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Metal Based Drugs: Current Use and Future Potential

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Abstract

Besides the remarkable therapeutic success of anticancer drugs such as cisplatin, carboplatin and oxaliplatin, metallodrugs have also shown promising results in the treatment of diseases other than cancer. They have been developed to treat/cure a variety of ailments viz. diabetes, ulcer, rheumatoid arthritis, inflammatory and cardiovascular diseases etc. The enzymes in our body and many drugs of organic nature require traces of metal ion for proper functioning. Due to a wide variety of coordination spheres, ligands design, oxidation states and redox potential, coordination and organometallic complexes are supposed to alter the kinetic and thermodynamic properties of the complexes towards biological receptors. Thus, chelation causes drastic change in biological properties of ligands as well as metal moiety. Metal complexes are supposed to exert their effect by inhibition of enzymes, interaction with intracellular biomolecules, enhanced lipophilicity, alteration of cell membrane functions and arrest of cell cycle etc. The review includes the current use and future potential of some metal based drugs used/showed promising results in the treatment of diseases/conditions such as diabetes, ulcer, infection, mania and hypertension etc. which are being developed as therapeutic agents during the recent past.

Keywords: Metallodrugs, Anti-diabetic, Antimanic, Antiulcer, Antihypertensive.

Introduction

Metals and metal complexes have played key role in the development of modern chemotherapy (1). For example, anticancer platinum drugs appear in more chemotherapy regimes than any other class of anticancer agents and have contributed substantially to the success achieved in treating cancer over the past three decades. Metals can play an important role in modifying the pharmacological properties of known drugs after coordinating to a metal. The resulting prodrugs

have different physical and pharmacological properties, allowing the drug to be released in a controlled fashion or at specific location. This approach may lead to the rescue of drugs that have failed because of poor pharmacology or high toxicity. For example, complexation of nonsteroidal anti-inflammatory drugs to copper overcomes some of the gastric side effects of these drugs [2]. Release of cytotoxins such as nitrogen mustards from redox-active metals such as cobalt in the hypoxic regions of solid tumors has the potential to improve drug activity and reduce toxicity [3]. The metal based drugs are also being used for the treatment of a variety of ailments viz. diabetes, rheumatoid arthritis, inflammatory and cardiovascular diseases as well as diagnostic agents [4-6]. In medicinal chemistry, metal complexes have received limited attention as compared to organic compounds. In fact, many organic compounds used in medicine do not have a purely organic mode of action and require traces of metal ions directly or indirectly for activation or biotransformation. Our health, aging, physiological disorders and diseases are related to the state of the metal ions and their complexes with biomolecules in the body. Traces of metals are essential for the biological processes as about 30 - 40 % of all known proteins including metalloenzymes require metal cofactors (e.g., Fe, Cu, Zn, Ni, Mn) for their proper folding into an active three dimensional (3-D) structure [7-8]. The iron porphyrin complex of hemoglobin in red blood cells (RBCs) for oxygen transportation and storage, the magnesium porphyrin complex of chlorophyll in green plants for photosynthesis, and cobalt in the coenzyme B12 for the transfer of alkyl groups from one molecule to another molecule, are some of the examples of the role of metal ions in biological systems. The amount of metals present in the human body is approximately 0.03% of the body weight. Low metal ion concentrations may be harmful for the body. It has been reported that in cancerous parts of the kidney, the concentrations of Cd, Cr, Ti, V, Cu, Se, and Zn were found to be at a lower level than in the non-cancerous parts [9]. Ligands having electron donor atoms like N, O, S, and P etc. may form coordination bond with metal ion. Chelation causes drastic changes in biological properties of ligands as well as metal moiety and in many cases it causes synergistic effect of metal ion and ligand both [10-11]. A few well known metallopharmaceuticals include platinum (Pt) anticancer agents cisplatin, carboplatin and oxaplatin, arsenic (As) anticancer agent arsenic trioxide, orally active gold (Au) anti-rheumatoid agent auranofin, selenium (Se) anti-inflammatory agent ebselen, lithium (Li) anti-manic depressive agent lithium carbonate, aluminum (Al) and zinc (Zn) anti-ulcer agents scrlfate and polaprezinc [12-13]. Various mechanisms have been proposed for their action including inhibition of enzymes, interaction with intracellular biomolecules, enhanced lipophilicity, alteration of cell membrane functions and arrest of cell cycle etc.

