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Metal Complexes as Prospective Antibacterial Agents

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1. Introduction

Ninety elements occur naturally on earth. Out of these, nine are radioactive and among the remaining eighty one that could support life, sixty one are metals. Our bodies are 3% metal. Thus, it is surprising that some of the most serious challenges to human life, externally, the pollutants cadmium, mercury and lead are attracting more attention, whereas internally, there is a constant battle against sodium and calcium that are rejected by cells and accumulated elsewhere in the body during the ageing process. Furthermore, some diseases release metals into the blood stream. Their use in the fight against diseases was first described by Schubert in 1965. Man just like other vertebrates requires cations of the metals to facilitate a great many essential life processes. Moreover, many of the metals are essential for all other forms of life process. 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.

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.

This could probably be attributed to our increased awareness of personal and family health. Most of the major classes of pharmaceutical agents contain examples of metal compounds which are in current clinical use. Inorganic compounds (metal complexes) have been used to treat various diseases and ailments for many centuries.

Introducing metal ions into a biological system may be carried out for therapeutic or diagnostic purposes, although these purposes overlap in many cases. Yet despite the obvious success of metal complexes as diagnostic and chemotherapeutic agents, few pharmaceutical or chemical companies have serious in-house research programs that address these important bioinorganic aspects of medicine. Metals not only provide templates for synthesis, but they also introduce functionalities that enhance drug delivery vectors. It should be recognized that traditional studies of inorganic drugs at a fundamental level are not complete without a program on metal pharmacology. Many organic drugs require interaction with metals for activity. They interact with metals at their target site or

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during their metabolism or disturb the balance of metal ion uptake and distribution in cells and tissue. The unique properties of metal complexes tend to offer advantages in the discovery and development of new drugs. The metal complexes are amenable to combinatorial synthetic methods, and an immense diversity of structural scaffolds can be achieved. Metal centers are capable of organizing surrounding atoms to achieve pharmacophore geometries that are not readily achieved by other means. Additionally, the effects of metals can be highly specific and can be modulated by recruiting cellular processes that recognize specific types of metal-macromolecules interactions.

Understanding these interactions can lead the way towards rational design of metallo-pharmaceuticals and implementation of new co-therapies. Metal complexes appear to provide a rich platform for the design of novel chemotherapeutic drugs. We can choose the metal itself and its oxidation state, the numbers and types of coordinated ligands and the coordination geometry of the complexes. The ligands can not only control the reactivity of the metal, but also play critical role in determining the nature of secondary coordination-sphere interactions involves in the recognition of biological target sites such as DNA, enzymes and protein receptors. Also the ligands themselves can sometimes undergo biologically-important redox reactions or other modifications(e.g hydrolysis) *in vivo* mediated by the metal. These variables provide enormous potential diversity for the design of metallodrugs. Metal-ligand (coordination) bonds are usually much-weaker than covalent bonds and so ligand substitution reactions will be common in biological media. Most metallodrugs are therefore, pro-drugs. They can undergo ligand substitution and redox reactions before reaching the target site. A displaced ligand may itself attack a target site and controlled ligand release can play a role in the mechanism of action. The ongoing battle against resistance of organism towards drugs is far over. The importance of developing new drug chemotherapeutic drugs cannot be over emphasized. This trend was in the past initiated by the successes of metal-containing antitumor drugs such as cisplatin. Over the last four decades thousand of Inorganic drugs have been screened for their medicinal activity in a wide range of diseases, but only a handful have made it into the clinic.

Huge success was achieved in the area of anticancer drugs and antimicrobial drugs. Some of the metal-based drugs already in market are cisplatin (anticancer drug), cardolite (myocardial imaging agent drug), silverderma (skin burn drugs marketed in Spain by Aldo Union), flammazine (Skin diseases drug marketed by Durpha) and Matrix metalloproteinase inhibitors (cancer and inflammatory disease marketed by British Biotech). The main objective of this paper is to review some of the previous work done by researchers with the hope of shielding light on the need to develop new drugs. We shall also draw together some of the work carried out by our group within our laboratories in the field of metal-containing Antibacterial agents.

2. Resistance of drugs

One way of restoring the activity of organic drugs for which resistance has emerged is to modify the structure to contain a metal, and some of these compounds are metal complexes. As early as 1975, it was reported by Edwards *et al*, (1975) that substituting the aromatic groups in the antibiotics penicillin and Cephalosporine with ferrocenyl moieties produced compounds with altered antibacterial activity compared to the starting materials. Against various strains of *Staphylococcus aureus*, ferrocenyl penicillin showed comparable activity to

benzyl-penicillin and also β -lactamase, which is one of the enzymes responsible for bacterial resistance to penicillin-type antibiotics. 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)

Majority of these complexes were found to possess higher antimalarial activities than their parent drugs. 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 motifs such as ferrocene circumvents chloroquine resistance. Since the parasite needs iron for its development inside the red blood cells. Attempt was made by Biot *et al*, (1999) to insert a ferrocenyl group into the side chain of chloroquine, thus, producing a hybrid compound called Ferroquine (Figure 1). They combined poison (chloroquine) and bait (ferrocene) in the same molecule.

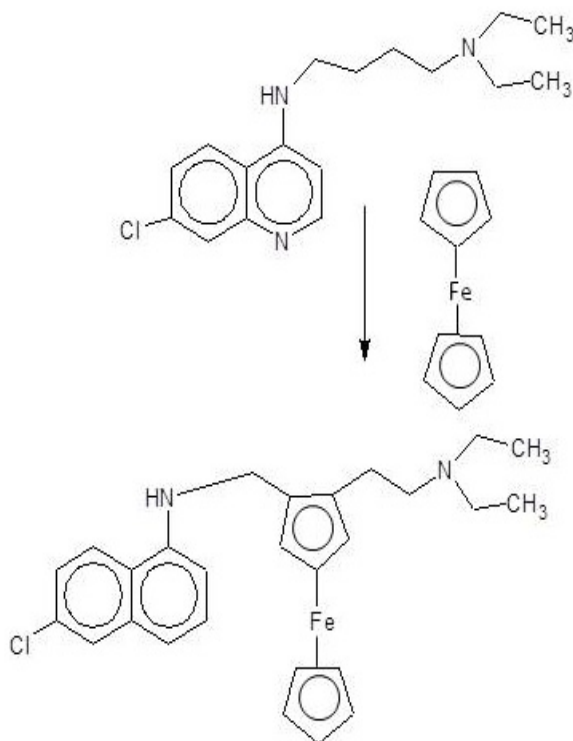


Fig. 1. Ferroquine

Ferroquine synthesized by them was found to be much more potent in mice than chloroquine. Tests have shown that ferroquine is active against both chloroquine sensitive and chloroquine resistant strains of *Plasmodium* and that it is safe and effective in mice, as well as being non-mutagenic. It was discovered that even when resistance to the drug builds up in mice, it can be reversed. The complex is a good candidate for further development. It is a promising organometallic analog of chloroquine..

They also used the same strategy to incorporate ferrocene into mefloquine. The pathway used for the synthesis of the ferrocenic mefloquine (Figure 2) includes coupling of an aminomethyl substituted ferrocene carboxaldehyde with a lithioquinoline compound. Mefloquine is covalently linked to a substituted ferrocenyl unit. The complexes exhibited a broad strong hydroxyl absorption band (3000cm^{-1}) characteristic of a hydroxyl group coordinated to an iron atom. (Biot *et al.* 2000).

The ^1H -NMR and mass spectra of the two diastereoisomers of the complex were similar except for the resonance of the Fe-CH-OH proton. The resonance of diastereomer (A) appeared at 8-6.5ppm (singlet, 1H) and resonance of diastereomer (B), appeared at 8 - 6.2 ppm due to a different anisotropic zone of ferrocenic skeleton.

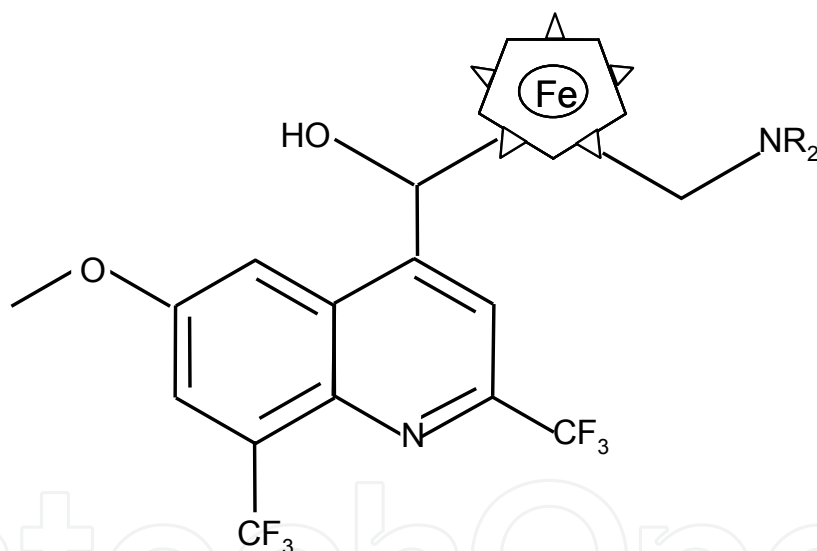


Fig. 2. Ferrocenic mefloquine

Artemisinin ferrocenic complexes were synthesized by Delhaes *et al* (2000). Novel ferrocenic artemisinin derivatives were found potent as artemisinin (QHS). Their antimalaria activity and affinity to bind with Ferritoporphyrin (IX) were studied. All the compounds showed capacity to bind with ferritoporphyrin (IX) resulting from the addition of different drugs concentrations. The association stoichiometry of compounds to Ferritoporphyrin (IX) was found to be 1:2.

Our research group also contributed to efforts being made to search for novel chemotherapeutic drugs against the resistant strains of *Plasmodium falciparum*. The synthetic strategy involves enhancing the activity of antimalarial drugs through the incorporation of transition metals into their molecular structures. In 1997, Obaleye and Nde-aga reported the

preparation and characterization of amodiaquine hydrochloride and chloroquine complexes. They reported that Amodiaquine HCl coordinated through O-H and N-H to the metal ion and chloroquine coordinated to the metal ion through (N-H), (C-N) and (C=N) functional groups acting as either a bidentate or tridentate ligand. All the complexes possessed antimalarial activity as confirmed by studies on mice infected with *Plasmodium yoelli*. Obaleye *et al* (2009) carried out *in vivo* antimalarial activities and toxicological studies of some quinoline methanol metal complexes. Antimalarial activities of these complexes were investigated using mice infected with *Plasmodium berghei*. The results showed that four of the metal complexes $[(\text{MeFH}^+)_2\text{Fe}(\text{SO}_4)_2]^{2-}$, $(\text{MeFH}^+)\text{CuCl}_4\cdot 4\text{H}_2\text{O}$, $[\text{Fe}(\text{QUIN})\text{Cl}_2\cdot \text{H}_2\text{O}]\text{SO}_4\cdot 3\text{H}_2\text{O}$ (Figure 3) and $[\text{Zn}(\text{QUIN})\text{ClSO}_4]_\infty$ exhibited significant higher antimalarial activity ($P < 0.05$) than chloroquine and their parent ligands respectively.

