Inorganic Therapeutics: Metal based drugs

PG Third Semester

Bioinorganic Chemistry-V

Lecture 14 & 15

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Contents

- Inorganic therapeutics
- Chelate therapy
- Metal based drugs

Books/References used and suggested

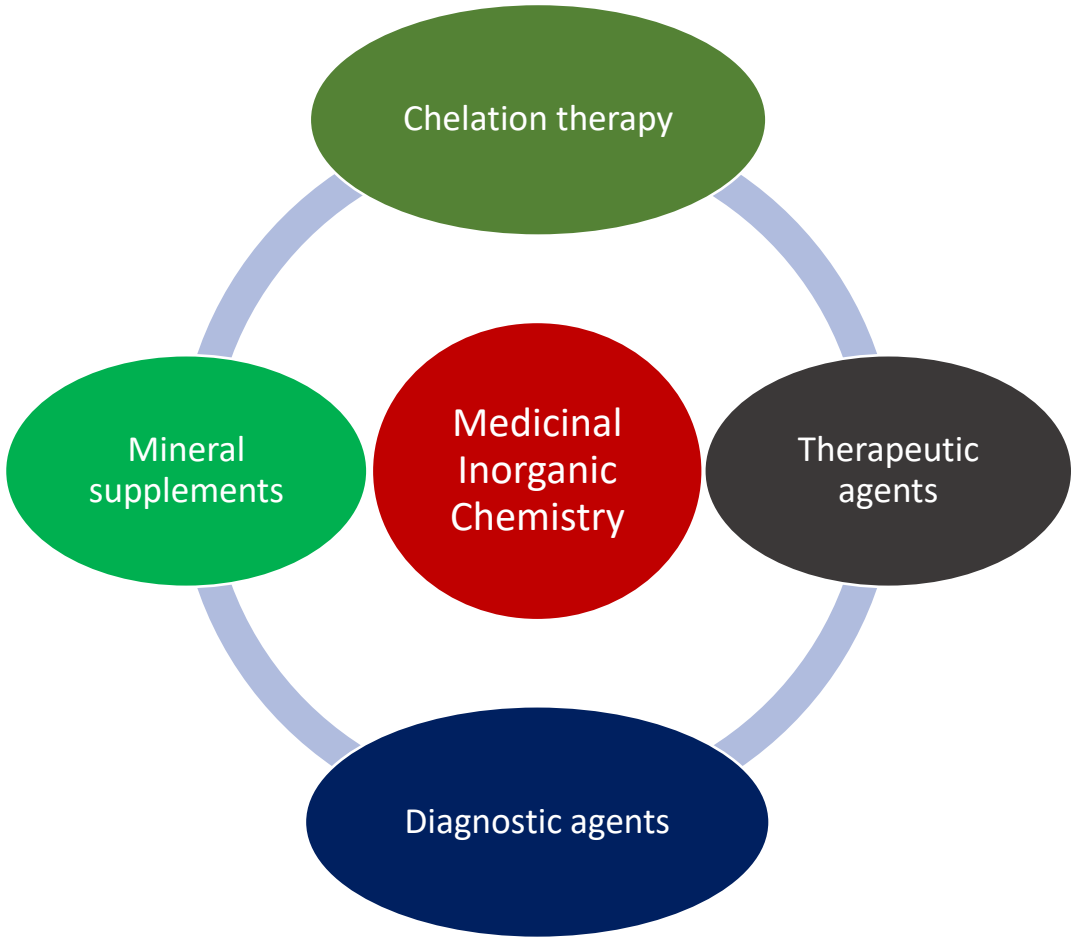
- Bioinorganic Chemistry by Bertini, Gray, Lippard and Valentine
- Inorganic Biochemistry by Cowan
- Bioinorganic Chemistry by A. K. Das
- Oxford Chemistry Primer by Fenton

History of Inorganic Medicinal Chemistry

- Medicinal inorganic chemistry is not a new discipline
- Cu was used to sterilize water in Egypt as far back as 3000 BC
- Chinese and Arabian were using Au in a number of medicines over 3,500 years ago.
- Hg_2Cl_2 was used as diuretic during the Renaissance period in Europe
- Paul Ehrlich (founder of chemotherapy) developed the arsenical-Salvarsan, as a drug in treatment of Syphilis in early twentieth century.
- Medicinal inorganic chemistry was kickstarted by the discovery of bacteriostatic and anticancer properties of Ru-polypyridyl complexes (F. Dwyer in 1950's) and strengthened by discovery of anticancer properties of Pt-ammine complexes (B. Rosenberg in 1969).

