Medicinal Uses of Inorganic Compounds – 1

B S Sekhon and Leena Gandhi

In this two part article, we describe some aspects of inorganic drugs that bridge the areas of inorganic chemistry and medicine. In this first part, we describe the therapeutic potential of inorganic compounds as neurological, anticancer, antimicrobial, antiulcer, antiviral, anti-inflammatory, cardio vascular and insulin-mimetic agents.

Introduction

The inorganic chemists' extensive knowledge of coordination, ligand exchange, photophysical and redox properties of metal ions have helped in understanding the interactions of inorganic compounds with biological molecules. Pharmaceutical industries, which have been dominated by organic drugs, are now focusing much attention on inorganic drugs because (i) many activities of metal ions in biology have stimulated the development of metal-based therapeutics; (ii) inorganic drugs are likely to be transferred in the body by oxidation and ligand substitution reactions. Metal complexes continue to find therapeutic applications for the treatment of a wide variety of human ailments. The science of medicinal chemistry began with the discovery of metal-based drugs to treat syphilis. Now, metal/metalloid elements such as platinum, titanium, bismuth, arsenic, antimony, selenium, silver, gold, vanadium, copper, manganese, germanium, iron, ruthenium, gadolinium and technetium are incorporated into many important therapeutic drugs and diagnostic imaging agents. Worldwide sales of inorganic drugs are growing rapidly. Although about 26 elements in the periodic table are considered essential for mammalian life, both essential and non-essential elements can be used in the drugs. Inorganic compounds used as drugs and diagnostic agents (*Table* 1) are described here.

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Keywords
Inorganic drugs, therapeutic agents, metal-based drugs, metal complexes.

Element	Compound	Use
Ag	Silver sulphadiazine	Antibacterial
Al	$Al(OH)_3$	Antacid
As	Salvarsan, Melarsen, Tryparsamide	Antimicrobial
Au	Gold(I) thiolates	Antitumour
	Auranofin	Antiarthritic
	Au(I) diphosphine complexes	Antiviral
Ba	Barium sulphate	X-ray contrast
Bi	Bismuth subsalicylate, colloidal bismuth citrate, ranitidine bismuth citrate	Antacid, antiulcer
Br	Sodium bromide	Sedative
Cr	Chromium complexes	Antidiabetic
Cu	Copper histidine complex	Supplement for Menkes Disease treatment
Co	Coenzyme B_{12}	Supplement
Fe	Sodium nitroprusside	Vasodilator
	Fe(III) desferrioxamine chelates	Antimicrobial
Gd	Gd metallotexaphyrins	MRI contrast agent. PDT, Radiopharmaceuticals
Hg	Mereurochrome	Antiseptic
I	I_2	Antiseptic
	$Na^{131}I$	Diagnosis of Thyroid
Li	Li_2CO_3	Manic depression
Lu	Lutetium complexes	PDT
Mg	MgO	Antacid, laxative
Mn	Mn-SOD complexes	Superoxide scavengers MRI contrast agent
Pt	Cisplatin, carboplatin	Anticancer
Ru	Ru(III) complexes	Anticancer
Sb	Pentostam, N-methylglucamine antimonate	Antileishmanial
Si	$Al_2(OH)_4Si_2O_5$	Antidiarrhoeal
Sn	Tin(IV) ethyl etiopurpurin	PDT
Tc	^{99m}Tc (V) propyleneamine oxime	Diagnostic imaging
Ti	Titanocene dichloride, bis(β-diketonato) Ti(IV)	Anticancer
V	bis(maltolato) oxovanodium(IV) bis(glycinato) oxovanodium (IV) bis(methylpicolinato oxovanadium (IV)	Antidiabetic
W	Polyoxometallates	Anti-HIV activity
Zn	ZnO	Skin ointment
	Zn(II)bicyclam complexes	Antiviral
	Zinc citrate	Supplement
Zr	Zr(IV) glycinato	Antiperspirant
Se	Ebselen : (2-phenyl-1,2-benzisoselenazol-3(2H)-one	Synthetic antioxidant Anti-inflammatory neuroprotective agent
	Phenylaminoalkyl selenide: (4-hydroxy-α-methyl-phenyl-2-aminoethyl selenide)	Antihypertensive
	Selenazofurin	Antineoplastic and antiviral agent
	Selenotifen	Anti-allergic agent

Table 1. Examples of inorganic compounds used as drugs and diagnostic agents.

Neurological Agents

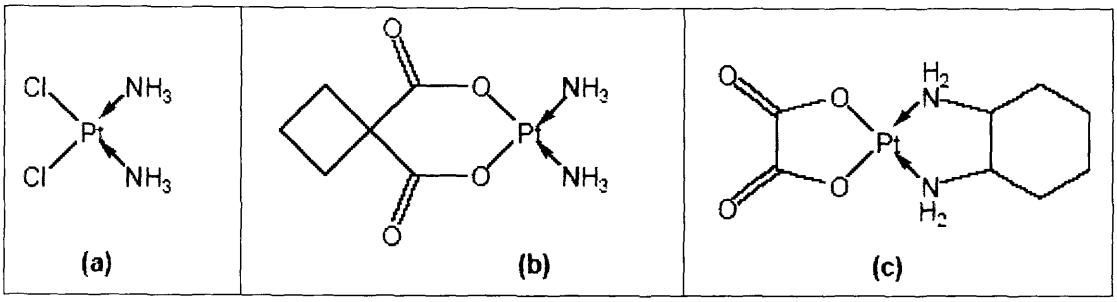
Lithium like alcohol can influence mood. Lithium drugs such as lithium carbonate Li_2CO_3, are used for the treatment of manic-depressive disorders, most likely through an effect on the transmission of neuronal signals. Li(I) interferes with the biochemistry of Mg (II) which is of similar size. Lithium (I) acts as an uncompetitive inhibitor of inositol monophosphatase that hydrolyses inositol phosphate into inositol and phosphate. According to the 'inositol depletion' theory of bipolar disorder treatment, the therapeutic effect of lithium is to block inositol recycling via inositol monophosphatase inhibition, and thus reduce inositol levels in the cell. Li^+ blocks the release of the aquation product phosphate from the active site by binding to Mg-Inosine monophosphate and thereby forming MgLi-Inosine monophosphate, which is inactive. Glycogen synthase kinase-3 (GSK-3) is a critical, negative regulator of diverse signaling pathways. Growing evidence also suggests a link between GSK-3, bipolar disorder, and the therapeutic effects of Li^+. Li^+ acts as a specific inhibitor of the GSK-3 family of protein kinases *in vitro* and in intact cells. For example, lithium is known to increase the inhibitory N-terminal phosphorylation of GSK-3, but the target of lithium responsible for this indirect regulation has not been identified