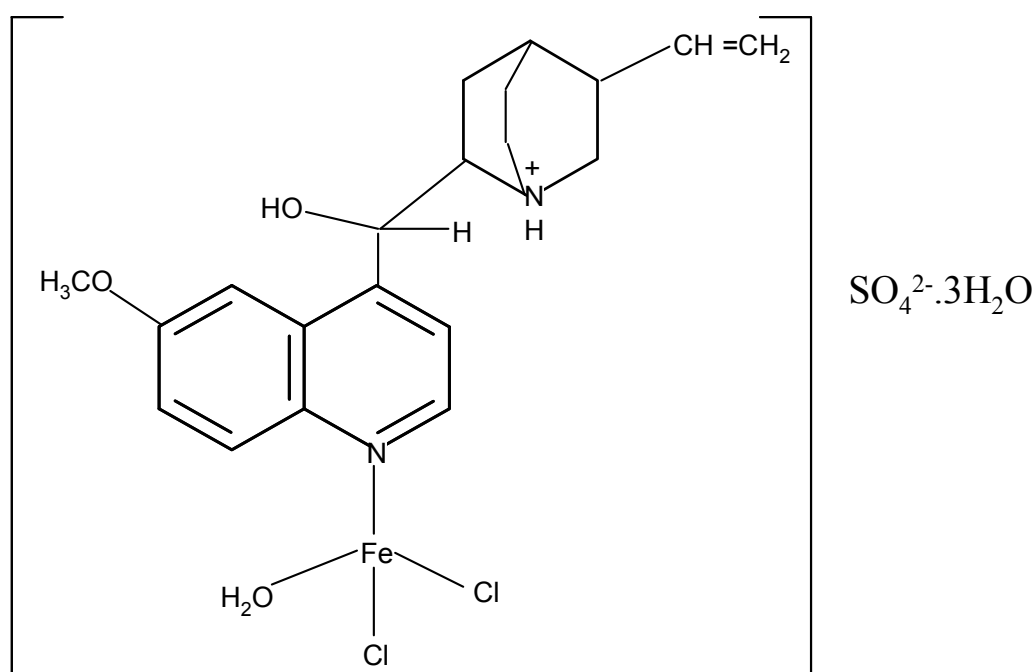
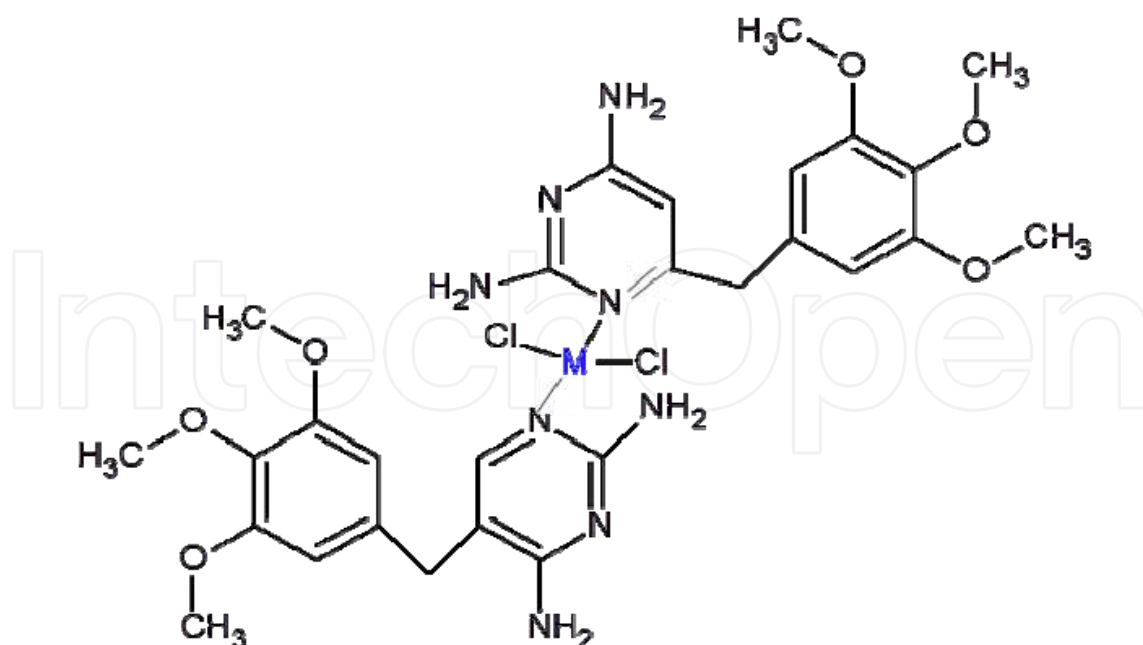


Fig. 3. Structure of $[\text{Fe}(\text{QUIN})\text{Cl}_2\cdot \text{H}_2\text{O}]\text{SO}_4\cdot 3\text{H}_2\text{O}$

The effects of these complexes on alkaline phosphatase (ALP) activity of kidney, liver and serum of Albino rats were investigated. Based on the results obtained, the complexes were found to be non-toxic and possess better antimalarial activity than the conventional antimalarial chloroquine. Tella and Obaleye (2010) synthesized two metal complexes of Co(II) and Cd(II) Trimethoprim. A distorted tetrahedral geometry is suggested for their structures (figure 4) and Trimethoprim behaves as a monodentate ligand.

The metal binds through the pyrimidine N(1) of the ligand. The complexes have been screened for antiplasmodial activity against *plasmodium berghei* and the results show that they are less active than the parent ligand. Toxicological study was carried out by investigating the effect of administration of the complexes on Alkaline phosphatase activity of kidney, liver and serum of Albino rats and they were found to be nontoxic. It can be seen from these studies by our group that incorporation of metal into molecular structure can either enhance the antimalarial activity or less or even make it the same.



M= Co(II) or Cd(II)

Fig. 4. Structure of Trimethoprim metal complexes

Similarly, many organic drugs used to treat the parasitic diseases *leishmaniasis* and *chagas* disease, as well as those used to treat *helminth* worm infections are becoming increasingly ineffective due to drug resistance. *Leishmania donovani*, which causes Leishmaniasis, transferred via bite of a sandfly, infects approximately 10-15 million people worldwide. The disease may be fatal if not treated and effectiveness of traditional organic drugs such as Pentamidine, Amphotericin B, Aminosidine and Antimonials is declining due to drug resistance (Ashford *et al*,1992; Quellette *et al*,1993). Pentamidine one of the organic antiparasitic drugs, has been complexed to several different metal centres and its activity has been evaluated against different parasite species. Of these an Organo-osmium derivative was found to have a 7.5 fold higher therapeutic index than pentamidine alone in treating leishmaniasis curing infected mice in a single dose(Loiseau *et al*,1992; Zinsstag *et al*,1991; Mesavalle *et al*,1993).

3. Anticancer metal complexes

Metal-based drugs are the most widely used drug in chemotherapy. The gallium, titanium salts have been shown to have anti-cancer activity. In the mid-1960s, Bennett Rosenberg and his co-workers(1965) serendipitously discovered that cis-dichlorodiammineplatinum(II) (cis-[Pt(NH₃)₂Cl₂], cisDDP, cisplatin) exhibited antitumor activity but trans isomer, trans-[Pt(NH₃)₂Cl₂], did not. Cisplatin, (cis-[PtCl₂[(NH₃)₂]) also known as cis-DDP (Figure 5) is perhaps the best known example of a small molecule metal-containing drug. The history of the discovery and development of Cisplatin remains a remarkable scientific story. Its use and effectiveness in cancer chemotherapy since entry into the clinic in the late 1970s has been thoroughly documented (Lippert, 1999; Kelland *et al*, 2000; Wong and Giandomenico,1999). Cisplatin is cited for treatment of germ-cell cancers, gestational trophoblastic tumors, epithelial ovarian cancer and small cell lung cancer as well as for

palliation of bladder, cervical, nasopharyngeal, esophageal, head and neck cancers. Cisplatin is a truly remarkable drug, in that for the last 30 years, it has been used to treat more than 70% of all cancer patients.

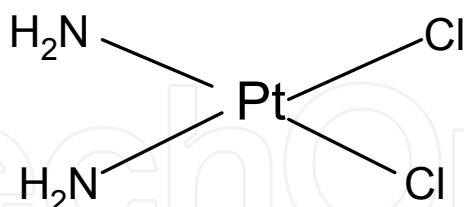


Fig. 5. Structure of cisplatin

Despite this success, there is still a limited range of tumors sensitive to cisplatin intervention. Some cancers are inherently resistant (O' Dwyer *et al*, 1999; Highley *et al*, 2000). Due to this shortcomings, the second- generation compounds based on the cisplatin structure were developed in an attempt to improve toxicity and/or expand the range of useful anticancer activity. Carboplatin entered the clinic in 1998, principally in response to the necessity to reduce the toxic side effects of the parent drug (Christian, 1992). Despite the lower toxicity, carboplatin is essentially active in the same set of tumors as cisplatin and a broader spectrum of activity is not indicated. The problem associated with the use of cisplatin have driven the development of new inorganic anticancer therapies such as medaplatin and oxaliplatin (Van Rijt and Sadler, 2009). Progress to develop many chemotherapeutic transition metals drugs has been quite slow. Metallocenes and metallocene dichloride are potential candidates e.g. Titanocene compound (TiCl₂Cp₂). Titanocene dichloride was first recognized as an anticancer agent by Koepf and Koepf-Maier, (1979) and until recently being evaluated for activity against cisplatin resistant ovarian and metastatic renal-cell carcinomas (Clarke *et al*, 1999). The drug seems to bind to the protein in a similar way to iron, resulting in the cyclopentadienyl ligands being released (Guo *et al*, 2000) and allowing the titanium metal to be delivered to the cancer cells. Titanocene dichloride demonstrates general anti-proliferation activity and has been shown to be effective against five types of cancer cells (Koepf-Maier and Koepf, 1987). Other metallocenes have more specific activity for example ferrocifens. Ferrocifens (Figure 6) was synthesized by Jaouen and Co-workers in 1994. They inserted ferrocene into molecular structure of Tamoxifen. Tamoxifen in form of its active metabolite hydroxyltamoxifen, is widely used in cancer hormone therapy and belongs to a class known as the Selective oestrogen receptor modulators (SERMS). It was discovered 20 years ago. It is used at all stages of the disease and recently, it has been shown to have a role in the prevention of cancer. It is however, only effective in 60% of cases and can cause problem of resistance when used for long time. Tamoxifen also increases the risks of endometrial (uterine) cancer and blood clotting in the lungs. Due to these shortcomings, Jaouen and co-workers in 1994 developed new SERMS that are as active as tamoxifen against as many types of breast cancer as possible. In order to find alternative SERMS, they decided to attach metallocenes to tamoxifens with the hope of improving its effect (Jaouen *et al*, 2000)

One series of Ferrocifens was made by replacing the aromatic phenyl in the β position of tamoxifen with an aromatic ferrocenyl of slightly greater bulk and lipophilicity, ferrocifen was synthesized via Mc-Murry coupling reaction. Ferrocifens has higher antiproliferative

effect against (ER $_{\alpha}$ - and ER $_{\beta}$ +) breast cancers than tamoxifen. The process of conversion is shown below (figure 6).