The importance of metal complexes as imaging agents for various diseases including heart disease and brain disorders etc. have also been recognized. They are able to determine specific aspects of disease such as tissue hypoxia, and can detect molecular phenomenon such as multi-drug resistance. Metal centers, being positively charged, favorably bind to negatively charged biomolecules (proteins and nucleic acids) and offer excellent tools for understanding of more specific biological processes including the formation of thrombi and the imaging of infection etc. By means of scanning techniques viz. gamma scintigraphy, positron emission tomography (PET) and magnetic resonance imaging (MRI), tissues and organs with radiolabelled compounds can be visualized and such visualization facilitates the detection of abnormalities in their function. Radionuclide complexes are used for diagnosis, as contrast media and as therapeutic agents. A ^{99m}Tc radiopharmaceutical (^{99m}Tc -SESTAMIBI), known as cardiolite, is an established radiopharmaceutical for myocardial perfusion imaging. A wide variety of coordination spheres,

oxidation states, and redox potentials of coordination and organometallic complexes give kinetic and thermodynamic properties of complexes towards biological receptors. We have recently reviewed the recent developments in the field of anticancer metallopharmaceuticals [14]. The present review includes the current use and future potential of some metal based drugs used/showed promising results in the treatment of diseases such as diabetes, ulcer, microbial infection, mania and hypertension etc.

Metal compounds as anti-diabetic agents

Many metal complexes have been synthesized and evaluated to overcome the problems of painful insulin injection and side effects for type 1/type 2 diabetes mellitus (DM). Although, chromium [15], manganese [16], molybdenum [17], copper [18-19], cobalt [20], zinc [21] and vanadium ions [22-23] have been reported to exhibit insulin-mimetic or enhancing properties *in vitro* and *in vivo*, vanadium seems to be the most promising one, especially when coordinated to certain organic ligands. The insulin like effect of vanadium salts on cells [23, 24] and diabetic animals [25-27] has stimulated research into the clinical use of vanadium compounds as insulin mimetics. Vanadium, an essential trace element, is present in almost all mammalian tissues and binding with intracellular phosphate, glutathione and ascorbate [28].

Under physiological conditions vanadium exists in three oxidation states of V^{III} , V^{IV} and V^V . Many V^{IV} compounds containing $VO(L)_2$ motif, where L= ligand containing a variety of O, O; N, O; N, S; and S, S donor atoms, have been synthesized and tested as insulin mimics [29-31]. Both vanadyl (VO^{2+} , O. S. +4) and vanadate (VO_4^{3-} , O. S. +5) ions have shown insulin mimetic effects. It is suggested that they act probably by the inhibition of enzymes such as phosphatases, ATPases, nucleases, kinases etc. involved in the carbohydrate/fat metabolism due to vanadium's peroxidase action [32-33]. Vanadate esters of sugars mimic phosphate esters and act as kinase inhibitors and monovanadate esters inhibit a number of nucleases [34-36]. In biological system, transferrin-mediated transportation and metabolism [37-39] of the vanadyl ions have been proposed and they bind with protein and other cellular molecules with O and N atoms [40]. Also an elevated level of glutathione (GSH) and enhanced glutathione S-transferase (GST) activity were observed in the liver of rats when vanadium was given in drinking water [41]. Vanadyl ion in the presence of hydrogen peroxide has shown lipid peroxidation in isolated rat hepatocytes [42].

However, vanadyl is less toxic than the vanadate ion. Vanadyl complexes with maltol (3-hydroxy-2-methyl-4-pyrone) and kojic acid (3-hydroxy-2-hydroxymethyl-4-pyrone) which possess insulin mimetic activity and low toxicity profile, have been proposed for clinical use in humans. Oxovanadium(IV) with maltol/ethylmaltol has shown enhancing insulin mimetic activity in experimental diabetic animals in recent years. The orally active complex bis(maltolato) oxovanadium(IV) or BMOV (Fig. 1a) is three times more active than $VOSO_4$ and shows low toxicity and enhanced tissue uptake. Recently, V^V -dipicolinato complex has shown more insulin enhancing effect compared to BMOV. New orally active β -diketonato complexes such as $VO(acac)_2$ and bis(α -furancarboxylato) oxovanadium(IV) [43] have shown glucose lowering ability comparable to BMOV and possess high water solubility and less toxicity when orally administered in diabetic rats. Vanadium complex, bis(pyridine-2-carboxylato) oxovanadium(IV) [$VO(pic)_2$] has shown higher insulin-mimetic activity than $VOSO_4$ [44]. Despite promising antidiabetic properties, vanadium compounds have been associated with

several toxic effects including diarrhea, dehydration, hepatotoxicity, nephrotoxicity, teratogenicity and reproductive dysfunctions. Further, detailed studies are required to improve the therapeutic potential and to reduce the side effects of the vanadium compounds.