Lithium drugs such as lithium carbonate Li_2CO_3, are used for the treatment of manic-depressive disorders.

Anticancer Agents

Metal compounds can bind tightly to biomolecules such as DNA to kill cancer cells. Cisplatin [*cis*-diamminedichloro platinum (II)] (*Figure* 1a), one of the leading metal-based drugs, is widely used in the treatment of testicular cancer. It is a neutral square planar complex of platinum (II). The mode of action of cisplatin is due to release of chloride ions on crossing cell membrane. Then a charged species is formed on hydrolysis, which is attracted to anionic DNA. For the drug to work according to the proposed mechanism, it must hydrolyze in the right place; if it hydrolyzes in the blood before it gets to the chromosomes within the cell, it will be more likely to react with the nontarget

The mode of action of cisplatin is due to release of chloride ions on crossing cell membrane.



Figures 1a-c.

species. Fortunately for the stability of the complex, the blood has approximately 0.1M in chloride ions, forcing the hydrolysis equilibrium back to the chloro complex. Once the drug crosses the cell membrane into the cytoplasm it finds a chloride ion concentration of only 4mM. The cytotoxicity of cisplatin originates from its binding to DNA through N_7 site of guanine and the formation of covalent cross-links involving 1,2-intrastrand d(GpG). Binding of cisplatin to DNA causes distortion of helical structure and results in inhibition of DNA replication and transcription. Platinum complexes that are currently in clinical use or approved for clinical use or in clinical trials are shown in *Figure* 1. (Cisplatin *Figure* 1a, carboplatin *Figure* 1b, oxaliplatin *Figure* 1c).

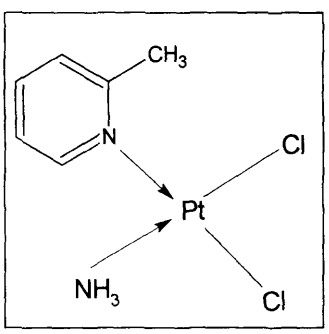
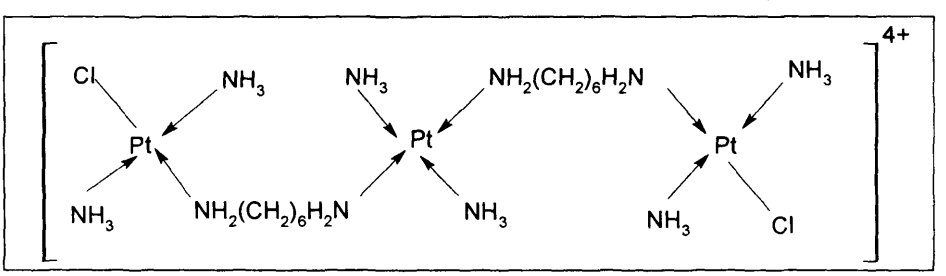
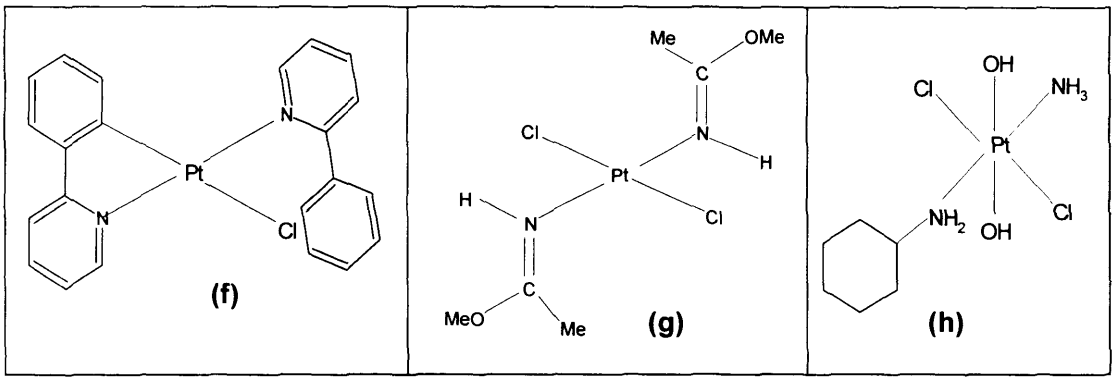


Figure 1d.

Cis-amminedichloro(2-methylpyridine) platinum(II) called ZD0473 (*Figure* 1d) is a new platinum based therapeutic compound to overcome resistance to standard platinum drugs mentioned above. The second class of multinuclear platinum complexes that bind to DNA in a manner different from that of cisplatin contain two, three or four platinum centers with both *cis* and/or *trans* configuration. A representative trinuclear complex BBR 3464 (*Figure* 1e) exhibits activity against pancreatic, lung and melanoma cancers. BBR 3464 is a highly charged (4^+)

Figure 1e.





