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# A SYSTEMATIC REVIEW ON METAL COMPLEXES OF SOME MEDICINAL COMPOUNDS

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**Abstract:**

Metal ions plays an important role in biological processes and also in metal homeostasis. Metal imbalance in body may cause several diseases. To overcome such condition various derivatives of drugs are complexed with different metals like Cu, Zn, Mn, Ni, Co, Pt, Cd, Fe, Hg etc. Drugs like captopril, acyclovir, Biguanides, Theophylline, Chloriquine, triazole, Nicotinic acid and their derivatives hold medicinal properties such as ant neurodegenerative, anticancer, antioxidant, antimicrobial, anti-inflammatory, and antidiabetic activities. This article shows the synthesis of some novel mixed legand complexes of Cu, Mn, Ni, Zn, Cd , Pt ,Fe and Co and their activity over its legand. It also shows the basic structure and its chemical moiety. In contrast, the metal complexes of both metformin and phenformin were protease inhibitors with potency at therapeutic concentrations. Biguanide–metal complexes were more potent cysteine protease inhibitors than either the biguanide or metal ions alone, i.e., synergistic. The process of synthesis of metal complexes of captopril, theophylline, nicotinic acid, chloroquine, biguanides, diphosphate, acyclovir and triazoles were explained and stable compounds were formed. The metal complexes of theophylline shows antioxidant activity. The potential of metal complexes (Cu and Mn) of nicotinic acid was explained. The metal complex of chloroquine diphosphate shows good antimalerial activity. The platinum complexes of acyclovir shows antiviral and anticancer activity. Pt metal complex of acyclovir was compared with cisplatin molecule. Zn, Ni, and Cd metal complexes of triazole were explained. The good antibacterial activity against gram negative and gram positive was explained. Antifungal activity was also seen. These activities explained the good potential of metal complexes of derivatives than its original molecule or its legand. Cu and Sn complexes were also prepared from derivative of triazole. The process of synthesis of derivative (legand) of triazole was also explained in this article. In this article, we focus on the chemistry of metal complexes of drugs derivatives and their activities with particular reference to different metals.

**Key Words:** Metal complexes, Captopril, Theophylline, Nicotinic acid, Biguanides, Acyclovir & Triazide.

**Introduction:**

Metals are essential cellular components selected naturally to function in several indispensable biochemical processes for living organisms. Metal complexes are important in catalysis, materials synthesis, photochemistry, and biological systems. Medicinal chemistry can exploit the unique properties of metal ions for the planning latest of new drugs. The use of metals and their salts for medicinal purposes has been present throughout history. With the advancement within the field of chemistry the role of transition metal complexes as therapeutic compounds is becoming increasingly important. Recent advances in chemistry have made possible formation of number of transition metal complexes with organic ligand of interest, which can be used as therapeutic agent.

**Importance of Metals and Their Complexes:**

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 within the normal functioning of organisms. 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 [1].

**Therapeutic Use of Metal Complexes:**

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 event 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 [2].Transition metal complexes are cationic, neutral or anionic species in which a transition metal is coordinated by ligands [3]. Transition metals exhibit different oxidation states and may interact with variety of charged molecules. This activity of transition metals has started the event of metal based drugs with promising pharmacological application and should offer unique therapeutic opportunities [4].

**Basic Structure and Activity of Metal Complex:**

With the development of electronic theory of valency in the beginning of the present century, much progress in understanding of the structure and behavior of metal complexes has been made. A complex compound consists of a central metal atom or cation to which several anions and/or neutral molecules are bonded. The latter are called ligands. The ligands are disposed about the central metal ion in a regular geometric manner. The total number of donor groups directly bonded to the central metal ion is called the coordination number of the central metal ion. With few exceptions, free ligands have at least one atom with lone pair of electrons. In complex formation, the lone pair m of electrons may be considered to be donated by the ligands to the electron deficient central metal ion. Certain ligands are capable of coordinating to the central ion through two or more donor atoms appropriately situated in the molecule leading to the formation of ring structures. The coordination of such ligands is called chelation. The term 'Chelate' from Greek word 'Chele' (meaning crab's claw) was introduced in 1920. To describe those complexes that result from a combination of an electron donor with a metal ion to form a ring structure. The compounds capable of forming a ring structure with a metal are designated as ligands. Ligands having the potential to form the rings are called chelating agents. They are often associated with additional complex stability, particularly when the rings are five membered. If the metal is not in a ring, the compound is called simply a metal complex. A ligand molecule containing only two electron donating groups is designated as "bidentate" and is able to form only a single ring; if it contains three electron donating groups, it is "tridentate" and may form two rings in an interlocked complex; the prophyrine are able to form a number of interlocked ring systems with metals and are designated as "polydentate" structures. The size of the rings in chelate compounds is of interest with respect to both the stability and occurrence.

The 5- and 6-membered chelate rings are most common and usually show the greatest stability. If the complex forming ligand supplies both electrons for chelation, then the bond is classified as a coordinate covalent bond and by convention is represented as M--X, where M is the metal and X is the ligand. If one electron is supplied by the metal and one by the ligand (normal coordinate bond), the bond is shown as M-X. 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 [1].

**Deregularities of Metals in Body:**

Deregulations of number of these essential metals during normal biochemical processing are implicated within the development of varied pathological disorders, like cancer [5]. These cellular functions only require the “trace metals” in miniscule but tightly regulated amounts. Research has shown significant progress in utilization of transition metal complexes as drugs to treat several human diseases. Transition metals exhibit different oxidation states and can interact with a few negatively charged molecules. These properties of transition metals led to the event of metal-based drugs with promising pharmacological application and unique therapeutic opportunities. The advances in chemistry provide better opportunities to use metal complexes as therapeutic agents.

**Importance of Metal Complexes in Various Diseases:**

These complexes have great diversity in action. Medicinal inorganic chemistry can exploit the unique properties of metal ions for the design of new drugs. This has, for instance, led to the clinical application of chemotherapeutic agents for cancer treatment, such as cisplatin [6].