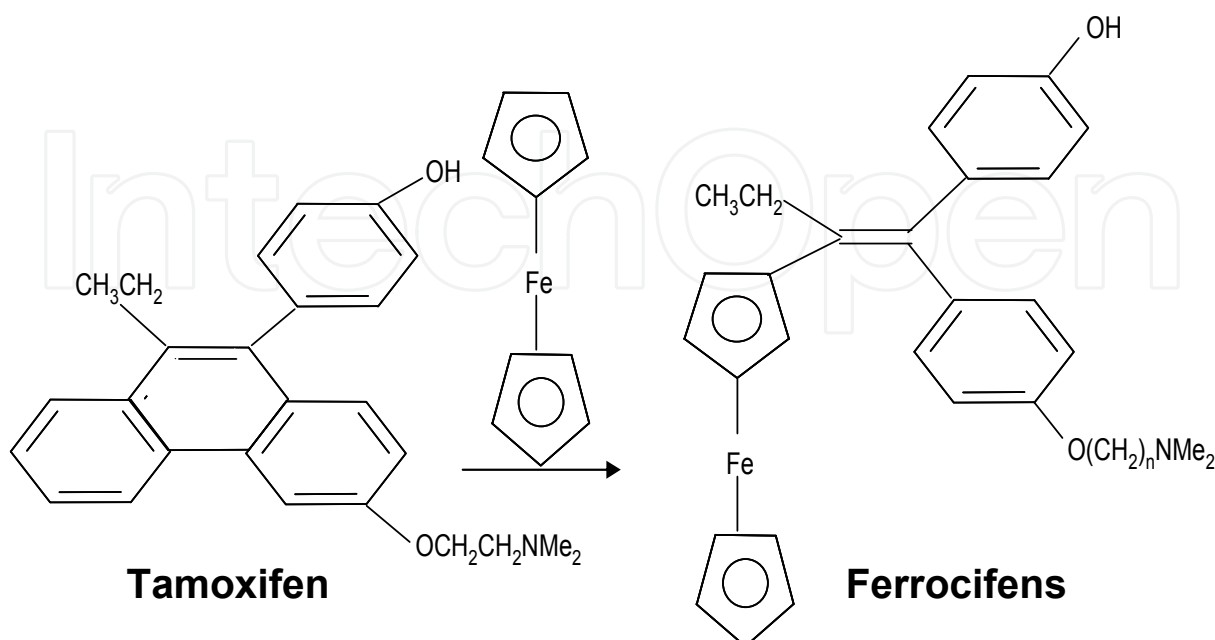
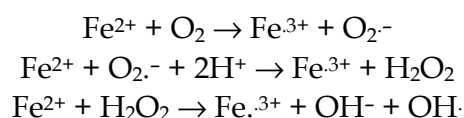


Fig. 6. Structure of Ferrocifens

It has been widely reported in the literature that the cytotoxic effect of ferrocene complexes (Fe $^{2+}$) is associated with their oxidation to ferricinium type (Fe $^{3+}$) radical and O $_2^{\cdot-}$ radical. Thus,



O $_2^{\cdot-}$ radicals are only slightly reactive towards DNA, but OH \cdot radicals are very reactive and provoke various types of lesions, making these radicals highly genotoxic.

By introducing an organometallic function that liberates OH radicals within the cell via an oxidant/antioxidant cascade, we have the SERMS (and possibly for other systems) a potential solution to a difficult and essentially paradoxical problem. Combining metallocenes with other organometallic centres such as Gold provides another means of modifying drug activity and specificity. In this case the complex shows promising activity against bladder and colon cancers (Violette *et al*, 1995). Complexes of group VIII B metals especially Rhodium, Indium and Platinum have been reported to have considerable antibacterial activity and induce lysis in *Lysogenic bacteria*. Platinum II and IV amino halide complexes were found to have antitumor activity (Adrien, 1985). Dinuclear Platinum(II) complex [Pt $_2$ -N,N'-bis(2-dimethylamino oxamide) Cl $_4$] was prepared by reaction of K $_2$ PtCl $_4$ with the ligand N, N'-bis(2-dimethylamino oxamide) in aqueous solution (Messori, *et al*, 2003). X-ray diffraction analysis revealed that the platinum ions simultaneously bound to the ligand, on opposite sides. The coordination environment of both platinum centers is square planar with identical NOCl $_2$ donor sets. Preliminary

in vitro studies point out that the dinuclear Platinum complex exhibits significant growth-inhibiting properties on a panel of cultured human tumor cell lines, although less pronounced than those of cisplatin.

Several recent studies(Adrien,1985; David, 1972; Messori, *et al* 2003) investigated twenty six inorganic compounds for antiviral and anticancer activity. These included metal complexes of already established anticancer drugs such as six mercaptopurine. It was suggested that the transfer of metal ion from the ligand to the viruses associated with cancer was a mechanism for releasing the anticancer drug in the locality of the tumor. Metal chelates of dl- methionine and ethionine were prepared, antibacterial activity were attributed to the ligands that render the metal ion fat soluble and thus made it capable of acting within the cell(Adrien, 1985).

Komeda *et al* (2000) reported another four azole bridged dinuclear platinum(II) complexes. All the four complexes were found to show much higher cytotoxicity than those of cisplatin.

4. Anti-inflammatory agents

Metal complexes of organic drugs have also been used as anti-inflammatory and anti-arthritic agents. Extensive research is being conducted into Au, Cu and Zn anti-inflammatory drugs that have fewer side effects with similar or higher efficacy than the parent organic drugs commonly in use. Gold compounds were first used in 1929 by French doctors to treat rheumatoid arthritis(Shaw, 1999; Snyder *et al*,1987) and remain important in the treatment of rheumatic diseases. Several injectable transition gold complexes like sodium aurothiomalate, aurothioglucose and sodium aurothiopropanol are used clinically in the treatment of severe cases of rheumatoid arthritis. (Rafique *et al*, 2010) The developments of orally Auranofin(also known as Ridaura was a major improvement over the early "injectable gold" preparation which were polymeric). Zhuo *et al* (2000) and Sorenson,(1976) reported the synthesis and characterization of anti inflammatory Zn(II) and Cu(II) complexes of indomethacin. The studies were undertaken in order to reduce the side effects associated with the clinical use of indomethacin and related carboxylate-containing nonsteroidal anti-inflammatory drug (NSAID). NSAID drug exhibits favorable anti-inflammatory, analgesic and antipyretic properties, but it has undesirable side effects of inducing gastro-intestinal ulceration and haemorrhages. The complexes of indomethacin are superior to uncomplexed indomethacin for treatment of a range of conditions and most importantly reduce considerably lower incidences of gastro-intestinal damage.

Investigation of anti-inflammatory activity of complexes of diclofenac was carried out by Kovala-Demertzi *et al*,2000, 2001). Diclofenac is one of the widely used non-steroidal anti-inflammatory drugs (NSAIDs.) The Binuclear copper(II) complex of diclofenac $[\text{Cu}(\text{L})_2(\text{H}_2\text{O})]_2 \cdot 2\text{H}_2\text{O}$ was found to have an anti-inflammatory profile superior to diclofenac when inhibiting inflammations due mainly to the activation of lipooxygenase and or to the complement systems. Other metal complexes of diclofenac synthesized by this group are Co(II), Ni(II) and Pd(II). These complexes exhibit a superior anti-inflammatory profile, inhibiting inflammations and phagocytosis and act as antioxidant compounds, properties that are absent in diclofenac.

The group also synthesized and characterized organotin complexes of Diclofenac (Kourkoumelis *et al.*, 2003). The complexes were found to be dimeric. The anti-inflammatory activity of complexes were not investigated. Extensive work was also carried out on the complexation of piroxicam with organometallic compound. Di Leo *et al*, 1998 synthesized Platinum(II)-piroxicam (Figure 7) complex by reaction of ziese salt $K(PtCl_2)(\eta^2-C_2H_4).H_2O$ with piroxicam in ethanol. The complex $PtCl_2(\eta^2-C_2H_4).(Hpir)] \cdot 0.5C_2H_5OH \cdot$ was synthesized. Platinum was linked to two chloride ions trans to each other, N(1) atom from the pyridyl ring of piroxicam and to an $\eta^2-C_2H_4$ molecule.

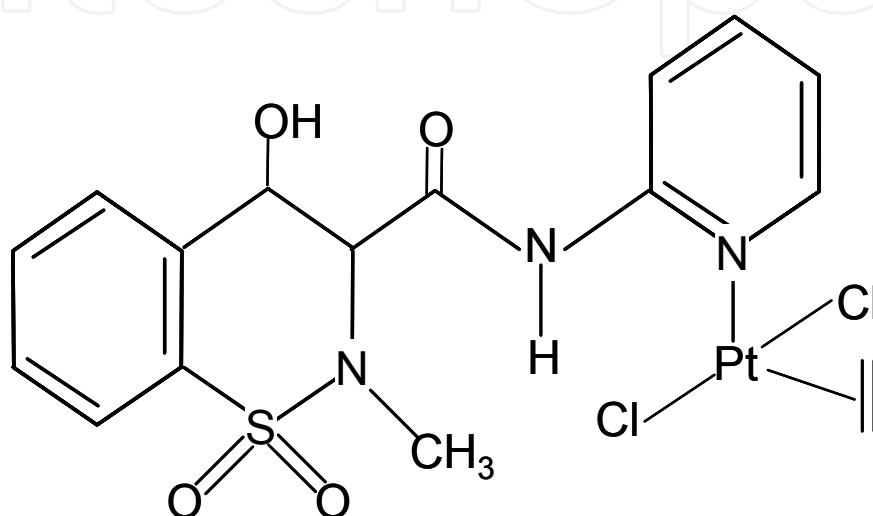


Fig. 7. Structure of Platinum(II)-Piroxicam

5. Antifungal agents

Many metal complexes have powerful antifungal activities and are already in common day to day use such as silverderma (Silver complex of sulfadiazine) and Flammazine (Zinc complex of silverdiazine.)

