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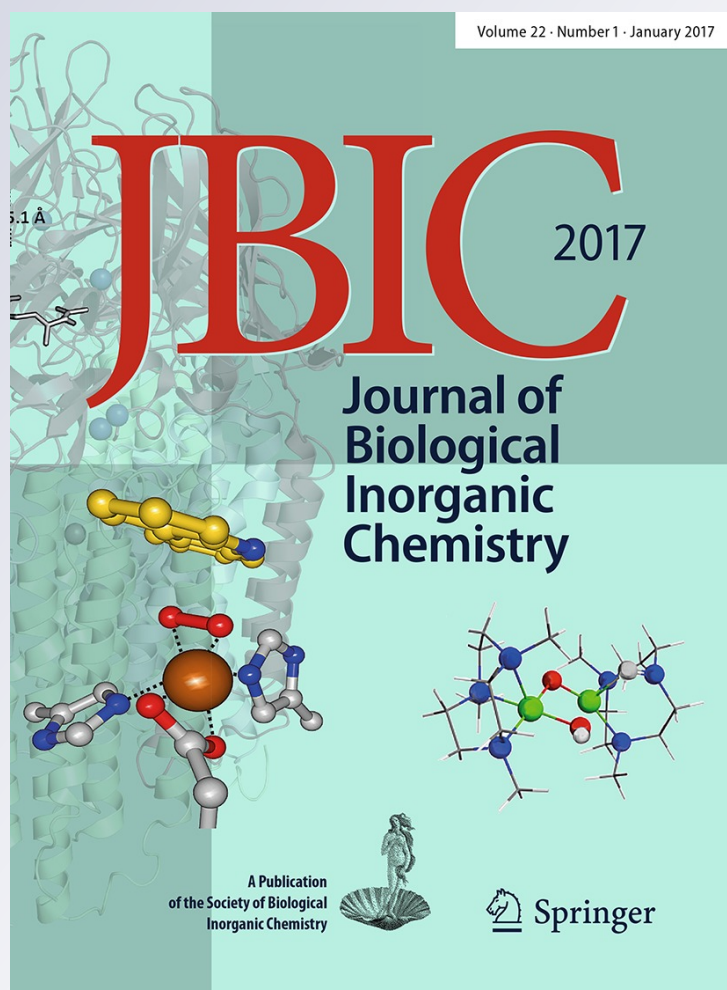
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Some nontoxic metal-based drugs for selected prevalent tropical pathogenic diseases

Saliu A. Amolegbe¹ · Caroline A. Akinremi² · Sheriff Adewuyi² · Amudat Lawal³ · Mercy O. Bamigboye³ · Joshua A. Obaleye³

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Abstract Metal coordination of bioorganic compounds from both natural and synthetic products is not only gaining recognition in drug design and medicinal inorganic chemistry research, also they are being considered in the improvement of the bioactivity of drugs. What is done in this paper is a review of recent advances in the study of coordination-driven drug delivery, i.e., metal-based drugs (MBDs). The role of some late first row transition metal ions namely Fe, Cu and Zn in the biological activities of metallodrugs such as antimalarials and antimicrobials are highlighted. It was revealed that the interaction between these bio-essential transition metal ions and the organic drugs could enhance the diagnostic and therapeutic potentials of such formed drugs. This is because such interactions were proved to have improved the stability, bioavailability and cell delivery functions of the metallodrugs. Emphasizing on the challenge of metal ions toxicity, the researchers concluded on the need for the development of MBDs to combat drug resistant parasites without causing injury to normal cells. This would be of significance in addressing the concern World Health Organisation of ameliorating the increasing mortality rate in developing countries.

Keywords Metal-based drugs · Non-toxic · Target cell · Tropical pathogens · Metalloenzymes

Abbreviations

MBDs	Metal-based drugs
CQ	Chloroquine
CQDP	Chloroquine diphosphate
QN	Quinine
ACT	Amoxicilin trihydrate
MAMDs	Metal antimalarial drugs
MAMcDs	Metal antimicrobial drugs
ATP	Adenosine triphosphate
mRNA	Messenger ribonucleic acid
tRNA	Transfer ribonucleic acid
rRNA	Ribosomal ribonucleic acid
DNA	Deoxyribonucleic acid
DDS	Drug delivery system

Introduction and scope

Non-toxic and bio-essential metal-based drugs (MBDs) with improved biological activities act either as diagnostic or chemotherapeutic agents. This along with their predominant presence in iron (Fe), copper (Cu) and zinc (Zn) metalloenzymes than in free organic compounds underscores the significance of medicinal inorganic chemistry [1–5]. Tropical diseases still pose a serious threat to human existence despite numerous formulations of vaccines. Unfortunately, malaria and number of other deadly infectious diseases predominate in Africa, thus threaten the growth and survival of the continent. In addition, many of the drugs available for the treatment of these diseases have become ineffective and impotent because of the development of multidrug-resistant strains by the

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diseases. Indeed, this has made some of these drugs to be toxic to human tissues.

Interestingly, the discovery of metallopharmacy with recent input of therapeutic MBDs towards an excellent drug delivery against pathogens is not only well known, but is receiving much interest in biomedical research [6–8]. The MBDs take the advantage of the metal–drug bond, hydrophilicity, redox reaction which make them very efficacious and boost the potency of bioactive compounds for physiological-friendly system. What makes the complexes significant to include the fact of their ability to be metal-antimalarial and metal-antimicrobial agents [9–19]. However, scientists continue the effort to design new drugs and strategies for diagnostic and therapeutic purposes. In line with this focus and in continuation of our interest in metal ions with chemotherapeutics molecules, we X-rayed a few non-toxic MBDs for improved biological activity.

It is well known that the naturally occurring metal ions like iron (Fe) [20], cobalt (Co) [21, 22] and many other biomolecules assist in the biomedical applicability of metallodrugs as a good strategy for the human body system. Many of such biometals are used for therapeutic or diagnostic purposes in spite of the toxicity of heavy metals as evidenced in literatures [23]. Generally, the non-covalent bonding of the metal complexes contributes to the stability of the metallodrugs and to their target-specific delivery. Most of the known metal-containing pharmaceuticals have been developed in academic laboratories or by relatively small or ‘start-up’ pharmaceutical enterprises [24–26]. The current applications of successful metallopharmaceuticals include the platinum anticancer drugs [27, 28]; the ^{99m}Tc - and other radionuclides containing radiodiagnostic agents [29, 30]; the Gd(III) complexes for magnetic resonance imaging (MRI) [31, 32]; β -emitting radiotherapeutic compounds [33]; complexes involving vanadium [24, 34] as insulin mimics; Cr(III)-compounds as intermediaries in activating insulin receptors [35, 36]. These applications confirm the potential of metal complexes for both therapeutic and diagnostic purposes.

No doubt, interest in iron, copper and zinc (II) ions (so called late first row transition elements) was borne out of their biological relevance as they are associated with various biomolecules related to essential physiological activities. [37–39]. The efficacy of chelating treatment is influenced by a number of factors including metal ion specificity and the pharmacokinetics and metabolism of the chelating ligand. New chelating agents continue to be sought and the contribution of Hider and Liu adding further to recent developments in iron chelators for therapeutic applications [40]. Moreover, from a biological point of view, some metal ions, such as copper, function as a key cofactor in a diverse array of biological redox reactions [41].

Although many important reviews have addressed series of MBDs the need to report the nontoxic potent MBDs, which do not have adverse effects is crucial. Consequently, a few drug complexes particularly those of (iron, copper, zinc ions) as new drug designs or chemotherapeutics agents are examined. The structural features are important components for understanding the biological activity of MBDs. Therefore, emphasis is on the so called non-toxic late first row transition metal complexes of antimalarial and antimicrobial/bioactive compounds and their features such as the metal-binding into enzymes and their inhibitory mechanism.

Chemotherapeutic agents: ranges of malaria and bacterial therapies

Malarial therapy

Malaria is one of the endemic diseases; it transmitted through a female anopheles mosquito vector. Malariology from inception utilizes aminoquinoline (e.g., chloroquine) as first class antimalaria drug for disrupting the DNA of plasmodium parasites. Quinine, a cinchona alkaloid with novel therapeutic activity, was isolated first by Pelletier and Caventru in 1820. More classes of antimalarial drugs are listed below (Fig. 1). The mechanism of most antimalarial drugs involves attacks on the asexual forms of erythrocyte life cycle or mutations of the parasitic enzymes. Unfortunately, a major setback in the control of malarial is the loss of antimalarial activity of the drugs because of resistance of the pathogens. One of such drugs is artesunate.

