneumonia, fever and so on are prescribed various medications. Commercially available drugs in market shows slow or less effect against bacterial, viral and fungal species, on other hand some bacterial, viral and fungal species are completely resistant to the drug. It's time to develop new more potent drug against drug resistant bacteria, viruses and fungus. The emergence and spread of pathogens resistant to many available drugs is of great concern. The situation is critical in Africa as a result of the spread of resistance to the inexpensive drugs widely used for treatment of diseases such as malaria and tuberculosis. As an alternative, a number of metallic ion-drug combinations are being assayedand suitable ones recommended. However the question about cost and adequacy of the supply necessitate the need to identify new novel agents [1-2].

The lipophilicity of thedrug is increased through the formation of chelates and drug action is significantly increased dueto effective permeability of the drug into the site of action. Interaction of various metal ions withantibiotics may enhance their antimicrobial activity as compared to that of free ligands. Metal ions bond 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.

Recently, attention has been drawn to studies of the antitumor activities of inorganic especially metal complexes. From the initial discovery of the anticancer properties of the inorganic complex cis-platin, many metal complexes have been tested for anticancer activities especially platinium(II) compounds,which has meant new advance in cancer medicine research.[3-6].

Generally iron complexes are used in the transport of oxygen in the blood and tissues. An adultat rest consumes 250ml of pure oxygen per minute, this oxygen carried by the metal complextransport system known as heme, allowing the oxygen to leave the blood when it reaches thetissue. The hem group is metal complex, with iron as central metal atom, which bind or releasemolecular oxygen. 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 inorganiccomplex cisplatin was discovered, today more than 50 years, it is still one of the world's bestselling anticancer drug. Metal complexes formed with other metals like copper, gold, gallium,germanium, tin, ruthenium, iridium was shown significant antitumor activity in animals.Titanium complexes, gold complexes alsoshow significant antitumor activity. In the treatment of ovarian cancer ruthenium compoundscontaining arylazopyridine ligands show cytotoxic activity. Now a day's metal complex in theform of nanoshells are used in the treatment of various types of cancer [7-8].

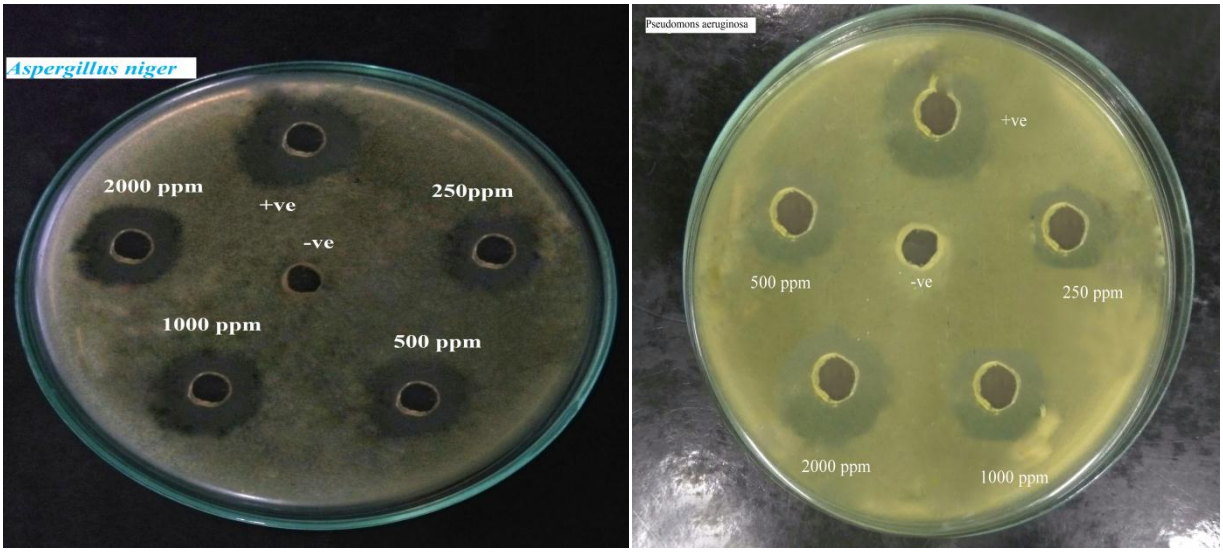
Methods to measure antimicrobial activity

1. Agar disc diffusion method for antibacterial activity

Antibacterial activities of complexes are tested by Agar disc diffusion method. Here nutrient agar media is prepared and autoclaved under 121°C at (15 lb) pressure for 15 min sterilization. After sterilization nutrient agar plates holding 30 ml of the media. In each plate four different concentration sterilized disc is soaked with four different concentration complexes and other with ligand drug. After 24 h of incubation at 37 ± 1°C the zone of inhibition in agar plates are observed, measured and photographed. The growth of inhibition zone is calculated using complex and ligand against pathogenic bacteria.

