EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 9
137-149
Year: 2020

A SYSTEMATIC REVIEW: APPLICATION OF METAL COMPLEXES IN MEDICINAL COMPOUNDS

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Article Received on 29/06/2020 **Article Revised on 19/07/2020** **Article Accepted on 09/08/2020**

ABSTRACT
Transition metal complexes have been of much interest over the last years, largely because of its various applications in biological processes and potential applications in designing new therapeutic agent. The metal complexes offer a great diversity in their action such as; anti-inflammatory, anti-tubercular, anti-infective and anti-diabetic compounds. The aim of this review is a detailed analysis of the usefulness of the metal complexes of some medicinal compounds over the parent ligand. The synthesis and alteration in the pharmacological and/or pharmacotechnical properties of coordination complexes of many pharmaceutical substances like glimepiride, ciprofloxacin, amoxicillin, ampicillin, lansoperazole, isoniazide, naproxen and mixed complexes with transition metals and rare earth metal were studied in this review. The activity of the complexes was usually found to be increased in comparison to parent drug. The influence of certain metals on the biological activity of these compounds has prompted a considerable increase in the study of their coordinatioin behaviour. This review illustrates the role of metals, progresses in synthesis of metal based drugs and their application.

KEYWORDS: Metal complexes, better efficacy, improved activity, synthesis, applications.

INTRODUCTION

Metal complexes are also known as coordination compounds, which include all metal compounds. Metal complex may be a structure consisting of a central atom (or) ion (metal) bonded with anions (ligands). Compounds that contain a coordination complex are called coordination compounds. Metals are Lewis acid due to their charge, when dissolved in water they form hydrated compounds.

The coordination complexes are studied since 1798 starting with the Tassaert studies, and till nowadays significant progresses are made within the inorganic and organic chemistry concerning the synthesis, characterization, and application of this massive group of metal complexes. Concerning their structure, complexes were considered those compounds which don't fit within the classical theory of valence, meaning that the mixture ratio of the elements whether exceeded their valences. This coordination theory elaborated by Alfred Werner indicated that the secondary valences of the elements are involved in the formation of the second-order combinations leading to the actual representation of the complexes formed by the primary coordination sphere marked between brackets [central atom (ligand)] and therefore the second coordination sphere (ionization sphere) coming outside of the brackets. The central atom can be any chemical element; meanwhile, the ligands can be ions, atoms, or neutral molecules, which can act as donors.[1] Neutral molecules or mono-/polyatomic anions which have one or more unshared electron pairs can act as mono-/polydentate ligands, the latter ones form complexes with cyclic structure known as chelates. A huge number of pharmaceutical substances behave in vivo or in vitro conditions as ligands and chelating agents.[2]

One of the foremost important properties of metallic elements is their ability to act as Lewis acids that form complexes with a spread of Lewis bases. A metal complex consists of a central metal atom or ion that's bonded to atleast one or more ligands (from the Latin ligare, meaning "to bind"), which are ions or molecules that contain one or more pairs of electrons which will be shared with the metal. Metal complexes are often neutral, like $Co(NH_3)_3Cl_3$; charged, like $[Nd(H_2O)_9]^{3+}$; or charged, like $[UF_8]^{4-}$. Electrically charged metal complexes are sometimes called *complex ions*. A *coordination compound* contains one or more metal complexes.

Natural metal complexes in the body

Natural metal complexes consisting of a central metal atom or ion (especially of the 3D transition metals) are involved during a many biological mechanisms among which photosynthesis, transport of oxygen in blood,

coordination of some metabolic processes, pathological states, enzymatic reactions, etc., albeit the metallic ions represent only 3% of the body composition. Many biomolecules (amino acids, peptides, carboxylic acids, etc.) can form metal complexes with different stabilities having biomedical importance.[3]

Metal ions bond with ligands in some process, and to oxidize and reduce in biological systems.The important metal present within 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. An adult at rest consumes 250ml of pure oxygen per minute, this oxygen carried by the metal complex transport system referred to as heme, allowing the oxygen to depart from the blood when it reaches the tissue. The heme group is metal complex, with iron as central metal atom, which bind or release molecular oxygen.

Role of metal ions in body

Metal ions play many critical functions in humans. Deficiency of some metal ions can cause disease like pernicious anemia resulting from iron deficiency, growth retardation arising from insufficient dietary zinc, and heart condition in infants owing to copper deficiency. The ability to know at the molecular level and to treat diseases caused by inadequate metal-ion function constitutes an crucial aspect of medicinal bioinorganic chemistry. Metal ions are required in biology for its role as pharmaceuticals also as diagnostic agents. Metals are endowed with unique characteristics that include redox activity, variable coordination modes, and reactivity towards organic substrates. Due to their reactivity, metals are tightly regulated under normal conditions and aberrant metal ion concentrations are associated with various pathological disorders, including cancer. For these reasons, coordination complexes, either as drugs or pro-drugs, become very attractive probes in medicinal chemistry. In nature, many biological systems make extensive use of metal ions, like zinc and copper, which play critical roles for the normal functioning of organisms.[4]

Transition metals such as copper, iron, and manganese, among others, are involved in multiple biological processes, from electron transfer to catalysis to structural roles, and are frequently associated with active sites of proteins and enzymes.

The use of transition metal complexes as therapeutic compounds has become more and more pronounced. These complexes offer an excellent diversity in their action such as; anti-inflammatory, anti-infective and anti-diabetic compounds. Considerable efforts are made for the evolution of transition metal complexes as drugs. Beside several limitations and side effects, transition metal complexes are still the most widely used chemotherapeutic agents and make a large contribution to medicinal therapeutics.[5]

Benefits of metal complexes[6]

1. Metal complexes and products containing oligoelements are widely used in therapy due to increase in pharmacodynamic properties.
2. Complexation improves the aqueous solubility and thermal and acid stabilities.
3. Metal complexes of some compounds result in their bioavailability enhancement.
4. Metal complexes results in decreased toxicity of some metal ions.
5. Metal complexes with transition metal result in improvement of pharmacotechnical properties.
6. The structure-activity relationship of drugs could be predicted by complexation.
7. Drug complexation experiments can also help medicinal chemists to predict some dosage form incompatibilities, explain the mode of action of some drugs, and devise new methods of drug analysis.
8. Metal complexes are also helpful in drug analysis and control.