Figures 1f-h.

species and binds to DNA. The interstrand cross-links appear to account for antitumour activity.

Monofunctional platinum(II) complexes with one normal and one cyclometalated 2-phenylpyridine ligand (*Figure* 1f) show high antitumour activity against cisplatin resistant cell lines. The *trans* analog of cisplatin (II) is inactive but substitution of one or both ammine ligands in *trans*-diamminedichloro platinum (II) with more bulky ligands such as planar aromatic amines, alkyl amines, imino ethers, piperidine, piperazine or 4-picoline has displayed significantly cytotoxicity against cisplatin resistant cancer cells. Representative examples of *trans* complexes are shown in *Figures* 1g–h and these have different DNA binding modes from that of cisplatin.

During the recent years many ruthenium compounds were found to have very promising anticancer activity. Ruthenium complexes with oxidation state 2+ or 3+ display antitumour activity. Due to the octahedral structure of Ru(II) and Ru(III) complexes as opposed to the square-planar geometry of Pt(II), ruthenium antitumour complexes probably function in a manner differently than cisplatin. The ruthenium (III) complexes namely Na *trans*-[Ru(Im)(Me_2SO)Cl_4], (ImH)*trans*-[Ru(Im) (Me_2SO)Cl_4 (Im= imidazole *Figure* 2a) and [Ru(II) (η^6-arene) (en)X]$^+$ (X = Cl or I, arene = p-cumene or biphenyl, en = ethylenediamine, *Figure* 2b) display antitumour activity especially against metastatic cancers

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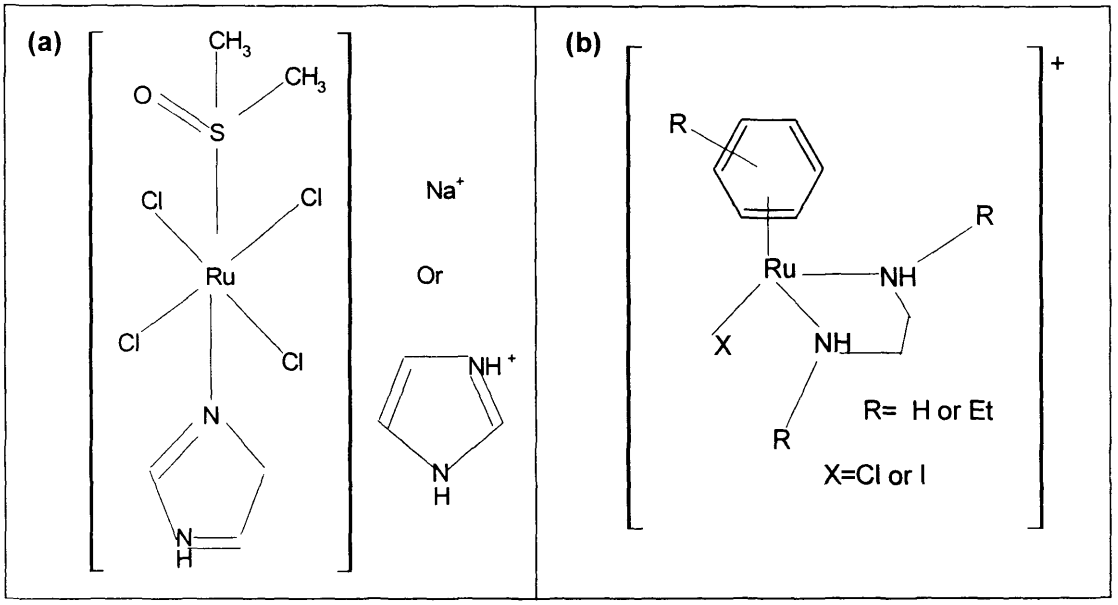

Figures 2a-b.

Ru(III) complexes tend to be more biologically inert than related Ru(II) complexes. Interestingly, it has been demonstrated that Ru(II) complexes are far more reactive towards DNA than Ru(III) and it is therefore possible that the anticancer activity of Ru(III) involves initial reduction to Ru(II) at the tumour site, promoted by the altered physicochemical environment in tumour cells (*vide supra*). If this hypothesis is correct then Ru(III) complexes are essentially prodrugs[1]. In addition to DNA binding, ruthenium compounds interact with proteins including serum transferrin and albumin, and it is likely that both activities contribute to the anticancer properties of the compounds. Since tumors rapidly utilize oxygen and other nutrients and the development of new blood vessels (known as neovascularization or angiogenesis) often fails to keep pace with tumor growth, there is usually a lower O_2 content (hypoxia) in tumor. Consequently, cancer cells depend more on glycolysis for energy and generate an excess of lactic acid, which lowers the pH in tumor cells. Due to these metabolic differences, the relative electrochemical potential inside tumors is generally lower than in the surrounding normal tissue, particularly at the center of the tumor. These differences in tumor relative to normal cell me-