Navarro *et al*, (2001) synthesized and characterized complexes of Copper (II) and Gold (I) with Clotrimazole and ketoconazole. It was found out that the ligands coordinated to Gold through imidazole N(1) atom of each ligand with linear structure. The clotrimazole and ketoconazole coordinated to copper (II) through N (3) of the ligand atom with square planar structure. The new compounds were tested for *in vitro* activity against cultures of *epimastigotes* of *trypanosoma cruzi*. At concentration equivalent to 10.6M of total clotrimazole and ketoconazole in dimethylsulfoxide, all the complexes exhibited higher inhibitory activity than their respective parental compound. Sanchez-Delgado *et al*(1993) reported enhancement of efficacy of complex of Ruthenium clotrimazole against *trypanosome Cruzi* as compared to clotrimazole ligand. Bankole *et al*(1979) reported the synthesis of organosilicon derivatives of p-aminosalicylic, salicylic and benzoic acids. It was discovered that the presence of silicon in the p-aminosalicylic acid- silicon complex- prolonged and increased the antitubercular activity of p-amino salicylic acid in the body. The reaction scheme for the synthesis of p-aminosalicylic acid silicon complex is shown below (Figure 8).

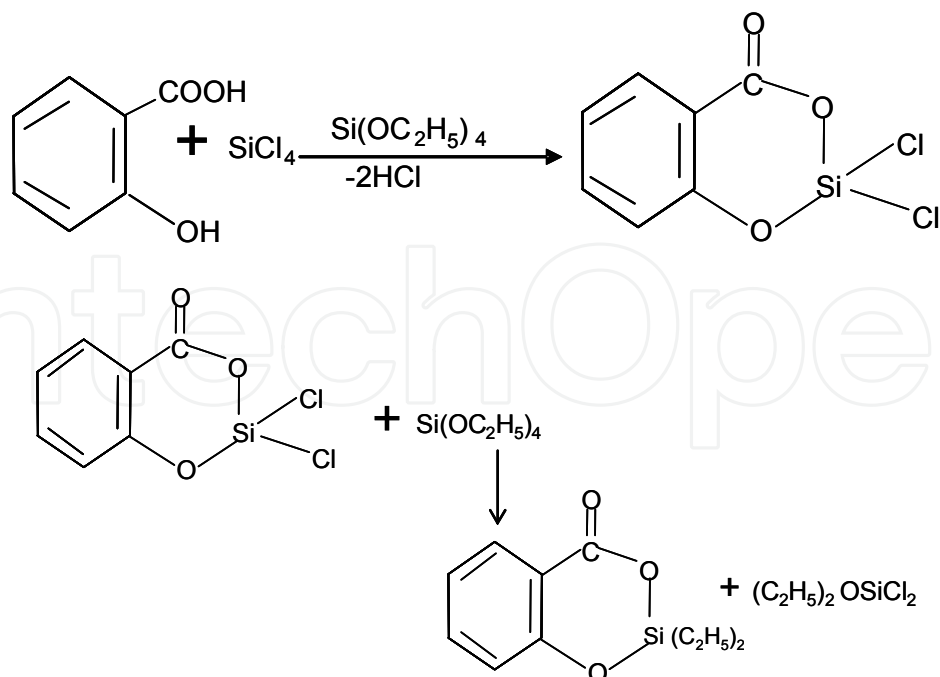


Fig. 8. Structure of Para-aminosalicylic acid silicon complex

6. Antihypertensive agents

Hypertension can be a long term illness and it is becoming increasingly common, severely limiting the quality of life of the sufferer. Because of the long term nature of the condition and therefore the long term nature of the medication, there is a strong incentive to develop drugs that can regulate blood pressure without causing side effects or becoming resistant over the course of the treatment. Many of the current leading therapies are based on organic drugs, although some inorganic compounds also exhibit excellent activity.

Anion of Sodium nitroprusside anion can be used to release NO in biological system and has been investigated as a potential hypotensive (Tuzel,1974). Sodium nitroprusside can be administered by infusion and reduces blood pressure within two months, the effect depending on the rate of NO release. Other similar compounds have been studied for potential application as vasodilators including vanadium, cobalt and molybdenum analogues(Hayton,2002).

Essien and Coker, (1987) reported the complexation of antihypertensive drug with calcium. Calcium nifedipine(Figure 9) was synthesized by reaction of calcium salt with nifedipine. The infrared spectrum revealed a strong evidence of possible complexation occurring at the carbonyl group ($\text{C}=\text{O}$) of the nifedipine. Two atoms of calcium complexed each to one pair of $\text{C}=\text{O}$ groups of 2 molecules of nifedipine.

Recently, Golcu *et al*,(2005) carried out the synthesis of binuclear copper (II) complex of Antihypertensive drug Pindolol. The biological activity of the parent drug pindolol was compared with the complex. The binuclear $\text{Cu}(\text{II})$ complex of pindolol was found to be highly active against *Bacillus megaterium*, *Aeromonas hydrophilia*, *Escherichia Coli*, *Candida albicans* bacteria and *Saccoramyces cerevisia*, *Rodotorula rubra*, *Kluyveromyces fragilis* yeasts. However, the free ligand was found not to be against these bacteria and yeasts.

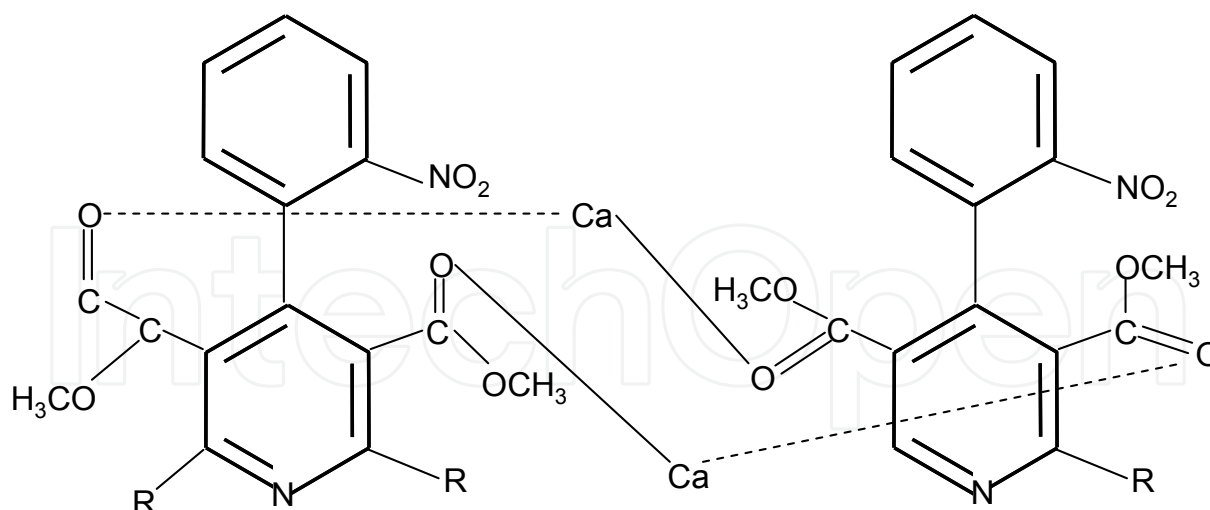


Fig. 9. Structure of Nifedipine - Ca.

7. Antibiotics agents

Many metal complexes have powerful antimicrobial activities and some of them are already in market. Silver bandages for treatment of burns.

A lot of antimicrobial metal complexes synthesized by researchers appeared in literature. We shall review some of these work. Emphasis will also be laid on the work carried out. Behrens *et al.* (1986) synthesized the transition metal complexes of Nalidixic acid.

Nalidixic acid is used in the clinical treatment of urinary tract infections caused by *gram-negative bacteria*. The mode of coordination of the drug was investigated by spectroscopic studies. From the spectra data, nalidixic acid anion binds through the carboxylate group either as a chelate or as bridge to give polymeric structure. Zupanicic *et al.* (2001) synthesized $[\text{CfH}_2]_2[\text{ZnCl}_4] \cdot 2\text{H}_2\text{O}$ from Ciprofloxacin and ZnCl_2 in dilute HCl. The compound was shown to be ionic consisting of tetrachlorozincate(II) dianion and two protonated monoatomic ciprofloxacin molecules. The second one which is a complex $[\text{Cu}(\text{Cf})(\text{H}_2\text{O})_3]\text{SO}_4 \cdot 2\text{H}_2\text{O}$ was synthesized by Turel *et al.* (1999). The complex was prepared by direct reaction of copper sulphate pentahydrate with ciprofloxacin in distilled water. X-ray crystallographic studies showed that the ciprofloxacin atom is bonded to the metal through carbonyl oxygen and carboxylic oxygen atom. Water molecules also coordinated to the copper.

Obaleye *et al.* (2001) synthesized and characterized metal (II) complexes of tetracycline HCl (Figure 10). For Mn, Fe, Zn, Co and Cd metals, the coordination of the metal to tetracycline is through one of the hydroxyl bands of tetracycline and oxygen of the carboxamide group, the proposed structures of the complexes were tetrahedral.

For Ni and Cu, the proposed structure of the complexes (Figure 11) were still tetrahedral, but the coordination is via oxygen of the $\nu(\text{C}=\text{O})$ and hydroxyl band of the drug. By using well-known antibiotics. Ogunniran *et al.* (2007) complexed Ampicillin Trihydrate, Chloramphenicol and Oxytetracycline with Ni(II), Fe(III) and Co(II) chloride salts. Thus, the three ligands acted as terdentate. The values of Zone of inhibition for *E. Coli*, *S. Aureus* and *K. Pneumonas* revealed enhanced antimicrobial activities upon complexation with metal salts.

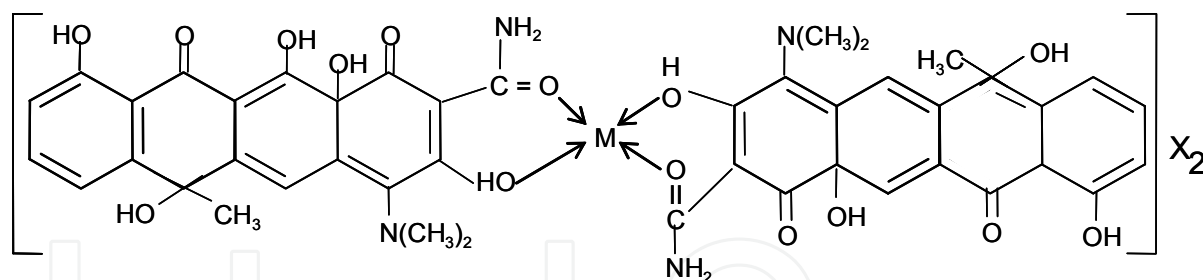


Fig. 10. Metal complexes Tetracycline [M = Mn, Fe, Co, Zn or Cd (II)].