2. Agar well diffusion method for antifungal activity

Potato Dextrose Agar (PDA) plates are smeared by a spreader with fungal spores of candiada Albicans, AspergillusNiger and allowed to dry for 1 min. After that, agar plates are punched or a hole is made with a sterile cork borer and 30 µL of solution of metal complex within various concentrations was added. The inhibition zones are measured after 48 h of incubation at 30 °C.



Antimicrobial and Antifungal activity of transition metal complexes with drug

In recent times good numbers of transition metal drug complexes have been reported in literature possessing antimicrobial, antibacterial, antifungal, anti-inflammatory and antitumor properties.Transition metal complexes synthesized from drug as ligands have drawn significant interest of researchers in the medical science because of their biological activity. At present times, drug resistance against different pathogens is one of the major causes of morbidity and mortality. It is assumed that novel antimicrobial drugs would play crucial role in biological monitoring of diseases. In recent times, many transition metal complexes possessing antimicrobial, antibacterial, antifungal, anti-inflammatory and antitumor properties have been reported [9].

Metal complexes as potential Antimicrobial and Antifungal activity:-

Muhammad Imran et.al. Check antimicrobial activity against gram positive and gram negative bacterial strain of metal coordination complexes of ciprofloxacin-imines and with first transition series metal ion like Cu(ii),Ni(ii),Co(ii), and Zn(ii). Coordination complexes shows good zone of inhibition against bacterial species comparatively standard drug.

A. Stojkovi*et al* studied that solubility of complexes of Ciprofloxacin hydrochloride metallic ion *in vitro.*Interaction studies revealed that drugsolubility and dissolution were impaired to different extents in dependence on the typeof the metallic complex like aluminium, calcium, zinc and iron on drug solubility and dissolution [10].

Wise and co-workers,[11] determined the MIC of ciprofloxacin and norfloxacin, in comparison with those of other antimicrobial agents using the agar plate dilution method. All the plates were incubated in air at 37^{O}C for 24hrs[11]. The MIC of Ciprofloxacin for 90% of *Enterobacteriacea, Pseudomonasaeruginosa, Haemophilus influenzae*, *Neisseriagonorrhoeae, Streptococci, Staphylococcus aureus* and *Bacteriodes fragilis* strains were between 0.008 and 2 mg / ml[11].

The minimum inhibitory concentrations (bacteriostatic) (MIC) and the minimum bactericidal concentrations (MBC) of the ligands and iron(III) complexes of ciprofloxacin iron complexes have been determined.[12] The ligand and iron complexes showed antimicrobial effect against the tested organism species except against the molds of *Penicillim*and *Aspergillus* as presented.[12] *Neisseragonorrhoea*was the most sensitive organism to thefluoroquinolones and their complexes.[12] The metalcomplexes showed comparable activity or greater activity against some of the microorganisms in comparison to the parent compounds.

The antimicrobial activity of Ti, Y, Pd and Ce metal complexes had been evaluated against three gram-positive and three gram-negative bacteria and compared with the reference drug moxifloxacin.[13] The antibacterial activity of Ti(IV) complex was reported to be significant for *E. coli* and highly significant for *S. aureus*, *B. subtilis*, *Br. otitidis*, *P. aeruginosa* and K. oxytoca compared with free moxifloxacin.[13]

The activity of the complexes against *Mycobacterium tuberculosis* virulent strain was determined.[14] Both, Pd(II) and Pt(II) complexes with sparfloxacin were the most active within each series inhibiting bacterial growth at 0.31 mg/mL.[14] The same MIC was found for the Pt(II) complex with gatifloxacin.[14] On the other hand, the least active complexes of the series were the Pd(II) complex with ciprofloxacin and the Pt(II) complex with ofloxacin, which exhibited MIC¼ 1.25 mg/mL.[14] Although the complexes have not shown better antitubercular activity than free gatifloxacin, in general all of the complexes exhibited good activity and, all but one of them were more active than rifampicin.[14]