Chemistry of Inorganic elements in medicine

- Coordination compounds have been extensively used in the treatment, management and diagnosis of disease.
- Therapeutic chelating agents have been used to remove excess metals from body (metal detoxification).
- The ideal ligand (antidote) should be specific for toxic metal and non toxic itself and its complexes.
- The ligand should be selective and form highly stable complexes with toxic metal.
- The complexes should be water soluble, readily excretable and should not be metabolized.
- HSAB principle is important for selectivity in metal detoxification.
- The most important aspect is the identification of donor group.



Key areas of medicinal inorganic chemistry

Chelate Therapy

- Therapeutic chelating agents have been in use to remove excess metals ions from the body such as Wilson disease (Cu-excess), Fe-overload, toxic metals (Pb(II), Cd(II), Hg(II))
- Development of chelate therapy is based on

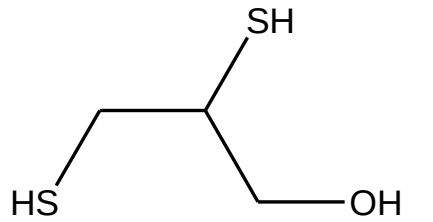
1. Determination of the site of action of the poison
2. Determination of donor group arrangement responsible for binding the metal (HSAB)
3. Synthesis of chelating agents having the same donor group arrangements
4. Chelate compounds can reverse the enzyme inhibition caused by the metal
5. Critical evaluation of the compound to assess its ability to perform efficiently in vivo.

- The ideal ligand should be specific for the toxic metal &, non toxic itself & as its complex.
- Chelating agent should form highly stable complex with the metal ion to be removed that are water soluble, & so readily excretable & it should not be metabolized

Chelating drugs with –SH groups

2,3-dimercapto-1-propanol (BAL)

- First used in the treatment of poisonous gas Lewisite ($ClCH=CHAsCl_2$) during world war II
- BAL can be used against As poisoning by complexation, excreted through urine.
- In acute Cu-poisoning and in Wilson's disease BAL used as antidote.
- Although Hg is soft, BAL cannot be used because their resulting complex is highly toxic.
- In case of As, the complex is unstable in aqueous solution with respect to aerial oxidation and local anaesthetic is required for intramuscular administration of BAL.
- Sometimes hypertension, vomiting and sweating are also observed on BAL administration
- The use of BAL is therefore questionable.



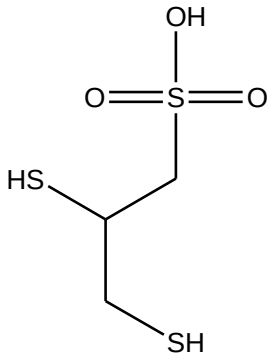
2,3-dimercapto-1-propanol

2,3-dimercapto-1-propan-sulfonic acid or Unithiol (DMPS)

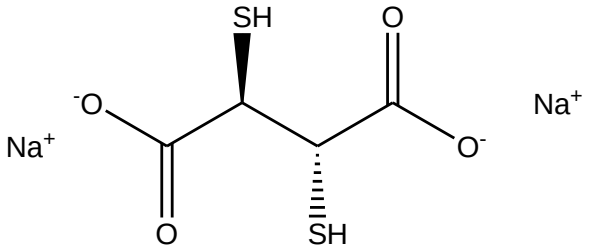
- DMPS is water soluble and has a number of clinical advantages over BAL.
- Due to its strong complexing power, high LD50 value (less toxicity) and water solubility, unithiol is used in the detoxification of metals like As, Hg, Tl etc.

Disodium meso-2,3-dimercaptosuccinate (DMSA)

- DMPS is also water soluble and can be given in drinking water.
- It is of low toxicity with LD50 value 30 times more than BAL.
- It can also detoxify As, Hg and many other soft metals under suitable conditions



2,3-dimercapto-1-propansulphonic acid

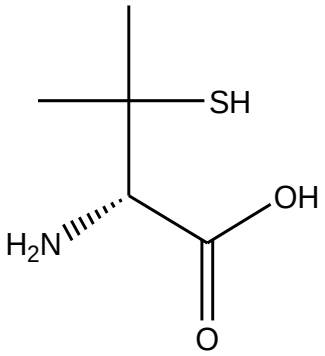


disodium meso-2,3-dimercaptosuccinate

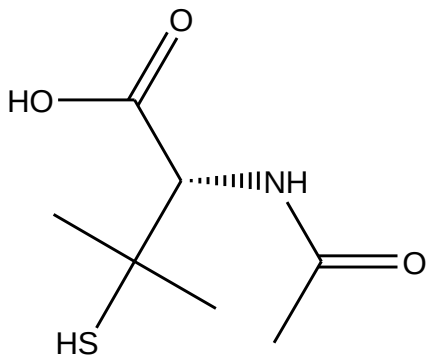
- DMSA and unithiol do not facilitate the entry of Hg(II) into brain (BAL complex is soluble in lipid and hence enters brain cell), but concentrate it in liver and kidney, making it available for excretion.