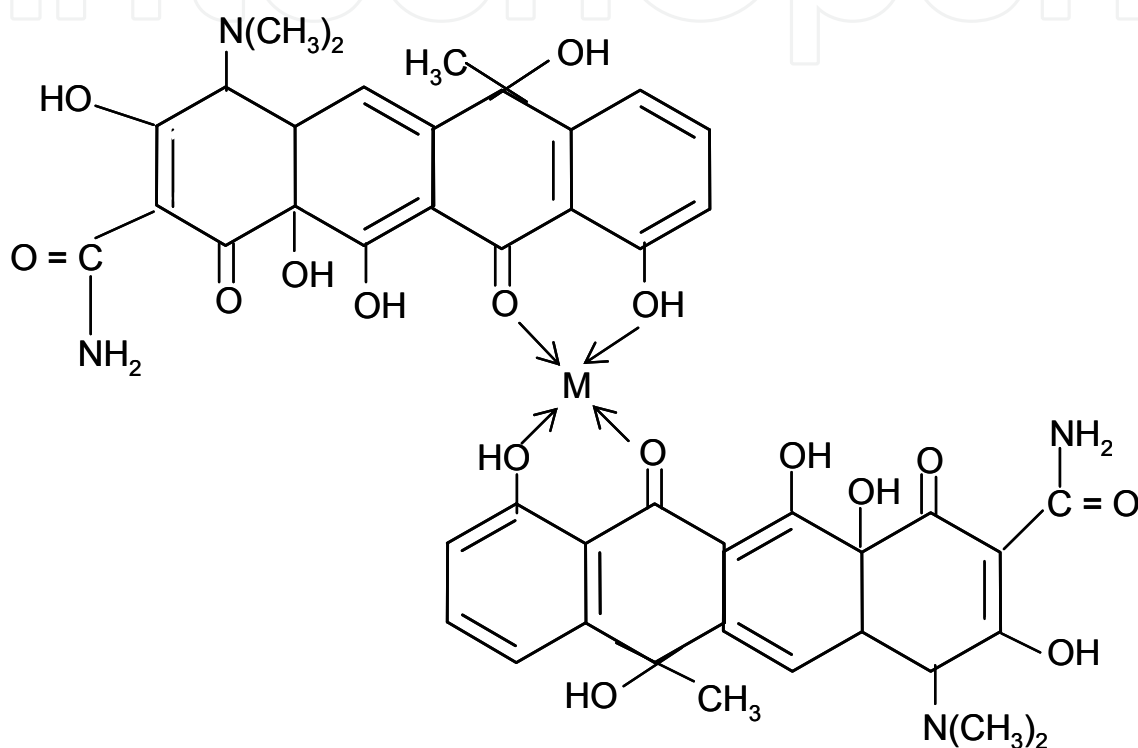


Fig. 11. Metal complexes of Tetracycline [Cu(II) or Ni(II)].

In 2007, Obaleye and co-workers synthesized two iron(II) complexes of ciprofloxacin by reaction of the ligand with iron(III) Chloride hexahydrate in different solutions. $[\text{Fe}(\text{Cip})_2\text{Cl}_2]\text{Cl} \cdot 6\text{H}_2\text{O}$ and $(\text{H}_3\text{Cip})\text{FeCl}_4\text{Cl} \cdot \text{H}_2\text{O}$ were prepared. The antibacterial activities of the products against 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 dose of the ciprofloxacin drug and the metal complexes were administered to albino rats and the results showed that the metal complexes are not toxic.

Attempt was also made to incorporate metal salts into mixed ligands. Cu and Co complexes of mixed sulphadiazine-cloxacillin were synthesized and characterized (Tella *et al*, 2010). Infra-red spectra revealed that coordination of the metal to the sulphadiazine is through nitrogen of the pyrimidine and sulphonyl groups while in cloxacillin, coordination with the metal occurred through the oxygen of the carbonyl group of β -lactam ring. Octahedral structure was proposed for the complexes. Antimicrobial screening was also evaluated which showed that the complexes exhibit higher activities than their corresponding ligands.

Recently, Tella *et al.*,(2011) investigated the possibility of transition metals coupling of antibiotics into cellulose. Chelates of Co(II), Zn(II) and Mn(II) cellulose- Antibiotics(Figure 12) were synthesized to form insoluble immobilized matrix with antibiotics. It can be established from this study that it is possible to form active immobilized antibiotics by simple chelation with metal salts.

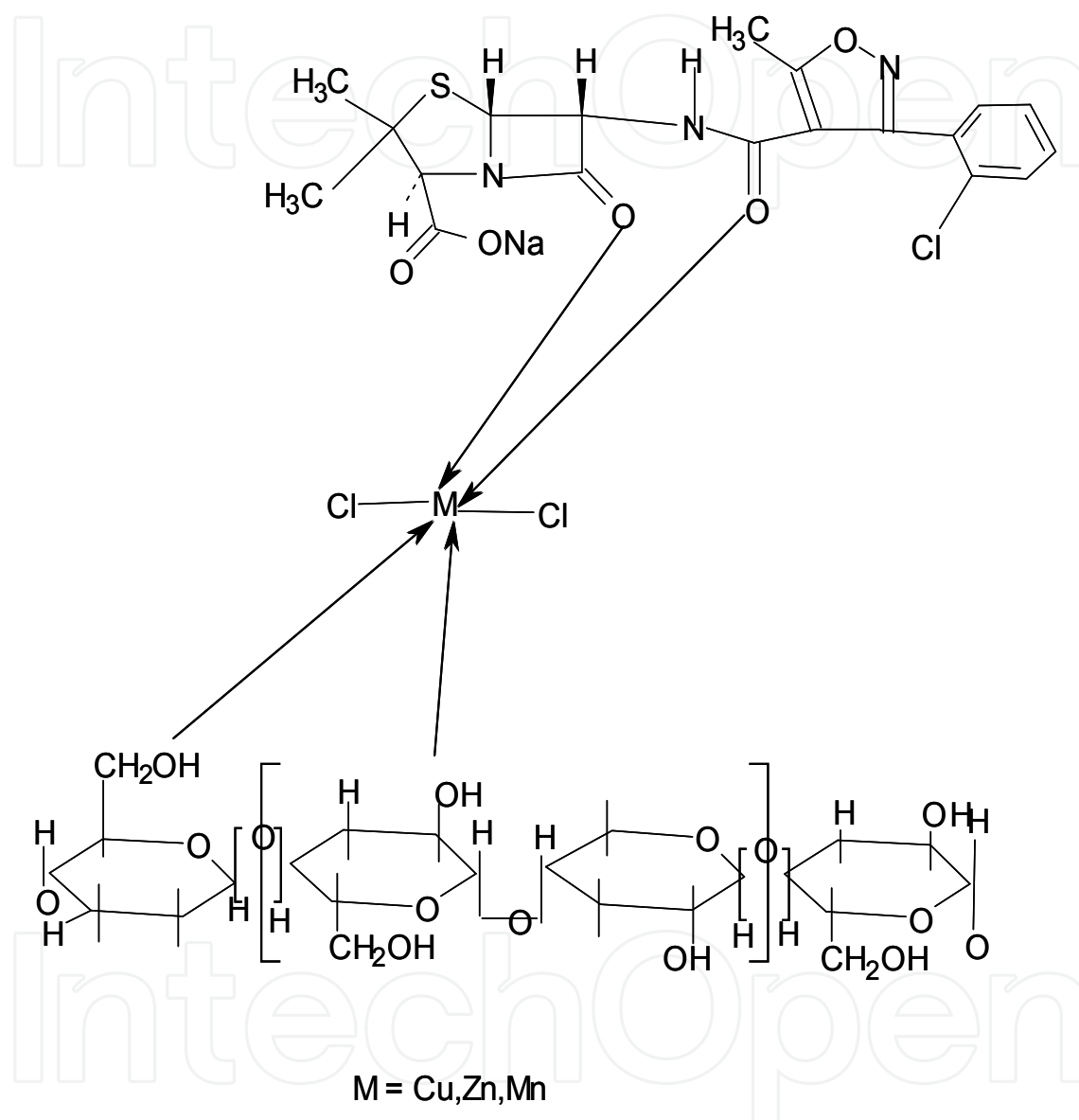


Fig. 12. Metal cellulose-Antibiotics Chelates.

From the antibacterial studies carried out, the products might be of greater applicability as food packaging material, antibacterial surface(water storage tanks, industrial membranes and chromatographic columns)..

8. Antibacterial agents

Casanova *et al.* (1993) synthesized single-crystal complex of $[Zn (\text{sulfathiazole})_2] H_2O$. The sulfathiazole was found to act as a bidentate ligand, chelates to two Zn ion as a bridge

through the N thiazole and N amino atoms. Rudzinski *et al* (1982) prepared several Sulfonamide -schiff base complexes of selenium(IV)(Figure 13) and tellurium(IV) (Figure14). Selenium coordinated through azomethine nitrogen, hydroxyl oxygen of the sulphonamide schiff base with chloride ion of the selenium salt to complete octahedral structure, while tellurium coordination site is only azomethine nitrogen, with chloride ion of the tellurium salt to complete the octahedral structure.

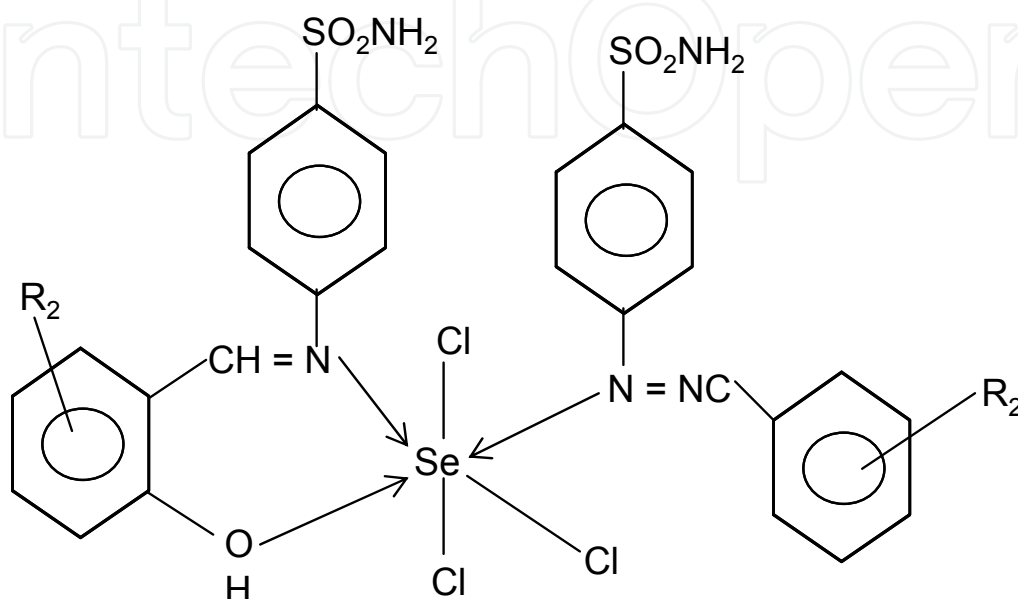


Fig. 13. Selenium (IV) sulphonamide Schiff base complex

The complexes were found to be active against bacterial even better than the parent ligand.