Platinum Complexes as therapeutic agents

Cisplatin: Platinum compounds, particularly cisplatin, are the heartbeat of the metal-based compounds in cancer therapy. Clinical use of platinum complexes as an adjuvant in cancer therapy is based on the desire to achieve tumor cell death and the spectrum of activity of the candidate drug. Such complexes are mostly indicated for the treatment of cervical, ovarian, testicular, head and neck, breast, bladder, stomach, prostate and lung cancers. Their anticancer activities are also extended to Hodgkin's and non-Hodgkin's lymphoma, neuroblastoma, sarcoma, melanoma and multiple myeloma.[7] Although resistance to cisplatin emerged, it was the fundamental basis that triggered the finding of alternative metallic compounds with improved anticancer and pharmacokinetic properties. On this basis, alternative platinum compounds were derived. Carboplatin, oxaliplatin, satraplatin, ormaplatin, aroplatin, enloplatin, zeniplatin, sebriplatin, miboplatin, picoplatin, satraplatin, and iproplatin are all products of deep research of platinum complexes.

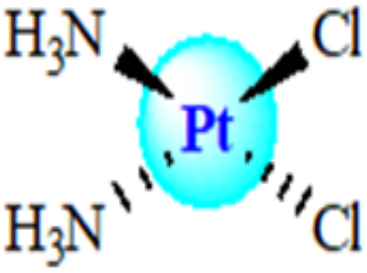
The side effects of cisplatin treatment are severe and include the dose-limiting nephrotoxicity, neurotoxicity, ototoxicity, and emetogenesis. The ''second-generation'' compounds based on the cisplatin structure were developed in attempts to improve toxicity and/or expand the range of useful anticancer activity.

Carboplatin: Carboplatin entered the clinic in 1998, principally in response to the necessity to reduce the toxic side effects of the parent drug. Despite this lower toxicity, carboplatin is essentially active in the same set of tumors as cisplatin and a broader spectrum of activity is not indicated.[8]

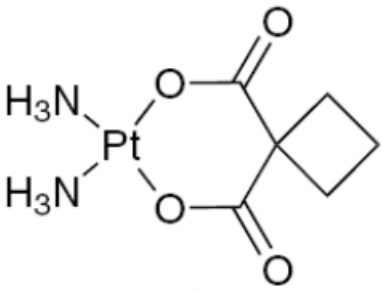
Oxaliplatin: Oxaliplatin was initially launched in France in 1996 and formally available in the countries of Europe

in 1999 and the US in 2002. This is a platinum-based drug with oxalate and diaminocyclohexane ligand (DACH). The DACH plays a major role in cytotoxicity and protects it against cross-resistance with cisplatin and oxaliplatin. It is licensed to be used as a combination therapy with other chemotherapeutic agents in the management of colon cancer and non-small-cell lung cancer.[9] This drug has better safety profile than cisplatin, as such is used in patients who cannot tolerate cisplatin.[10]

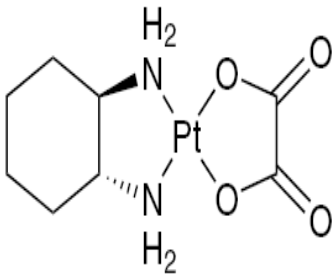
Satraplatin: Satraplatin, *bis*-(acetate)-ammine dichloro-(cyclohexylamine) platinum (IV), is the first orally bioavailable platinum drug. This drug exhibits varying pharmacodynamics and pharmacokinetic properties relative to other platinum compounds and hence may possess a special spectrum of anticancer activities.[10] The anticancer activities of satraplatin span through platinum-sensitive and resistant cell lines, including cervical, prostate, ovarian and lung cancers. Nonlinear pharmacokinetics was one major challenge encountered during the initial studies of satraplatin that led to the study being abandoned. Satraplatin has undergone several phases of clinical trials. Phase III clinical trials examined satraplatin and prednisolone combination against refractory cancer.[11] Satraplatin is currently targeted in phase I, II and III trials in combination with other drugs such as docetaxel in the treatment of prostate cancer.



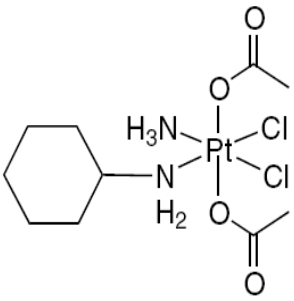
Cisplatin



Carboplatin



Oxaliplatin



Satraplatin

Metal complexes as anti-diabetic agent

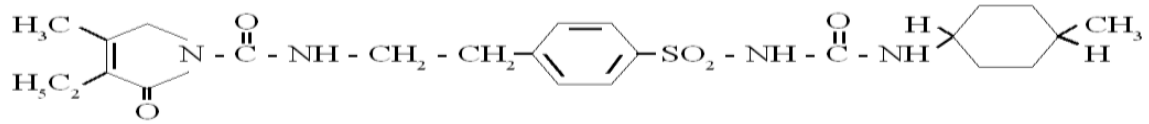
Samarium complex of glimepiride

In recent years, much attention is given to the utilization of suphonyl ureas because their high complexing nature with essential metals. Sulphonyl ureas are effective for non-insulin dependent diabetes mellitus.[12]