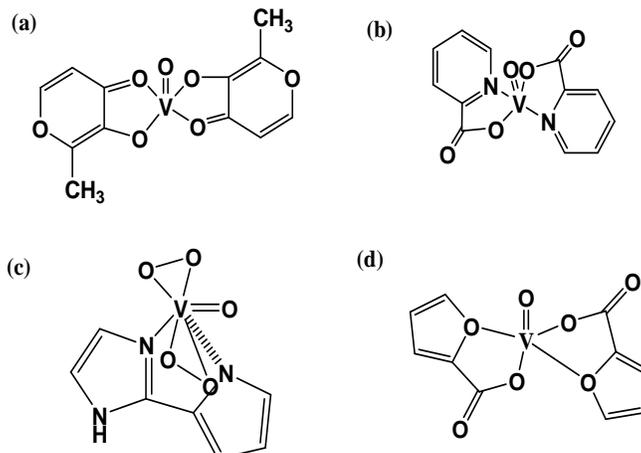


Fig. 1. Structures of insulin mimetic vanadium complexes: (a) BMOV (b) VO(pic)₂ (c) [OV(O₂)₂{2-(2'-py)-Imi}]⁻ vanadium(IV) and (d) Bis(α-furancarboxylato) oxovanadium(IV)

Metal compounds as anti-inflammatory agents

The copper bracelets have long been used as a folk remedy for the treatment of arthritis [45]. In 1940s, Cu-complexes such as cupralene [46] and dicuprene [47-48] had been evaluated for their antiarthritic properties. Many Cu-complexes of anti-inflammatory drugs (Fig. 2) have been found more active in animal models than either their parent Cu(II) salt or NSAID. Cu(II) complex of salicylate has been found about 30 times more effective than aspirin as an anti-inflammatory agent. In addition, Cu(II) complexes of many non-anti-inflammatory agents exhibited anti-inflammatory action. The pharmacological activity of these complexes has been proposed to be due to its inherent physico-chemical properties of the complex itself rather than that of its constituents. It was suggested that salicylates may deliver Cu to target cells in the body. SOD activity, redox potential, lipophilicity and stability constants may be useful parameters in evaluating the biological activity of these Cu compounds.

The possible modes of anti-inflammatory action of the Cu complexes may include inhibition of SOD activity [49], inhibition and stabilization of polymorphonuclear leukocytes (PMNL), inhibition of phospholipase A₂, inhibition of lipid peroxidation and microsomal NADPH oxidation [49] and modulation of nitric oxide synthetase (NOS) activity [50]. The role of Cu complexes in free radicals scavenging and the activation of lysyl oxidases (collagen cross-linking enzymes) are also proposed modes of action.

Inhibition of the release of tissue necrosis factor-alpha (TNF-α), IL-1 and IL-2 from macrophages by Cu-carboxylates is also reported. They also exhibit a marked SOD-mimetic activity. NO may also be important in the mode of action of Cu-NSAIDs because NO has a variety of pharmacological and pathophysiological actions in the body. The structure and stability of the Cu-NSAID complexes have been shown to be a critical determinant of their activity and toxicity. For example, the anti-tumor activity of the monomeric Cu(II) complex of aspirin ([Cu(Asp)₂(Py)₂]) is reportedly more effective than the dimeric [Cu₂(Asp)₄] complex.