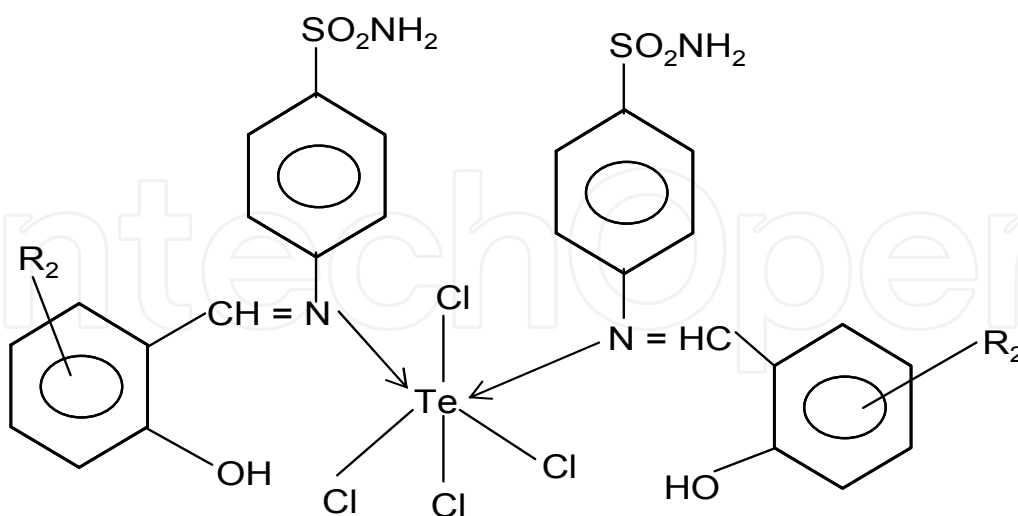


Fig. 14. Tellurium (IV) sulphonamide Schiff base complex

These two complexes proved to be biologically active as evidenced by pharmacological tests. Garcia-Raso *et al* (2000) synthesized single crystal of zinc-sulfamethoxazole complex $[\text{Zn}(\text{sulfamethoxazolato})_2(\text{pyridine})_2(\text{H}_2\text{O})_2]$ (Figure15).

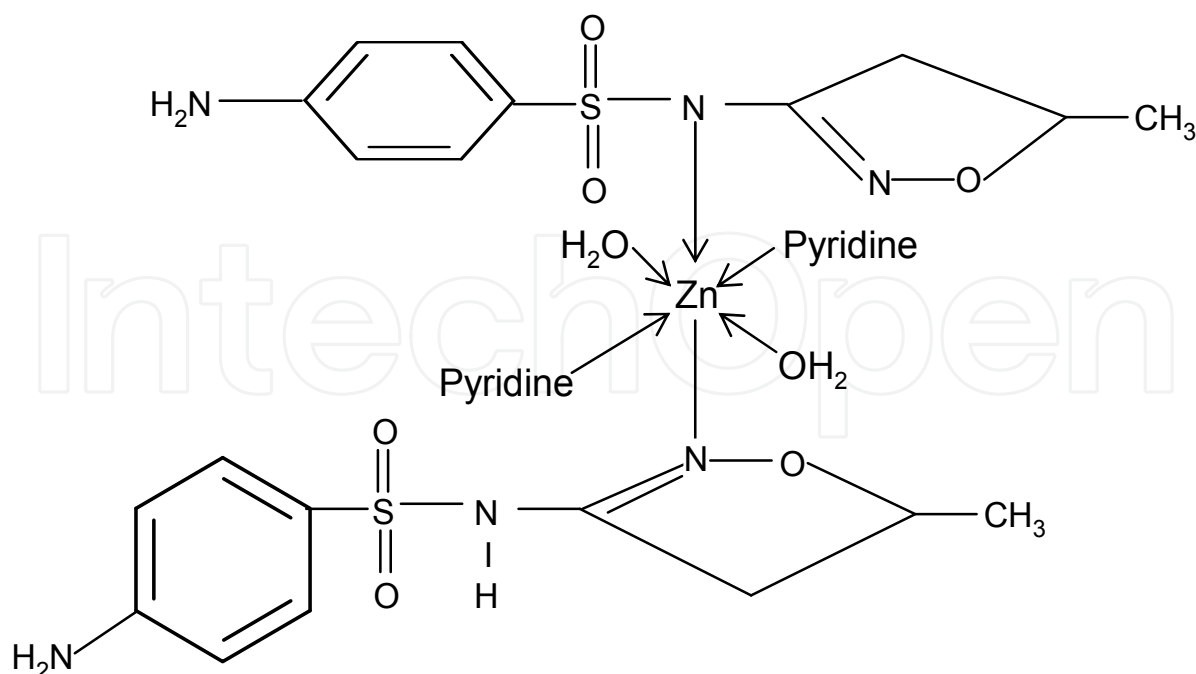


Fig. 15. Zinc sulfamethoxazole complex

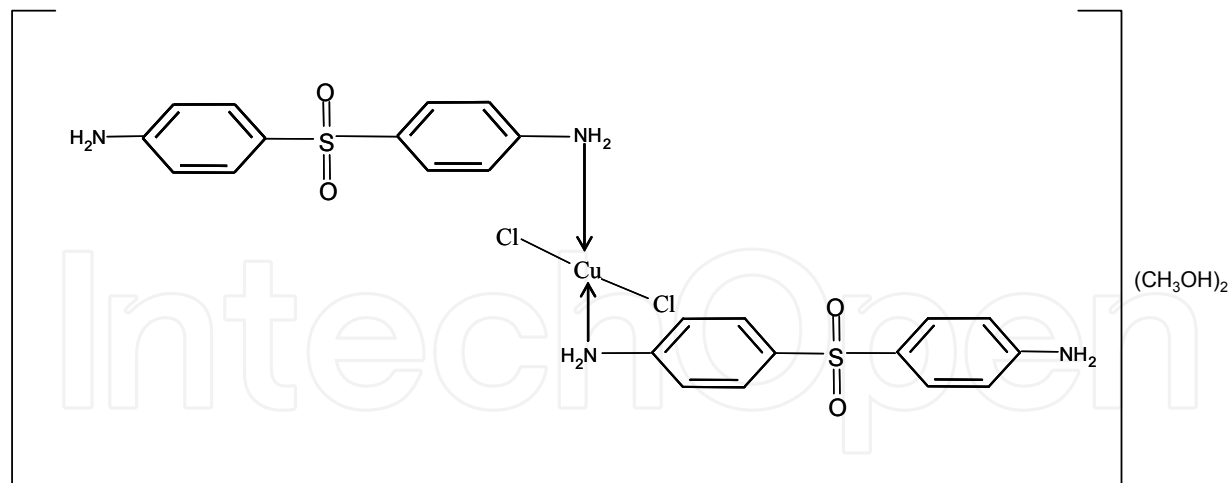
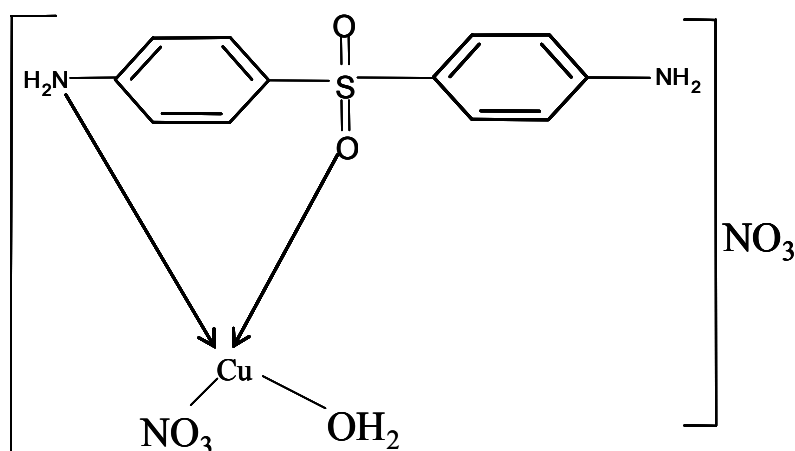
The geometry around Zn(II) ion can be described as a slightly distorted compressed octahedron. Two pyridine and two isoxazole N atoms are located in the equatorial plane and two oxygen atoms of two water molecules are placed in the apical positions.

Ajibade and Kolawole, (2008) reported trivalent complexes of sulphadiazine. The complexes were tested for in-vitro activity against cultures of the resistant strains of *Plasmodium falciparum*, *Tripamastigotes T.B. rhodesiense* and *Amastigotes L. donovani* to determine their antiprotozoa activities. The Fe(III) complex is more active than the other complexes against the parasitic protozoa.

Recently, our group studied mode of coordination and Antimicrobial activities of complexes of some sulphonamides. Tella and Obaleye(2009) synthesized five complexes of copper (II) 4,4-diaminodiphenylsulphone (Dapsone) using copper salts of counter ion(sulphate, nitrate and chloride) in different reaction media(Solvents). The structure of the compounds were elucidated by spectroscopic techniques. Dapsone coordinated to the metal in monodentate and bidentate manner. with all the complexes having tetrahedral structures (Figures 16 and 17)

The biological activities data showed that the complexes are more active against *Escherichia coli*, *Klebsiella pneumonia* and *staphylococcus aureus* than the free ligand.

Antimalarial activities of the complexes and the ligand were investigated using mice infected with *Plasmodium berghei*. All the complexes exhibited lower activity than the ligand and chloroquine. Toxicological studies carried out showed that the complexes are not toxic, as indicated from the effect of administration of the complexes on alkaline phosphatase activities of kidney, liver and serum of Albino rats. The serum ALP activity showed no significant change($P>0.05$), suggesting non-damaging effect on the plasma membrane of liver and kidney cells.

Fig. 16. Structure of $[\text{Cu}(\text{DAP})_2\text{Cl}_2](\text{CH}_3\text{OH})_2$ Fig. 17. Structure of $[\text{Cu}(\text{DAP})(\text{NO}_3)(\text{H}_2\text{O})]\text{NO}_3$

Metal complexes of sulphadimidine synthesized by Tella and Obaleye (2009) were established to possess higher antibacterial activities than the ligand. The complexes showed greater activities against the *Escherichia coli*, *Klebsiella pneumonia* and *staphylococcus aureus*. This is in agreement with the findings of other researchers.