The antibacterial potential against *Helicobacter pylori* and other microorganisms of thefluoroquinolones, norfloxacin, ofloxacin,ciprofloxacin, sparfloxacin, lomefloxacin, pefloxacinand gatifloxacin, with bismuth has beeninvestigated.[15] These compounds were found topossess strong activity against *Helicobacter pylori* with a minimum inhibitory concentration of 0.5 mgL–l.[15] They also exhibited moderate activity against *Escherichia coli, Staphylococcus aureus*, *Bacillus pumilus*and *Staphylococcus epidermidis*.[15] Thesebismuth-fluoroquinolone complexes have thepotential to develop as drugs against *H. pylori* related ailments.[15] Bismuth-ciprofloxacin complexwas found to be most potent against *E. coli* with *MIC* of 0.05 mgL^{-1}.

The complexes were tested against different strains of bacteria at concentrations of 20 mg/ml, 15mg/ml and 10mg/ml. The Co(II) complex showed higher activities against all the tested strains (*E.coli, Salmonella typhi,Klebsiella, Pseudomonas, Streptococcus pyogenes, Corynebacterium pneumoniae* and *Bacillus subtilis*) similar to the parent drug [16] except against *Staphylococcus aureus.* Large inhibition zones (21- 40 mm) was shown by Ni(II) complex for all the test strains except against *staphylococcus aureus*. Similar activities were observed against *Salmonella typhi, Klebsiella pneumoniae, Pseudomonas aeruginosa, Streptococcus pyogenes* and *Bacillus subtilis*.

Increased activity was shown against *Escherichia coli* and *Corynebacterium pneumoniae* compared to the parent drug. In Cu(II) complex no activity was found against *Staphylococcus aureus*, but increased activity was observed against *E. coli, Salmonella typhi, Streptococcus pyogene, Klebsiella pneumoniae, Pseudomonas aeruginosa,Corynebacterium pneumoniae* and *Bacillus subtillis*compared to the parent drug[16]

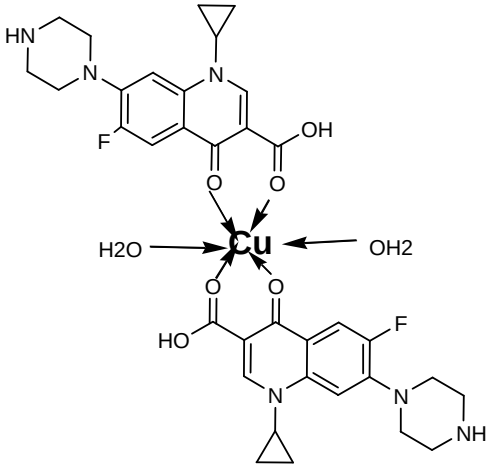
The anti-MTB activity of the compounds was determined by the REMA (Resazurin Microtiter Assay) method according to Palomino *et al*, 2002 [17]. Stock solutions of the tested compounds were prepared in dimethyl sulfoxide (DMSO) and diluted in Middlebrook 7H9 broth (Difco) supplemented with oleic acid, albumin, dextrose and catalase (OADC enrichment - BBL/Becton Dickinson), to obtain final drug concentration ranges of 0.09-25 μg/mL. The isoniazid was dissolved in distilled water, and used as standard drug. A suspension of the MTB H37Rv ATCC 27294 was cultured in Middlebrook 7H9 broth supplemented with OADC and 0.05% Tween 80. The culture was frozen at -80 ºC in aliquots. After two days was carried out the CFU/mL of a aliquot. The concentration was adjusted by 5x105 CFU/mL and 100 μL of the inoculum was added to each well of a 96-

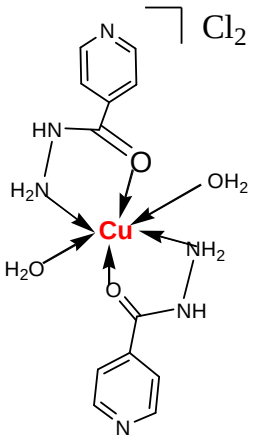
well microplate together with 100 µL of the compounds. Samples were set up in triplicate. The plate was incubated for 7 days at 37 °C. After 24 h, 30 µL of 0.01% resazurin (solubilized in water) was added. The fluorescence of the wells was read after 24 h in a TECAN Spectrafluor. The MIC was defined as the lowest concentration resulting in 90% inhibition of growth of MTB[18]

