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Isoniazid, Ciprofloxacin and Chloroquine Containing Transition Metal Based drug as Potential Antimicrobial, Antifungal Agent: A Short Review

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Abstract: Antibiotic resistance has been growing at an alarming rate and consequently the activity of antibiotics against Gram-negative, Gram-positive bacteria and fungal spores has dropped very fast day to day. Due to this there is a very strong need to synthesis new substances that have good anti-bacterial, anti-fungal activity as well as having new mode of action. Inorganic compounds particularly metal complexes have played an important role in the development of new metal based drugs complexes. A significantly rising interest in the design of metal complexes as drugs and diagnostic agents is currently observed in the area of scientific inquiry, specifically termed medicinal inorganic chemistry. In this review article we have focused on research undertaken over the past few decades which has sought to possess pharmacological screenings like anti-microbial, anti-fungal, anti-oxidant action of isoniazid, ciprofloxacin and Chloroquine containing synthetic transition metal complexes.

Keywords: Isoniazid, Ciprofloxacin, Chloroquine, Metal complexes, Antibacterial, Antifungal, Anti-Tuberculosis, Anti-Cancer etc.

1. Introduction:

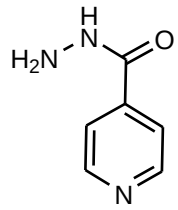
Metals have played an important role in medicine for years, ever since human being started to walk on the planet. Many are essential to our diets in varying quantities, although people have only recently realized their significance. Around 5000 years ago the Egyptians used copper metal to sterilize water and gold was used in a variety of medicines in Arabian and China, but the practice emanated from the value of pure metal rather than from therapeutic

effects. Our bodies are 3% metal. Metal coordination complexes provide a rich platform for the synthesis of novel chemotherapeutic drugs. We can choose the transition metal for the synthesis of complexes with drug because of its variable oxidation state. Metals not only provide templates for synthesis, but they also introduce functionalities that enhance drug delivery vectors. Many organic drugs require interaction with metals for activity. They interact with metals at their target site or during their metabolism.

Isoniazid metal complexes have enjoyed a lot of attention due to its antituberculostatic, antidepressant and antibacterial properties (*Zhang Y et al,* 1993). Tuberculosis, caused by Mycobacterium tuberculosis (MTb), is the second leading cause of death from an infectious disease and it is surpassed by the human immunodeficiency virus (HIV) (*Md. Saddam Hossain et al,2017, WHO, 2009-2011*). Tuberculosis (tubercle bacillus) that kills between 2 and 3 million people every year in the world (*T. Aboul-Fadl et.al, 2010 , M. C. D. S. Lourenco,2008*). It is the only disease which does not require any vector for transportation from one person to another or to cross the physical boundary of the countries (*M. Shahar Yar,2008*). WHO declared TB as a global emergency but since that time, no new drug have successfully been developed for the treatment of the disease. With the global emergence of multidrug-resistant tuberculosis (MDRTB), there is an urgent need to develop more potent and fast acting anti-TB drugs. The researchers now a day are trying to discover isoniazid containing new metal based drugs that would be most effective against TB. In this review we explored the overview application of isoniazid based metal complexes.

Many synthetic drugs have been discovered over the years for the treatment of malarial disease like chloroquine, sulphadoxine and pyrimethamine being among the most effective. However, malarial parasites resistant to these drugs are now widespread in America, Asia and Africa. Resistance to antimalarial drugs first to chloroquine and then to others was first noticed in the 1950s and since then, it has spread all over the world. Resistance of Plasmodium falciparum to chloroquine has become a major health concern of developing world. Therefore, it becomes highly necessary to come up with alternative antimalarial drugs with different structures and mode of action to deal with the development of resistance to the drugs in current use. Many researchers worked extensively on discovery of new therapeutic

drugs to combat this problem of resistance. A number of papers on modification of the structure of the existing antimalarial drugs by incorporation of metals into their molecular structure appeared in literature. Notable among them are those of (*Spacu et al,1968; Wasi et al,1987 ; Hubel et al, 2000; Biot et al,1999; Navarro et al, 2001; Sanchez-Delgado et al, 1993 and Tsangaris et al, 1974, Biot et al.2000*). The most recent and remarkable is the work carried out by Biot and co-workers. They inserted ferrocene(organometallic compound) into molecular structure of some antimalarial drugs.There is strong evidence that significant structural change to the side chain either through altering its length or through the introduction of more structural motiys such as ferrocene by *Biot et al, (1999).*From the literature review (*Shaban, et al,2000*) reported the determination of mixed Chloroquine and Pyrimethamine metal drug complexes.