9. Vitamin metal complexes

Vitamins are essential for the normal growth and developments of a multicellular organisms. Once growth and development are completed, vitamins remain essential nutrients for the healthy maintenance of cells, tissues and organ that make up a multicellular organisms. It has been established that complexation of metal with vitamins enhances the activity of the vitamins. Many workers made attempt to synthesis metal complexes of thiamine. From early complexation studies, it was evident that thiamine and its derivatives do not readily form true complexes with direct metal-thiamine bonds but instead, they give ionic salts mainly of the type $(\text{HT})^{2+}(\text{MX}_4)^{2-}$ due to the net positive charge on the thiazolium ring and the easy protonation of pyrimidine N(1) atom. Such ionic salts synthesized by them are $[\text{ThH}]^{2+} [\text{HgCl}_3]^{2-}$, $[\text{ThH}]^{2+} [\text{CdCl}_4]^{2-}$ and $[\text{ThH}]^{2+} [\text{HgCl}_4]^{2-}$. (Garcia-Raso *et al*, 2000,

Richardson,1975). However, the successful preparation and structure determination of $\text{Cd(Th)Cl}_3 \cdot 0.6\text{H}_2\text{O}$, $\text{Cd(Th)Cl}_3 \cdot 2\text{H}_2\text{O}$, Cu(Th)Cl_2 , $\text{Zn(Th)Cl}_3 \cdot 0.4\text{H}_2\text{O}$ (Hadjilias, 1983; Gramer,1984; Bencini,1987) proved that metal-thiamine complexes exist. Another study on vitamin is the work carried out by Mosset *et al*(1978). They synthesized Cd(Py)Cl_2 from reaction of aqueous solution (pH=6.5) of equimolar amount of pyridoxine and cadmium chloride. From NMR and X-ray structural studies, the structure consists of infinite chains of Cd-bridge-Cd. The Cd atom, in an octahedral environment is bound to three chlorine atoms and three oxygen atoms of the ligand. Two chloride ions make a double bridge between two equivalent cadmium atoms. The pyridoxine molecule acts as a bidentate ligand through two oxygen and as a bridge between two equivalent atoms. Zinc complex of pyridoxine was also reported by Thompson *et al*(1980). $[\text{Zn(Py)}_2(\text{H}_2\text{O})_2](\text{NO}_3)_2$ was synthesized from reaction of zinc nitrate and pyridoxine. The X- ray crystallographic studies revealed that Zinc atom lie on centers of symmetry and are chelated to the 4-amino methyl and phenolate groups of pyridoxine zwitterions. Octahedral coordination is completed by water molecules. Dakovic *et al* (2008) reported the synthesis of nicotinamide metal complexes of Zn(II) and Hg(II). The nicotinamide with carboxamide group in the meta-position to the pyridine nitrogen atom acts as a monodentate -N ligand for the zinc(II) and mercury (II) ion coordinating to metal ions through the pyridine nitrogen atom and leaving both carboxamide moieties available. The biological activities of all these complexes were not investigated. It can be seen from literature review that there is little or no work carried out on investigation of biological activities by many researchers. Attempt was made by our research group to investigate antimicrobial activities of vitamin-metal complexes. Investigation of antimicrobial activities of transition metal complexes of vitamin C was carried out. Obaleye *et al.* (1994) ; Obaleye and Ojiekwe, (1983) synthesized and screening Co(II), Zn(II), Mn(II),Fe(III),Hg(II),Cu(II) and Cd(II) complexes of vitamin C against four strains of bacterial species- *Escherichia coli*, *Klebsiella pneumonia*, *staphylococcus aureus* and *Bacillus subtilis* and two fungal species- *Aspergillus flavus* and *Aspergillus niger*. The complexes have little or no activity on the bacterial species studied. Generally, percentage inhibition of Ascorbic acid on fungal species was the greatest among all compounds tested.

10. Antidote

Metal complexes have been used as antidote since 1945, for chronic intoxication arising from therapy or household contamination or hasten excretion of radioactive element. These antidotes circulate in the blood stream without causing much depletion of the body 's essential metals. A lot of ligands have been used as antidote to combat metal poisoning. Dimercaptol is used to counter poisoning by compound of gold and mercury. The use of ascorbic acid as a possible antidote was demonstrated by Key pour *et al.* (1986).

In an attempt to discover possible antidote for drug or metal poisoning. We investigated the interaction of pyrimidine and sulphonamide drugs with some transition metals by determining their stability constants in order to assess their potentiality as antidote for metal-overload poisoning(Tella and Obaleye, 2010). The stability constant(β) were found to be log 10.68, 5.5 and 4.8 for Trimethoprim, sulphadiazine and sulphadimidine with respect to metal salts. The order of stability constants(β) was found to be $\text{Cu(II)} > \text{Fe(III)} > \text{Ni(II)} > \text{Co(II)} > \text{Zn(II)}$ in accordance with Irvin-williams series. The stability constant data revealed that this ligand may be used as antidote or chelating agent for medical treatment of metals overload or poisoning.

11. Conclusion

The structure of known biologically active molecules is modified to result in new molecules known as metal coordinated complexes. The goal of such modification is to get a molecule that is improved in some way, such as potency, stability, reduced side effect or targeted delivery. The improvement is achieved without sacrificing the molecules' desirable properties. In this paper, we have been able to shed light on effort made so far by our group and other researchers in discovery of new antibacterial agents by modification of existing known biological agents through the incorporation of metal into their molecular structure. We have been able to establish that some of these complexes are biologically active than their parent ligands, making them promising candidates to join league of metal-based drugs already in market. It should be known that traditional studies of organic drugs at a fundamental level are not complete without a parallel program on metal pharmacology. In general, because metal can undergo ligand exchanges, metal complexes are pro-drugs, ligand substitution can activate the metal complex toward binding to target molecules.

It should be recognized that a metal is not just a metal : it is a metal ion plus its ligand. The metal ion plus the ligand determine the biological activity.

We should know that despite the obvious success of metal complexes (Cisplatin, Silverderma, Flammazine and others) as chemotherapeutic agents, few pharmaceutical companies have serious in-house research programs that address these important bioinorganic aspects of medicine. Research programs in organic and metallo-drugs should not be seen as mutually exclusive. They overlap extensively and the combination is likely to be a powerful force for the future.

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13. References

- [1] Adrien, A. (1985). *Selective Toxicity*, 7th Ed. Chapman and Hall, New York, 432- 468.
- [2] David, R.W. (1972). Anticancer drug design involving complexes of amino acid and metal ions. *Coord. Chem. Review*, 5, 123-133
- [3] Messori, L., Shaw, J., Camalli, M., Mura, P., Marcon, G. (2003). Structural features of a new dinuclear platinum (II) complex with significant antiproliferative activity. *Inorg. Chem.* 42, 6166-6168.
- [4] Komeda, S., Lutz, M., Spek, A.L., Chikuma, M., Peedijk, J. (2000). New antitumor – active Azole – bridged dinuclear platinum (II) complexes synthesis, characterization, Crystal structures and Cytotoxic studies. *Inorg. Chem.* 39, 4230 – 4236.
- [5] Zhou, Q., Hambley, T.W., Kennedy, B. J., Ley, P. A Turner, P., Warwick, B., Biffin, J. R., Regtop, H. L. (2000). Synthesis and characterization of Anti-Inflammatory Dinuclear

- and Mononuclear. Zinc Indomethacin complexes. Crystal structures ($\text{Zn}_2(\text{Indomethacin})_4(\text{L})_2$) and ($\text{Zn}(\text{Indomethacin})_2(\text{L})_2$) *Inorg. Chem.* 39, 3742-3748
- [6] Sorenso, J.R.J. (1976). Copper Chelates as possible active forms of the antiarthritic agents. *J. Med. Chem.* 19, 135-148.
- [7] Navarro, M., Fajardo, E.J., Lechmann, T; Delgado, R.A., Atencio, R., Silva, P., Liva, R., Urbina, J.A. (2001). Toward a novel metal-based chemotherapy against tropical diseases; synthesis and characterization of new copper (II) and Gold (I) Clotrimazole and ketoconazole complexes and evaluation of their activity against trypanosome cruzi. *Inorg. Chem.* 40, 27, 6879 - 6884.
- [8] Sanchez - Delgado, R.A., Lazard, K., Rincon, L., Urbina, J., Hubert, A.J., Noels, A.N. (1993). Toward a novel metal based chemotherapy against tropical diseases II. Enhancement of efficacy of clotrimazole against *trypanosoma cruzi* by complexation to Ruthenium in $\text{RuCl}_2(\text{clotrimazole})_2$. *J. Med. Chem.* 36, 2041-2043.
- [9] Bankole, F.O. (1979). Organosilicon derivatives of salicylic acid. *J. Pharm. and Med. Sci.* 4(5), 249-250..
- [10] Essien, E.E., Coker, H.A.B. (1987) Interaction of nifedipine with calcium. *The Nig. J. Pharm.* 18(4)21-22.
- [11] Obaleye, J.A., Adeyemi, O.G., Balogun, E.A. (2001). Some metal tetracycline Complexes: Synthesis, characterization and their effects against malaria parasites. *Int. J. Chem.* 11(2), 101-106.
- [12] Casanova J., Alzuet, G., Ferrer, S., Borrás, J., Garcia - Granda, S., Perez - Carreno, E. (1993). Metal Complexes of sulfanilamide Derivatives Crystal structure of $[\text{Zn}(\text{sulfathiazole})_2] \cdot \text{H}_2\text{O}$. *J. Inorg. Biochem.* 51, 689-699.
- [13] Rudzinski, W.E., Aminabhavi, T.M., Biradar, N.S., and Patil, C.S. (1982). Biologically active sulfonamide Schiff base complexes of Selenium (IV) and Tellurium (IV). *Inorg. Chim. Acta.* 67, 177-182.
- [14] Richardson M.F., Franklin, K., Thompson, D.M. (1975). Reaction of metals with vitamins I. Crystal & molecular structure of thiamium tetrachlorocadmate monohydrate. *J. Am. Chem. Soc.* 97, 3204-3209.
- [15] Hadjiliadis, N., Yannopoulos, A. (1983). Complexes of Mercury (II) with Thiamine. *Inorg. Chim. Acta*, 69, 109-115.
- [16] Gramer, R.E., Maynard, R.B., and Evangelista, R.S. (1984). Synthesis, crystal and molecular structure of a Cu (II) complex of vitamin B1, $\text{Cu}(\text{thiam})\text{Cl}_2$. *J. Am. chem. Soc.* 106, 111-116.
- [17] Bencini, A., Borghi, E. (1987). Complexes of vitamin B1 with Transition metal ions Crystal and molecular structure of $\text{Zn}(\text{thiamine})\text{Cl}_3 \cdot 0.4\text{H}_2\text{O}$. *Inorg. Chim. Acta.* 135, 85-91.
- [18] Mosset, A., Nepveu-juras, F., Haran, R., Bonnet, S.S. (1978). Complexation of the vitamin B₆ with Cd^{2+} cation: NMR and X-ray structural study. *J. Inorg. Nucl. Chem.* 40, 1259-1263.
- [19] Thompson D.M., Balenovich, W., Hornich, L.H. M., Richardson, M.F. (1980). Reactions of metal ions with vitamins. The crystal structure of a Zinc complex of pyridoxamine (vitamin B₆). *Inorg. Chim. Acta.* 46, 199-203.
- [20] Obaleye, J.A., Orjiekwe, C.L. (1983). Synthesis and characterization of copper (II) and Zinc (II) complexes of Ascorbic acid. *Int. J. Chem.* 4, 37.
- [21] Zupančić, M., Turel, I., Bukorec, P., White, A.J.P., Williams, D.J. (2001). Synthesis and characterization of two novel Zinc (II) complexes with ciprofloxacin. Crystal structure of $(\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{F})_2 \cdot (\text{ZnCl}_4) \cdot 2\text{H}_2\text{O}$. *Croatica Chemica Acta.* 74(1), 61-74