**1) Captopril:**

Chemical moiety-Proline Derivative (fig 1.1) ($C_5H_9NO_2$) which is pyrolidine-2-carboxylic acid and it belongs to five member ring in a molecule.

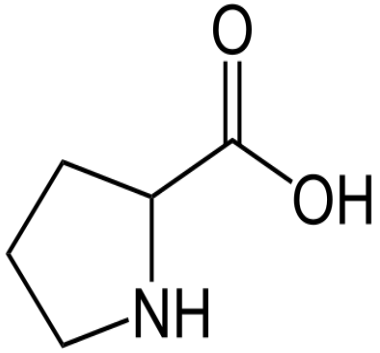


Figure 1.1: Structure of proline

Captopril (CPL) (Fig 1.2), 1-(3-mercapto-2-D-methyl-1-oxoproppyl) -l-proline (S,S), is used therapeutically as an antihypertensive agent. It acts as a potent and specific inhibitor of angiotensin-converting enzyme. It is used in the management of hypertension, in heart failure, following myocardial infarction and in diabetic nephropathy.

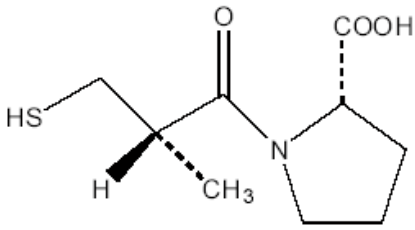


Figure 1.2: Structure of Captopril

As a representative of the ACE-inhibitor class of antihypertensive, captopril (CPL), was studied for several reasons: first, it seems to be one of the most widely used drug of the group and, secondly, because it contains several donor groups, namely COOH, C=O, SH and proline nitrogen [7]. In the late 1980's the first publications appeared on the interaction between CPL and copper/zinc [8]. In these studies however, the system copper (II)–CPL was investigated always in the presence of other ligands, capable of keeping copper in +2 oxidation state so as to prevent its reduction. The ideas regarding the new possible functions of captopril have spread later in several directions, in order to explain different aspects of the physiological effect of the drug [9].
The stability of those complex combinations depends on: The character of the metal ion generating the complex, the character of the ligand, the relative affinity of the donor atoms for the acceptor atoms and ions and the affinity for electrons of the central metal atom and with the basic character of the ligand. The participation of some given functional groups within a metal bond depends on its level of competition within the prevailing neighbouring functional groups, also as on the competition of the protons and of the metal ions with the potential donor atoms.

**General Procedure for Preparation of Metal Complexes:**

Synthesis A: Composition of [Me(CPL)nXm], where Me = Mn, Cd, Ni, Zn, Co and X = $[HgI_4]_2$-. 0.68g $HgCl_2$ were dissolved, by heating, in 20mL distilled water; potassium iodide was added in the solution till the complete solubilisation of the initially formed precipitate of mercury iodide (II). The obtained solution, containing the complex anion $[HgI_4]_2$- is treated, under continuous stirring, with 60 mL solution containing in grams the amount of salt of the metals needed to complexate 1g of captopril. The obtained precipitates of different colours are filtered through a Buchner funnel, washed 3 times with warm water and alcohol and then dried in an exicator on a filter paper. The captopril forms complexes with transition metals such as Zn, Cd, Ni, Co, Mn in the presence of the $[HgI_4]_2$- anion of tetraiodomercuriat type [10].
Synthesis B: Composition of the captopril complex of copper(II), $Cu_2IICPL_2(H_2O)$ in aqueous solution at a molar ratio of Cu:CPL=1:2 and ambient temperature, copper(II) is reduced to copper(I) which forms with an excess of captopril a yellow diamagnetic complex CuICPL, quite stable kinetically as a solid substance, when isolated and dried immediately after its formation and precipitation. In air, but only in the presence of $H_2O$, copper(I) in the complex is easily oxidized by $O_2$ to copper(II), and the corresponding green copper(II) complex of captopril $Cu_2$ $IICPL_2(H_2O)_2$ is made, which is kinetically and thermodynamically stable.

Cu and Hg complexes of captopril: The study of Cu(II) and Hg(II) captopril interactions were performed in aqueous (deionized) solution, employing copper sulfate and mercury nitrate as metal cations sources. The dissolution of captopril during a 1:1 (mo:mol) or 1:2 Cu(II) solution are identical (in the uncertainty interval). So, can be concluded that an increase of the total amount of captopril in solution do not provoke "extra" captopril-copper interactions, probably due to the fact that all available coordination sites of $Cu^{2+}$ are already interacting. The most remarkable result's is related with the captopril-Hg(II) interaction, which it is 3.3 times most exothermic than the captopril-Cu(II) interactions. Such fact are often explained that Hg(II) may be a soft acid, whereas Cu(II) may be a hard (or borderline) one. To the solid state $Cu_2(Cap)_2(H_2O)$ complex it has been verified that there are the participation of COOH, C=O and SH groups in coordination, along side $H_2O$, which is additionally included in the inner coordination sphere of copper . In the present work, it is assumed, to the aqueous solution captopril-Cu(II) interactions, a similar coordination feature [11].

**2) Theophylline:**

**Chemical Moiety**: Purine derivative **(**Fig 2.1)($C_5H_4N_4$)is heterocyclic aromatic organic compounds which have two rings in its structure.

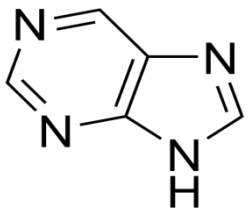


Figure 2.1: Structure of Purine

Theophylline is a methylxanthine (Fig 2.2) drug used in therapy for respiratory diseases.