Antibiotics

There are hundreds of different types of antibiotics based on their structures, function or mechanism of action. Many of these antibiotics are still suffering from a set back and a need for better chemotherapy continues to be a challenge. Classification based on mode of inhibition of antibiotics is summarized in Table 1 below [42]:

Biocoordination metal drugs complexes (MDCs)

The success recorded in the metallodrugs research field after cisplatin, $\text{cis-[Pt(NH}_3)_2\text{Cl}_2]$ anti-cancer drug has continued with even more breakthroughs [43]. As a matter of fact, metal-based bioactive agents have a potential advantage over other small molecular species in that characteristics transition metal coordination geometry, its redox

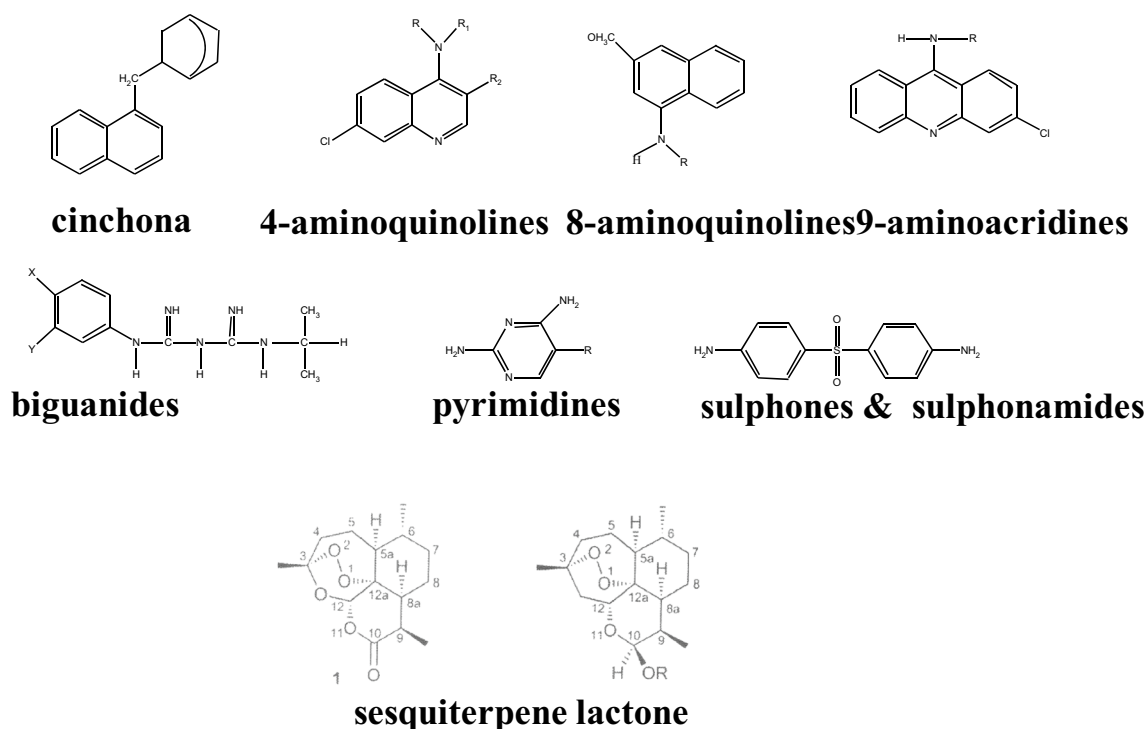


Fig. 1 Structural formulae of antimalarial drugs

state and ligand exchange allow one to fine-tune reactivity and affinity properties in a distinct fashion [44]. However, the central role of metals as therapeutic and diagnostic agents in the treatment of many human diseases is undisputed as can be judged by the use of iron anti-malarials, zinc in mammalian metalloprotein physiological activities; copper in the treatment of Menke's disease; antimony in anti-leishmanial/anti-protozoals, bismuth in the treatment of ulcers, gold in anti-arthritic drugs; silver in antimicrobials; and platinum in anti-cancer drugs; gold and arsenic in the treatment of rheumatoid arthritis and syphilis [45–47]. Up until now, record shows that about 24 elements are actively involved in biological activity and 14 of them which include iron, copper and zinc are bio metal ions [48].

It is clear that the novel way through which the metal-containing bioactive compounds (drugs) work to combat drug resistance by targeting the DNA or proteins of pathogens has boosted new routes in drug design technology in 21st century. In this paper, many of these metal-based drugs (MBDs) are hereby thoroughly addressed. Focus is placed on the Chemistry and Biology of the late first row transition metals such as antimalarials and antimicrobials. Attention will also be paid to the evaluation of the toxicological activity of the MBDs.

Toxicity of metal containing drugs

The need to subject bioactive metal-based drugs (MBDs) to clinical trials to check their toxicity level is not negotiable as this would explain and add value to their inhibitory activity. Many MBDs particularly anticancer and anti-tumor agents have been reported but the progress towards their being marketed is hampered because they failed toxicological screening [49]. Speciation of metal based drugs on toxicity characterization includes acute, sub chronic and chronic type is known. The most toxic are Hg, Pd, Cd and As while the least are iron and zinc which are regarded as bio essential metal ions [50–52]. Of particular interest is the required metal concentration level in the body because when the limit is exceeded, this may cause toxic and hazardous effects on human health. Abernethy et al. had reported limits of the metals for drugs considering their lethal effect above the permissible dose level (PDL) [50]. Elsewhere, it is reported that inorganic arsenic As(III), As (V) ions are very poisonous while arsenates are of limited toxicity. Methyl mercury and Cr(VI) ion are not highly toxic but are carcinogenic while cadmium causes kidney damage [51].

However, toxicity has been regarded as a relative term because the so-called “toxic ions” can usually be tolerated

Table 1 Properties of some common antibiotic drugs

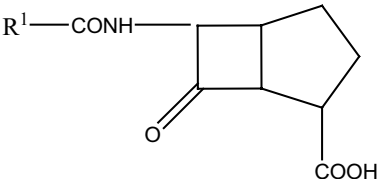
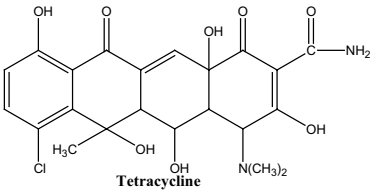
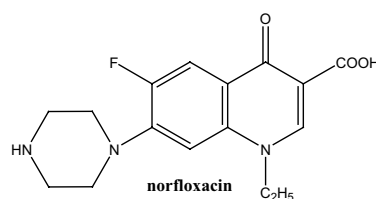
Antibiotic group	Function / mechanism of action	Examples	Representative structure
1. Cell wall synthesis inhibition			
β -lactams	Inhibits the synthesis of bacterial cell wall (peptidoglycan)	Penicillin G Methicillin Cephalothin	
2. Protein synthesis inhibition			
Aminoglycosides	Bind to small ribosomal subunit (30S) and interfere with protein synthesis	Gentamicin, neomycin	
Tetracyclines	Bind to 23S rRNA of large ribosomal subunit (50S) to inhibit peptide chain elongation	oxytetracycline Erythromycin, clindamycin	
Macrolides	Same as above	Chloramphenicol	
3. Nucleic acid synthesis inhibition			

Table 1 continued

inhibition

Quinolones and Fluoroquinolones Inhibit DNA gyrase and bind to topoisomerase IV thereby blocking DNA replication and transcription

Ciprofloxacin, norfloxacin



Rifampin Inhibits bacterial DNA-dependent RNA polymerase

Rifamycin, rifacilin

4. Cell membrane disruption

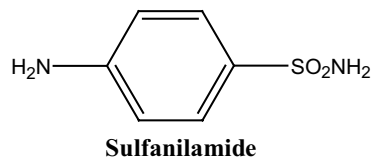
Polymyxin B Binds to plasma membrane and disrupts its structure and permeability properties

Polymyxin B, polymyxin 3-D Complex structure

5. Antimetabolites

Sulfonamides Inhibits folic acid synthesis by competing with p-aminobenzoic acid (PABA)