- [22] Turel, I., Golic, L., Ramirez, O.L.R. (1999). Crystal structure and characterization of a new Copper (II) cirpofloxacin (cf) complex $[\text{Cu}(\text{cf})\text{H}_2\text{O}]_3\text{SO}_4 \cdot 2\text{H}_2\text{O}$. *Acta. Chim. Slov.* 46 (2), 203-211.
- [23] Spacu, P., Gheorghiu, K., Nicolaescu, A. (1968). Coordination Compounds of Ni (II) and Ni (III) with Paludrine. *Coord. Chem. Reviews*, 12, 413-415.
- [24] Wasi, N., Singh, H.B., Gajanana, A., Raichowdhary, A.N. (1987). Synthesis of metal complexes of antimalarial drugs and *in-vitro* evaluation of their activity against *Plasmodium falciparum*. *Inorg. Chim. Acta.* 135(2), 133-137.
- [25] Obaleye, J.A., Nde-aga, B.J. (1997) Some antimalarial drug metal Complexes. *Afr. J. Sc.* 1, 10-12.
- [26] Tsangaris, J.M., Baxevanidis, G.T., Zeitschrift Naturforschung, Teil Bi (1974). Complexes of Quinine with Copper (II), nickel (II), Cobalt (II) and Chromium (III) Chlorides. *Zeitschrift fuer Naturforschung*, 29 (7/8) 532-537.
- [27] Ogunniran, K.O., Tella, A.C., Alensela, M., Yakubu, M.T. (2007) Synthesis, physical properties, antimicrobial potentials of some antibiotics complexed with transition metals and their effects on alkaline phosphatase activities of selected rat tissue. *Afr. J. biotech.* 6(10), 1202 -1208.
- [28] Keypour, H., Silver, J., Wilson, M.T., Hamed, M.T. (1986). Studies on the reactions of ferric ion with Ascorbic acid. A study of solution chemistry using Mossbauer Spectroscopy and stopped-Flow techniques. *Inorg. Chim. Acta*, 125, 97-106.
- [29] Biot, C., Delhaes, L.A., N'Daiye, C.M., Maciejewski, L., Camus, D., Dive, D and Brocard, J.S. (2000). Synthesis and potential metabolites of ferrochloroquine and related compounds. *Bioorg. Med. Chem.* 7, 2843-2846.
- [30] Biot, C., Delhaes, L., Abessolo, H. (1999). Novel Metallocenic compounds as antimalarial agents: Study of the position of ferrocene in chloroquine. *J. Org. chem.* 589, 1, 57-65.
- [31] Delhaes, L., Biot, C., Berry, L., Maciejewski, L., Camus, D., Brocard, J.S., Dive, D. (2000). Novel ferrocenic Artemisinin derivatives: Synthesis, *in-vitro* antimalarial activity and affinity of binding with ferrophotoporphyrin (IX) *Bioorg. Med. Chem.* 8, 2739.
- [32] Hubel, R.; Polborn, K.; Knizek, J.; Heinrich, N and Wolfgang B. (2000). Metal complexes of Biologically important ligands CXXVI Palladium (II) and Platinum (II) complexes with the antimalarial drug mefloquine as ligand. *Anorg. Allg. Chem.* 629, 1701-1708.
- [33] Di Leo, D., Berrettin, F and Renzo, C. (1998) Synthesis of Platinum(II)-Piroxicam Compounds. Crystal structure of trans-dichloro(η^2 -ethene(Piroxicam)Platinum(II). *J. Chem. Soc. Dalton Trans*, 1993-2000.
- [34] Garcia-Raso, A., Fiol, J.J., Rigo, S., Lopez-Lopez, A., Molins, E., Espinosa, E., Borrás, E., Alzueta, G., Borrás, J., Castineiras, A. (2000). Coordination behaviour of sulfanilamide derivatives, Crystal structure of $[\text{Hg}(\text{Sulfamethoxypyridazinato})_2]$, $[\text{Cd}(\text{Sulfadimidinato})_2(\text{H}_2\text{O})] \cdot 2\text{H}_2\text{O}$ and $[\text{Zn}(\text{Sulfamethoxazolato})_2(\text{pyridine})_2(\text{H}_2\text{O})_2]$. *Polyhedron*, 19, 991 - 1004.
- [35] Obaleye J.A, Tella, A.C and Arise, R.O (2009). Advances in Natural and Applied Sciences, 3(1), 43-38.
- [36] Ashford, R, Desjeux, P, de raadt, P (1992). *Parasitol. Today*, 8, 104
- [37] Quellette, M, Papadopolou, B (1993). *Parasitol. Today*, 9, 150
- [38] Loiseau, P M, Craciunescu, D.G, Doadriovillarejo J.C, Certedfombona, G, Gayral, P. (1992). *Tropical medicine and Parasitology*, 34, 110.
- [39] Insstag, J; Brun, R; Craciunescu, D.G; Iglesias, E.P (1991). *Tropical medicine and Parasitology*, 42 : 41
- [40] Mesa valle, C.M; Mortaleda Lindez, V; Craciunescu, D; Alonso, M; Osuna, A (1993). *Arzneimittel Forsch Drug Res.* 43: 1010.

- [41] Rosenberg, B; Van camp, L ; Krigas, T.(1965). *Nature*, 205, 698.
- [42] VanRujt, S.H and Sadler, P.J.(2009) *Drug Discovery Today*. 14, 23/29, 1089-1097
- [43] Lippert B(1999). Ed, *Cisplatin : Chemistry and Biochemistry of a leading Anticancer Drug*, Wiley-VCH, New York.
- [44] Kelland, L.R; Farell, N.P.(2000). *Platinum-based drugs in Cancer Therapy: Human Press*, Totowa, New Jersey.
- [45] Wong, E;Giandomenico, C.M.(1999), *Chem. Rev.* 99, 2451-2466.
- [46] Christian, M.C.(1992). *Semin. Oncol.* 19,1970.
- [47] O'Dwyer, P.J; Stevenson, J.P; Johnson, S.W.(1999) Clinical status of cisplatin, carboplatin and other platinum-based Antitumor Drugs. in *cisplatin: Chemistry and Biochemistry of a leading Anticancer Drug ; Lippert, B; Ed. Wiley-VCH, New- York*, 31-72.
- [48] Rafique, S; Idress, M; Naim, A; Albar, H and Athar, A.(2010). *Biotechnology and Molecular Biology Reviews*, 5(2), 38-45.
- [49] Highley, M.S; Calvert, A.H. (2000) *Clinical Experience with Cisplatin and Carboplatin ; Kelland, L.R; Farell, N.P; Eds: Human Press, Totowa N.J.* 89-113.
- [50] Shaw, C.(1999). Gold Complexes with anti-artritic, Antitumor and Anti-HIV Activity; In *uses of inorganic chemistry in medicine*, Farell, N; Ed. Cambridge, 26-57.
- [51] Jaouen, G; Top, S; Vessieres, A; Leclercq, G; Quivy, J; Jin, L; Groisy, A.(2000). *CR. Acad. Sci. IC*, 3,89.
- [52] Tella, A.C and Obaleye, J.A.(2009). *E-journal of Chemistry*,6(S1), s311-S323.
- [53] Violette, M; Gautheron, B; Kubicki, M.M; nifantev, I.E; Fricker, S.P(1995). *Metal-based Drugs*, 2, 311.
- [54] Koepf-Maier, P; Koepf, H.(1987). *Chem. Rev.* 87, 1137.
- [55] Snyder, R.M; Mirabelli, C.K; Crooke, S.T.(1987), *Semin. Arthritis Rheum*, 17, 71-80.
- [56] Guo, M.L; Sun, H.Z; Mc Ardle, H; Gambling, L; sadler, P.J.(2000). *Biochemistry*, 29, 10023.
- [57] Koepf, H. Koepf-Maier, P.(1979). *Angew Chemie*, 91, 509.
- [58] Clarke, MJ; Zhu, F.C; Frasca, D.R.(1999). *Chem. Rev.* 99,2511.
- [59] Edwards, E.I; Epton, R; Marr, G.(1975). *J. Orgnometal. Chem.* 85, c23.
- [60] Tella, A.C and Obaleye, J.A.(2010). *Int.Chem. Sci.*, 8(3), 1675-1683.
- [61] Tuzel, H.I(1974).*Clin. Pharmacol.*14, 494.
- [62] Hayton, T.W; legzdins, P; sharp, W.B(2002). *Chem.. Rev.* 102, 935.
- [63] Tella, A.C and Obaleye, J.A(2010). *Orbital-The Electronic Journal of Chemistry*, 2(1), 11-26.
- [64] Tella, A.C and Obaleye, J.A.(2010). *Int. J. Biol. Chem. Sci.*4(6), 2181-2191..
- [65] Ajibade,P.A and Kolawole, G.A.(2008). *Bulletin Chem. Soc. Ethiopia*, 22(2), 261-268.
- [66] Tella, A.C; Obaleye, M.O and Obaleye, J.A(2010).*Integrated Journal of Science and Engineering*, 9, 1,58-63.
- [67] Kourkoumelis, N; Demertzis, M.A; Kovala- Demertzi, D; Koutsodimou, A; Moukarika,A.(2004). *Spectrochimica Acta Part A* 60, 2253-2259
- [68] Golcu, A; Dolaz, M; Dager, E.K.(2005). *KSU Journal of Science and Engineering*, 8(1),4-9.
- [69] Behrens, N.B and Diaz, G.A(1986). *Inorganica Chimica Acta.* 125,21-26.
- [70] Dakovic, M; Popovic, Z; Giester, G; Rajic-Linaric,M.(2008). *Polyhedron*,27, 465-472.
- [71] Obaleye, J.A and Famurewa, O.(1989). *Biosci. Res. Commun.* 1, 87.
- [72] Obaleye, J.A; Akinremi, C.A; Balogun, E.A and Adebayo, J.O.(2007). *African Journal of Biotechnology*,6(24), 2826-2832.
- [73] Tella, A.C ; Obaleye, M. O and Akolade, E.O.(2011). *Middle- East Journal of scientific Research*,7(3),260-265.
- [74] Obaleye J.A.,Orjiekwe C.L. and Famurewa O.(1994).Effects of Some Novel Ascorbic Acid-Metal Complexes on SelectedBacterial and Fungal Species. *J.Sci.I.R. of Iran* 5(4) 154-157.

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