Medicinal Uses of Inorganic Compounds – 2

B S Sekhon and Leena Gandhi

Left. B S Sekhon is currently Head of the Department of Biochemistry and Chemistry, Punjab Agricultural University, Ludhiana. His main research interests are in coordination chemistry and bioinorganic chemistry.

Right. Leena Gandhi is a PhD student in the Department of Biochemistry and Chemistry, Punjab Agricultural University, Ludhiana. Her main research interests are coordination complexes particularly of drugs with biologically important metal ions.

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In the first part of this article, we described medicinal uses of inorganic compounds relating to cancer care, infection and diabetic control, neurological, cardiovascular and inflammatory diseases. This article contains further information on the medicinal uses of inorganic compounds as therapeutic and diagnostic in chelation therapy, as antihypertensive and anti-ulcer agents, metal superoxide dismutase mimics, metal activation of organic drugs, radiopharmaceuticals, magnetic resonance imaging contrast agents and photodynamic therapy.

Chelation Therapy

In theory all metals whether 'nutritional' or not are toxic when in excess. Metals such as arsenic, lead, mercury, cadmium etc. which do not have a role in normal body function are toxic in any amount. Chelation may be used to deliver essential metals into and remove toxic metals from the body. Chelation therapy in medicine is generally regarded as using chelating agents to remove toxic heavy metals from the body. The chelating agent binds to the metal in the body's tissues, forming a chelate complex, which is then released to the bloodstream. The chelate is filtered out of the blood by the kidneys and excreted in the urine. The choice of chelating agent depends on which metal is involved. Common chelating agents and their uses are given in *Table* 1 .The structures of some chelates involving metal-chelating agent systems are shown in *Figures* 1a-e. While EDTA (ethylenediamine tetra-acetic acid) is a perfectly legitimate therapeutic for the removal of metal ions in heavy metal poisoning, it is as yet unproven as a treatment for atherosclerosis.

Anti-hypertensive and Anti-ulcer Agents

Antihypertensive agents are proposed to be substrates for

Compound / Structure of chelate	Uses
Desferrioxamine (Desferal®) (*Figure* 1a)	Treatment of iron-overload patients (from multiple transfusions) with thalassaemia
Eferiprone (1,2-dimethyl-3-hydroxypyrid-4-one) (*Figure* 1b)	Treatment of iron-overload patients (from multiple transfusions) with thalassaemia
Histidine	For the treatment of copper overload in Wilson's disease (an inherited disorder in which excessive amounts of copper accumulate in the body)
Copper-histidine chelate [Cu $(His)_2$] (*Figure* 1c)	To supplement copper deficiency (Copper is deficient in most tissues of Menkes disease patients)
Copper- 3,3-dimethylcysteine (*Figure* 1d)	In treatment of arsenic, mercury and lead, and other heavy metal poisoning. Also for the treatment of Wilson's disease, a genetic disorder in which the body tends to retain copper
Dimercaprol (2,3-dimercapto-1-propanol) (*Figure* 1e)	For removal of arsenic, mercury and antimony
Magnesium disodium EDTA	Treatment of cardiovascular disease
Calcium disodium versanate ($CaNa_2$-EDTA)	Treatment of lead toxicity
Calcium salt of diethylene triamine pentaacetic acid	To reduce the amount of plutonium retained in the human body
Metallothionein (a protein of low molecular mass, 6000 to 7000 Da, contains 30% cysteine)	Cadmium complexation in the liver binds 4-8 Cd and / or Hg atoms, (tetrahedrally coordinated by cysteine ligands)
Lanthanum carbonate (Fosrenol™)	Fosrenol binds to dietary phosphate in the stomach and reduces phosphate absorption

Table 1. Various chelating agents/compounds used in chelation therapy.

dopamine beta-monooxygenase (DBM). Phenyl-2- aminoethyl selenide (PAESe, *Figure* 2a-I) and 4-hydroxy-α-methyl-phenyl-2-aminoethyl selenide (*Figure* 2a-II) are excellent substrates for DBM and exhibit antihypertensive activity.