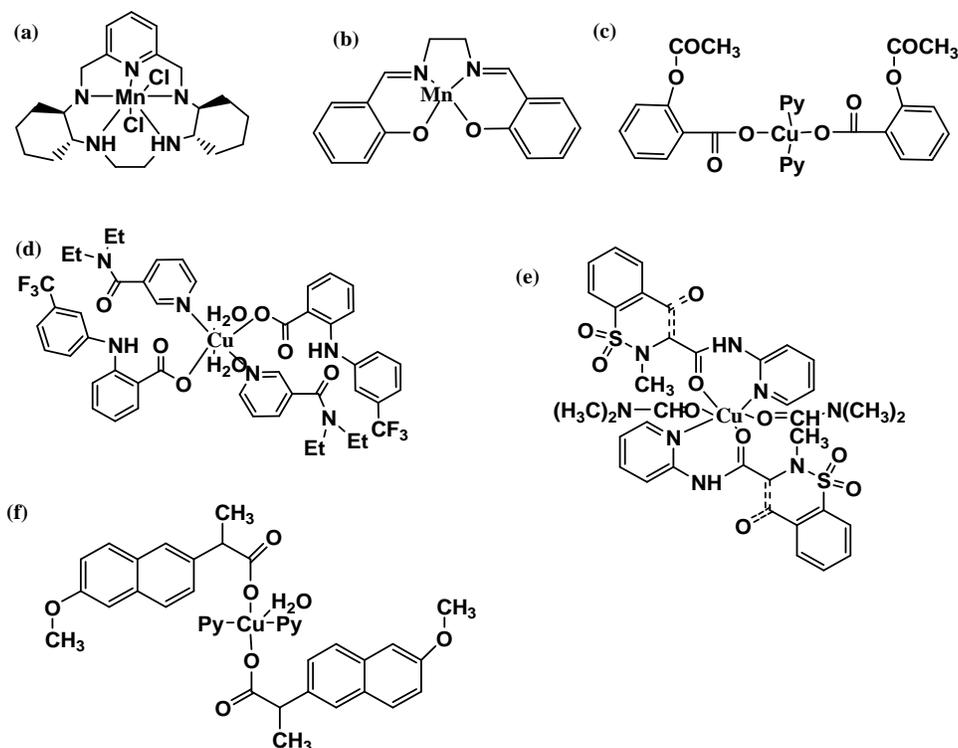


Fig. 2. Structures of some anti-inflammatory manganese and copper complexes: (a) & (b) Manganese compounds as SOD mimetics (c) Cu(II) complex of aspirin [Cu(Asp)₂(Py)₂] (d) Cu(II) complex of flufenamate (e) Cu(II) complex of piroxicam and (f) Cu(II) complex of naproxen [Cu(Nap)₂(pyridine)₂]

A large number of transition metal complexes of non-steroidal anti-inflammatory drugs (NSAIDs) such as tolmetin, naproxen, ibuprofen, flufenamic acid, indomethacin, diclofenac, aspirin, piroxicam etc. have been reported. Vanadium complexes with the NSAIDs - tolmetin, ibuprofen, naproxen and aspirin have been recently prepared and evaluated for anti-inflammatory activity. Some vanadyl complexes of anti-inflammatory drugs containing carboxylate ligands have shown promising results [51].

The complexes such as Gold(I) thiomalate [myocrisin (Autm)_n], gold(I) thioglucose [solganol (Autg)_n] and auranofin [2,3,4,6-tetra-*o*-acetyl-1-thio-β-D-glucopyranosato-(S)-triethylphosphine gold(I)] have been successfully used over many years for the treatment of rheumatoid arthritis [52-54].

Metal compounds as antimanic agent

Lithium carbonate, used in manic depressive psychosis (MDP) for the treatment of recurrent mood changes, is the only drug of its kind to exert prophylactic effect in MDP [55-56]. It is neither sedative nor euphoric but on prolonged administration, it acts as mood stabilizer in MDP. It gradually suppresses the episode of acute mania in 1-2 weeks and continued treatment prevents cyclic mood changes and hence markedly reduced sleep time in manic patients is normalized. The medicinal importance of lithium has been recognized since 1949. Lithium salts significantly increase the number of neutrophil granulocytes and, to a lesser extent, also the number of eosinophil granulocytes and lymphocytes, but the average number of erythrocytes

does not change significantly. Patient tolerability to lithium carbonate therapy is very good. It can also be used to treat patients with chronic leucopenia following chemotherapy or radiotherapy. The limited use of lithium carbonate in psychiatric disorders such as pathological aggression and reduction in acute or attempted suicide is also recognized. Lithium salts have also proved their clinical effectiveness worldwide for other indications viz. alcohol abuse and aggression, epilepsy, tardivedys-kinesia, schizophrenia, Huntington's chorea, premenstrual syndrome, migraine and cluster headaches.