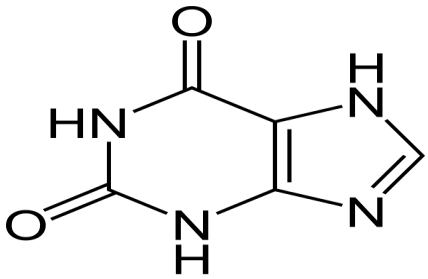

Figure 2.2: Structure of xanthine

It aids in relaxation of bronchial smooth muscles, lowers blood pressure, increases renal blood flow and has some anti-inflammatory effect. Its formula is: $C_7H_8N_4O_2$, (3,7-dihydro-1,3- dimethyl-1H-purine-2,6-dione or 1,3-dimethylxanthine).

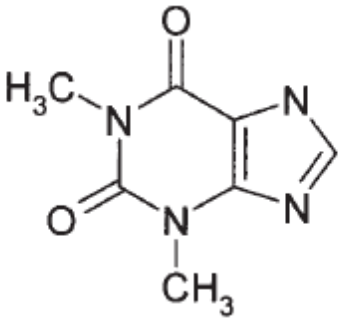

Figure 2.3: Structure of Theophylline

Theophylline (Fig 2.3)(1, 3-dimethylxanthine) referred to as purine base and constitute an important class of anti-inflammatory Agent . Theophylline has biological importance as it is structurally related to nucleic acids components and thus can be used as a drug for the treatment of asthmatic bronchitis and chronic obstructive bronchitis under a variety of brand names and as anticancer drugs [12]. The interest in metal complexes of theophylline is stimulated by the fact that certain purine-metal complexes have been found to have therapeutic value as diuretics . It is also important to study the mode of binding of the ligand with the metal. Moreover, the study of the behavior of theophylline as a ligand can be useful for elucidating the metal and interligand interactions involving the purine bases of nucleic acids or their nucleosides, because the theophylline molecule are often considered as a model for the nucleoside guanosine [13].

**General Procedure for the Synthesis of the Transition Metal (II) Complexes:**

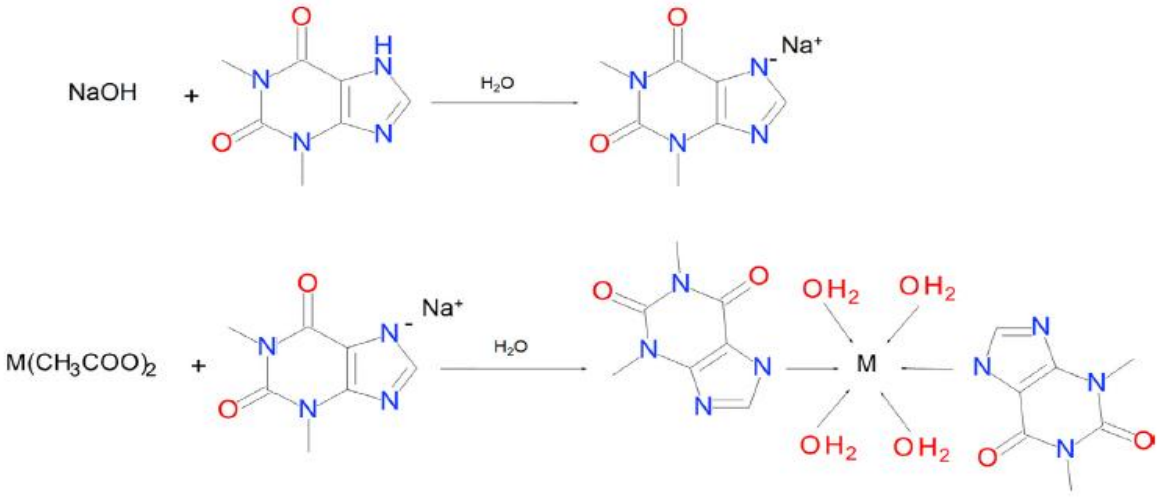


Figure 2.4: Procedure Used in Synthesis

Synthsis A*:* 1.80 g theophylline (TEO) is dissolved in a warm environment in 100mL distilled water heated up to 70°C. The obtained solution was treated with a solution that contains 0.005 moles (≈1.0 g) $Cu(CH_3COO)_2 \cdot H_2O$ dissolved in 50 mL distilled water. The reaction mixture was stirred at temperature for 30 min. The obtained green precipitate is filtered using a Buchner funnel, is washed several times with washing water that for 100mL solution contains 0.2 g theophylline and 0.2 g copper acetate, and then with distilled water heated up to 70°C, then with some alcohol and ether. Then, the substance will be dried in open air on a filter paper or in vacuum. In the same way, the other new complexes are obtained, but instead of the copper acetate, cobalt, zinc

or cadmium acetates were used. The elemental analysis gives a coordination ratio of 1:2 metal:theophylline with the presence of two crystallization water molecules, the formula being $[Me(TEO)_2](CH_3COO)_2 \cdot 2H_2O$ [12].

Synthesis B: Complexes were synthesized following the procedure as shown in fig 2.4. The sodium salt of the ligand was prepared by theophylline (2 mmol) dissolution in 40 mL fresh NaOH (2 mmol) solution. The latter was heated up to 80 C and subsequently added to aqueous solution of the respective metal acetate (1 mmol in 25 mL). The reaction mixture was kept under stirring in 60 C for 2 h. All complexes were isolated by filtration, washed with hot water and dried on air [14].

**Antioxidant Activity:**

The antioxidant activity of the metal complexes and theophylline was evaluated by measuring scavenging ability of the DPPH (2,2- diphenyl-1-picrylhydrazyl) free radical [15].

**Antibacterial and Antifungal Activities:**

Theophylline complexes were screened for antibacterial and antifungal activities by micro-dilution broth method using Mueller-Hinton broth and Mueller-Hinton broth with 5% lysed sheep blood for growth of non-fastidious and fastidious bacteria, respectively or the Mueller-Hinton broth with 2% glucose for growth of fungi. Minimal inhibitory concentration (MIC) of the tested derivatives were evaluated for the panel of the reference microorganisms from the American Type Culture Collection (ATCC), including Gram-negative bacteria (*Escherichia coli* ATCC 25922, *Salmonella typhimurium*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, Gram-positive bacteria (*Staphylococcus aureus*), *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Micrococcus luteus*, *Bacillus subtilis*, *Bacillus cereus*, *Streptococcus pyogenes*, *Streptococcus pneumonia*, *Streptococcus mutans* and fungi (*Candida albicans*), *Candida parapsilosis*, *Candida glabrata* [16].