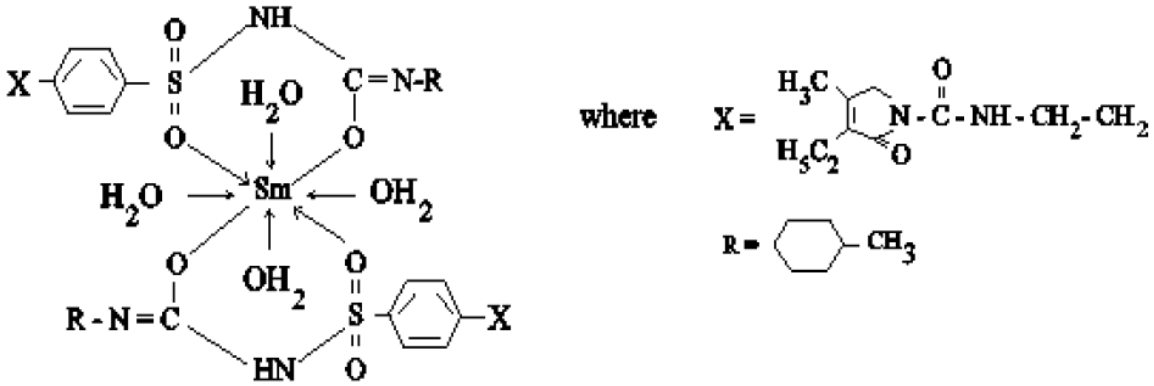
These compounds are completely absorbed on oral administration. They are metabolized by liver and are excreted predominantly through urine.Complexation of sulphonyl ureas with rare earth's metals have been studied in detail by several workers. A perusal of available literatures shows that systemic study on complexation samarium with variours hypoglycemic drugs is relatively more important.[13]

Synthesis

A weighed quantity of glimepiride (2mol.) was dissolved in minimum quatity of 80% DMF. The samarium trioxide solution was prepared by dissolving it separately in the same solvent. A few drops of alkali NaOH solution was added to metal solution to increase the solubility. Metallic solution was added slowly with stirring into the solution of ligand at room temperature maintaining the pH between 6 to 8 by adding dilute NaOH solution and refluxed for 2-4 hours at 80°C.[14],[15] The solutions were left for crystallization at room temperature for 18-20 hours, shiny grey coloured crystals of complex were obtained which were filtered,washed, dried and then their melting points determined were recorded.



Structure of glimepiride



Structure of glimepiride-samarium complex.

Antidiabetic activity

The isolated glimepiride-metal complex were found to be stronger as compared to the parent drug. Hence as compare to standard synthetic drug the glimepiride-samarium complex is having more hypoglycemic activity.[16] The hypoglycemic effect of glimepiride as well as metal complex were investigated on the blood sugar levels of male wistar rats by Oral glucose tolerance test.[17] Hypoglycemic activities of the complex shows more blood glucose lowering effect as compared to parent ligand. Calculating the toxicity in the complexes and on many trials on monkey's and men the complex may be introduced as medicine in future.[18]

Cu (II) and Fe (III) complexes of glimepiride

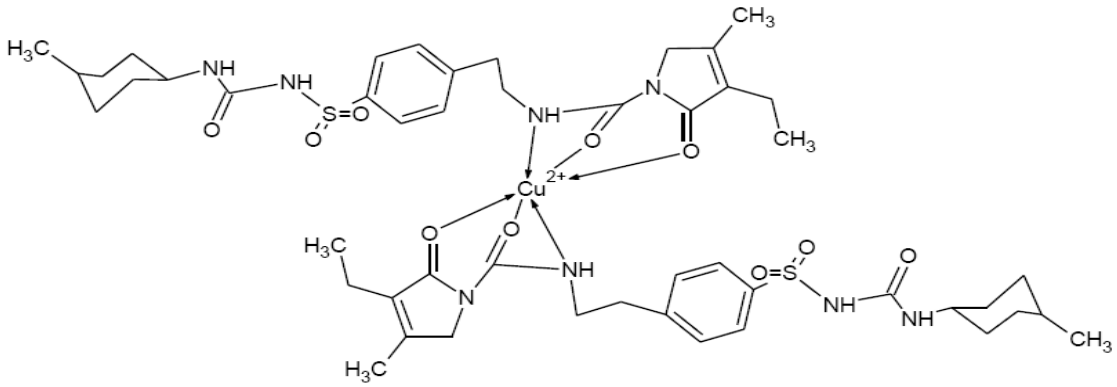
Copper sulfate treatment in diabetes has demonstrated helpful impacts with protection of β-cell work by decreasing free radicals or thorough lessening in glucose levels.Glimepiride is a third era sulfonylurea drug utilized for the treatment of type 2 diabetes which brings down glucose level by animating the arrival of insulin through pancreatic beta cells and by inciting expanded action of intracellular insulin receptors. Complexation of sulphonylureas with transition and inner transition metals has been considered in detail.[19]

Synthesis of the [Cu(GMP)2] complex

(1) The complex was prepared following reported procedure.[20] The copper solution was prepared by dissolving 4.26 g (0.025 mol) of CuCl2.2H2O in 25 ml ethanol. The solution of the metal salt was added slowly with stirring in separate 20 ml of ethanol solution of 12.25 g of glimepiride (0.025 mol) at room temperature maintaining the pH between 6.0 - 6.5 by adding dilute solution of NaOH. On refluxing the mixture for 3 hours and cooling, the complex separated**.** The complex formed was washed with ethanol, recrystallized, filtered andfinally dried in vacuum. The yield was recorded.

(2) **Synthesis of complex**

Complex was synthesized by mixing the solution (DMF) metal salt solutions with that of ligand in 1:2 molar ratios, respectively and refluxing the mixture for 3.5 to 4 h. The dark green precipitate of [Cu(C24H34N4O5S)2(H2O)2] and red brown precipitate of [Fe(C24H34N4O5S)2(H2O)2] formed was filtered, washed with DMF, dried and weighted, melting point of the complex was recorded.[21]



Proposed structure for [Cu(GMP)2] complex.