D-penicillamine (DPA - 3,3/-dimethyl cysteine) and N-acetyl- D-penicillamine (NAPA)

- D-penicillamine is therapeutically active but corresponding L isomer is toxic
- LD50 value is much higher than BAL and can be orally administered.
- DPA uses its S, N, O binding site to bind Hg(II), CH_3Hg(II), Cu(II), Au (I), Pb(II) etc.
- Possibility of depletion of essential elements like Zn and Cu are also there with DPA.
- In Wilson's disease, use of DPA is clinically recommended (intense purple coloured multinuclear complex linked through S and N atoms).
- DPA has also been used in the treatment of rheumatism and arthritis.
- In NAPA, presence of acetyl group makes it more lipophilic and also less toxic than DPA.
- Due to its lipophilicity, NAPA is used more effectively to detoxify CH_3Hg^+ from erythrocyte cells.



D-penicillamine



N-acetyl-D-penicillamine

Polyaminocarboxylic acid as chelating agent

- Polyaminocarboxylic acids (EDTA, CDTA, DTPA, puchel) are administered intravenously or intramuscularly as solution of their Ca-salts.
- Use of H_4EDTA is prohibited as they can form complexes with both toxic and essential metal ions (deplete serum calcium).
- Na_4EDTA salt is toxic and therefore mixed complexes Na_2CaEDTA is used to prevent rapid Ca depletion.
- Similarly to avoid depletion of Zn(II), Zn_2EDTA, Na_3ZnDTPA are used.
- In Pb(II) poisoning, Na_2CaEDTA is administered intravenously, Pb replaces Ca in the chelating agent and excreted via urine.
- EDTA complexes can also be used for removing Hg(II), Fe and other metals.
- Na_2CaEDTA can also detoxify Co and Cd poisoning.
- DTPA and its derivative puchel can be used for Pu detoxification.

Desferrioxamine (DFO) as chelating agent

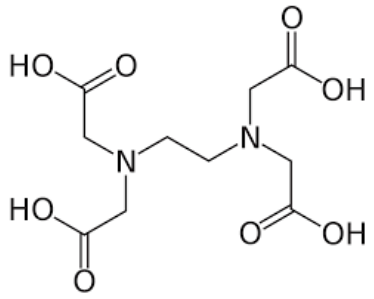
- Naturally occurring siderophores (desferrioxamine) with hydroxamic acid groups.
- Highly specific to reduce Fe toxicity
- Desferrioxamine B (desferal) injection is clinically well established to remove Fe load from the patients suffering from genetic disorders (Cooley's anaemia, thalassemia, hemosiderosis, hemochromatosis etc.)
- Desferrioxamine is poorly absorbed and may lead to allergic and skin reactions, neurological and renal effects.
- 1,2-dimethyl-3-hydroxypyridine-4-one (L1, promising, rapidly absorbed and commercially cheaper) is under clinical trial.
- Can be useful for treating Fe and Al overload. However, is associated with some side effects like gastric, joint pain and even Zn depletion

Aurintricarboxylic acid as chelating agent

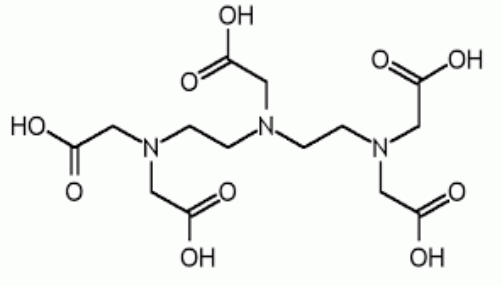
- Be poisoning is common amongst workers in the light alloy industries.
- Aurintricarboxylic (aluminon) is recommended to treat excess Be.