Metal compounds as antimicrobial agents

In recent decades, the problems of multi-drug resistant microorganisms have reached an alarming level in many countries around the world [57-59]. A number of recent clinical reports describe the increasing occurrence of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and other antibiotic-resistant human pathogenic microorganisms in the United States and European countries [60]. Infections caused by these microorganisms pose a serious challenge to the humanity and need for an effective therapy has led to search for novel antimicrobial agents. Metal complexes may be an alternative to conventional organic drugs because complexation may lead to synergistic effect of metal ion and ligand both. Many metal complexes of quinoline group of antibiotics viz. ciprofloxacin, norfloxacin and tetracycline were evaluated and reported to possess enhanced activity than antibiotic alone. Recently, bismuth-norfloxacin complex is reported to possess enhanced antimicrobial activity than norfloxacin alone [61]. It is believed that the enhanced activity is due to increased bioavailability of the complex. Hence transportation of organic ligands into bacterial cells can be facilitated by the formation of metal complexes. Pd(II) complex of tetracycline (Fig. 3a) has been reported to have potency sixteen times more than parent compound against *E.coli* HB101/pBR322, a bacterial strain resistant to tetracycline whereas Pd(II) complex of doxycycline (Fig.3b) is two times more potent than doxycycline against resistant strain [62]. Antimicrobial activity of organotin(IV) complexes with isatin and *N*-alkylisatin bithiocarbonohydrazones has also been reported [63]. Silver and mercury salts have a long history of use as antibacterial agents [64-66]. The antifungal effect of copper ions has been known for many years. Copper(II) and silver(I) complexes of 2-pyridyl-1H-benzimidazoles have shown considerable antimicrobial activity [67]. Bismuth compounds also show moderate antibacterial activity. Bismuth therapy provides short-term effects requiring administration of relatively large, frequent doses, which increase the chances of toxicity. The poor water solubility of bismuth is the limiting factor. The antimicrobial activity of bismuth complexes towards Gram-negative bacteria has been reported to be dependent on the iron uptake system. The iron is essential for the growth of *H. pylori*. Efficient iron acquisition is thought to be an important virulence factor for this bacterium [68]. Bismuth compounds are also used in medicine for the treatment of syphilis, tumors, in radioisotope therapies, reduction of renal toxicity of cisplatin etc.[69]. Zinc gluconate (Fig. 3e) has shown antiviral activity and used to treat common cold.

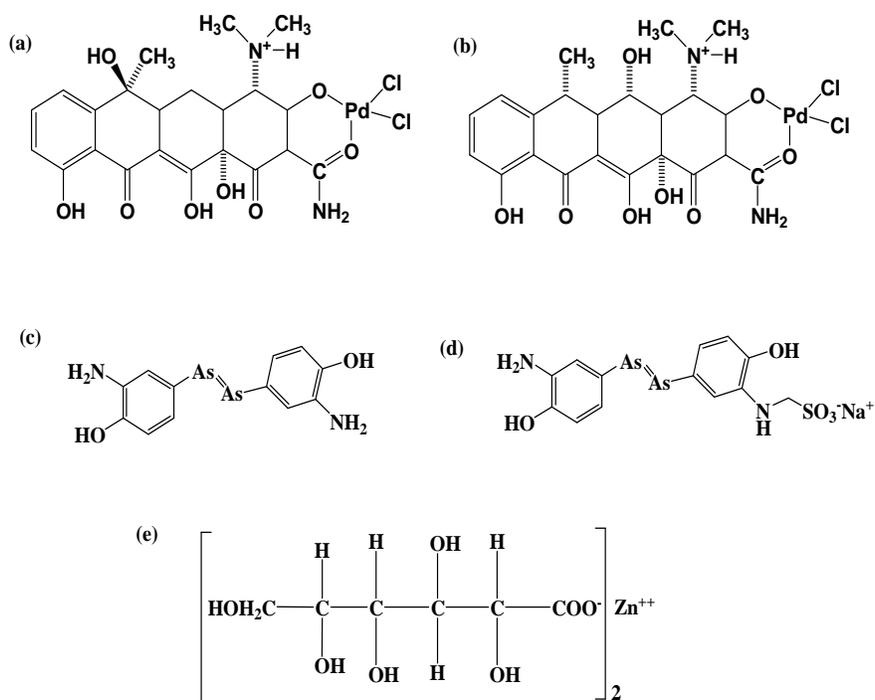


Fig. 3. Structures of some promising antibacterial, antiparasitic and antiviral agents: (a) Pd(II) complex of tetracycline (b) Pd(II) complex of doxycycline (c) Salversane (d) Neosalversane and (e) Zinc gluconate