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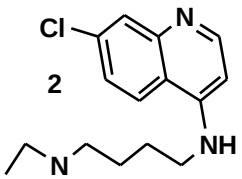

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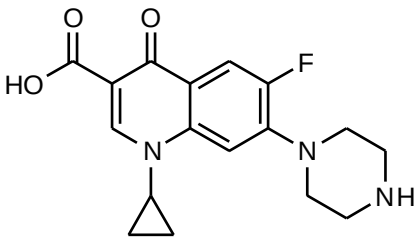


C

Structure A) Isoanizide B) Chloroquine C) Ciprofloxacin

Numerous research papers have described the bactericide and fungicide properties of various mixed ligand complexes of metal ions with isoniazid and hydrazone derivatives.3,4(*KRIZA et.al.2009, Narang et.al 1996).*As per literature survey transition metal ions particularly in 3-

d series has been subjected for detailed investigation (*Carlin, 1965*). Co-ordination compounds have employed greatly in the field pharmaceutical, medicine and therapeutics, micro management and diagnosis of diseases (*Fenton, 1995).* Cu2+ cation has extensively discussed that due to it slew of low-molecular-weight, Cu 2+ has as proved that it can act against various diseases such as rheumatoid, turberculosis, gastric ulcers, and cancers (*Guangguo Wu, 2003; Sorenson 1976; Brown, 1980; Williams, 1971; Ruiz, 1995).*When drug administrated as a metallic coordination complex, they shows increased pharmacological and toxicological properties are exhibited. In the third generation quinolone family Ciprofloxacin (cpf) was widely considered as the best one. Crystal structure of metal complexes with cpf has been reported greatly. (*Guangguo Wu, 2003; Turel, 1997; Turel, 1998; Yang, 1999; Wang, 2000).* Currently, the structure of quinolone-metal complexes have been focused, however, the research on the nature of complexes is neither comprehensive nor deep (*Zhengde Tan, 2012; Turel, 1997; 1994; Parker, 1998; Rodriguez, 1984*). Ciprofloxacin can usually act as a bidentate ligand through the pyridone oxygen and one carboxylate oxygen. In the literature, diverse transition metal complexes of ciprofloxacin have been structurally characterized (*Ketan, 2012; R.Saranya, 2017*).

Isoniazid, an anti-tuberculosis (TB) drug has been coordinated with chromium, molybdenum, and tungsten metal carbonyls and three new zero-valent complexes fac-[M(CO)3(isoniazid)3] (M = Cr, Mo, and(isoniazid = 4-H2NHNOCC5H4N) have been synthesized by *Jesudural D and et al.*An isonicotinoyl dithiocarbazic acid (IN-DtczH) ligand, synthesized from isoniazid, was complexed with transition metals and evaluated for anti-mycobacterial activity as well as toxicity towards human-transformed rhabdomyosarcoma (RD) cells in vitro by *Shamsher Singh Kanwar* . Complexes with Ni, Co and Zn showed MIC of 2, 2 and 50 µg/ml against Mycobacterium tuberculosis H37Rv, and 10, 100 and 50 µg/ml against a multidrug-resistant strain of M. tuberculosis. *Bamigboye M. O and et al.* were synthesized Mn2+, Fe2+, Cu2+, Co2+, Zn2+, Cd2+ complexes of mixed of Trimethoprim-Isoniazid. *K P Deepa and et al.* synthesized five new metal chelates of omega-bromoacetoacetanilide isonicotinylhydrazone. The ligand behaved as a tridentate complexes. They also carried out antifungal studies of these compounds against four selected pathogenic