Sulfasalazines, sulfisoxazole



Isoniazid Inhibit lipid synthesis

Isoniazid

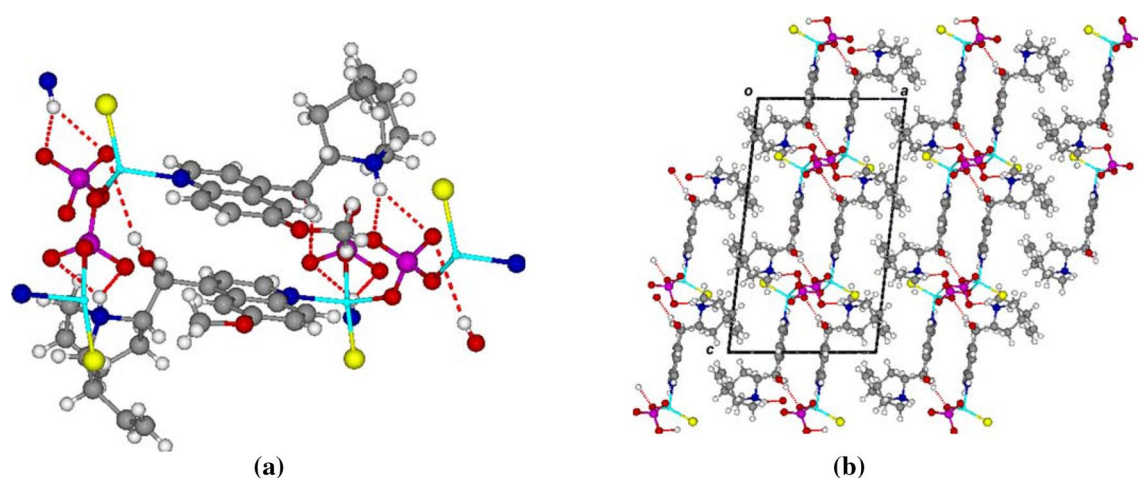


Fig. 2 **a** Hydrogen bonding of type O–H...O and N–H...O (bifurcated) and **b** molecular packing in the crystal structure of the zinc (II) complex of quinine hemisulfate. Adapted from Ref. [56]

in low concentrations, and may exhibit biological values within the limit ranges. On the other hand and biologically essential elements may impair health if dosage is in excess [53]. Some first row metal ions considered to be bio-essentials ligated by drugs are described herein.

Metal-antimalarial drugs (MAMDs)

The lethal effect of the pathogens on human life particularly the plasmodia resistance to the antimalarial drugs, poses a serious challenge to the control of the world endemic disease—Malaria. Biomedical researchers have attributed this resistance to several factors which include the insolubility and decomposition of the drugs. Bioinorganic chemists are faced with the challenge of how to overcome this problem. One way of stabilizing the drugs would be through the incorporation of metal ions which would allow them to be deposited in the target cell without any degradation or loss in composition. Another method would be to bring about a sequestration reaction through the use of the metal ions to remove toxic molecules in the body. Given the importance of iron metabolites in malaria physiology and toxicity, various metal chelators have been used as antimalarials with high activity [54]. The strategy is based upon the known principles that: (a) all microorganisms need iron and some other metal ions for their growth and replication; (b) microorganisms secrete siderophores, small molecular weight, water soluble molecules that bind extracellular iron(III) with high affinity with the resulting metal complexes binding to selective surface receptors for internalization through a multistep process, and (c) iron deprivation impacts preferentially parasitic growth compared to mammalian cells [55].

Structural investigations with many other characterizations of metal coordination drug for application in biomedical research have been reported. Obaleye et al. [56] described a novel tetrahedral geometry zinc ions coordination through oxygen, chlorine and N(4) atom of an antimalarial drug quinine hemisulfate which produced polymeric [chlorosulphato (2-ethenyl)-4-azabicyclo[2.2.2] oct-5-ylum-(6-methoxyquinolin-4-yl) methanol zinc(II)]. The crystal packing of this intended antimalarial drug, obtained from the single-crystal X-ray diffraction analysis, revealed that the quinine forms a zigzag coordination polymeric complex with the Zn(II) ions through extended chains –ZnCl–O–SO₂–O–Zn–O–SO₂–O–ZnCl– (see Fig. 2). The molecular parking showed the presence of intermolecular hydrogen bonding interactions between the zinc(II) complex polymeric chains depicting bilayer conformational arrangement by a twofold rotation axis.

The antiplasmodial activity of the quinine-zinc complex had been studied and the inhibition of parasitic growth measured by the inhibition of schizont formation in freshly collected infected blood samples from malaria patients was significantly better than chloroquine (CQ) the control drug ($p < 0.05$) [57, 58]. Two potential antimalarial metal complexes: $[\text{LH}^+]_2 \cdot [\text{CuCl}_4]^{2-} \cdot 4\text{H}_2\text{O}$ and $[\text{LH}^+]_2 \cdot [\text{CdBr}_4]^{2-} \cdot 2\text{CH}_3\text{OH}$ (L = mefloquine) have been characterized using X-ray crystallographic analysis. The compounds contain opposite chirality solvated salts (DL-erythro- α -2-piperidylum-2,8-bis(trifluoromethyl)-4-quinolinemethanol) tetrachlorocuprate(II) tetrahydrate and bis(DL-erythro- α -2-piperidylum-2,8-bis(trifluoromethyl)-4-quinolinemethanol) tetrabromocadmiate(II) bis(methanol), respectively. The ionic structures with an asymmetric unit comprising two protonated monocationic mefloquine molecules of opposite chirality, $(\text{MX}_4)^{2-}$ [M = Cu or Cd] and

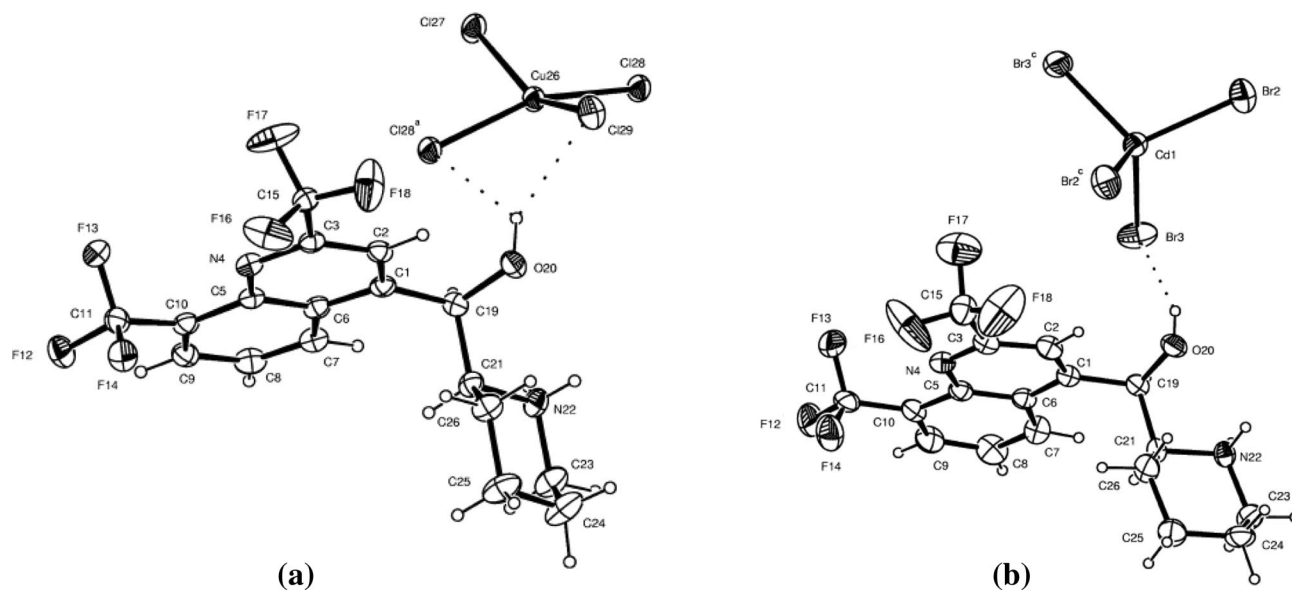


Fig. 3 ORTEP views of **a** the protonated mefloquine molecule (L) and the tetrachlorocuprate ion in $[\text{LH}^+]_2 \cdot [\text{CuCl}_4]^{2-} \cdot 4\text{H}_2\text{O}$ and **b** the protonated mefloquine molecule and the tetrachlorocadmuate ion in

$[\text{LH}^+]_2 \cdot [\text{CdBr}_4]^{2-} \cdot 2\text{CH}_3\text{OH}$, with thermal ellipsoids of 50% probability. Adapted from Ref. [59]

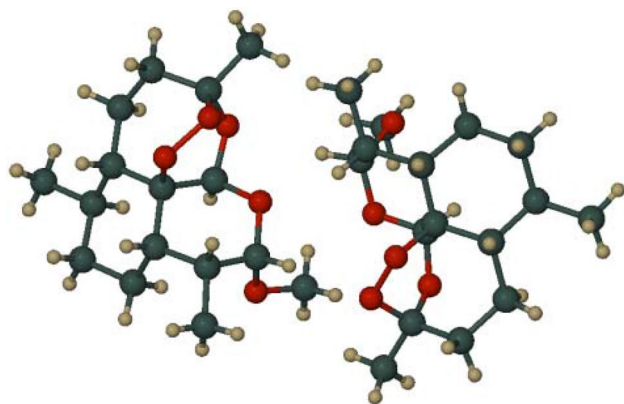


Fig. 4 The two crystallographically independent molecules of artemether. Adapted from Ref. [61]

disordered solvent molecules. The $[\text{CuCl}_4]^{2-}$ anion adopts the commonly observed flattened tetrahedral geometry, whereas the $[\text{CdBr}_4]^{2-}$ anion is in tetrahedral configuration (see Fig. 3). It is opined that the molecular conformation of the drug complex crystal contains some useful biological relevance [59].