Anti- Diabetic Activity

The hypoglycemic activities (acute test) of glimepiride and [Cu(GMP)2] complex after 2 hours, there were no significant differences (P<0.05) in the sugar level of the complex ([Cu(GMP)2] 312.50b±17.08). This may be due to slow release of the compound from the synthesized metal complex. After 4 hours, 6 hours and 8hours, a significant decrease (P<0.05) in blood glucose level was observed in animal group treated with ([Cu(GMP)2] complex 283.25c±10.01 to 161.00c±14.63). The Cu complex showed significant reduction in blood sugar level more than the parent drug itself (glimepiride drug). This indicates that Cu complex shows more hypoglycemic actions. The results are in alignment with the findings that metals are‘’insulin mimetic’’ and can play a role as anti-diabetic potential elements. Comparison of the hypoglycemic effects of the complex with the parent drug shows that the metal complex has better hypoglycemic effect.[22]

Metal complexes as antibacterial agents

Metal (II) complexes of ciprofloxacin

Ciprofloxacin (CFL) is a synthetic, broad-spectrum fluoroquinolone antibacterial agent for oral administration. It is active against a wide variety of aerobic gram-negative and gram-positive bacteria. After some research, it came to light that antibacterial drugs become more effective against bacteria upon chelation/coordination with the transition metal ions. Transition metals are present in very low concentrations in vivo, and their ligand environment can be considerably altered. This change in balance between the metal ion and drug ligand may have profound effects upon the activity of a drug against potentially susceptible bacteria. This formation may increase the bioavailability of either the metal ion or the drug ligand or both.[23]

Fluoroquinolones have broad spectrum of antimicrobial activity, high bioavailability, good penetration into tissues, long serum half-life and safety. These have made the compounds very attractive agents for treating numerous infectious diseases. The site of action of FQs has been pinpointed to a subunit of that remarkable enzyme, DNA gyrase which unwind the supercoiled DNA helix prior to replication and transcription.[24]

Synthesis

Preparation of ciprofloxacin-cobalt(II) complex

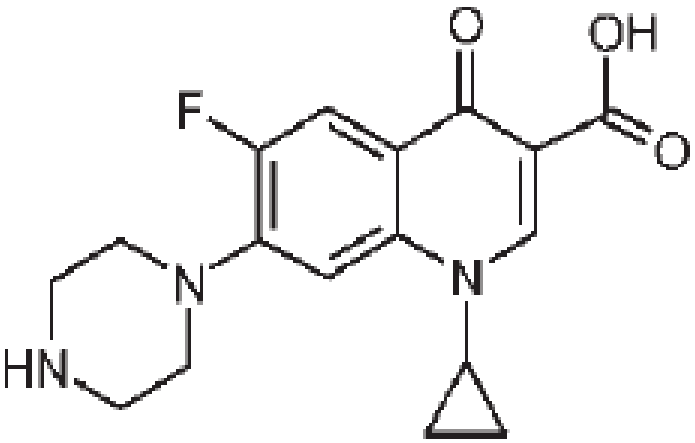
The complex was prepared by using the method adopted by dissolving 10mmole (3.31g) ciprofloxacin in 20ml hot methanol. Five millimoles (5mmole), (1.189 g) cobalt(II) chloride hexahydrate dissolved in 10ml hot methanol was added with constant stirring and refluxed for 2hours. The mixture was then transferred to a beaker and left in a refrigerator for 30minutes. The brown precipitate was washed with (3 x 5)ml portions distilled water and dried in dessicator over anhydrous calcium chloride for three days.[25],[26]

Preparation of ciprofloxacin-ni(II) complex

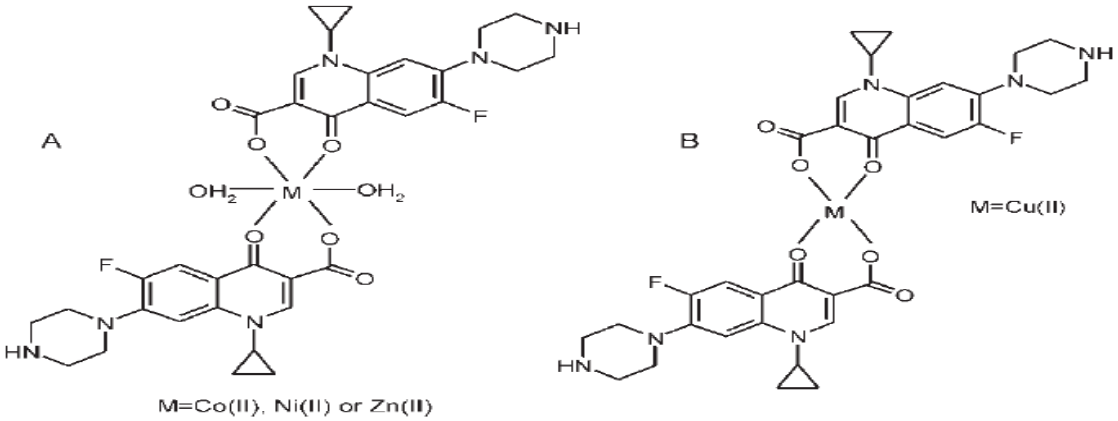
The complex was prepared by dissolving 20mmole (6.62g) of finely powdered ciprofloxacin in 20ml hot methanol. Ten millimole (2.377g) of nickel((II) chloride hexahydrate was dissolved in 10ml hot methanol. The two solutions above were mixed and refluxed for 2 hours with constant stirring. The mixture was then carefully poured into a beaker and cooled to room temperature before filteration. The precipitate was washed with (3 x 5ml) portions methanol and also with distilled water. The precipitate was dried using similar procedure already described.

Preparation of ciprofloxacin-copper(II) complex

Ten millimole (3.31g) ciprofloxacin drug was dissolved in 20ml hot methanol and mixed with 5mmole (0.853g) copper(II) chloride dihydrate dissolved in 10ml hot methanol. The mixture was refluxed with constant stirring for 2 hours. The content was then transferred to a beaker and cooled to room temperature. After filtration, the green precipitate was washed with 3 - 5ml petroleum ether followed by distilled water. The precipitate was dried as described above.