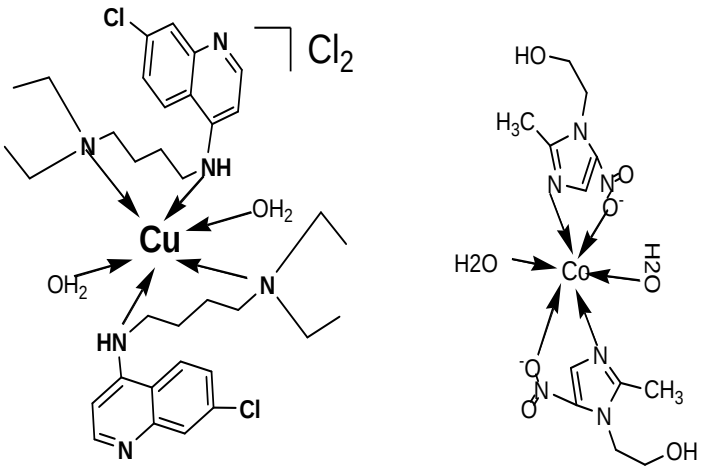
Metal Complexes of Schiff Bases

A metal surrounded by cluster of irons or molecules named as Schiff bases which are products of primary amines condensed with aldehydes (or) ketones (RCH=NR', where RPR' are alkyl and (or) aryl substituents.Apart from antimicrobial, antifungal, antiviral activity, Schiff bases with their metal complexespossess anti-inflammatory, allergic inhibitory, antioxidant and analgesic action. Example- Furansemicarbazone metal complexes exhibit significant antihelmintic and analgesics activities [19].Schiff base with metals such as thallium, molybdenum, manganese, zinc, cadmium, copper andsilicon form complexes show impaired antimicrobial property when compared with Schiff base.Example- Schiff base of pyrolidone, pyridone with O-phenylenediamine and their metalcomplexes show better antibacterial activity [20].Schiff base with metals such as Arsenic, antimony and bismuth show considerable antifungalproperty against *A.niger*and *A.alternata.* Example Schiff bases and their metal complexesformed between furan (or) furylglycoxal with amines show antifungal activity against variousorganisms [21].Schiff base of silver complexes show considerable antiviral activity. Example silver complexes inoxidation state showed inhibition against cucumber mosaic virus [25].Kadam et.al to check antibacterial activity was determined by measuring thediameter of zones showing complete inhibition in (mm) at500µg/ml concentration. At this concentration, Ni(II) complexshows better antibacterial activity over Cu(II)and Fe(II) coordinationcomplexes of Chloroquine.

Proposed Structures of some Drug metal coordination complexes







Conclusion

In this review work, the antimicrobial activity of transition metal complexes with N,O donor ligand has been discussed to develop new antimicrobial agents and antifungal agents with great success. A large no. of metal complexes exhibited good position for the development of new classes of highly potent antimicrobial agents and antifungal agents. The role of transition metal complexes as therapeutic agent is becoming increasingly significant. Synthesis of metal drug coordination complexes is not easy task and also shows more number of side effects. Besides these limitation transition series metal drug coordination complexes as drug more pronounced.

References

[1]. GG Mohammed; M.M Omar and A.M Hindy. Turkey J. Chem. 2006, 30 (3): 361-382

[2]. Mustapha A. N., Ndahi N. P., Paul B. B. and Fugu M. B. J. Chem. Pharm. Res., 2014, 6(4):588-593

[3]. Lumme P, Elo H, Jane J. Antitumor Activity and metal complexes of the first transition series. Tranbis(salicylaldoximato) copper(II) and related copper(II) complexes, a novel group of potential antitumor agents. Inorg Chim Acta 1984;92:241-251.

[4]. Bruek MA, Bau R, Noji M, Inagaki K, Kidani Y. The crystal structures and absolute configurations of the antitumor complexes P+ (oxalato)(IR, 2R-Cyclohexane. Diamined and P+(malonato)(IR, 2R-Cyclohexadiame). Inorg Chim Acta 1984;92:279-284.

[5]. Hegmans A, Qu Y, Keland LR, Roberts JD, Farrell N. Novel approaches to polynuclear Platinium prodrugs. Selective Release of CrytotoxicPlatiniumSpemidine species through Hydrolytic clearage of Carbonates. Inorg Chem 2001;40:6108-6114.

[6]. Kopf-Maier P. Complexes of metal other than platinium as antitumor Agents. Eur J Clin Pharmacol1994;47:1-16.