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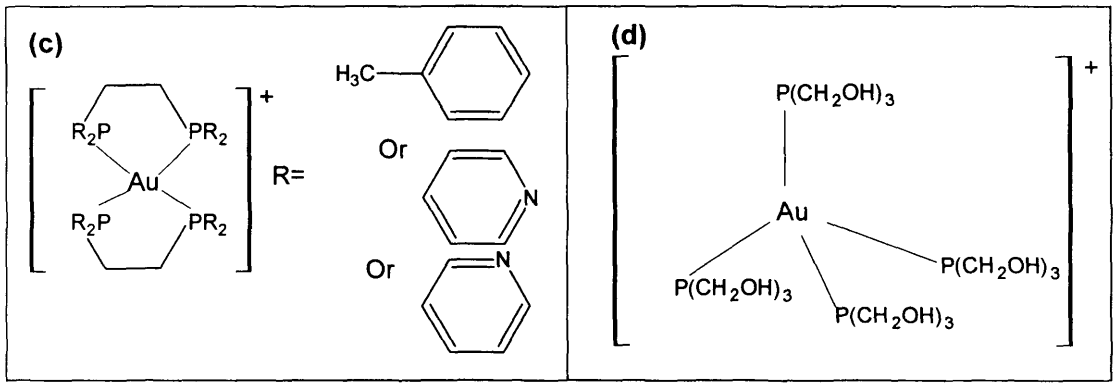


Figures 2c-d.

tabolism should favor the production of Ru(II) relative to Ru(III) in tumors, compared with normal tissue.

Tetrahedral gold (I) complexes with 1,2-bis-(diphenylphosphino) ethane; 1,2,-bis-(dipyridylphosphino)ethane; tetrakis-((tris (hydroxymethyl)-phosphine) gold (I) complex and chlorotriphenylphosphine-1,3-bis-(diphenylphosphino) propane gold (I) complex display antitumour activity (*Figures* 2c,d). Their cytotoxicity is mediated by their ability to modify mitochondrial function and inhibit protein synthesis. Other examples include titanocene dichloride (*Figure* 2e) and bis (β-diketonato) Ti (IV) complex called budotitane (*Figure* 2f).

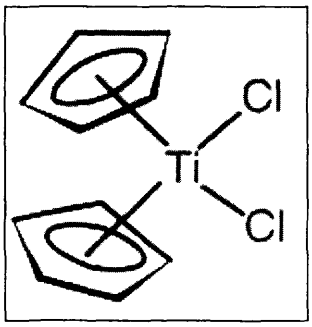
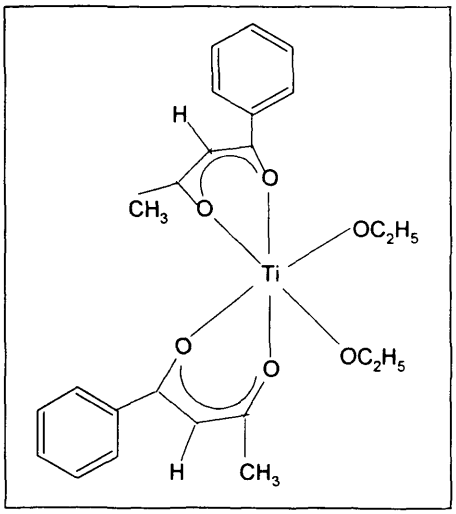


Figure 2e.

Figure 2f.

Antimicrobial Agents

Elrich in 1910 introduced 'Salvarsan' for the treatment of syphilis (*Figure* 3a). A few other arsenic compounds namely tryparsamide (sodium N-carbamoylmethylarsanilite), melarsen [N-(4,6-diamino-s-triazin-2-yl)arsanilic acid], diphetarsone (disodium N-N-ethylenediarsanilate) and p-uriodobenzenearsonic acid are being currently used for the treatment of trypanosome and amoeba mediated diseases. The therapeutic effectiveness of Salvarsan is due to its oxidized arsenoso compound, which is the active form. This form binds to sulphydryl (-SH) compounds present in and essential for microbial cells through covalent bond, and thus causes



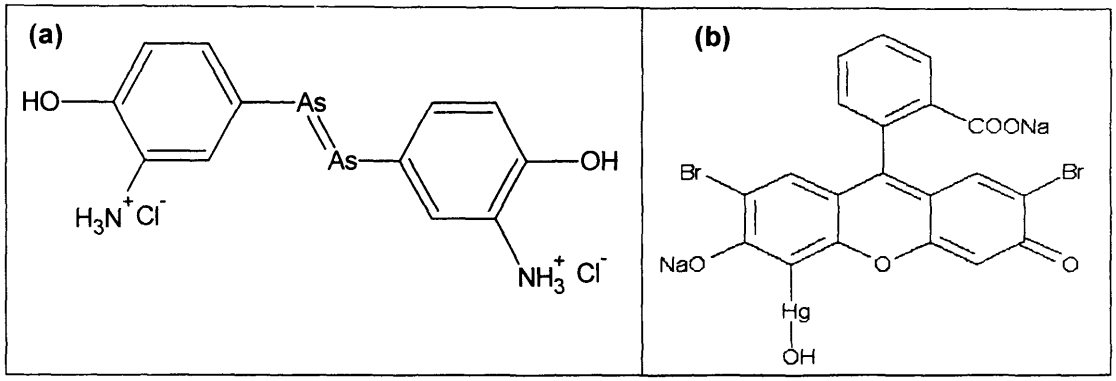
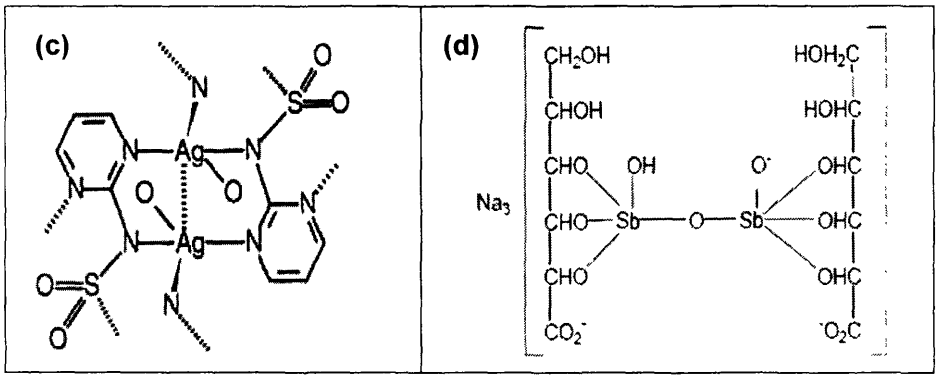