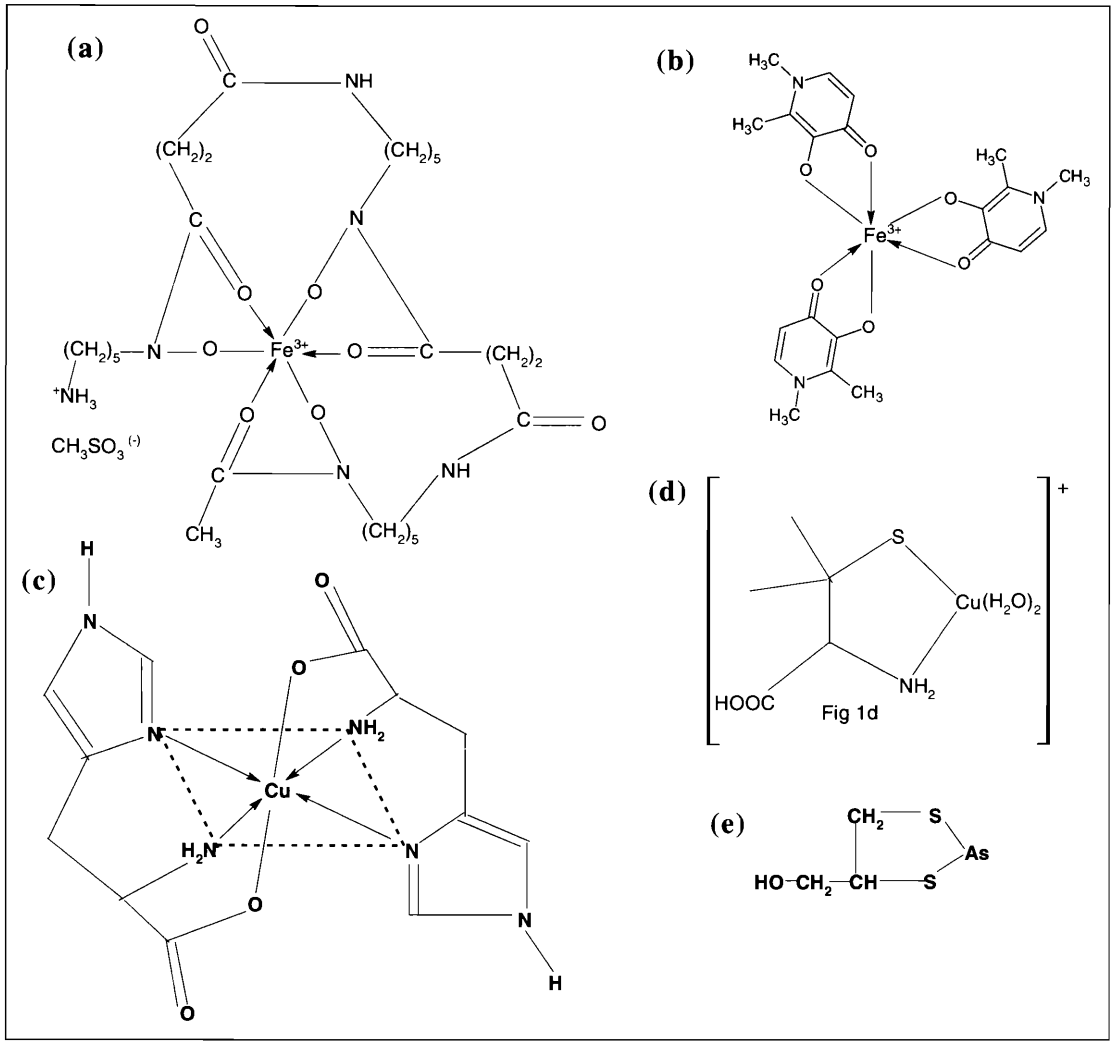


Figure 1(a)-(e).