Structure of ciprofloxacin.



Proposed structure of the metal(II)–CFL complexes.

Antimicrobial activity

Antimicrobial activities of the parent drug (ligand) and the metal(II) complexes were tested against different species of bacteria (Gram-positive and Gram-negative) namely: S. aureus, E. coli, P. aeruginosa, K. pneumonia and B. dysenteriae. The metal(II) complexes exhibited a marked enhancement in ciprofloxacin activity against all the test bacterial strains compared to the parent antibiotic, ciprofloxacin (L).

It has been suggested that those ligands have nitrogen and oxygen donor systems might inhibit enzyme activity, since the enzymes which require these groups for their activity appear to be especially more susceptible to deactivation by the metal ions upon chelation.[27]

Iron (III) complexes of ciprofloxacin, cloxacillin, and amoxicillin[28]

Synthesis of iron (III) complex of ciprofloxacin. CiprofloxacinHCl (1mmole) was dissolved in aminimum quantity of distilled water. To this solution FeCl3 (0.5mmole) dissolved in absolute ethanol was added.The mixture was stirred continuously with magnetic stirrer at room temperature for 3 hours. The resulting red solution was transferred into an evaporating dish and allowed to evaporate slowly at room temperature for one week. The red crystals formed were purified by recrystallizing in a minimum quantity of ethanol and weighed.

Synthesis of iron (III) complex of cloxacillin. Cloxacillin powder (1mmole) was dissolved in dioxane (100 mL). To this solution an ethanolic FeCl3 solution containing 162.5mg of FeCl3 in ethanol (10 mL) was added. The mixture was stirred continuously for 4 hours at room temperature at the end of which clay-brown crystals separated from the solution. The mixture was filtered and the crystals were washed thoroughly with dioxane, dried in a desiccator, and weighed.

Synthesis of iron (III) complex of amoxicillin. Amoxicillin powder (1mmole) was dissolved in methanol (100 mL) in a beaker. FeCl3 (1mmole) was put in another beaker containing ethanol (10 mL). The two solutions were put in a round bottom flask and stirred with a magnetic stirrer under reflux maintained at 40∘C for 4 hours. The resulting green solution, which was foaming, was transferred into an open beaker and allowed to stand for 1 week. The green crystals obtained were washed thoroughly with small quantity of ethanol, dried, and weighed.

Antimicrobial activity

Ciprofloxacin complex shows improved antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* in comparison there to of the ligand. It had almost the same activity against *Pseudomonas aeruginosa*, *Escherichia coli*, and *Shigella* spp. as the ligand and lower activity against *Salmonella typhi* when compared to that of the ligand.

Iron (III) complexes of cloxacillin and amoxicillin showed decreased antibacterial and antifungal activities in comparison to those of the corresponding ligands. This could be attributed to loss of some essential pharmacophoricmoieties due to coordination with the metal ion.The sites used for dative bonding with the central metal ion are no longer available for binding with the biological receptors in the microorganisms.

Metal complexes of proton pump inhibitor

Investigations are happening on the formation of metal complexes with benzimidazole ligand. Benzimidazole and its derivatives play an important role in analysis and in several biological reactions.Benzimidazole derivatives exhibit antibacterial,antihelmintic and insecticidal activities.[29] Transition metal complexes containing benzimidazole are widely used as catalysts for hydrogenation, hydroformaylation, oxidation and others reactions.[30]

Copper complex of lansoprazole

Synthesis of copper complex

For the synthesis of complex of Lansoprazole-copper, 2 mol of the ligand was dissolved in 100ml of acetone – water mixture (60:40) and added slowly to a solution 1mol of copper chloride solution(solvent acetone–water (60:40) mixture). The mixture was refluxed for 3 hours, cooled and filtered. A brown colored crystalline complex

was separated. The complex was washed with acetone – water mixture, dried and weighted (yield 32%) and melting point was recorded.[31]

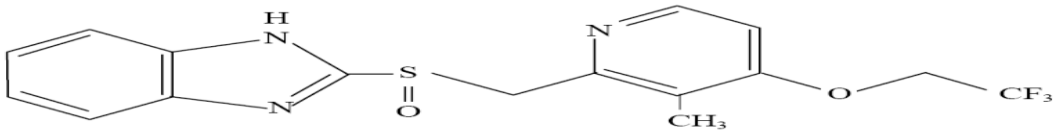


Fig. 1: Structure of lansaprozole

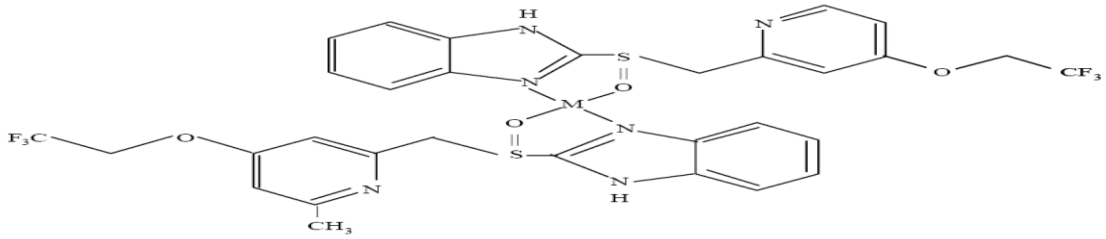
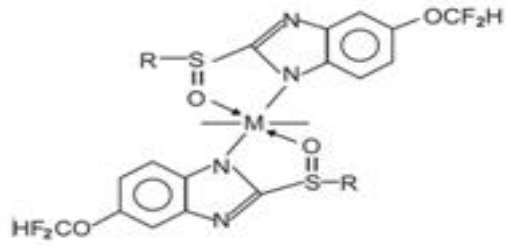


Fig. 2: Structure of Lansoprazole-copper Complex

Complexes of pantoprazole with transition metal ions [Vo(II), Cu(II) and Cd(II)][32]

Synthesis of the complexes

Pantoprazole metal complexes were prepared by mixing of Pantoprazole and the metal salt in 1:1 molar ratio and refluxing the mixture for 5-6 hours over water bath. The solution on nconcentration gave insoluble complex, which was filtered washed and dried (after recrystallisation) in vaccume. The complexes were stored in airtight bottles.