Goncalves et al. [60] described conformational arrangement by the single-crystal structural analysis of four antimalarial quinoline derivatives derived from the mefloquine drug.

A series of Fe(III), Zn(II) and Cd(II) complexes bearing artemisinin derivatives of powder artesunate was prepared. The X-ray diffraction single crystal of arthemeter

(see Fig. 4) was obtained through a series of reactions with artesunate as the starting material [61].

Pseudo-octahedral geometry of copper(II) ions bearing 3-arylazo-4-hydroxy-1,2-naphthoquinones with nitrogen and oxygen coordination sites rather than through the 1,2-carbonyl oxygen is reported including other similar copper complexes synthesized from the ligand derivatives with their antimalarial activity [62]. Record has it that the first row transition metals being considered in this review particularly iron shows higher antimalarial activity when bound with quinine (QN), its derivatives, metallocenes, etc. [63, 64]. Of particular interest is ferroquine antiparasitic activity among its analogues towards inhibiting β -haematin disease cell through the oxygen radical species [65]. Structure–activity relationship of chloroquine (CQ) analogues–piperazine-tethered heterodimers (see Fig. 5) was observed to play a key role in the antimalarial activity of the iron chelators against CQ-strains and resistant *Plasmodium falciparum* [39].

In the search for novel drugs against resistant parasites, the effect of metal ions on the biological activity of some antimalarials including chloroquine drug (CQ) of Mn(II), Co(II), Pt(II) and Cu(II) ions was investigated. The metal complexes showed good in vitro activity with values ranging from 0.16 to 2.7 μM . $[\text{Pt}(\text{CQ})_2\text{Cl}_2]$ exhibited the highest antiplasmodial activity ($\text{IC}_{50} = 0.16 \mu\text{M}$) followed by $[\text{Mn}(\text{TMP})\text{Cl}_2\text{CH}_3\text{OH}]$, ($\text{IC}_{50} = 1.1$) and $[\text{Cu}(\text{pym})_2(\text{CH}_3\text{COO})_2]$ (TMP = trimethoprim; pym = pyrimethamine). $[\text{Co}(\text{TMP})_2\text{Cl}_2(\text{CH}_3\text{OH})_2]$ showed a weaker antiplasmodial activity ($\text{IC}_{50} > 5$). All

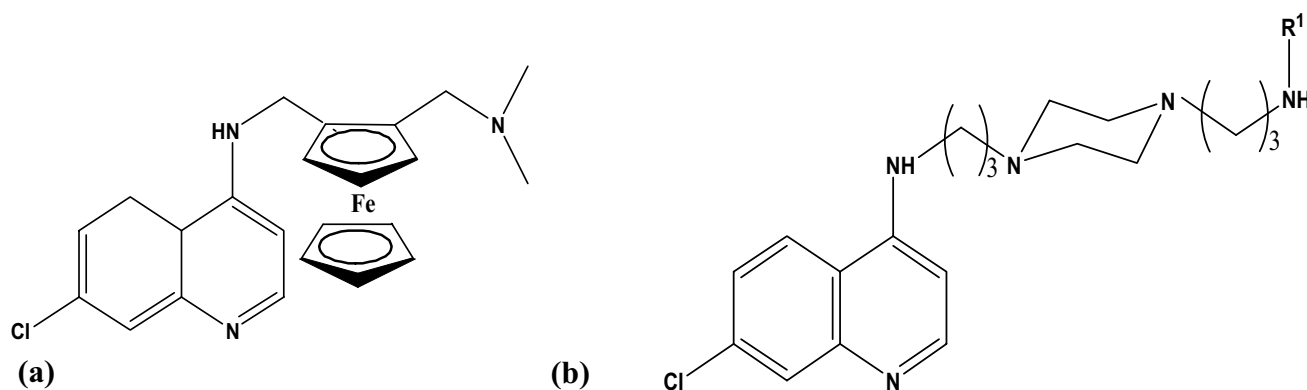


Fig. 5 Antimalarial drugs: (a) Ferroquine (FQ) (b) N1-(7-chloro-4-quinolyl)-1, 4-bis (3-aminopropyl)piperazine moiety

the complexes showed relatively good antitrypanosomal activities in the micromolar level against *Trypanosoma cruzi* and *T. b. rhodesiense* except the Cu(II) complex of pyrimethamine. Both the Mn(II) and Co(II) complexes of trimethoprim showed enhanced activities against *L. donovani* [66]. Late transition metals were used to stabilize QN drug in the search for a more potent antimalarial drug. The work extended to the toxicological and stability properties of the four tetrahedral metal-based antimalarial drugs [Co(QN)Cl₃], [Fe(QN)Cl₂H₂O]SO₄·3H₂O, [Cu(QN)ClSO₄] and [Cd(QN)ClSO₄]. Cu(II) complex with the least ionic size showed the highest stability constant and less toxicity compared to the QN, thus combining some of the useful properties of the metallopharmaceuticals for complete drug delivery. We succeeded in synthesizing tetrahedral Co(II) complexes of pyridine-2-carboxamidazones analogues with better antimalarial activity against *P. falciparum* [67, 68].

In vitro activities greater than 30 µg ml⁻¹ ED₅₀ values of a distorted square planar copper(II) complex *cis*-[dicloro(N¹-2-acetylthiophene-pyridine-2-carboxamidrazone)] was attributed to the advantage of the copper complexation [69]. A result of higher antiparasmodial activity against *Plasmodium berghei* of Fe(III) complex bearing 4-amino-N-pyrimidin-2-ylbenzene sulphonamide (APS) compared with other metal complexes of Mn(II), Co(II), Ni(II), Cu(II) and Cd(II) and the parent drug had appeared in literature [70]. However, Sanchez-Delgado group reported a new antiparasitic agent [Au(PPh₃)(CQ)]PF₆ obtained by reaction of AuClPPh₃ with chloroquine (CQ) and KPF₆ in CH₃CN. The CQ binds through the pyridinic N(1) atom to the gold metal centre and through PPh₃ ligand. The structure of the ionic complex is linear. This novel gold-chloroquine complex was found to be more active in vitro against cultures of chloroquine resistant strains of *Plasmodium falciparum*, and also against *Plasmodium berghei* (rodent malaria) both in vitro and in vivo study. The IC₅₀ value (determined as the CQ-based

concentration of the drug) for [Au(PPh₃)(CQ)]PF₆ was 3 × 10⁻⁹ M, that is about 22 times lower than the concentration of CQ required for chloroquine diphosphate CQDP (6.7 × 10⁻⁸ M) against *P. berghei*, whereas its in vivo parasitemia counting was 84% compared to the free CQ. The authors noted that the synthesized gold complex of the CQ drug performed excellently well as a chemotherapeutic agent and much better than chloroquine diphosphate (CQDP) and other previously reported metal-CQ complexes [71]. Nevertheless, the recent discovery of metal coordination tetraazamacrocyclic complexes particularly cyclen and cyclam as antimalarial chemotherapeutic agent is acknowledged [72].

Metal-antimicrobial drugs complexes (MAMcDs)

Metal-based antibiotics are an efficient means of drug delivery as they conduct a high percentage of a drug's bioactivity against its target biomolecules; they could also play a role in the homeostasis of metal ions. Metal complexation of antibiotic drugs is a new strategy for the development of better diagnostic and therapeutic agents. They are very effective and could disrupt antibiotics resistant strains. Some metal ions, e.g., iron, copper and zinc can influence a drug-induced metalloenzymes inhibition mechanism in some pathogens that are responsible for infections, influenza, tumour, inflammation, etc. [73]. Thus, extensive investigations regarding the therapeutic effects of antibiotics coordinated with transition metals continue to be of interest in bioinorganic research.