[7]. Loo C, Lin A, Hirsch L, Lee MH, Borton J, Halas N, West J, Drezek R. Nanoshell enabled photonics based imaging and therapy of cancer. Technol.cancer.Res.Treat. 2004, 3(1):33-40.

[8]. K.Hariprasathet al J. Chem. Pharm. Res., 2010, 2(4):496-499.

[9]. Omima M.I. Adly, Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy Volume 95, September 2012, Pages 483-490

[10]. Stojkovi} et al., Acta Pharm. 64 (2014) 77–88.

[11]. Wise R, Andrews JM, Edwards LJ. In Vitro Activity of Bay 09867, a New Quinoline Derivative, Compared with those of other Antimicrobial Agents. AntimicrobAgs Chem 1983;23:559-564.
[12]. Obaleye JA, Akinremi CA, Balogun EA, Adebayo JO. Toxicological studies andantimicrobial properties of some Iron(III) complexes of Ciprofloxacin. Afr J Biotech 2007;6:2826-2832.
[13]. Sadeek SA, El-Shwiniy WH, El-Attar MS. Synthesis, characterization and antimicrobialinvestigation of some moxifloxacin metal complexes. Spec. Acta Part A: Molecular and Biomolecular Spectroscopy 2011;84:99-110.
[14]. Vieira LMM, de Almeida MV, Lourenço MCS, Bezerra FAFM, Fontes APS. Synthesis and antitubercular activity of palladium and platinum complexes with fluoroquinolones. Eur J Med Chem 2009;44:4107-4111.
[15]. Shaikh AR, Giridhar R, Megraud F, Ram Yadav M. Metalloantibiotics: Synthesis, characterization and antimicrobial evaluation of bismuth-fluoroquinolone complexes against Helicobacter pylori. Acta Pharm 2009;59:259-271. (against S. aureus with MIC of 0.125 mgL–1,bismuth-sparfloxacin complex against S. epidermidis with MIC of 0.125 mgL–1 and bismuth
[16]. Shaikh AR, Giridhar R, Megraud F, Ram Yadav M. Metalloantibiotics: Synthesis, characterization and antimicrobial evaluation of bismuth-fluoroquinolone complexes against Helicobacter pylori. Acta Pharm 2009;59:259-271. (against S. aureus with MIC of 0.125 mgL–1,bismuth-sparfloxacin complex against S. epidermidis with MIC of 0.125 mgL–1 and bismuth
[17]. Palomino, J.C.; Martin, A., Camacho, M.; Guerra, H.; Swings, J.; Portaela, F. Antimicrob. Agents Chemother. 2002, 46, 2720- 2722.
[18]. Mariana Poggi et al.J. Mex. Chem. Soc. 2013, 57(3), 198-204
[19]. Latha KP, vaidya VP &Keshavayya J. Synthesis, characterization and biologicalinvestigations on metal complexes of 2-acetyl naptha (2,1-b) furan semicarbazone, J Teach ResChem, 2004, 11, 39-48.
[20]. Gaur S, Phsicochemical and biological properties of Mn(II), Ni(II) and chelates of Schiff bases, Asian J Chem, 2003, 15, 250-254.
[21]. Dhakrey R and Saxena G, Synthesis of Ni (II) complexes with heterocyclic aldehyde Schiff base, J Indian Chem Soc 1987, 64, 685-686.
[22]. Meng F, Zhao Q, Lim XinY. Yingyong Hu axue, 2002, 19, 1183-1185
[23]. Obaleye JA, Akinremi CA. Synthesis, characterisation and antimicrobial studies of some copper (II) complexes of mixed fluoroquinolone ligands. Nigerian Society for Experimental Biology (NISEB) Journal 2011;11:233-242. 61. Obaleye JA, Akinremi CA. Synthesis, characterisation and antimicrobial studies of some copper (II) complexes of mixed fluoroquinolone ligands. Nigerian Society for Experimental Biology (NISEB) Journal 2011;11:233-242.
[24]. Sobhi M. Gomha, Nabila A. Kheder, Mohamad R. Abdelaziz, Yahia N. Mabkhot, Ahmad M. Alhajoj, A facile synthesis and anticancer activity of some novel thiazoles carrying 1,3,4-thiadiazole moiety, Chemistry Central Journal, 2017, 11:25.
[25]. Mukesh Shankarrao Kadam1,*, Sachin Atmaram Khiste2, Satish Ashruba Dake3 andBhimrao Chintamanrao Khade4,* Anti-Infective Agents, 2020, Vol. 18, No. 4