Angiotensin converting enzyme (ACE) is a zinc metalloenzyme and is responsible for the hydrolysis of decapeptide angiotensin I to angiotensin II (octapeptide), and angiotensin II acts on blood vessels to make them narrow and cause hypertension. By blocking or inhibiting the action of ACE, the conversion to angiotensin II is interrupted and blood pressure is lowered. Copper complexes of organic ligands that act like ACE inhibitors and other examples are given in *Table* 2.

The amino terminal Cu(II)- and Ni(II)-binding (ATCUN, a short, three-residue) motif in proteins has been implicated in

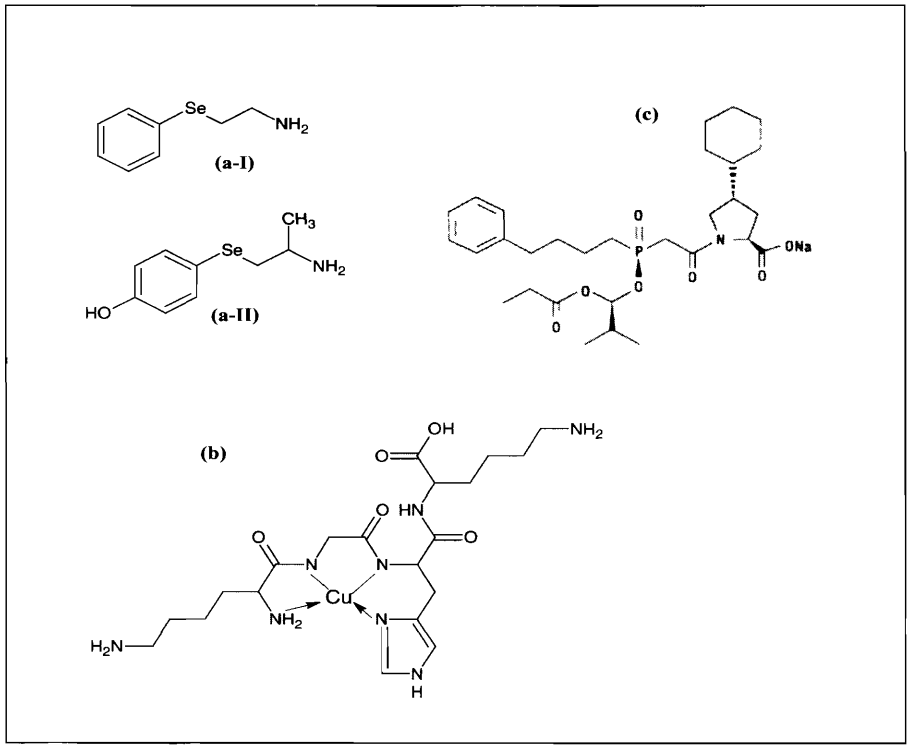


Figure 2.

DNA cleavage and has been shown to have antitumor activity. The copper complex [KGHK-Cu]$^+$ (peptide containing sequence KGHK (*Figure* 2c) demonstrates catalytic inactivation of human ACE at sub-saturating concentrations, under oxidative conditions.

Examples of anti-ulcer compounds are given in *Table* 2. After ingestion of colloidal bismuth subcitrate (CBS), the bismuth derivatives formed in the acid environment of the stomach bind strongly to the proteins in ulcerated tissue to form a protective layer which shields it from aggressive factors and allows it to heal.