**3) Nicotinic Acid:**

**Chemical Moiety:** Pyridine (fig 3.1) ($C_5H_5N$) is heterocyclic organic compound which is structurally related to benzene by a nitrogen atom,with one methine group replaced by nitrogen atom.

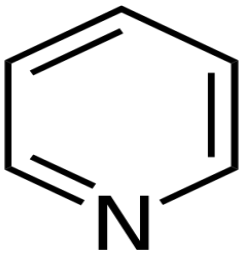


Figure 3.1: Structure of Pyridine

Nicotinic acid (fig 3.2) is an organic compound also known as vitamin B3. It is colorless, water soluble solid having formula $C_6H_5NO_2$.

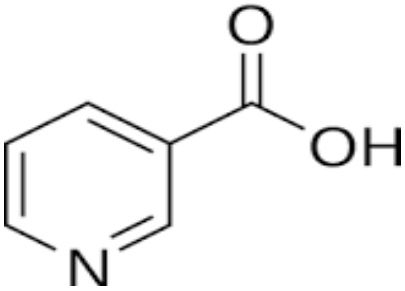


Figure 3.2: Structure of nicotinic acid

It is derivative of pyridine with carboxyl group at 3-position.Insufficent Nicotinic acid cause diseases like anemia, headache, tiredness, nausea, skin infection. Its chronic deficiency causes pellagra. Nicotinic acid is useful in minimizing the chances of cardiovascular diseases [17]. Niacin is found in many foods i.e. chicken, beef, fish, peanuts. High dose of Niacin cause toxic effect like maculopathy (thickening of retina) which causes blindness [18]. It also causes elevation of blood sugar, Diabetes mellitus [19].

**$Cu^{+2}$ Complexes with Nicotinic Acid:**

It was stated that complexes of mixed ligand nicotinic acid with other carboxylic acids were synthesized. Studies showed that niacin or vitamin B3 was used as physiological and anti-hyper lipidemic functions. Cu complexes were tested and observed antimicrobial activity against Bacillus subtilis with 256μg/ mL that was minimum inhibition concentration. Cu complexes also showed super oxide dismutase (SOD) mimetic activity. Cu complex with maximum SOD activity possess highest occupied molecular orbital energy (HOMO). These properties showed potential for development of metallo vitamin based medicine [20].

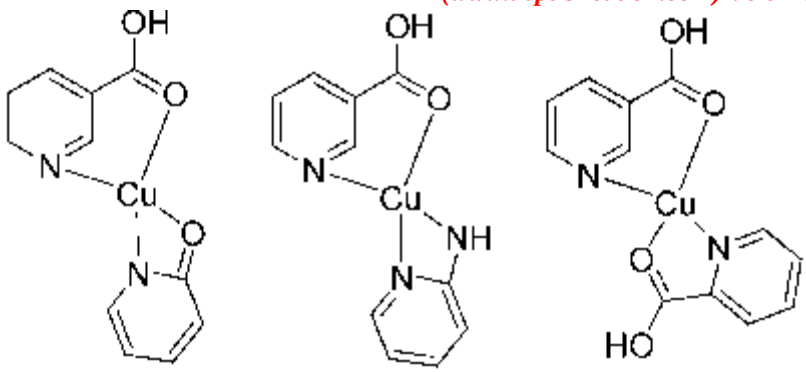


Figure 3.3: cu complexes of nicotinic acid

Thermal behavior of nicotinic acid and its sodium salt was done. The hydrated transition metal compounds were dehydrated and thermally decomposed in a single step. Different results such as the thermal stability, thermal decomposition and identification of the gaseous products formed in the process of decomposition of the compounds were found [21].

It was studied that copper nicotinic acid complex was used to treat fatty liver in which fat stores in cells of liver and caused problem in structure and functions of liver. It was applied on fatty liver of rat model. Cu nicotinate complex was applied for 4 weeks. Improvements were observed in rats. Fat droplets disappeared from liver sections. Liver weight, liver trans aminases and alkaline phosphates were decreased and nitric oxides, super oxides; lipid peroxides were changed to normal level. Cu complex was important for renewal of structure and functions [22]. Complex of nicotinic acid with manganese in sodium Meta silicate ligand was also formed [23].

**Potential of Metal Complexes of Nicotinic Acid:**

Nicotinic acid complexes of Cu(II) and Mn(II) show various activity against antimicrobial, anti-inflammatory, analgesic, anti-tubercular, anticancer etc. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic nicotinic acid nucleus. Thus nicotinic acid complex of Cu(II) and Mn(II) offers better pharmacodynamic characteristics.

**4) Chloroquine Diphosphate:**

**Chemical Moiety:** Chloroquine ($C_{18}H_{26}ClN_3$) Chloroquine (fig 4.1) (CHQ) [7-chloro-4-(4-diethylamino-1methylbutylamino) quinoline] is relatively well tolerated drug initially developed for the treatment of malaria. CHQ has, however, since accrued a plethora of uses within the treatment and amelioration of several other diseases and conditions due of its lysosomotropic properties.

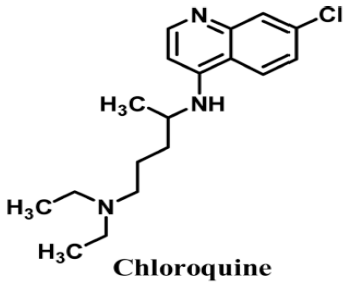


Figure 4.1

Chloroquine diphosphate (CQDP) (fig 4.2) is the phosphate salt of chloroquine, a quinoline compound with antimalerial and anti inflammatory activity.