Figure 3a-b.

their toxic effect. Mercurochrome (*Figure* 3b), an organic mercury compound, in 2% aqueous solution is used as a topical antiseptic. The application of silver-containing solution to the burned skin is an effective protection against the change of second-degree burn (redness and blistering) into third degree burn (complete destruction of all layers of skin). Silver sulphadiazine (*Figure* 3c), an insoluble polymeric compound releases Ag (I) ions slowly and is used clinically in the form of cream as an antimicrobial and antifungal agent to prevent bacterial infections in case of severe burns. This compound in colloidal silver form disables oxygen metabolism enzymes of virus, fungi, bacterium or any other single celled pathogen. Unlike pharmaceutical agents (for example sulfonamides) which destroy beneficial enzymes, colloidal silver leaves these tissue-cell enzymes intact. Antimony (V) drugs namely sodium stibogluconate (Pentostam, *Figure* 3d) and N-methylglucamine antimonate (Glucantime) are used clinically for the treatment of

Figure 3c-d.



leishmaniasis, a disease caused by intracellular parasites. N-methylglucamine antimonate has the same structure to that of sodium stibogluconate but with the CO_2^- groups being replaced by deprotonated $CH_2N(H)CH_3$.

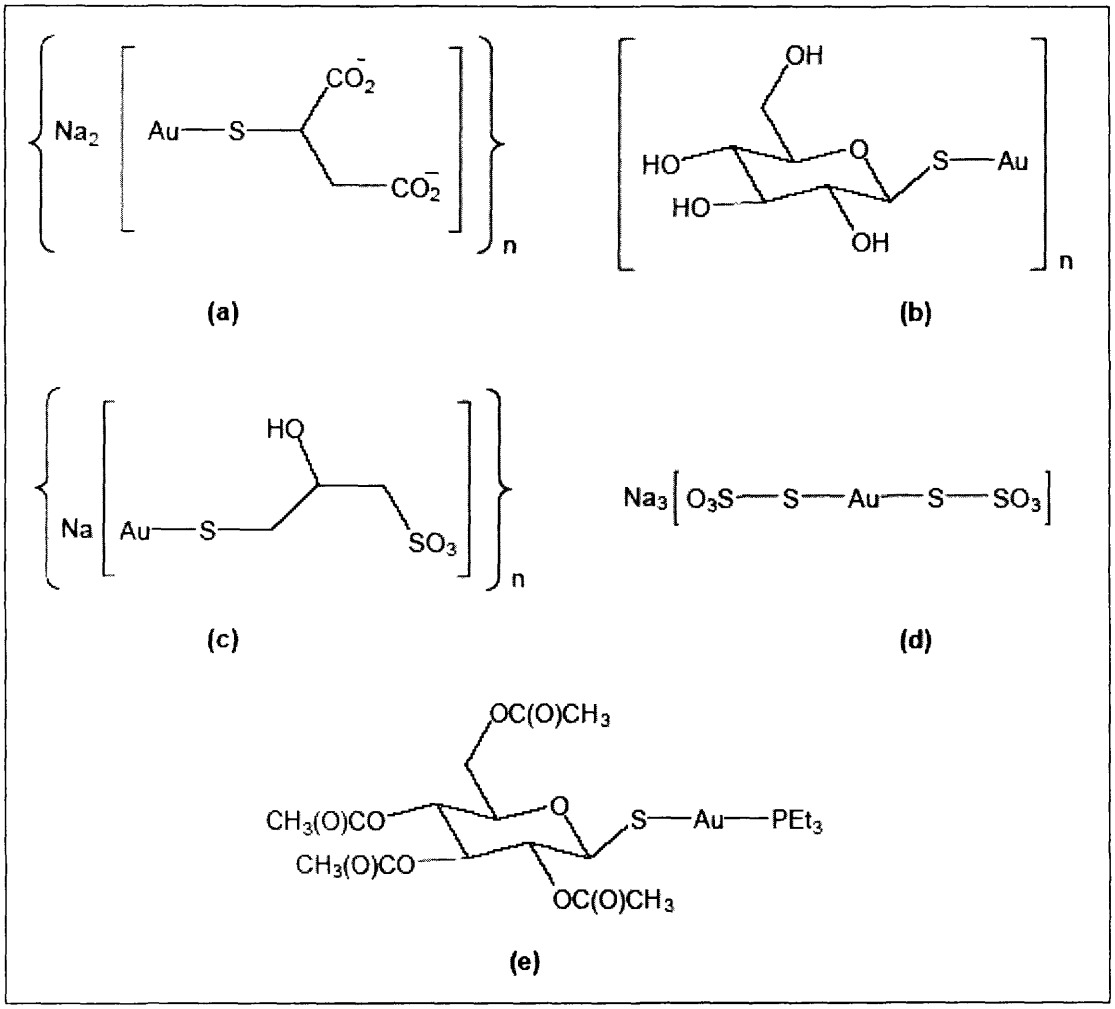
Antiviral Agents

Polyoxometallates, for example, $[NaW_{21}Sb_{29}O_{86}]$ $[NH_4]_{17}$ and $K_{12}H_2[P_2W_{12}O_{48}]$. $24H_2O$ exhibit antiviral activity. These are nanoscale assemblies of early transition metals (for example, vanadium, tungsten, molybdenum) with oxygen to form a variety of cage-like structures. Being negatively charged, these compounds bind to positive patches of HIV gp120 blocking binding to lymphocyte $CXCR_4$ receptor.