The Amoxicillin drug coordinated with metal ions has been screened for its antibacterial activity against several bacteria such as *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* while detailed analyses of their molecular structures have been done in several studies [74–80]. Recently, Refat et al. [81] carried out the synthesis,

characterization, thermal behaviour and biological screening of the Y(III), La(III), Ce(III) and Sm(III) complexes of the Amoxicillin trihydrate ligand (ACT). The metal complexation behaviour of ACT was studied extensively through infrared spectroscopy. The study revealed that amoxicillin behaves as an ionic tridentate ligand and coordinates to metals through its amino, imino and β -lactamic carbonyl groups. Thus, in these complexes the metal ion is coordinated with one ligand molecule and three waters resulting in the proposed octahedral geometries. The biological tests of these amoxicillin metal complexes showed antibacterial activity against four species of bacteria, namely *S. aureus*, *B. subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*, and two fungal species, *Aspergillus flavus* and *Candida albicans*. The active property of the free drug against the used strains is reduced by complexation. Antimicrobial activity of the Y(III) complex was slightly more enhanced against the tested bacteria, when compared with that of the other metal complexes. This was attributed to the smaller ionic radius and higher electronegativity; however, no effect on the *A. flavus* fungi was observed.

Adediji et al. [82] synthesized octahedral Fe(III) complex of mefloquine and tested it for antimicrobial activity. In contrast to earlier studies on mefloquine complexes, in this study mefloquine complexes behave as neutral tridentate ligands that coordinated through the hydroxyl and the two nitrogen atoms in the quinoline and piperidine rings in the structure, as found from the infrared spectra. The antimicrobial activities of mefloquine metal complex exhibited greater inhibition than the parent ligand.

Incorporation of some late transition metal ions (Fe, Co, Ni) into metronidazole ligand showed greater antifungal activity on the organisms, compared to the free metronidazole [83].

An attempt was made to prepare some mixed drugs with a view to comparing their biological activity with transition metal drug complexes. Lawal et al. [84] synthesized and investigated the antibacterial activity of metal complexes of mixed metronidazole-vitamin-C and the results gave enhanced biological activity of the latter over the free mixed drugs. Also the antibacterial activity of other bioactive mixed drugs, isoniazid-pyridoxine and sulfamethoxazole-cloxacillin when complexed with late transition metals, were found to be higher than that of the parent drugs [85, 86]. Previous works [87–91] on the thiamine drug indicated 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 $(HT)^{2+}(MX_4)^{2-}$ due to the net positive charge on the thiazolium ring and the easy protonation of pyrimidine N(1) atom. The results of the physical and spectroscopic data on the mixed ascorbic acid with thiamine and zinc(II) salt supported the formation of the complex [92]. Ascorbic

acid coordinates through the oxygen of the carbonyl group and that of the enolic C-2 hydroxyl group while thiamine hydrochloride coordinates through (N1) atom of the pyrimidine ring and another donor oxygen atom from water making the zinc(II) complex to form a distorted tetrahedral geometry. The biological activity of the zinc complex of mixed ascorbic- thiamine is yet to be investigated.

In the search for more potent drugs, Cu(II) and Fe(III) complexes bearing sulphadoxine and pyramethamine mixed antimalarial drugs have been considered by Oguniran et al. [93] The in vitro screening of the complexes against *E. coli*, *P. species*, *P. aeruginosa* and *S. typhi* using disc diffusion method indicated that the metal complexes exhibited better antibacterial activities as compared to the ligands.

The pathogenic inhibitory or therapeutic power of some organic or natural products like amino acids, imidazole, thiadiazole, urea, oxine, etc., containing N, S, O donor atoms has encouraged synthetic bioinorganic chemists to consider their metal-based bioactive compounds for chemotherapeutic activity [94, 95]. Our group [96] used bioactive ligand 2,5-diamino-1,3,4-thiadiazole derived from semicarbazide hydrochloride for preparing the Co(II), Ni(II), Cu(II) metal complexes. The complexes were characterized using elemental, infra-red, ultraviolet/visible, magnetic moment, atomic absorption, thin layer chromatography and molar conductance measurements. The IR data revealed that the ligand behaved as tridentate neutral ligand. It coordinated to the metal ion via sulphur and nitrogen of the amines, and the complexes gave octahedral structure. *In vivo* evaluation of the antimicrobial activities of the metal complexes showed greater activity against some bacterial species which include clinical cultures of *E. coli*, *S. aureus*, *K. species*, *N.gonorrhoea*, *S. typhi*, *S. species*, *P. species*, *P. aeruginosa* and *A. species* when compared to the parent uncomplexed ligands. The chelates do not show toxicity against the activities of enzymes from homogenates of liver, kidney and serum in experimental rats. Adediji, et al. [97] reported that the metal complexes of Mn(II) and Fe(III) with N- and S-donor ligand performed credibly as antipathogenic agent. We surveyed that many metal-based antimicrobial drugs showed better inhibition against pathogens than the uncomplexed drugs [98] Adejoro et al. [99] in their research work utilized PM3 semi-empirical quantum mechanical calculations to predict the geometries, thermodynamic parameters, vibrational frequencies, and band gaps of the new metal drug complex, dichlorobis(N-{4-[(2-pyrimidinyl-kN-amino)sulfonyl]acetamide)copper(II).

Recently, four transition metal complexes with mixed ligands derived from 8-hydroxyquinoline (HQ) and amino acids (AA), L-alanine and methionine, which gave better inhibitory performance over the uncomplexed N–O donor mixed ligands were studied. *In vitro* antimicrobial investigations of the metal complexes against standard bacteria

species showed significant inhibition. The copper complex showed the highest inhibitions against *P. aeruginosa* (ATCC27853) of 43 mm at 10 $\mu\text{g/ml}$. This was attributed to the enhanced kinetic lability of the alanine-amino acid ligand which, through Jahn–Teller distortion, may assist the ligand exchange and the binding to the organisms [100]. On the other hand, Sobola et al. synthesized Cu(II) functionalized schiff base complexes found to be very active antibacterial and antifungal potent [101].

Pantcheva et al. have extensively studied the complexation of polyether ionophorous antibiotics Monensin and Salinomycin with divalent metal ions and their antimicrobial and antitumor activities [102–110]. A series of complexes with biologically relevant, or with toxic metal ions, have been successfully synthesized and their structure was fully characterized by IR, NMR and/or EPR spectroscopic methods, as well as single-crystal X-ray diffraction analyses and mass spectrometry. The structural data indicated three possible ways of coordination of the studied antibiotics depending on the chemical form of starting ligand (the acidic form or its sodium salt), the type of the metal ion and the reaction conditions. Complexes with the composition ML_2Cl_2 were obtained for the sodium Monensin [104] with Cu, Co and Mn; while $\text{ML}_2(\text{H}_2\text{O})_2$ complexes were isolated for the Monensin [102–104, 106, 107] and the Salinomycin [110] with Mg, Ca, Sr, Ba, Mn, Co, Ni, Cu, Zn and Cd. Complexes with the composition $\text{ML}(\text{H}_2\text{O})$ were obtained for both Monensin [105] and Salinomycin [108] with the heavy metal ions Hg and Pb. Interestingly, the biometal(II) complexes of the polyether ionophores exhibit stronger antimicrobial activity against the aerobic Gram(+)-microorganisms *B. subtilis*, *B. mycoides* and *S. Lutea* [102–104, 106, 107] as compared to the non-coordinated antibiotics. Similar trends were observed in the in vitro anticancer tests against permanent human tumour cell lines and virus-transformed animal tumour cell lines, revealing that the Monensin complexes with Mg(II), Ca(II), Mn(II) and Co(II) ions showed higher activity than the free ligand against the virus-induced transplantable tumours in chicken (hepatoma, LSCC-SF-Mc29) and in rat (sarcoma, LSR-SF-SR) [109]. The anticancer activity tests of the Mg, Ca, Mn, Co, Ni and Zn complexes of the monensic acid (MonH) against the human tumour cell lines 8MGBA (glioblastoma multiforme), A549 (lung cancers), MCF-7 (breast), HeLa (uterine cervix) and HepG2 (liver) showed a decrease in the tumour cell viability and proliferation in a time- and concentration-dependent manner [110]. The metal(II) complexes studied (especially those of Co(II), Ni(II) and Zn(II) ions) have been proved to express stronger cytotoxic and cytostatic activities than the non-coordinated monensin antibiotics. The recent results on the acute toxicity in mice outlined the effect of metal(II) ion complexation on the toxicity profiles of these two antibiotics [111]. The results

confirmed once again that the presence of biometal(II) ion enhances significantly the antimicrobial and antitumor activity of the studied antibiotics, as well as the acute toxicity values in some cases; however, these are heterogeneous and require more detailed studies. In summary, all obtained results for the tested antibiotics confirm that the complexation of the biologically active compounds with the essential bio-metals could be effectively applied as a strategy to improve the properties of the starting drug.