Redox Chemistry in Medicine

(i) *Metal Superoxide Dismutase Mimics and Peroxynitrite Control*

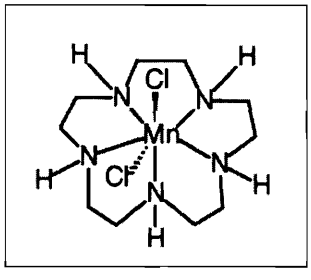
Superoxide dismutase (SOD) is an important antioxidant to

Compound	Uses
Phenyl-2-aminoethyl selenide (PAESe, *Figure* 2a-I)	Exhibits dose-dependent antihypertensive activity
4-Hydroxy-α-methyl-phenyl-2-aminoethyl selenide (*Figure* 2a-II)	Exhibits restricted central nervous system permeability and oral antihypertensive activity
Fosinopril sodium (*Figure* 2b) (ACE inhibitor)	Blood pressure lowering
Copper complex $[KGHK\text{-}Cu]^+$ (*Figure* 2c) (ACE inhibitor)	Blood pressure lowering
Colloidal bismuth subcitrate $[K_3 (NH_4)_2 [Bi_6O_3 (OH)_5 [HCit)_4]^-$	Treatment of upset stomach and prevention of ulcers
Sucralfate complex $C_{12}H_{14}O_{11}(SO_3Al(OH)_2)_8 \cdot (Al(OH)_3)_x \cdot (H_2O)_y$, where x is 8 to 10 and y is 22 to 31.	Treatment of upset stomach and prevention of ulcers

Table 2. Examples and uses of anti-hypertensive and anti-ulcer agents.

control the free radical reactions related to superoxide generated in biological system. However, its large molecule and short lifespan *in vivo* limit its clinical use. SOD mimics function as SOD to catalyze the dismutation of superoxide. Metal-dependent SOD mimics have several advantages. They are cheap low-molecular-weight-molecules, which can cross cell membrane easily. The SOD mimics are potential pharmaceutical agents for treatment of cardiovascular, inflammatory and neurological disorders. The free radical superoxide, $O_2^{-\cdot}$, reacts with nitric oxide, NO, to form damaging peroxynitrite, $ONOO^-$.

Figure 3.



Peroxynitrite readily reacts with transition metal centers in SOD and SOD mimics. Manganese and iron porphyrins have been shown to react catalytically with peroxynitrite ($ONOO^-$). Complex in *Figure* 3 inhibits coronary tissue injury and neutrophil accumulation into coronary tissue *in vivo*. The cobalt substituted-polyoxometalate $K_7[CoAlW_{11}O_{39}] \cdot 15H_2O$ and the simple $CoCl_2 \cdot 6H_2O$ are efficient catalysts for peroxynitrite decomposition and their activities are comparable to MnTMPyP.

(ii) *Metal Activation of Organic Drugs*

Bleomycin sulphate is used in combination chemotherapy for treatment of head and neck cancer. Bleomycin (BLM) is a DNA-cleaving glycopeptide antibiotic and a potent anticancer agent, which is activated by picking up its endogenous iron metal within the body. The cytotoxicity of bleomycin is believed to result from its ability to coordinate iron ion to form O_2 -Fe(II)-BLM complex which accepts an electron to form an active specie O_2^{2-}-Fe(III)-BLM which is believed to cleave DNA and RNA and ultimately destroy the cancer cell.

Radiopharmaceuticals

As diagnostics, radiopharmaceuticals are used to light up a particular tissue or an organ type in the body, for example, a tumor, the heart or the thyroid gland and help to assess the pathological state of the tissue. As therapeutics, they are used to destroy that tissue. Gamma emitters are preferred for diagnostics and alpha or beta emitters for radiation therapy. Radionuclide Technetium-99m (^{99m}Tc) is the radioisotope of choice. Cardiolite (*Figure* 4a) is used for myocardial perfusion imaging and Ceretec (*Figure* 4b) is used in the evaluation of stroke. The heart takes up ^{99m}T in these compounds and can be imaged.