fungal strains using a cup-plate technique. Both the ligand and its metal chelates were active against all fungal strains investigated. However, the chelates were found to be more active than the ligand. *Elena Pahont and et al* Hydrazone complexes of Cu(II), Co(II), Zn(II), Ni(II) and Pt(II) with N-isonicotinoyl-N0-(3-metoxy-2hydroxybenzaldehyde)-hydr azone (HL) were synthesized and characterized by different physico-chemical techniques. Spectral data showed that hydrazone behaves as tridentate ligand through the azomethine nitrogen, phenolate and keto oxygen atoms. For the copper (II) complexes, metal– ligand bonding parameters were evaluated from the EPR spectra. The antibacterial activity against Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus and Candida albicans strains were studied and compared with those of free ligand. The complexes showed significant antimicrobial activity against the Gram-positive bacteria Staphylococcus aureus and Candida albicans in comparison to the control drugs.

K. S. PATEL and et al. Synthesis of Cu(II), Ni(II), Co(II), and Mn(II) Complexes with Ciprofloxacin and Their Evaluation of Antimicrobial, Antioxidant and Anti-Tubercular Activity. In Ciprofloxacin complexes, the metal coordinated to the ligands through the oxygen of the carbonyl group. The compounds were subjected to antimicrobial, antioxidant and anti-tubercular activity screening using serial broth dilution method and Minimum Inhibitory Concentration (MIC) is determined. Mn(II) complex has shown significant antifungal activity with an MIC of 6.25 µg/ml while Cu(II) complex is noticeable for antibacterial activity at the same concentration. Anti-TB activity of the ligand has enhanced on complexation with Ni(II) and Co(II) ions. While Ni(II) complex shows superior antioxidant activity than other complexes. All the metal complexes were more potent bactericides and fungicides than the ligand. All complexes were characterized based on elemental analyses, and IR, UV–VIS–NIR and EPR spectroscopy, as well as by thermal analysis and determination of their molar conductivity and magnetic moments.

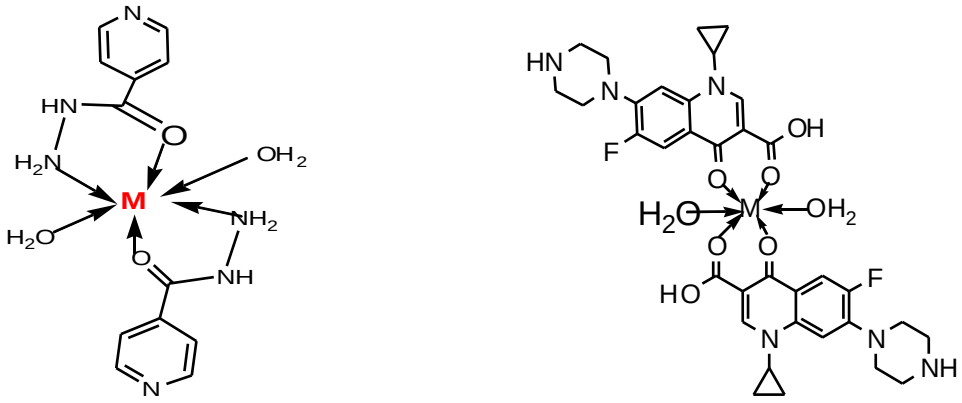
Obaleye et al. (2007) Toxicological studies and antimicrobial properties of some Iron(III) complexes of Ciprofloxacin. Two iron(III) complexes of Ciprofloxacin were synthesized by reaction of the ligand with iron(III) chloride in solutions. The nature of bonding of the ligands and the structure of the isolated metal complexes were elucidated on

the basis of their physical and spectroscopic studies. The infrared spectra suggest that two classes of compounds were obtained: molecular complex in which the ligands were bidentately bonded to the metal through the ring carbonyl oxygen and one of the oxygen of the carboxylate group. The antibacterial activities of the products against various microorganisms were tested and it was established that their activities were comparable with those of their parent drug. Toxicological studies were carried out in which therapeutic doses of the Ciprofloxacin drug and the metal complexes were administered to albino rats and the results showed that the metal complexes are not toxic.