Other metal-drug complexes

The metal drug complexes are gaining interest in metallopharmacy and is noteworthy to mention some other drug candidates like anticancers [3, 112, 113] antituberculosis [114–116], antitumors [17], antivirals [117, 118], neurochemicals [119], etc. Ejidike and Ajibade in 2015 [120] prepared biometal(II) butan-1-one Schiff base (DEPH_2) analogues as DPPH and ABTS radical scavenger potential towards inhibiting reactive oxygen species (ROS) which involves in etiopathogenesis of numerous chronic diseases like atherosclerosis, hypertension and coronary heart disease.

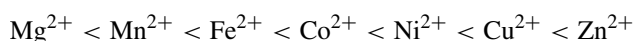
Discovery of a new dinuclear copper (II) complex of DNA nucleobase (adenine) and phenanthroline for cancer therapy has been unfolded with satisfactory anti-proliferative potency against Hela and Caco-2 cancer cells [3]. Renfrew et al. [121] reported the use of cobalt(III) prodrug of curcumin as a vehicle for the delivery and release of curcumin in the hypoxic tumour cells where the cobalt(III) prodrug is reduced to cobalt(II). Although the cisplatin is a famous anticancer drug, recently Kurzwernhart et al. [122] showed that ruthenium(II) arene complexes with bidentate flavonoid ligands have higher anticancer and antioxidant activity when compared with their free flavonoids. From the results, topoisomerase(II) inhibition and cytotoxicity of the ruthenium–flavonoid complexes over the parent flavonoids was based on complexes' advantage of almost 10-fold higher water-solubility than the free ligands and their ability to remain intact in solution for several days.

Davarski et al. [123] synthesized bis-thiourea metal complexes characterized with enhanced antiphytoviral activity. From the result, the highest augmentation of the antiphytoviral activity was obtained in secondarily infected leaves by complexation of diallyl bis-thiourea with Cu^{2+} , Ni^{2+} and Co^{2+} . Diallyl bis-thiourea reduced the virus concentration by 50%, while the corresponding Cu^{2+} , Ni^{2+} and Co^{2+} complexes caused a reduction of 81, 81, and 79%, respectively. In inoculated leaves the reduction caused by diallyl thiourea complexes was less. The corresponding values were 0% for diallyl-bisthiourea and 34, 41, and 7% for the complexes. The unsubstituted

and uncomplexed bis-thiourea caused only a small inhibition of PVX. But the corresponding complexes with Cu^{2+} and Co^{2+} inhibited PVX in inoculated leaves and the complex with Cd^{2+} in secondarily infected leaves remarkably. Diphenyl-bis-thiourea was nearly not antiphytoviral. The same is true for the most metal complexes with this substance. Only the corresponding Ni^{2+} and Fe^{2+} complexes inhibited PVX in secondarily infected leaves significantly. In the study by Barbosa et al. [116] synthesis of three antimycobacterium tuberculosis ruthenium(II) drugs were achieved by the equimolar reaction under reflux for 6 h of $\text{cis}[\text{RuCl}_2(\text{dppb})(\text{bipy})]$ and ligands 2-hydroxynicotinic acid (2-OHnicH), 6-hydroxynicotinic acid (6-OHnicH), and 3-hydroxypicolinic acid (3-OHpicH), in methanol. The octahedral geometry of the ruthenium complexes was confirmed by X-ray crystallographic structural analysis. In addition, the investigation revealed that the coordination of the ligands (2-OHnic, 6-OHnic and 3-OHpic) to the ruthenium centres promoted an increase in antitubercular activity, where in some cases the minimum inhibitory concentrations (MICs) for the complexes are much better than those of some “second” and “first” line drugs used in current therapy.

DNA-binding of metal–organic based drugs: metalloenzymes

Cell metabolism of microbes or parasites is biogenic metal ion co-factor dependent [124]. Metal ions are required both in biochemical or biophysical cellular machinery because they are natural constituents of proteins as they connect with unfolded or folded polypeptide bonds of proteins like histidine, thiolates, cysteines. Also they serve as a nucleation site that directs polypeptide folding along a specific pathway in the free-energy landscape [125]. The metal-binding proteins are a biological phenomenon and are instrumental to a wide range of essential tasks ranging from nucleic acid, protein structure stabilization to enzyme catalysis in oxidation–reduction reaction and hydrolytic reactions. They activate many essential life processes such as respiration and photosynthesis among others [126–128]. The molecular mechanisms of these biological applications are not entirely understood. These cellular or extracellular metalloproteins biochemistry tasks are metal ions specific and selective [129]. The physical and chemical properties of proteins tend to select, particularly, the essential divalent metal ions in biological systems with a ranked order of preference that follows the Irving-Williams series [130]:



Matrix metalloproteins have also been studied in the design of small organic ligands bind and inactivate

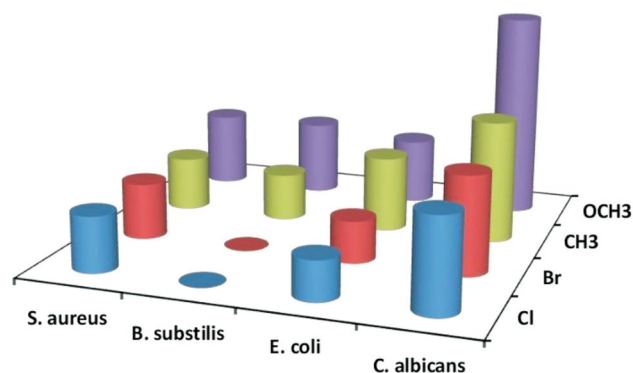


Fig. 6 Antimicrobial activity of the o-vanillin derivatives of the Schiff base ligands. Adapted from Ref. 101

metalloenzymes [131]. Certain factors have been identified which influence the metal binding in protein. These include valence, ionic radius, coordination geometry, ligand number, second-shell ligands, effects of the protein matrix, and ligand characteristics (net charge, dipole moment and polarizability, charge-donating/-accepting ability, and denticity) [132, 133]. Proteins of Pathogens can be “lured” through cell machinery to bond to excess and or foreign biogenic metal ion from extracellular concentrated metal-chelator (referred to as drug) for protein re-structuring through sequestration reaction and simultaneously make the release of the drug for attack on the cell possible and, therefore, destroy the pathogen cytoplasm [125, 129]. It is against this backdrop that a metal based drug is devised as a delivery system for disease therapy in biological fluids. Furthermore, drug release phenomenon is possible through interaction of DNA with metal chelate based on static electronic potential effect as conceived in Fig. 6. However, an extensive biochemistry detail of microbial cellular metalloproteins concept is beyond the scope of this review. It is important to note that bigger volumes of reviews on metalloregulatory proteins have been documented elsewhere [134–136].

We exploited the possible stable coordination chemistry of biogenic metal ion-protein complexes due to the cellular metal homeostasis [137–139] as evidence for the sufficient contact of drug with microbe or plasmodium parasites [140]. This informs our argument for the use of metal complexes as drug targets for cancer, HIV and malaria therapies among others (Figs. 7, 8, 9).