Anti-inflammatory Agents

Gold-based drugs prescribed for the treatment of rheumatoid arthritis are disease-modifying anti-rheumatoid drugs and are known to inhibit the progression of the disease and, in some cases, cause remission. Gold (I) is the most stable state *in vivo* and this fact has been used in the design of drugs of most of the gold compounds that have been approved for clinical use. There are two classes of gold (I) complexes used in chrysotherapy: (i) the gold (I) thiolates, and (ii) phosphine gold (I) thiolate. The representative examples of class I drugs are (a) Myocrisin, sodium aurothiomalate, (b) Solganol, aurothioglucose, (c) Allochrysine Limière, sodium aurothiopropanol sulphonate, and (d) Sanocrysin, sodium aurothiosulphate (*Figures* 4a-d).

The examples of class I drugs are generally polymeric complex (gold: ligand ratio of 1:1) with linear Au (I) thiolate–S bridging. The second class comprises only one example namely, auranofin, triethylphosphino gold (I) tetraacetylatethioglucose (*Figure* 4e). This drug is monomeric and gold atom exists as linear geometry. Aauranofin, in the presence of calcium ions, is a highly efficient inducer of mitochondrial membrane permeability transition, potentially referable to its inhibition of mitochondrial thioredoxin reductase.



Figures 4a-e.

Basically gold drugs should be prodrugs, in that upon administration to patients, metabolism occurs with bond cleavage within the drug, which releases Au that is bonded to biologically relevant thiol and/or selenol groups. Selenols are able to bind some heavy metals more efficiently than thiols and, therefore, the selenocysteine of thioredoxin reductase appears as the target of organic gold inhibitors. Gold (I) compounds exhibit also a marked and specific reactivity with selenoenzymes such as glutathione peroxidase (GPx), iodothyronine deiodinase type I, and thioredoxin reductase; an enzyme recently shown to possess selenium at its catalytic site. Considering glutathione peroxi-

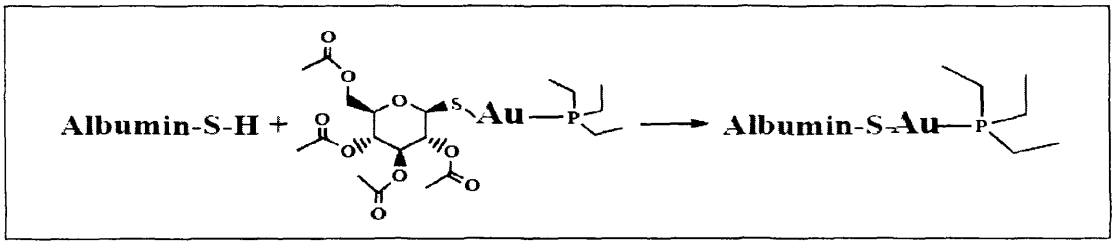


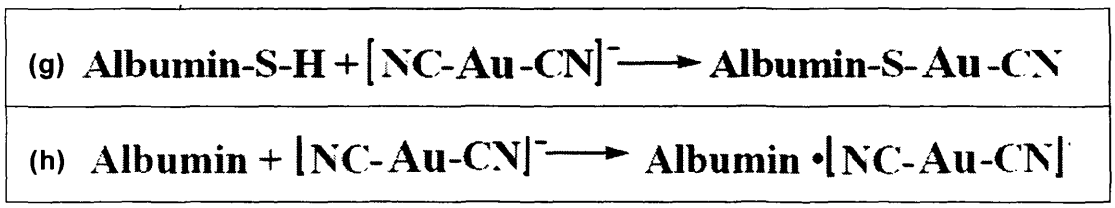
Figure 4f.

dase, gold (I) derivatives such as aurothiomalate, aurothioglucose and auranofin have been shown to exert their inhibitory action by forming a glutathionate-gold (I)-selenocysteine glutathione peroxidase ternary complex (GPxSe-Au-SG). Gold drugs are almost certainly transformed inside the body into more active species. It was found that most of the gold in circulation had become protein bound. The small amount of gold left in plasma that could be identified was the dicyangold (I) anion [Au $(CN)_2^-$].

One target site is the abundant blood protein albumin, to which gold binds very specifically at a single amino acid residue, the sulfur atom at amino acid residue number 34 (a cysteine residue, *Figure* 4f). Gold bound to albumin circulates in blood and is delivered to cells and tissues where it can inhibit enzymes which break down joint tissue.

There are two possible mechanisms for interaction between dicyanogold (I) and serum albumin that retain a two-coordinate gold (I): covalent or electrostatic. A covalent binding mechanism similar to that observed for gold drugs would involve the loss of a cyanide ligand in order to bind to the sulfur of cysteine-34 (*Figure* 4g). In an electrostatic binding mechanism, the dicyanogold (I) anion would bind intact to some positively charged region of the protein (*Figure* 4h).

Figures 4g-h.

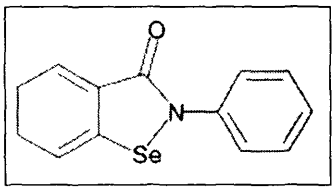


The other explanation relates to conversion of gold (I) administered in various drug formulations to aurocyanide and oxidized to gold (III) by the immune system.