Silver and silver containing compounds used as antimicrobial agents, are active even at low concentrations and have a low toxicity. Silver complexes with pyridine and purine nucleotides and nucleosides have antibacterial properties. They are active especially against *Pseudomonas* infections, where many other antibiotics are ineffective. Silver sulfadiazine (Fig. 4a) inhibits the growth of pathogenic microorganisms, including some species resistant to sulfonamides. It is especially effective against *P. aeruginosa*. The compound is used topically to reduce microbial colonization and the incidence of infections of wounds from serums. Silver releases slowly from the preparation and inhibits the microbial growth. Silver nitrate is still used to prevent ophthalmic disease in newborn children [70]. The mechanism of action of silver and mercury is through slow release of the active metal ion, thus inhibiting the thiol function in bacterial cell walls. There are examples where free ligands have no antimicrobial activity but complexation with silver produce antimicrobial activity. Examples of such complexes are {[Ag(L-Hasp)]₂} and {[Ag(LHasp)]₂}_n, [Ag(salH)]₂ and [Ag(NH₃)(salH)]₂. Silver complexes such as [Ag(hino)]₂ (where hino = 4-isopropyltopolone) [71] and silver(I) complexes of (R)-(+)- and (S)-(-)-2-pyrrolidone-2-carboxylic acid [72] are effective against some bacteria, yeasts and moulds.

Metal compounds as antiparasitic agents

Metal complexes of gold(Au), platinum(Pt), iridium(Ir), palladium(Pd), rhodium(Rh) and osmium(Os) have been reported to have activity against a variety of trypanosomatids. The enzymes, cysteine proteases have been found to play an important role in parasitic life cycles including *Schistosoma*, *Plasmodium*, *T. brucei*, *T. cruzi* and *Leishmania* in nutrition, host invasion, protein processing and evasion of the host immune response [73]. Arsenic and bismuth have been reported to be effective against trypanosomiasis and leishmaniasis, respectively.

Salversane and neosalversane (Fig. 3c & 3d) are well known for their antisyphilitic activity. The existing antimalarial drugs are now becoming less effective against *Plasmodium*. The emergence of resistance to chloroquine (an antimalarial drug) is one of reasons for an urgent need for new effective antiparasitic agents. In the search of better therapeutic results, gold and ruthenium complexes of chloroquine and clotrimazole have also been prepared and evaluated against *Plasmodium* [74-77]. Chloroquine complex of transition metal ruthenium, $[\text{RuCl}_2(\text{CQ})]_2$ (Fig. 4h) has been found to be 2-5 times more active than chloroquine diphosphate (CQDP) in *in-vitro* test against chloroquine-resistant strain of *P. falciparum* without any sign of acute toxicity. The incorporation of the metal produced an enhancement of the efficacy of chloroquine [77]. Some of these complexes have shown improved therapeutic results even in chloroquine resistant cases. Another examples where metal complexes have shown promising results include antimony compounds (Fig. 4 (e) & (f)) are used to treat leishmaniasis. The leishmanicidal activity of platinum complexes viz. *trans*- $[\text{PtCl}_2(\text{NBA})(\text{pz})]$ (NBA= *n*-butylamine, pz= piperazine) and *trans*- $[\text{PtCl}_2(\text{NH}_3)(4\text{-pippip})]$ (4-pippip=4-piperidino-piperidine) (4c & 4d) against promastigotes of parasite *L. infantum* was found to be 2.5 and 1.6 times higher than that of the cytotoxic drug *cis*-diamminedichloroplatinum(II), respectively. These compounds are reported to produce higher amount of programmed cell death in *L. infantum* promastigotes than cisplatin, which is associated with cell cycle arrest in G2/M [78].

Metal compounds as antiulcer agents

Bismuth compounds are commonly used for treating a variety of gastrointestinal disorders because of their antacid and astringent properties [79]. Colloidal bismuth subcitrate (CBS), bismuth subsalicylate (BSS) and ranitidine bismuth citrate are the most widely used drugs for the treatment of diarrhea, dyspepsia and peptic ulcers. The primary biological target of bismuth drugs is thought to be the bacterium *Helicobacter pylori*, the suspected causative agent for these gastric complaints. The mechanism of actions of these drugs is inhibition of synthesis of protein, ATP, cell wall and alteration of membrane functions. The widely used salts include tripotassiumdicitratobismuth, bismuth salicylate, Pepto-Bismol (BSS), and De-Nol (CBS). The combination of ranitidine (a histamine H₂-receptor antagonist) and bismuth citrate is marketed as Ranitidine Bismutrex for the management of peptic ulcer and ulcers associated with *H. pylori* [80]. Bi(III) is highly acidic in aqueous medium and oxygen-rich nature of the sugar carrier ligands leads to formation of di- and polynuclear-bridged complexes. Bismuth(III) remarkably forms stable complexes with GSH [81] and transferrin [82].