Muhammad imran and et al. (2007) In Vitro Antibacterial Studies of Ciprofloxacin-imines and Their Complexes with Cu(II),Ni(II),Co(II), and Zn(II). These ligands as well as their metal complexes were also evaluated for their antibacterial activity against several bacterial strains, such as Staphylococcus aureus, Bacillus subtilus, Salmonella typhae, and E. coli. It was found that metal complexes are more antibacterial as compared to uncomplexed ligands. On chelation the polarity of the metal ion will be reduced to a greater extent due to overlap of ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further it increases the delocalization of Π-electrons over the whole chelate ring and enhances the lipophilicity of complexes (23) *Tumer M and et.al(*1999).

Bhupinder Singh Sekhon et al.(2012) Transition metal-based anti-malarial drug. A number of potential metal-based anti-malarial drugs have become available. The various metal complexes used as effective anti-malarials include metals such as iron, gold, ruthenium, cobalt, rhodium, iridium, copper, cobalt, zinc, osmium and palladium. The most likely anti-malarial mechanism involving metal complexation occurs by heme aggregation inhibition. Metal-chelating agents seem to be promising therapeutic adjuvants for treatment of severe Plasmodium falciparum malaria infection, and the better activities observed against resistant parasites are probably due to the structural modification. Ferroquine has been found active against both chloroquine-susceptible and chloroquine-resistant Plasmodium falciparum and P. vivax strains. The derivatization of the fluoroquinolone, ciprofloxacin, with a ferrocene nucleus resulted in compounds which were found to be 10- to 100-fold more active than ciprofloxacin against P. falciparum chloroquine-susceptible and chloroquine resistance

strains. The potency of Ru(II) chloroquine complexes against resistant parasites was consistently higher than that of the standard drug chloroquine diphosphate. in this article they gives so many anti-malerial metallo -drug i.e. Ruthenium chloroquine [RuCQCl2]2, [RuII(η6-p-cymene)Cl2(CQ)], ruthenoquine, [Au(PPh3)(CQ)]PF6, [(CQ)Au(PPh3][NO3)]; [(CQ) Au(PMe3)][PF6]; [(CQ)Au(PEt3)][PF6]; [(CQ)2Au(Cl)2] Cl; [(CQ)Au(Cl)(SR)(Et2O)]Cl] displayed in vitro activity against CQ-sensitive and CQ-resistant strains of Plasmodium falciparum. The highest activity for this series was obtained for complex [(CQ)Au(PEt3)][PF6] , which was 5 times more active than chloroquine diphosphate (CQDP) against the CQ-resistant strain FcB1(*Navarro M and et al.2004, Blackie and et al 2003).*



(A) (B)

Fig. Proposed structure of A) metal ciprofloxacin complexes (M= Ni(II), Co(II), and Mn(II)) B)metal ciprofloxacin complexes (M= Cu(II), Ni(II), Co(II), and Mn(II))

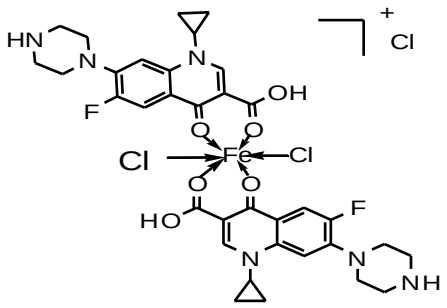


Figure 2. Di(ciprofloxacin)dichloro iron(III) chloride hexahydrate-[Fe(Cip)2Cl2]Cl.6H2O

2. Conclusion:

The chemistry of metal-drug interaction is significant and becoming popular. The efficacy of the drugs on complexation with metal ion is enhanced in many cases. This review article covered some of the recent literature of the metal-ion interaction with selected Isoniazid, Ciprofloxacin and Chloroquine and their comparative biological activities with respect to free Isoniazid, Ciprofloxacin and Chloroquine. The Isoniazid, Ciprofloxacin and Chloroquine represent a diverse class of bactericidal agents with multiple applications in ocular infectious diseases. Their action particularly targets to stop bacterial growth. Synthesis and structural modification in different generations of these compounds have led to improved bioactivity against wide resistant microbial species. This serves as a light cast for chemist interested in developing new design of drugs.

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