Selenium is an essential micronutrient in all known forms of life; it is a component of the unusual amino acid selenocysteine. Selenium, long known to be an important dietary 'antioxidant', is now recognized as an essential component of the active sites of a number of enzymes, and several additional mammalian selenoproteins. Mammalian thioredoxin reductase (TrxR) enzymes are important selenoproteins that, together with Trx and additional Trx-dependent enzymes, carry out several antioxidant and redox regulatory roles in cells. These roles include synthesis of deoxyribonucleotides with ribonucleotide reductase, reduction of peroxides or oxidized methionine residues with peroxiredoxins or methionine sulfoxide reductases, respectively, regulation of several transcription factor or protein kinase activities, as well as regeneration of many low molecular weight antioxidant compounds.

Se deficiency is associated with two human diseases (Keshena disease and Kashimbeck disease). Keshena disease is cardiomyopathy where multifocal necrosis and fibrosis of the myocardium occurs, presenting with muscle weakness and myalgia. Kashimbeck disease is an endemic osteoarthropathy and is characterized by chronic osteoarthrosis affecting fingers, toes and long bones and is found in children aged between 5 and 12 years. It is a progressive disorder that results in deformity and growth retardation. These conditions are improved by administration of sodium selenite or selenomethionine.

Figure 4i.



Other synthetic selenium-containing compounds have been reported to be undergoing evaluation as potential pharmacological agents. Ebselen [2-phenyl-1,2-benzisoselenazol-3(2H)-one (PZ 51/ DR3305)] (*Figure* 4i), a seleno-organic compound, which was designed to mimic the enzymatic activity of glutathione peroxidase, also reacts with peroxynitrite and can inhibit enzymes such as lipoxygenases, NO synthases, NADPH oxidase,

protein kinase C and H^+/K^+-ATPase. Ebselen is one of the promising synthetic antioxidants and a potential chemopreventive agent in inflammation-associated carcinogenesis and is currently undergoing clinical testing for the inhibition of stroke. Unlike many inorganic and aliphatic selenium compounds, Ebselen has low toxicity as metabolism of the compound does not liberate the selenium moiety, which remains within the ring structure. Both selenazofurin (2-β-D-ribofuranosylselenazole-4-carboxamide, selenazole) (*Figure* 4j), as an antineoplastic and antiviral agent, and selenotifen, as an anti-allergic agent, are examples of pharmacologically active organoselenium compounds that offer significant advantages over their corresponding sulfur analogs.

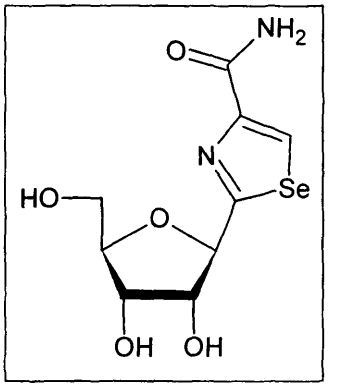
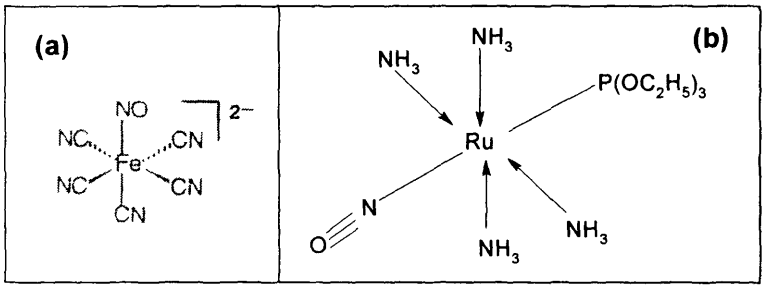


Figure 4j.

Cardiovascular Agents – Metal-Based NO Donors and Scavengers

NO is produced in the body and the physiological processes mediated by NO include neurotransmission, blood pressure regulation and immunological response. The low spin ferrous complex, sodium nitroprusside Na_2 $[Fe(CN)_5NO]$ $2H_2O$ (*Figure* 5a) is often employed for the treatment of hypertension to lower blood pressure in human subjects. The therapeutic effect of this compound depends on release of nitric oxide (NO), which relaxes muscles. It is activated by reduction *in vivo* to $[Fe(CN)_5NO]^{3-}$ in which an antibonding orbital becomes populated to facilitate the loss of NO. Ruthenium complexes exhibit both nitric oxide release and scavenging functions that can affect vasodilation. Structure of the ruthenium NO-releasing complex, *trans*-$[(NO)(P(OCH_2CH_3)(NH_3)_4Ru(II)]$ is shown in *Figure* 5b.

Figures 5a-b.



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On the other hand, overproduction of NO contributes to diseases such as sepsis, arthritis, diabetes and epilepsy. Effective scavengers of NO, such as K[Cl(EDTA)Ru(III)], may be useful in treating toxic shock syndrome by lowering the dangerously high level of NO in the bloodstream.