Proposed structures of these metal complexes.

Antibacterial activity

The Pantoprazole(PAN) show moderate inhibition with E.coli species with 1.9 mm inhibitory zone.The binary complex of PAN with Vo(II), Cd(II) metal ions show less activity as compared to parent drug PAN, whereas binary complex of Vo(II) show almost similar effect as PAN with E.coli.But binary complex of Cu(II) show higher antibacterial activity. The binary complexes of PAN with Staphylococci aureus also show such antibacterial activity. PAN inhibit the Staphylococci aureus species with 2.0 mm inhibition zone.Cu(II) show high inhibition activity against Staphylococci aureus species, whereas other complexes show moderate inhibition activity as drugs do.The results of antibacterial screening indicate that the metal complex show more activity than drug. This may be due to higher stability of the metal complex than the drug.

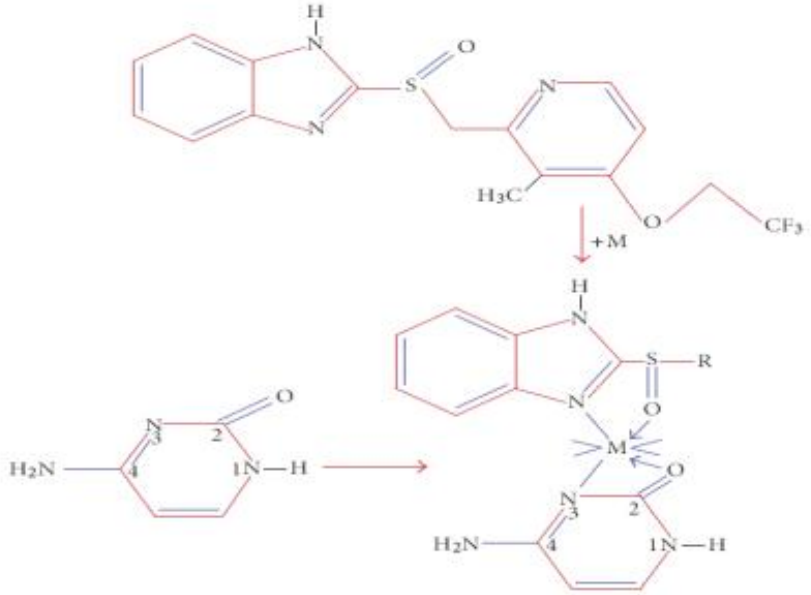
Mixed ligand complexes of inner transition metals with lansoprazole and cytosine

Considering the importance of drugs and their complexes it has been desired to synthesize and characterize some ternary complexes of inner transition metal [Th(IV), Ce(IV), Gd(III),Nd(III)] with a Benzimidazole derivative, lansoprazole, and cytosine. Lansoprazole being an antiulcer drug reduces gastric acid secretion and has successfully been used to heal and relieve symptoms of gastric or duodenal ulcers and gastroesophageal reflux.[33],[34]

Synthesis

The solid complexes were prepared by mixing the solution of metal salts [Th(NO3)4·4H2O, Ce(SO4)2·*x*H2O, Nd(NO3)3·6H2O,Gd(NO3)3·6H2O] with ethanolic solution of lansoprazole and cytosine in molar ratio 1 : 1 : 1. The resulting mixtures were then refluxed for 4-5 hours to give the precipitate.

After cooling at room temperature the solid complexes were filtered as fine precipitates. These precipitates were washedtwice with water. Then they were dried and stored in a desiccators containing dry calcium chloride. The compounds obtained were stable coloured solids.[35]



Proposed Scheme and Structure of representative ternary complex (M-Lanso-cyto).

Antifungal activity

The antifungal activity of the ligand, metal salts and the corresponding complexes was assayed simultaneously against *Aspergillus niger* fungus by paper disk method[36] at room temperature. The pure metal salts, and lansoprazole drug showed activity in *Aspergillus niger*. The zones of inhibition against microorganism were measured (in cm) after 48 hours of incubation. The mixed ligand complexes showed higher inhibition zone as compared to parent drug. The result of antifungal activity indicates that the complexes are more active than free ligand (lansoprazole drug).

Metal complexes of antitubercular drug

Tuberculosis, an infectious ailment influencing numerous organs of the body is an insidious granulomatous disease bringing about dismalness and mortality in human eras for hundreds of years.

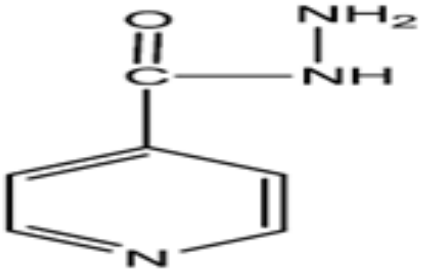
Effective TB treatment is difficult, thanks to the weird structure and chemical composition of the *Mycobacterium* cell membrane, which makes many antibiotics ineffective and hinders the entry of medicine.[37]

With the global emergence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) there is an urgent need to develop new anti-mycobacterial agents.