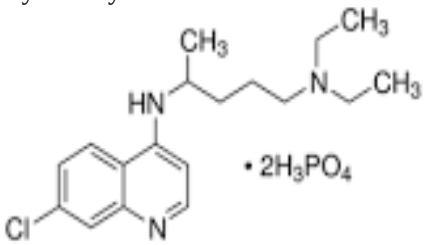


Figure 4.2: Chloroquine Diphosphate (CQDP)

Additinally, an overview of some of the novel uses of CHQ in the treatment of viral infections and cancer are presented [24]. A variety of metal complexes has been developed as possible anti-malarial agents [25]. Sanchez-Delgado and Navarro groups have proposed the modification of CQ through their corporation of a transition metal into the molecular structure. Indeed, several metal centres (Rh, Ru, Ir and Au) have been used

finding that the most significant results have been obtained for the centers of ruthenium [26, 27] and gold [28,29]. All metal-chloroquine (CQ) and metal-CQDP complexes were synthesized under $N_2$ using Schlenk technique.

The mechanism of action of these metal chloroquine complexes ($[RuCl_2(CQ)]_2$ and $[Au(CQ)(PPh_3)]PF_6$) were evaluated on two important targets, Fe(III) PPIX and DNA [13,14], finding that the main mechanism of anti-malarial action of those $[RuCl_2(CQ)]_2$ and $[Au(CQ)(PPh_3)]$ $PF_6$ complexes against resistant strains of P. falciparum was the inhibition of β-haematin formation. Both the enhanced activity and the ability of these compounds to lower CQ resistance are related to the high lipophilicity of the metal complexes and the important structural modification of the CQ structure imposed by the presence of the metal-containing fragment. Taking under consideration the importance of the interactions of those metal compounds with the precise targets Fe(III) PPIX and therefore the relevance inhibition of β-haematinin order to extend anti-plasmodial activity and avoid parasite resistance, the interaction of six metal-CQ (metal: Au, Pt and Pd) complexes with ferriprotoporphyrin, their ability to inhibit the haem aggregation at water/lipid interfaces and their anti-malarial activity against 3D7 and W2 strains (CQ-susceptible strain and CQ-resistant strain, respectively) were assessed within the present work. Worthy of mentioning, that the cytotoxic activity against the six tumor cell lines, of five of these metal-CQ complexes have already been reported [30, 31]. Synthesis and characterization of the new Pd $(CQDP)_2I_2$ complex were also explained.

**Procedure for Preparation of Metal Complexes:**

Synthesis and characterization of complex Pd $(CQDP)_2I_2$:

A solution of $K_2[PdCl_4]$ (65.3 mg, 0.2 mmol) in water (20 mL) was stirred until complete dissolution was achieved, an excess of KI was added. Then, CQDP dissolved in water (206.4 mg, 0.4 mmol) was added. The stirring was continued for 1 hr at room temperature, and a brown precipitate was obtained. This was collected by filtration,washed with water, and dried under vacuum [32].

**Antimalerial Activity:**

All tested metal-CQ and metal-CQDP complexes displayed very high anti-malarial activity against the CQS strain (37D), in general all metal complexes showed better activity than CQDP, except $Pd(CQDP)_2I_2$ which showed the less activity. Suggesting that, metals like gold and platinum achieved to enhance the antiplasmodial activity of CQDP. However, this trend was not observed when the studied metal complexes were tested against the CQR strain (W2), the result revealed that Pt $(CQDP)_2Cl_2$ was the most active compound of these series, followed by Au(CQ)(TaTg) and $Pt(CQDP)_2I_2$ which displayed similar antiplasmodial activity [33].

**5) Metformin, Proguanil and Phenformin:**

**Chemical Moiety**: Biguanides (Fig 5.1) ($C_2H_7N_5$)

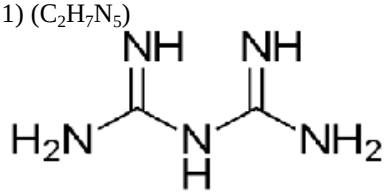


Figure 5.1: Structure of Biguanide

Various biguanide derivatives are used as antihyperglycemic and antimalarial drugs (e.g., 1,1-dimethyl biguanide(metformin) (fig 5.1) $C_4H_{11}N_5$, phenylethybiguanide (phenformin) (fig 5.4) $C_{10}H_{15}N_5$, proguanil (fig 5.3) ($C_{11}H_{16}ClN_5$) etc. Biguanides bind endogenous metals that inhibit cysteine proteases independently, e.g., $Zn^{2+}$, $Cu^{2+}$, $Fe^{3+}$.

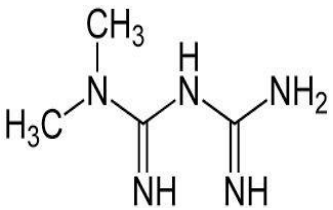


Figure 5.2: Metformin

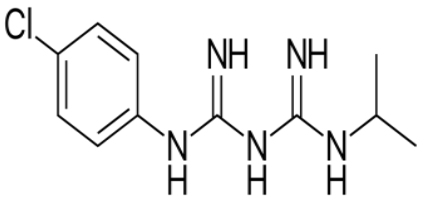


Figure 5.3: Proguanil

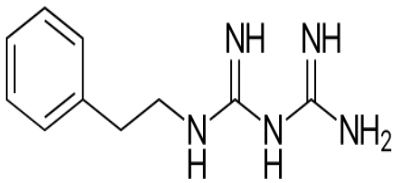


Figure 5.4: Phenformin

Various biguanide derivatives are reported to be metal-interactive inhibitors of cathepsin B from mammals and falcipain-2 from Plasmodium falciparum. Structural homologies were identified among the Phe-Arg protease substrate motif and therefore the metal complexes of phenformin and proguanil. Molecular modeling revealed that the position of the scissile amide substrate bond corresponds to the biguanide-complexed inhibitory metal when the phenyl groups are homologously aligned. Binding of the phenformin–metal complex within the site of human cathepsin B was modeled with computational docking. Similar to chloroquine, therapeutic extracellular concentrations of metformin, phenformin, and proguanil caused metal-interactive inhibition of lysosomal protein degradation as bioassayed in primary tissue using perfused myocardium [34].