Recently, capsule containing colloidal bismuth citrate, metroindazole and tetracycline has been approved for the eradication of *H. pylori* [83-84]. Several other bismuth salts such as $\text{Bi}(\text{NO}_3)_2 \cdot 5\text{H}_2\text{O}$, BiCl_3 , BiOCl and citrate (3-carboxy-3-hydroxypentane-1, 5-dioic acid) salts of bismuth are important for their widespread medicinal use.

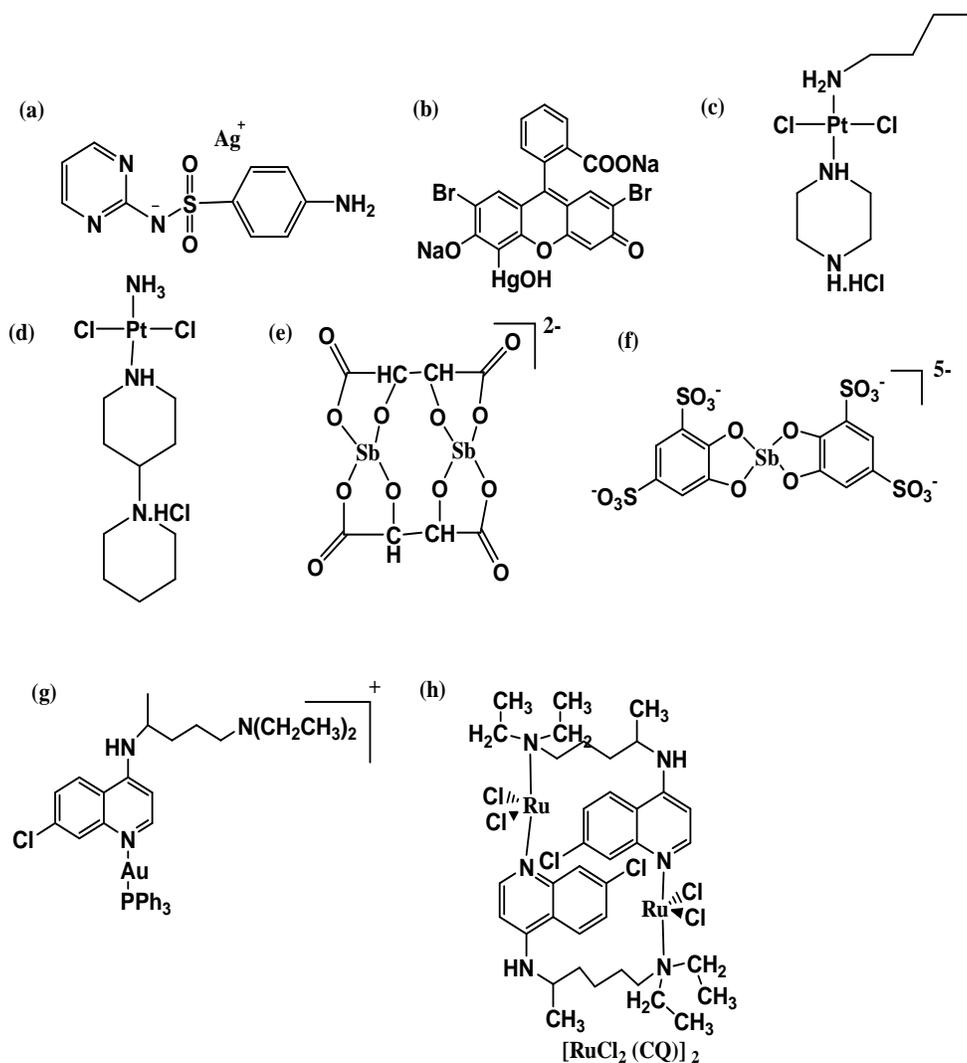


Fig. 4. Structures of some antibacterial and antiparasitic agents (a) Silver sulfadiazine (b) Mercurochrome (c) *trans*-[PtCl₂(NBA)(pz)] (d) *trans*-[PtCl₂(NH₃)(4-pippip)] (e) & (f) Antimony-based antiparasitic agents (g) Gold-based antiparasitic agent and (h) Ruthenium-based antiparasitic agent [RuCl₂(CQ)]₂