Technetium-99m labelled glycoprotein IIb/IIIa receptor antagonist DMP444 that is expressed on activated platelets may help physician to locate a blood clot using a gamma radiation

Suggested Reading

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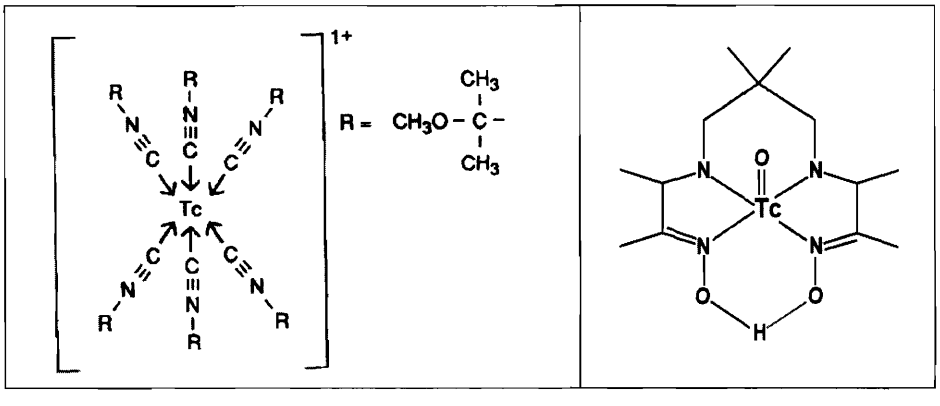

Figure 4a (left).
Figure 4b (right).

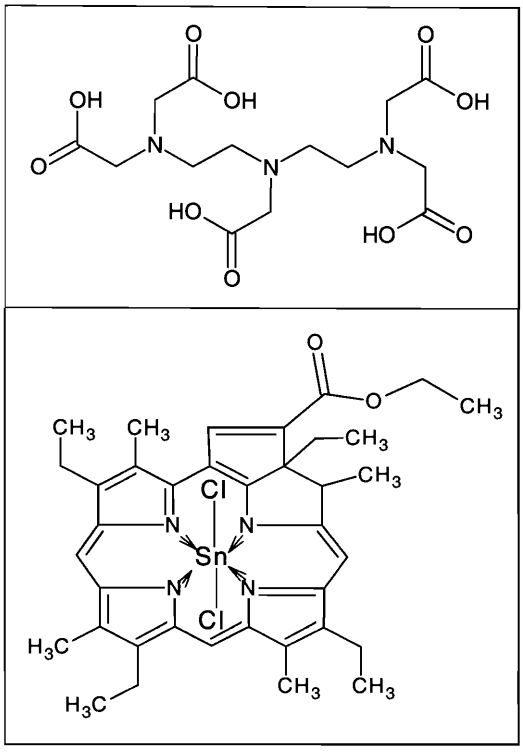

Figure 5 (top).
Figure 6 (bottom).

detecting camera. ^{131}I-Sodium iodide (α-particle emitter) is widely used for treatment of metastatic thyroid carcinoma and hyperthyroidism due to selective uptake of iodide by thyroid.

Magnetic Resonance Imaging Contrast Agents

MRI contrast agents are mostly inorganic compounds and common MRI contrast methods use approved Gd(III) or Mn(II) complexes with ligands shown in *Figure* 5 as potential imaging agents.

Photophysical Properties

Photodynamic therapy (PDT) is a method of cancer treatment involving the treatment of diseased tissues and cells with photo-sensitizers and visible light in an oxygen rich environment. Metal porphyrins (photosensitizers) absorb energy and transfer it to surrounding oxygen molecules. The singlet oxygen formed can damage proteins, lipids, nucleic acids and other cellular components, and thereby, destroys cancer cells. Tin(IV) porphyrin complexes as in *Figure* 6 and several lanthanide complexes are effective photosensitizers, which are promising in PDT of cancer treatment.

These drugs produce singlet oxygen following activation with 732 nm light.

Address for Correspondence
B S Sekhon
Department of Biochemistry
and Chemistry
Punjab Agricultural
University
Ludhiana 141 004, India.
Email:
sekhon224@yahoo.com

Future Perspective

The peptides labeled with different radionuclides (^{99m}Tc, ^{111}In , ^{123}I and ^{18}F) have potential as carriers for the delivery of radionuclides to tumors and infected tissues for diagnostic imaging and radiotherapy and may be the effective future tools as radiopharmaceuticals.