Mammalian cathepsin B and plasmodial falcipain are among major proteases contributing to the degradation of insulin and host hemoglobin. These and other cysteine proteases are partially inhibited by

endogenous metal ions. $Zn^{2+}$ and $Fe^{3+}$ are natural inhibitors of insulin and hemoglobin degradation, respectively. Upon drug administration the biguanide moiety forms metal complexes in proportion to the relative binding affinities and tissue availabilities of endogenous metals [35].

**Potential of Metal Complexes of Biaguanides:**

Inhibitory synergy among biguanides and metal ions was observed near the minimally effective inhibitory concentration of metal ions alone. At 1 uM, the $Zn^{2+}$–phenformin complex caused approximately 80% inhibition, which is more than the additive 25% inhibition caused by 1 uM phenformin and the 15–20% inhibition caused by 1 uM $Zn^{2+}$ under identical conditions. At higher concentrations of drug and metal, their combined actions were approximately additive in the range of 25–50% inhibitions caused by the independent agents. Cathepsin B was completely inhibited by less than 5 uM concentration of the $Zn^{2+}$–phenformin complex. Thus, phenformin–metal complexation eliminated the 30% subcomponent of reaction that was uninhibited by 100-fold. Higher concentration of metal-free phenformin alone. These results indicate that metal complexation converts the drug action from a weak, partial competitive inhibitor to a complete inhibitor with much greater potency. Whereas 20 uM metformin alone caused no falciparin inhibition, 20 uM $Fe^{3+}$ –metformin complex caused 80% inhibition, which was greater than the sum of independent inhibitions caused by these individual agents separately. At higher 40 uM concentration, the $Fe^{3+}$ –metformin complex caused 90% inhibition of falciparin activitymetformin markedly decrease the ongoing exogenous insulin requirement in type 2 diabetic individuals by 30–40% [34].

**6) Aclyclovir:**

**Chemical Moiety**: Guanosine (fig6.1) ($C_{10}H_{13}N_5O_5$), is a purine nucleoside in which guanine is attached to ribofuranose via a beta-N(9)-glycosidic bond.

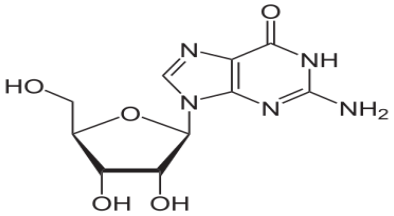


Figure 6.1: Structure of Guanosine

Acyclovir (fig6.2) [9-(2-hydroxyethoxymethyl) guanine, acycloguanosine] is currently used in antiviral therapy, respectively. Acyclovir is a nucleoside analogue with potent activity towards herpes virus infections.

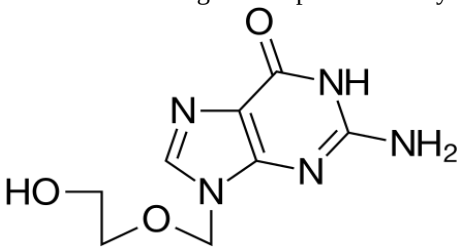


Figure 6.2: Structure of acyclovir

Acyclovir triphosphate is preferentially formed in infected cells and inhibits viral DNA synthesis either selectively interfering with viral DNA polymerase or leading to premature chain termination [36]. The metal-coordinating properties of acyclovir are of current interest (2-5) from a mechanistic point of view, some DNA polymerases containing ($Zn^{2+}$) and/or being activated by metal ions ($Mg^{2+}$ $Mn^{2+}$ or $Co^{2+}$). Moreover, metal complexes of acyclovir may exhibit antiviral activity different from that of the free ligand [37].

**Platinum Complex of Drug:**

Platinum(II) complexes with nucleosides and nucleoside analogues are also of current interest as model compounds; moreover, platinum(II) complexes with nucleotide derivatives of formula $[PtCI(NH_3)_2(Am)]^+$ (Am pyrimidine or purine have recently demonstrated activity in prelinical tumour screens, thus suggesting that also monofunctional DNA lesions might determine a cytotoxic effect [38].

**Synthesis of the Complexes:**

Preparation of cis-$[PtCI_2(NH_3)(L1)]$(L1-ACYCLOVIR): The compound was prepared by the method of Pochon and Kong by bridge splitting with acyclovir of the dimer $n[PtI_2(NH_3)]_2$ obtained from reaction of cis-$[PtI_2OqI\text{-}I_3)_2]$ with perchloric acid. The chloro compound could be obtained from the corresponding iodo species by precipitating the iodo ligands with a silver salt and adding KCI. The desidered product was formed in less than 50% yield [36].

Preparation of cis-$[PtCl_2L_2]$ (L2-monoacyclovir, L-L1,L2): The complexes were prepared by reaction of $K_2[PtC_{14}]$ and L in 1:2 molar ratio. Thus $K_2$ $[PtCI_4]$ (0.20 g, 0.5 mmol) in water (50 ml) was treated with L (1 mmol) and therefore the suspension was left to stir at temperature for 3d. The yellow precipitate was collected, washed with water, then with methanol, and finally with ether [39]

Preparation of cis-[PtCI($NH_3$)$_2$(L)]$NO_3$:This complex was prepared from cis-[$PtCI_2(NH_3)_2$] and L1 according to the method of Hollis et al. Cis-[$PtCI_2(NH_3)_2$](0.30 g, 1 mmol) and $AgNO_3$(0.15 g, 0.9 mmol) were stirred in dimethylformamide (DMFA) (30 ml) for 1 d. The resulting mixture was filtered and the stoichiometric amount of L1 (0.22 g, 1 mmol) was added to the filtrate. Stirring was resumed and continued for 1 d. After a second filtration, the solution was taken to dryness and the residue crystallized from water [39,40].