Complexes of isoniazid

Isoniazid, otherwise called isonicotinylhydrazide (INH),an antibiotic is among the principal line treatment pharmacological agents for the treatment of both inert and active tuberculosis.[38] It is active against not only mycobacteria, particularly Mycobacterium tuberculosis but is likewise effective against some atypical mycobacteria, such as M. kansasii and M. xenopi. Isoniazid is unique in that it goes about as a bactericidal agent against quickly dividing mycobacteria, while it is also bacteriostatic for the gradually developing mycobacteria making it a first line medication to battle bacteria which are otherwise hard to overcome by other common anti-infection agents because of their walling actions.[39] In the current years, issues on multidrug safe microorganism have been drawn closer at alarming level the world over. A very number of *Mycobacterium tuberculosis* strain end up plainly impervious to isoniazid and other first line medication of tuberculosis.[40]

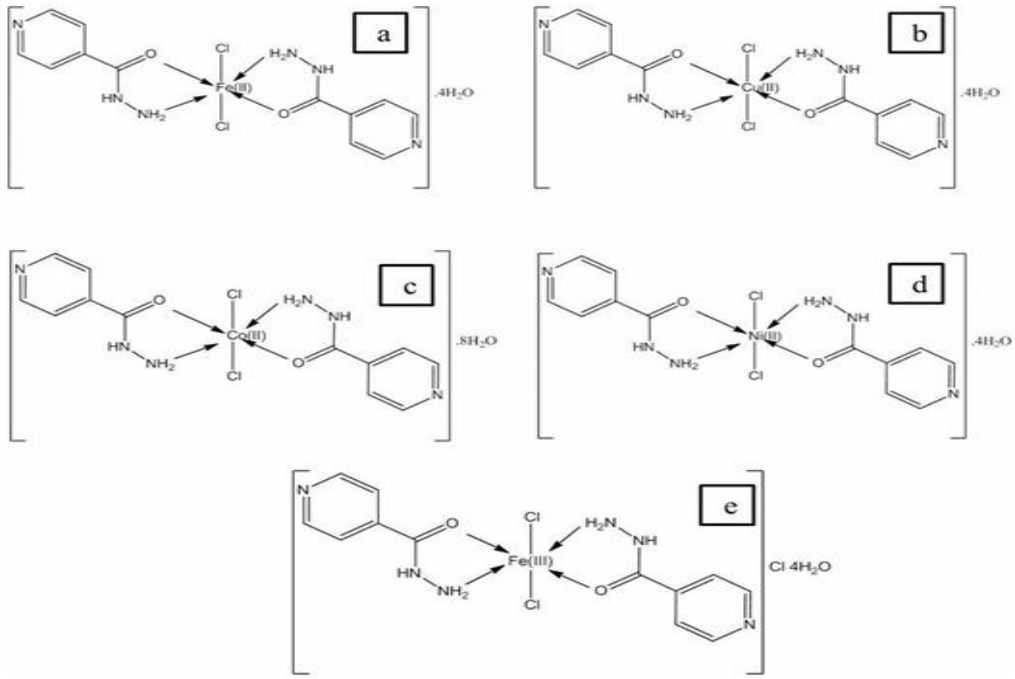
The science of metal coordination plays a noteworthy part in the field of biology and is used to investigate the metal complexes of natural drug molecules with the prospect of expanding their pharmacological actions and beating the resistance.



(Isoniazid)

Synthesis of complexes (INH)

Equimolar quantities of INH and metal salts (cobalt chloride) were weighed accurately on an analytical balance. Both were dissolved separately in the volumetric flask in methanol; each was introduced into a round bottomed flask. The mixture was refluxed on a water bath and allowed to heat for 4 hours with occasional stirring. After refluxed the mixture was allowed to cool at room temperature upon cooling crystals were formed at the bottom of the flask were separated out by filtration. The crystals were dried at 60ºC in an oven for 30 minutes. The same procedure was followed for the synthesis of Cu(II), Fe(II), Fe(III) and Ni(II) complexes of INH.[41]



Structures of Metal complexes of INH.

Antimycobacterial activity

Five reference multidrug resistant (i.e., resistant to isoniazid, pyrazinamide, ethambutol and rifampin) strains were used in this study for INH susceptibility test using the MGIT 960 system as per the manufacturer's instructions.

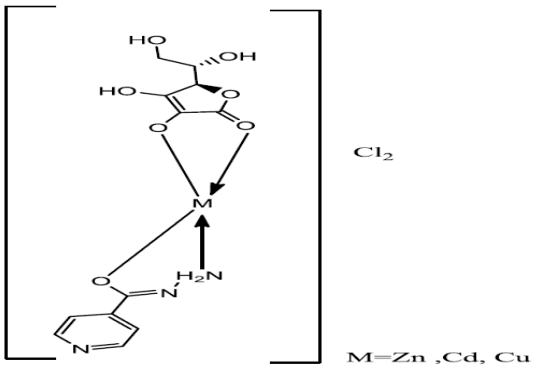
When parent drug and its Fe(II)-INH complex were tested for antimycobacterial activity they were found to resist the growth up to 2 weeks. The valuable results were obtained with complexes (Fe(III)- INH, Cu(II)-INH, Co(II)-INH, and Mn(II)-INH) in which growth of all five strains were retarded for 3 weeks. This showed that these complexes have the capability to resist the growth of mycobacteria and revealed that various derivatives of INH possess moderate activity against five strains as compared to INH and other first line anti TB drug (pyrazinamide, rifampicin and ethambutol) resistant strains of *Mycobacterium tuberculosis* for longer period of time. The promising activity of Fe(III)-INH, Cu(II)-INH, Co(II)-INH and Mn(II)-INH showed that they can be used to design further novel derivatives with better antitubercular activity.[41]

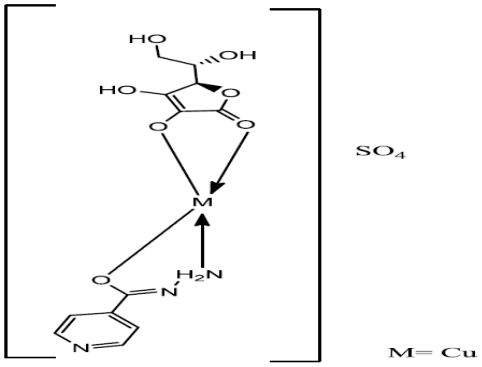
Mixed metal complexes of isoniazid and ascorbic acid