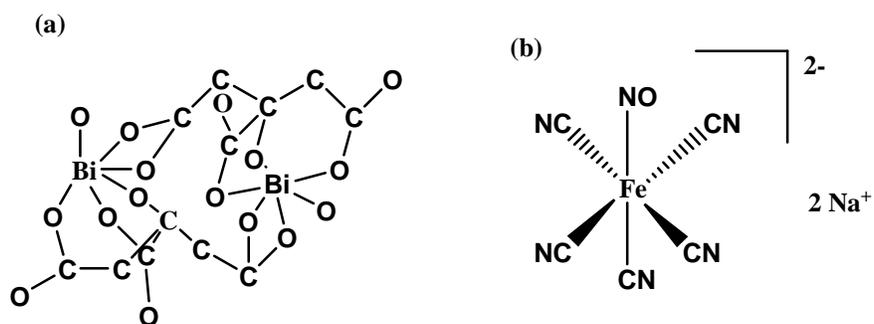


Fig. 5. Structures of some bismuth and Iron complexes: (a) Bismuth citrate dimer (b) Sodium nitroprusside

Bismuth therapy is associated with several side effects including neurological dysfunction, reproductive dysfunction due to lower serum testosterone levels and its toxicity is reversible over several weeks or months when bismuth intake is stopped [85-86].

Metal compounds as antihypertensive agents

The discovery of diverse biological roles of NO in physiology has stimulated and facilitated the development of NO targeted metallopharmaceuticals. The role of NO in physiological processes of neurotransmission, blood pressure regulation and immunological responses has been recognized. Sodium nitroprusside, $\text{Na}_2[\text{Fe}(\text{CN})_5\text{NO}]\cdot 2\text{H}_2\text{O}$ (Fig. 5b) is used clinically to treat hypertensive patients in emergency situations. However, toxicity involving accumulation of cyanide has limited its application. Ruthenium complexes exhibit both nitric oxide release and scavenging functions that can affect vasodilation and synapse firing. Simple ruthenium complexes are effective in suppressing the immune response by inhibiting T cell proliferation.

Ruthenium complex such as *trans*- $[\text{Ru}(\text{NH}_3)_4\text{P}(\text{OEt})_3(\text{NO})](\text{PF}_6)_3$ has shown similar antihypertensive activity but reduced toxicity when compared with sodium nitroprusside in animal studies [87]. *Trans*- $[\text{Ru}^{\text{II}}(\text{cyclam})(\text{NO})\text{Cl}](\text{PF}_6)_2$ has shown prolonged antihypertensive activity in both normotensive and acute hypertensive Wistar rats [88], showing its beneficial effect in controlled release of NO. Overproduction of NO is considered to produce peroxynitrite ONOO^- through reaction of NO with O_2 . The peroxynitrite plays a role in many other pathological conditions such as sepsis, arthritis, diabetes and epilepsy. Ruthenium-polyaminocarboxylate complexes are efficient NO scavenger [89-91] and demonstrating their therapeutic potential.

Conclusions and Perspectives

In this review, an overview of the metal based drugs which have shown promising results or used in the treatment of diabetes, inflammation, mental disorders, infection, hypertension etc. has been presented. It seems that opportunities exist to exploit metal and metal based drug candidates in the discovery and development of novel chemotherapeutic agents. The encouraging results of preclinical and clinical studies with metal compounds form the basis for further investigations towards the development of metallodrugs for better healthcare. Further, understanding of mechanism of action, cellular target and the properly designed metal compounds will increase the selectivity and the specificity of new metal compounds. It is clear that metal compounds offer new properties that cannot be found amongst purely organic agents. The therapeutic application of metal complexes is still an unexplored area of research and continued work in this area is warranted. Due to a wide variety of coordination spheres, ligands design, oxidation states and redox potential, coordination and organometallic complexes can systematically alter the kinetic and thermodynamic properties of the complexes towards biological receptors. Therefore, they offer opportunities for the design of novel agents for the treatment of a variety of diseases and conditions.

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