**Antiviral Activity:**

The antiviral activity was evaluated in vitro by the plaque reduction assay. For this purpose, 24 h growth VERO cell monolayers in 60 mm Petri dishes were infected with 0.5 ml of a Herpes Simplex-1 virus stock solution containing 500 Plaque Forming Units/ml. After 1 h incubation at 37 C the dishes were washed twice with sterile 25OM. PBS and a semisolid maintenance medium containing the drug under study was added. Each drug concentration was tested in triplicate and in three control cultures the cell medium contained only the appropriate amount of drug solvent (DMSO). After 48 h incubation, cell monolayers were fixed with methanol for 20 min, stained with Giemsa stain for 15 min and then the cytolysis plaques were counted. The 50% inhibitory concentrations ($ID_{50}$) were derived by interpolation from a log-linear plot of concentration-per cent plaque reduction outcomes [41].

The platinum-acyclovir complex maintains the antiviral activity of the parent drug acyclovir, though showing a minor efficacy on a molar basis ($ID_{50}$ 7.85 and 1.02 uM for platinum-acyclovir and acyclovir, respectively).

**Anticancer Activity:**

The platinum-acyclovir complex shows an in vitro growth inhibitory capability, expressed as 50% growth inhibitory concentration ($ID_{50}$) markedly less than of cisplatin: $ID_{50}$ 108 and a couple of 1aM, respectively. Nevertheless, the platinum-acyclovir complex features a selective in vivo antitumour activity and shows an equivalent efficacy of cisplatin in increasing the lifetime of animals treated with equitoxic dosages of the two compounds (%T/C 209 and 211, respectively). The platinum-acyclovir complex is smaller amount potent than cisplatin on a mole-equivalent basis. This behaviour might be related either to pharmacokinetic reasons, being platinum-acyclovir a charged compound, or to a different mechanism of action, as suggested by the absence of cross-resistance with cisplatin. Both cisplatin and platinum-acyclovir complexes were effective as cross-linking agents. In the case of Pt acyclovir, the rate of interstrand cross-link formation was slower than that of cisplatin, and also the extent of reaction was lower.

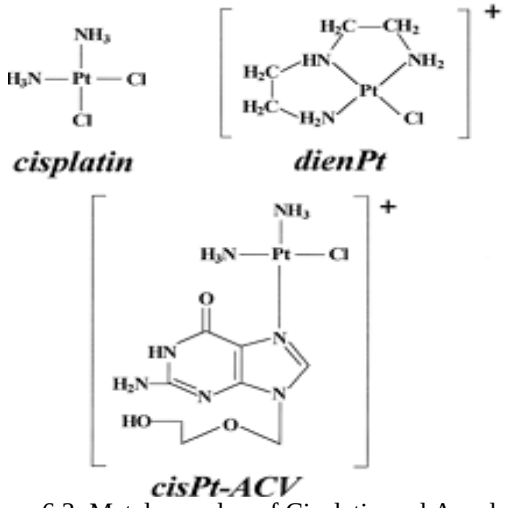


Figure 6.3: Metal complex of Cisplatin and Acyclovir

Platinum (II)-acyclovir complexe show that [PtCl($NH_3$)$_2$(acyclovir)]$NO_3$, is endowed with both antiviral and anticancer activities. On a mole-equivalent basis the platinum-acyclovir complex is less active than the parent drugs, but it shows the same activity of cisplatin when administered at equitoxic dosages to P388 leukaemia-bearing mice.

**7) Triazoles:**

Triazoles are five memberd heterocyclic compounds with formula $C_2H_3N_3$ containing three nitrogen and two carbon atoms. There are two types of triazole, the 1,2,3-triazoles and the 1,2,4-triazoles [42]. Amine and thione-substituted triazoles have been studied as anti-inflammatory and anti-microbial agents and other applications [43].

A group of triazoles such as (Figure 7.1) terconazole (1) has been widely used for the control of vulvovaginal moniliasis caused by *Candida albicans* and other *Candida* species, fluconazole (2) is a broad spectrum antifungal3 and trazodone (3) is used as an antidepressant5. Similarly, vorozole (4), anastrozole (5) and letrozole (6) potentially inhibit breast cancer.

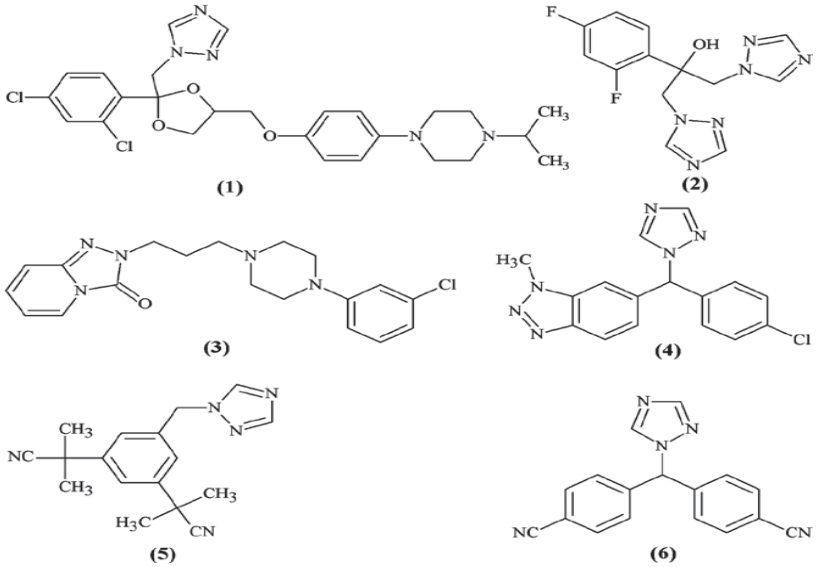


Figure 7.1: Structure of triazole compounds

**1) 4 amino-5-(pyridyl)-4H-1,2,4-triazole-3-thiol:**

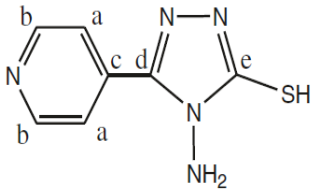

Figure 7.2: 4 amino-5-(pyridyl)-4H-1,2,4-triazole-3-thiol(Ligand)

Series of coordination complexes of Ni(II), Cu(II), Zn(II), Cd(II) and Sn(II) metal with 4-amino-5-(pyridyl)-4H-1,2, 4-triazole-3-thiol, as a ligand has been successfully prepared in alcoholic medium.