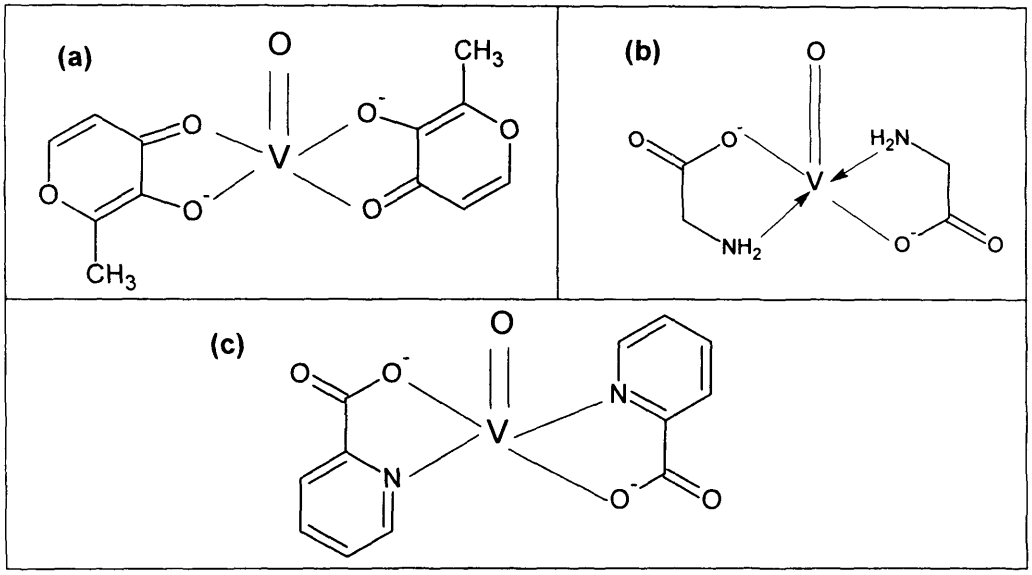
Insulin Mimetics

Vanadium supplementation has a potential role in maintaining blood glucose levels in diabetics. Bis (maltolato)-oxo-vanadium (IV) (BMOV, *Figure* 6a) has been marketed as a dietary supplement and is chelated form of vanadyl ion. In the solid-state complex, it has five coordinate square pyramid geometry with the oxo-ligand in the axial position and *trans* maltolato ligands. It is neutral, water-soluble and 2-3 times more potent than vandadyl sulphate $VOSO_4.H_2O$. Other vanadium compounds of promise are bis-(glycinato) oxovanadium (BGOV) (*Figure* 6b) and bis-(methylpicolinato) oxovanadium (IV) (*Figure* 6c). These compounds exert their action by regulating the cellular levels of tyrosine phosphorylation. In general, the vanadium insulin like behaviour seems to improve glucose management in insulin-dependent diabetes (Type I) while vanadium improves glucose tolerance and lower glucose levels in Type II diabetes.

Low-molecular weight chromium binding substance, a naturally occurring oligopeptide consisting of chromium (III), aspartic acid, glutamic acid, glycine and cysteine in 4:2:4:2:2 ratios activate insulin-dependent tyrosine protein kinase activity of insulin receptor.

Future Perspectives

There is enormous scope for the development of novel square planar gold (III) complexes for their antitumour activity as gold (III) is isoelectronic with platinum (II) and forms square planar complexes similar to that of cisplatin. Moreover, gold (III) also offers more synthetic variability. The understanding of the physiological processing of metal complexes, chemical mechanisms underlying cleavage of RNA and DNA targets and the



Figures 6a-c.

application of combinatorial chemistry may be helpful for the development of inorganic drugs. The coming years should be an exciting time for inorganic drugs.

Conclusion

Inorganic drugs have a major impact in modern medicine as these are used to diagnose a variety of diseases and conditions relating to cancer care, infection control, diabetic control, neurological, cardiovascular, anti-inflammatory diseases, ulcers-inhibition, and have promising therapeutic properties. Lithium carbonate is used for the treatment of manic-depressive disorders and germanium complexes act as antitumour agents. Gold (I) and gold (III) complexes, mononuclear and multinuclear platinum complexes show promise as antitumour agents while gold (I) complexes act as anti-rheumatic agents, and the possible mechanisms of therapeutic activity have been discussed. Selenium compounds show antioxidant, antineoplastic, anti-allergic and antiviral potential. Polyoxometallates show anti-HIV potential while vanadium compounds act as insulin mimetics. Ruthenium compounds with anticancer activity penetrate tumours through a transferrin-mediated process and bind to cellular DNA following intracellular activation by reduction.

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Errata

C P Navathe and S Nigam, *Resonance*, Vol.11, No.4, p.80-85, April 2006

Title

Understanding Vanishing Energy During Charging of Capacitor Level

should be read as

Understanding Vanishing Energy During Charging of Capacitor

Page 81, equation (2)

$$VC1 = \frac{VC_1}{C_1 + C_2} + \frac{VC_2}{C_1 + C_2} e^{\frac{-t}{RC}}$$

should be read as

$$V_{C_1} = \frac{VC_1}{C_1 + C_2} + \frac{VC_2}{C_1 + C_2} e^{\frac{-t}{RC}}$$

Page 81, equation (3)

$$VC2 = \frac{VC_1}{C_1 + C_2} - \frac{VC_1}{C_1 + C_2} e^{\frac{-t}{RC}}$$

should be read as

$$V_{C_2} = \frac{VC_1}{C_1 + C_2} - \frac{VC_1}{C_1 + C_2} e^{\frac{-t}{RC}}$$

Page 83, line 3

that $L \leq 0$

should be read as

that $L \neq 0$

Page 84, equation 12

$$E_{total}(t) = E_{C_1}(t) + EC2(t) + EL(t)$$

should be read as

$$E_{total}(t) = E_{C_1}(t) + E_{C_2}(t) + E_L(t)$$

Page 84, equation 12

$$= \frac{1}{2} C_1 [VC1(t)]^2 + \frac{1}{2} C_2 [VC2(t)]^2 + \frac{1}{2} L[i(t)]^2$$

should be read as

$$= \frac{1}{2} C_1 [V_{C_1}(t)]^2 + \frac{1}{2} C_2 [V_{C_2}(t)]^2 + \frac{1}{2} L[i(t)]^2$$

Page 84, Line 13

that $L \leq 0$

should be read as

that $L \neq 0$