INH is in a position to coordinate with metal cations through different chemical groups: heterocyclic nitrogen from the pyridine ring and/or carbonylic O and N atoms of the hydrazide group. For this versatility, it is also an interesting ligand from the chemical point of view.Vitamin C, known chemically as ascorbic acid, is an essential vitamin necessary for the treatment of scurvy.[42] Vitamin C has also been cited to act as biological hydrogen carrier for redox enzyme systems in cell metabolism.[43]

Synthesis of the Mixed Metal Complexes

The method described by[44] were used in the synthesis of the mixed metal complexes. Isoniazid 0.137 g (1 mmol) was dissolved in 20 ml ethanol; 0.176 g (1 mmol) vitamin C was also dissolved in 20 ml water. 20 ml of aqueous solution of 1 mmol of metal (M= CuSO4, CuCl2, ZnSO4, CdSO4) were added to the solution of isoniazid and Ascorbic acid in a (1:1:1) ratio. The precipitated complexes were filtered, washed, dried and kept in sample bottles for further analysis.





Antimicrobial Activity

The result of the antimicrobial studies showed that all the mixed complexes showed higher activity compared to the parent ligand isoniazid and ascorbic acid. The metal complexes showed enhanced activities compared to the free ligands, the copper complexes in all the cases studied proved to be a better antimicrobial agent compared to the ligands and other metal complexes. The presence of several potential donor sites, e.g. heterocyclic nitrogen from the pyridine ring, carbonylic Oxygen and N atoms of the hydrazide group, and amide nitrogen atoms make them versatile complexing agent with metal ions.[45]

Metal complexes of naproxen

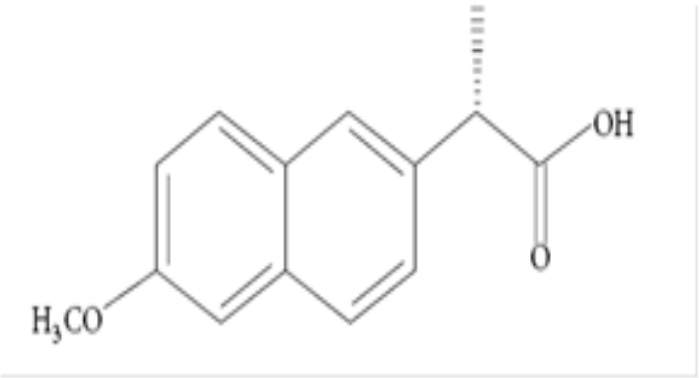
Nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most prescribed drugs worldwide as antipyretic, analgesic, and anti-inflammatory agents. However, the major limitation to NSAID use is the gastric and intestinal mucosal damage.[46] Much has been studied thus far to scale back the gastric toxicity of NSAIDs and during this regard, complex formation of NSAIDs with transition metals has long been recognized as an effective way of reducing gastric mucosal lesions caused by these drugs . Thus, the present study is performed to synthesize transition metal complexes of Naproxen and to observe their relative stability by conducting forced degradation studies. Forced degradation is an integral component of validating many analytical methods that indicate stability of the drug and detect different impurities coming from manufacturing processes.[47],[48]

Synthesis[49]

Step 1: Synthesis of Sodium Salt of Naproxen (HL). 0.82 gm (0.1 M) of Naproxen (ligand) was dissolved with 0.1M of sodiumhydroxide solution inwater to formthe sodiumsalt of Naproxen.Then the solution was sonicated for 5minutes and kept in room temperature. The potency of Naproxen must be considered before preparation. The reaction mixture was put on a water bath to evaporate until a crystal film appeared; upon cooling the white product separated out.

Step 2: General Procedure for Synthesis of Transition Metal Complexes.

Equimolar metal salts dissolved in water were added to the abovemixture so that the ratio *n (metal) : n (ligand)* of monovalent, divalent, and trivalent ions used was 1 : 1, 1 : 2 and 1:3, respectively, in each case and immediate precipitation occurred.Thenthe solidcomplexeswere isolated by filtration, washed until being free of chlorides with the corresponding solvent (methanol or water), and finally dried at room temperature.



Naproxen.

Forced Degradation Condition

TABLE 1: Types of degradation reactions and conditions.

Degradation reaction	Typical conditions
Elevated temperature	Exposed to 105°C heat, up to 3 hours
Acid hydrolysis	Treated with 1 N HCl up to 24 hours
Base hydrolysis	Treated with 1 N NaOH up to 24 hours
Oxidation	Treated with 10% H_2O_2 solution up to 24 hours
Reduction	Treated with 10% Na bisulfite solution up to 24 hours
Water hydrolysis	Treated with water up to 24 hours

Stability profile: Within the forced degradation study it had been found that Naproxen-metal complexes were the foremost stable compounds against any sort of forced degradation condition applied than parent Naproxen. The highest degradation of Naproxen was found by acid hydrolysis and it had been only 7.92%. Among the complexes, Naproxen-Iron complex was found most stable against the stressed conditions. The most probable reason for its higher stability than Naproxen is that the possibility of forming dimer or may be polymer structures. It was also revealed that the complexes have very high decomposition point than that of the parent Naproxen. That is why they are able to show better stability against stressed condition. This finding suggests that the metal derivatives of Naproxen can be more potent anti-inflammatory agent in human body with longer half-life as well as in the dosage form with longer shelf life when compared to the parent Naproxen.[49]

CONCLUSION

The synthesis of the metal complexes of medicinal compounds is becoming increasingly important owing to their improved pharmacological and pharmacotechnical property, beating the resistance and to expand the range of therapeutic agents available to treat a disease. Significant progress in the synthesis of platinum based anticancer drugs like cisplatin has been made and these drugs have proven to be highly effective in treating various types of cancers. The findings of the study suggested that most of the metal complexes studied provided an advantage of improved pharmacological activities and/or better stability than the parent ligands itself. The use of transition metal complexes as therapeutic compounds has become more pronounced. Development of metal complexes as drugs is not an easy task, considerable effort is required to get a compound of interest and there is need to synthesize new complexes with more properties.

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