**Synthesis of 4 amino-5-(pyridyl)-4H-1,2,4-triazole-3-thiol (ligand):**

A mixture of isonicotinic acid (1 g) (0.0072 mol) and (0.44 g) (0.008 mol) from potassium hydroxide, was dissolved in (10 ml) ethanol. After mixture was dissolved then (2 ml) (0.014 mol) from compound and was added slowly. The reaction mixture was stirred for 10 hours.Dry ether (10 ml) was added and therefore the yellow precipitate was filtered, washed with ether and dried. The salt was obtained in almost quantitative yield and was employed to the next step. The yellow precipitate (potassium salt) was added to an more than of hydrazine hydride (20 ml), and was refluxed with stirring until the evaluation hydrogen sulfide; it has been ceased by sugar of lead paper. After cooling the reaction mixture was filtered, and then was acidified by Hydrochloric acid to yield the white precipitate [44].

**Synthesis of this Ligand's Complexes:**

Ethanolic solution of the acceptable metal salts [Cupper (II) acetate, Tine (II) Chloride, Zinc (II) acetate dihydride, Cadmium (II) acetate and Nickel (II) acetate] was added to an ethanolic solution of 4-amino-5-(pyridyl)-4H-1,2,4- triazole-3-thiol in 1:2 (metal:ligand) molar ratio and refluxed for 2 hours, crystalline colored precipitates was formed at room temperature. The resulting solids were washed by hot methanol and left to dried and recrystallized from ethanol [45].

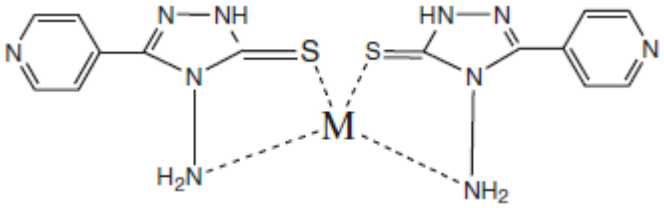

Figure 7.3: Proposed structure of complexed where M –Ni(II),Cu(II),Zn(II),Cd(II),Sn(II)

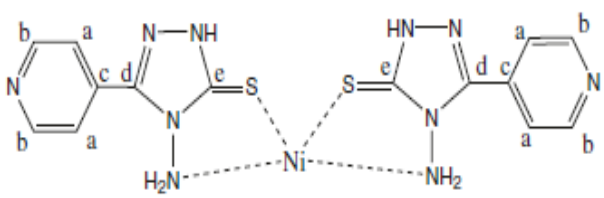

Figure 7.4: Complex of Ni(II)

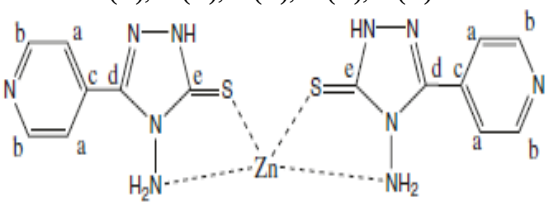

Figure 7.5: Complex of Zn(II)

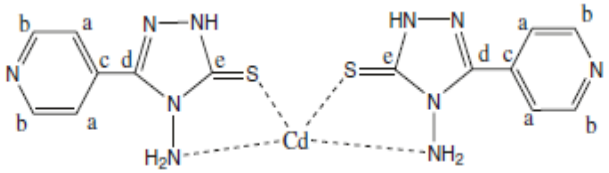


Figure 7.6: Complex of Cd(II)

The ligand 4-amino-5-(pyridyl)-4H-1,2,4-triazole-3-thiol was successfully synthesized. The ligand was treated to different metal ions salts to afford the corresponding complexes. It concluded that the ligand coordinated through amino and thiol groups to the metal atom leading to the formation of five member ring chelate [45].

**Activity of Metal Complexes [46]:-**

**Antibacterial Activity of Metal Complexes:**

These compounds have been investigated for *in vitro* antibacterial activity against four Gram-negative (*Escherichia coli, Shigella sonnei, Pseudomonas aeruginosa, Salmonella typhi*) and two Gram-positive (*Staphylococcus aureus, Bacillus subtilis*) bacterial strains, and antifungal activity against six fungal strains (*Trichophyton longifusus*, *Candida albicans*, *Aspergillus flavus*, *Microsporum canis*, *Fusarium solani* and *Candida glabrata)*.

**Antifungal Activity of Metal Complexes:**

Antifungal activities of compounds were studied against six fungal strains (*Trichophyton longifusus*, *Candida albicans*, *Aspergillus flavus*, *Microsporum canis*, *Fusarium solani* and *Candida glabrata).*

**Potential of Metal Complexes Over Legand:**

From the *in vitro* antibacterial and antifungal activity data shown against representative bacterial and fungal strains is evident that the legand and their Ni(II), Cu(II) and Zn(II) complexes were found to possess good antibacterial and antifungal activities however, the metal complexes showed more activity as compared to the simple triazole derivative.

**Conclusion:**

The process of synthesis of derivatives and their metal complexes were explained. It also shows that the formed metal complexes shows good potential over its legand. Cu and Hg metal complex of captopril shows good effect, while metal complex of theophylline shoes good antioxidant, antibacterial and antifungal activities .metal complex of nicotinic acid shows antimicrobial activity and super oxide dismutase mimetic acivity. The metal complex of chloroquine diphosphate shows better antiplasmodial activity. Biguanides metal complexes shows good inhibitory concentration for microbes. Also effect of metal complexes of acyclovir and triazole shows good anticancer, antiviral, antifungal and antibacterial effects.

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