Bacterial organelles are arranged in such a way that essential metal ions from the extracellular setting require special consideration for binding to their protein structure. The organs in Gram-negative bacteria for example possess an outer membrane (OM), a periplasmic space, and an inner cytoplasmic or plasma membrane through which the metal must pass before entering the cytosol;

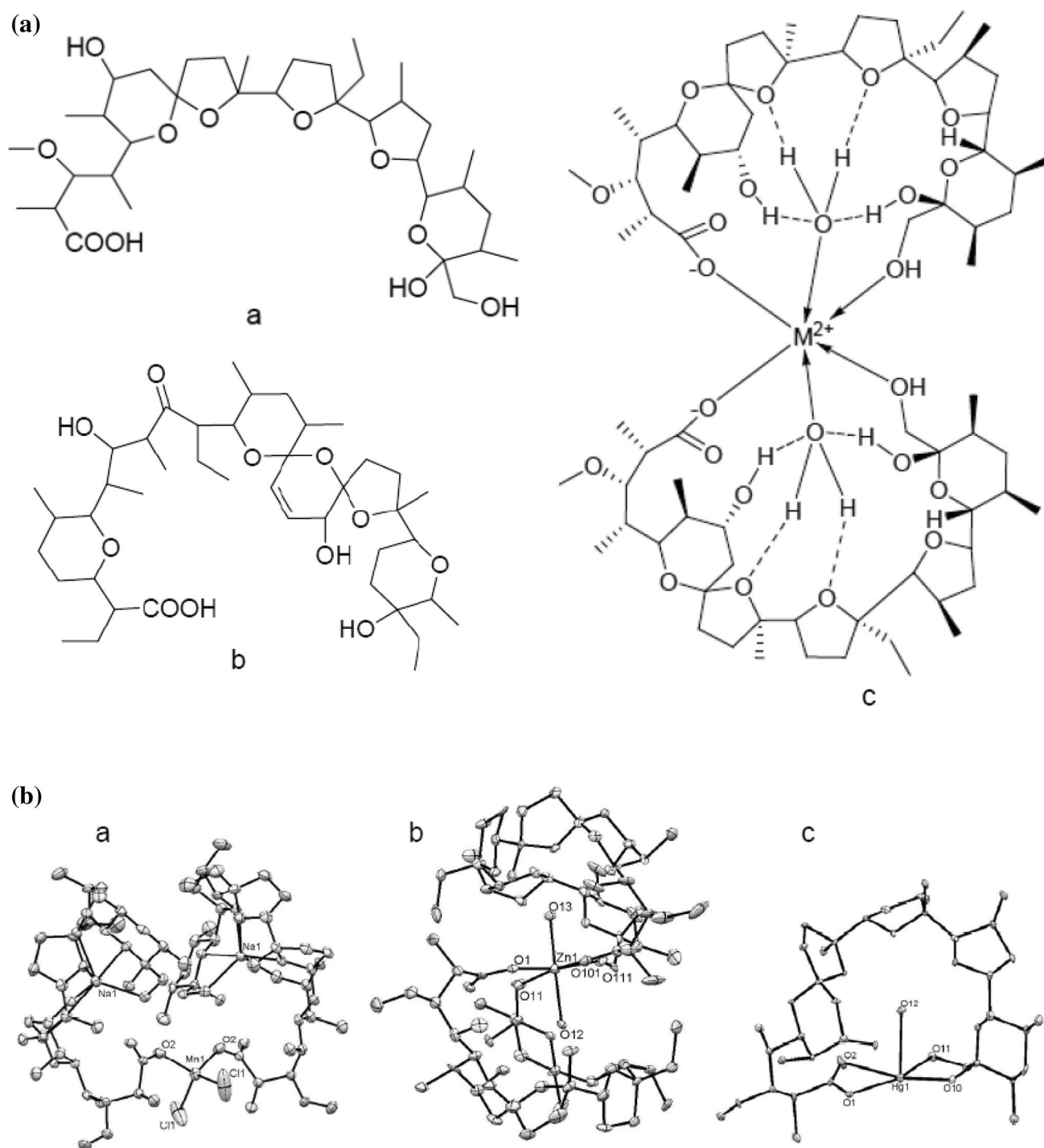


Fig. 7 a Structures of the **a** monensin acid (MonH), **b** Salinomycin acid (SalH) and() the complexes of Mon with M(II) biometals ($M = Mn, Co, Ni, Zn$) as evidenced from IR, 1H and ^{13}C NMR and massspectrometry (FAB-MS). Adapted from Refs. [102, 107].

b Crystal structures of the three different types of coordination of Monensin as seen in (a) $Mn(MonNa_2)Cl_2$; (b) $Zn(Mon)_2(H_2O)_2$ and (c) $Hg(Mon)(H_2O)_2$ Adapted from Refs. [102, 106]

Gram-positive bacteria, in contrast, lack a periplasm. Trimeric barrel proteins referred to as porins and that are embedded in the outer membrane allow, for nonselective passive diffusion of metal ions across the OM [129].

High-affinity active transport systems in the OM or that are embedded in the plasma or inner membranes (PM or IM) function to transport and release metal ions into the cytosol because of its concentrated active metal ions [141].

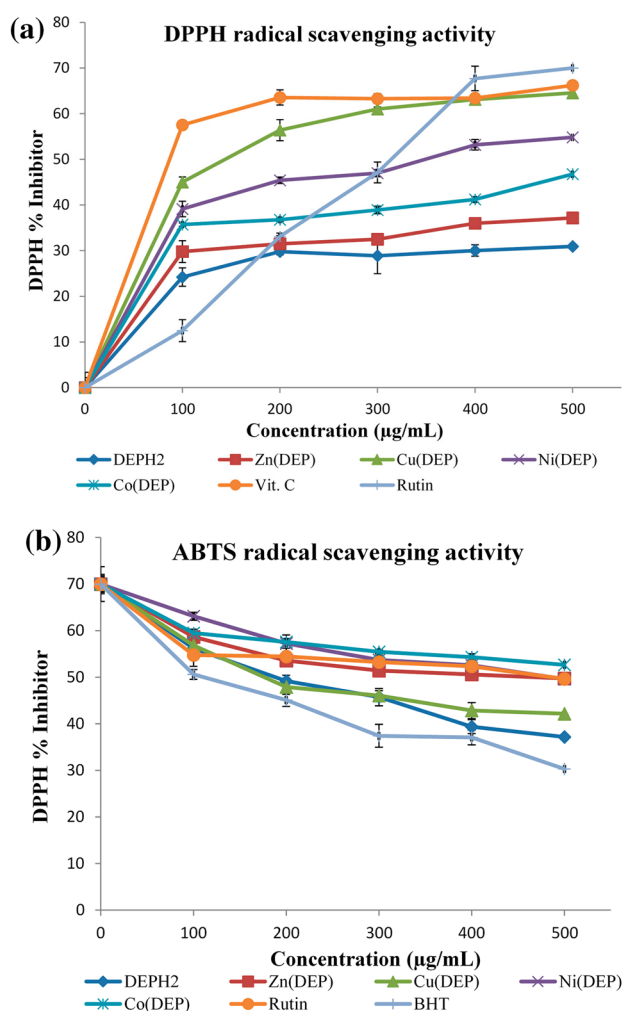


Fig. 8 **a** DPPH scavenging activity of DEPH_2 and $\text{DEPH}_2\text{-M(II)}$ complexes. **b** ABTS radical scavenging activity of DEPH_2 and $\text{DEPH}_2\text{-M(II)}$ complexes

Inner membrane transport systems are driven either by the hydrolysis of ATP on the cytoplasmic side of the membrane (e.g., by ATP binding cassette (ABC) transporters and P-type ATPases), or by coupling to an energetically favourable transfer of protons or other ions across the bilayer (e.g. by Nrm proteins and cation diffusion facilitator (CDF) proteins). The presence of additional layers

of extracellular lipopolysaccharide (LPS) or complex carbohydrate matrices, as well as a biofilm, is also likely to have a considerable impact on the rates and mechanisms of metal uptake and efflux [142]. Interestingly, another strategy for metal binding preferences and metallation of most metalloproteins in the bacterial periplasm is aided by maintaining the relative concentration of these pools (the Irving–Williams series) as an inverse function of the stabilities of the respective metal complexes. For example, magnesium enzymes always prefer to bind zinc, and these metals dominate the metalloenzymes without metal delivery systems. The buffered concentration of zinc is held at least a million-fold below magnesium inside most cells [143]. Essentially, metallochaperones as protein structures have been recognised for copper [144–147], nickel [148], and iron-sulphur protein biogenesis [149], and recent work shows that the periplasmic Zn(II) binding protein, YodA, has characteristics consistent with a role as a zinc chaperone in *E. coli* [150].

Particular attention is drawn to the bacterial homeostasis of structures and function copper, zinc and iron metals homeostasis vis-a-viz the metal–ligand geometry, nature and number of the coordinating atoms, since most of the other trace metals have been identified as parts of metalloenzymes. For example, manganese is found as a cofactor in mitochondrial SOD, inorganic phosphatase and in the photosynthesis system [124, 151, 152].

Iron cofactor metalloenzymes

Well-known examples of soluble redox-active metalloproteins in microbes are iron-sulphur (Fe–S) cluster proteins used for the synthesis of ammonia from nitrogen and hemebinding cytochromes used for oxygen carriage c-Type cytochromes, characterized by covalent attachment of iron-porphyrin at two cysteine residues are proteins implicated in electron-transfer processes in both eukaryotic and prokaryotic organisms. The biological chemistry of iron in living organisms as essential element or cofactor for many physiological reactions is enormous, however, its excess could be toxic at the molecular level where it reacts with peroxides to produce free radicals and destroy or infect disease cells. On

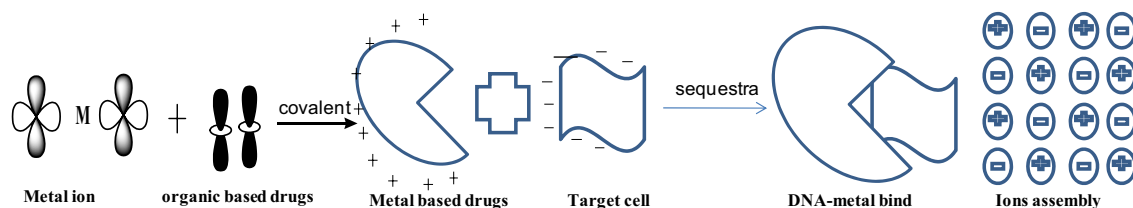


Fig. 9 Schematic illustration of Metal drug chelate in DNA binding of target cell

the other hand, shortage of iron could lead to a reduction in haemoglobin, a condition of anemia [125, 153].

Uptake of iron by either metal transporters or metal sensor bacterial proteins for biological activities has been widely reported [130, 154–160]. Iron is the next most common cofactor after zinc; it is estimated to be exploited by ~8 and ~6% of enzymes. These ions account for most (~18%) of the remaining fraction of metalloenzymes that are devoid of delivery systems. It should be noted that another subset of iron enzymes does have metal delivery systems and iron is commonly found in preassembled cofactors. The divalent ions of iron have similar ligand affinities, radii, coordination preferences, and salvation free energies, creating a distinct challenge for proteins to discern between these elements when they compete for a site [161]. Fe-requiring bacterial mostly survive in 100-fold higher in *E. coli* vs a chemically defined minimal medium [141], demonstrating an impressive concentration of iron within the bacterial cell. The role of iron and α -ketoglutarate as cofactors has been obtained. This binds unto lysine derivative proteins on histone H3 and affords the demethylase activity of GASC1 (gene amplified in squamous cell carcinoma 1) which directly demethylates H3K9me3 and H3K9me2 in vivo through a hydroxylation reaction producing formaldehyde and H3K9me1. This can constitute a new anti-neoplastic therapeutic modality. From the GASC1 modelling, its mechanism shows that residues H190, E192 and H288 form an essential part of the iron-binding groove of GASC1. On the basis of this in silico model the mutating H190 and E192 would be sufficient to abrogate the iron-binding ability of GASC1 and thus, also to inhibit its demethylation activity. In addition, mutant GASC1 has no detectable demethylase activity thereby indicating that the putative iron-binding residues are crucial to the demethylase activity of GASC1. This work goes further to check if GASC1 incubated with EDTA (chelating iron) is significantly less efficient in the absence of its cofactors. The ability of the demethylation reaction to occur in vitro without the addition of cofactors is probably due to the co-purification of cofactors (for example, iron and α -ketoglutarate) with recombinant GASC1 [162].

Copper cofactor metalloenzymes

Copper is an essential biogenic metal ion, present in the parts per million concentration range. It is a key cofactor in a diverse array of biological oxidation–reduction enzymatic reactions like pigmentation of tyrosinase, catecholamine production of dopamine hydroxylase, collagen and elastin formation of lysyl oxidase, blood clotting, etc. These involve either outer-sphere electron transfer, as in

the blue copper proteins and the CuA site of cytochrome oxidase and nitrous oxide reductase, or inner-sphere electron transfer in the binding, activation, and reduction of dioxygen, superoxide, nitrite, and nitrous oxide. The best characterized blue-copper protein with respect to the role of metals in folding is *Pseudomonas aeruginosa* azurin. It is coordinated by two histidine imidazoles (His46 and His117), one cysteine thiolate (Cys112), and two weaker axial ligands, sulphur of methionine (Met121) and carbonyl of glycine (Gly45) in a trigonal bipyramidal geometry [125]. Destruction of Cu^{2+} cofactor binding geometries of some natural proteins like kanamycin A in human serum albumin through the use of aminoglycoside antibiotics has been reported [163]. Aminoglycosides are among the antibiotics that are effective against Gram-negative and some Gram-positive bacteria. Their therapeutic action consists in binding to the bacterial ribosome through the peptide bond, decreasing the fidelity of mRNA translation and further preventing protein synthesis [164]. They can interfere with most molecules of the RNA group and ribosomal RNA, HIV-1 viral Rev, yeast tRNA hammerhead ribozyme and RNase P RNA [165–170]. Also, neomycin B displaces essential metal ions like Fe^{2+} or Pb^{2+} from major regions in intron RNA, inhibits splicing, and protects the catalytic core from cleavage [137, 138].

Zinc cofactor metalloenzymes

Zinc is one of the most commonly utilized metal cofactors (~16 and ~9% of all enzymes, respectively) [161]. They dominate the subset of metalloenzymes lack a defined delivery system and represent ~78% of this group. Potential difference of these zinc-containing enzymes is associated with several diseases including arthritis and cancer, so inhibition of the zinc active site is a good strategy for the design of a drug. Empirically, zinc is known to replace magnesium to inactivate enzymes including β -galactosidase [171], tyrosine kinases [172], and magnesium alkaline phosphatase [173, 174]. The calculated free energies for replacing magnesium with zinc in rigid or flexible sites implies that zinc will always be favoured over magnesium in mono- and binuclear binding pockets, with ΔG for replacement in flexible, neutral sites ranging from -10 to $-29 \text{ kcal mol}^{-1}$ [175]. Over expression of these zinc-containing enzymes is associated with several diseases including arthritis and cancer so inhibition of the active Zn active site(r4) is necessary. Representative proteins that use catalytic zinc ions are carboxypeptidases, carbonic anhydrase, and alcohol dehydrogenase. In addition, zinc ions often play structural roles in proteins [e.g., in superoxide dismutase (SOD) and zinc-finger motifs [123].

Activity of zinc metal binding to some proteins like histone under the influence JMJD2 demethylase can control

diseases [176]. Disulfiram which has been used clinically as an aldehyde dehydrogenase inhibitor (where it inhibits by irreversible modification of active-site cysteines [177]), has also been shown to eject structural Zn(II) from nucleocapsid p7 protein (NCp7) from HIV-1 [178] and ebselen to eject zinc ion from the protein capable to cause acute ischaemic stroke [179]. Series of sulphur- and selenium-containing compounds were screened as potential Zn(II) ejectors for inhibition of JMJD2A using a MALDI-TOF MS-based assay monitoring demethylation with varying level of Zn-ejection (Fig. 2) with the view to searching for highly specific therapy delivery [180, 181].

Zn²⁺ in Zn-Cys₄, Zn-Cys₃His, Zn-Cys₂His₂, and Zn₂Cys₆ cores of zinc finger (Zf) proteins is very important metal ions. As protein structural components that bind DNA, RNA, proteins, or small molecules, they are involved in many fundamental cellular processes such as replication and repair, transcription and translation, cell proliferation and apoptosis, metabolism, and signalling [182, 183]. When zinc ion is surrounded by protein molecule like Cys-rich it depicts a tetrahedral geometry (coordination number 4) as Cys- transfers more charge to Zn²⁺ than do the other amino acid and water ligands [184, 185] thereby reducing the metal's positive charge and electron-accepting ability [186]. The deficient or release of zinc ion can cause Zn bound S atoms of the Cys₃His core in HIV-1 nucleocapsid p7 protein and in the *E. coli* Ada protein (N-Ada) to be oxidized and, therefore, lead to loss of viral protein structure and function [182, 187, 188] without any lethal effect to cellular human functions [189]. This is a good strategy in drug activity. Its inhibitory activity on Wilson's disease has been reported [190].

Summary and future goals

This review focussed on metal complexes of some antiparasitic drugs and on recent contributions covering a wide area of Biocoordination Chemistry with the aim of understanding and enhancing the application of Inorganic Chemistry in medicine. The study has shown that Fe, Cu and Zn metal ions are not mere Chemical ingredients in drugs or supplements but play very important roles in antimalarial, antimicrobial and other chemotherapies. The cytotoxicity of the metal ions when bound to protein such as metalloenzymes for inhibiting DNA of pathogens was made clear under certain mechanisms. On drug resistant strains, most of the metal drug complexes investigated showed that the inclusion of metal ions leads to a more favourable therapy and diagnosis than do the free drugs. This occurred without any injury to the host mice. This raises hope in the first row transition metal chelate drugs as the next generation of chemotherapeutic agents for combating major tropical diseases. However, while synthetic

inorganic chemists seek and find opportunities in the inorganic diagnostic and therapeutic values of metal containing bioactive molecules, there is the need to prove that these “noble metal ions” are non-toxic [191].

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