Chelating antidotes for metal detoxification

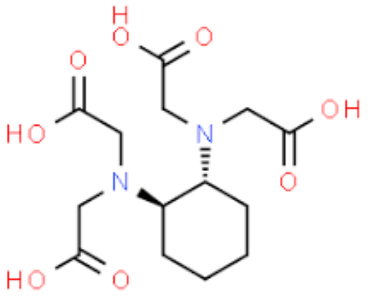
Metal	Chelating agent	Metal	Chelating agent
Al	DFO, L1	Cu	DPA, DMSA, DMPS, trien
Sb	DMSA, DMPS	Au	DMSA, DMPS
As	DMSA, DMPS, BAL, DPA	Fe	DFO, L1
Be	Aluminon	Pb	$Na_2CaEDTA$, DPA, BAL, DMSA
Bi	DMSA, DMPS	Mn	$Na_2CaEDTA$, $Na_2Ca(DTPA)$
Cd	$Na_3Ca(DTPA)$	Hg	DPA, NAPA, DMSA, DMPS
Ni	$Na_2CaEDTA$, DTCA	Pt	DTCA, DMSA



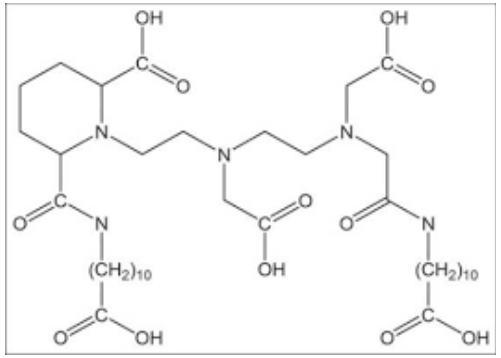
EDTA



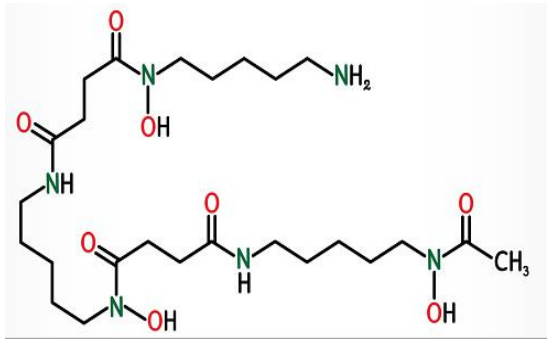
DTPA



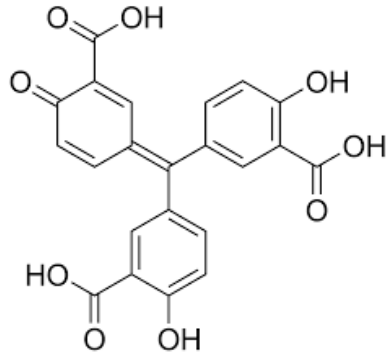
CDTA



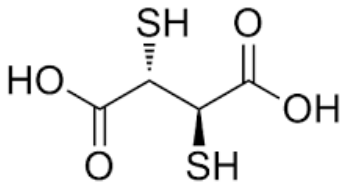
Puchel



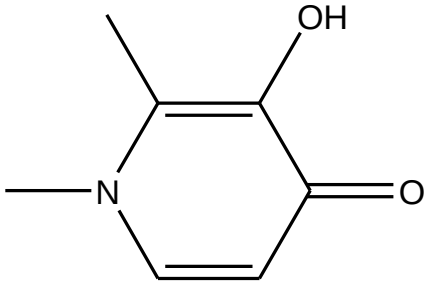
Desferrioxamine B



Aluminon

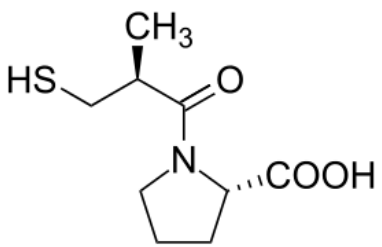


Succimer (DMSA)

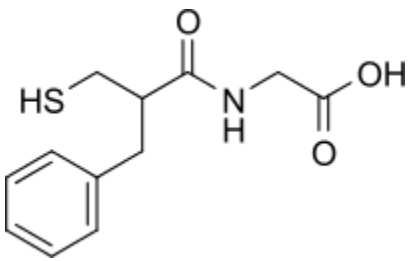


1,2-dimethyl-3-hydroxypyridine-4-one

- Ligands may also be used to target metalloenzyme and inhibit their undesirable activity which appear at the root of many physiological disorder.
- Zn-enzyme (Angiotensin converting enzyme) may catalyse the cleavage of decapeptide to octapeptide, raises blood pressure (hypertension). This may be controlled by EDTA or captopril, controls hypertension by binding with Zn.
- Thiorphan binds to Zn and deactivate the enzyme enkephalinases, and thereby reduces and controls the pain thereby acting as analgesic.



Captopril



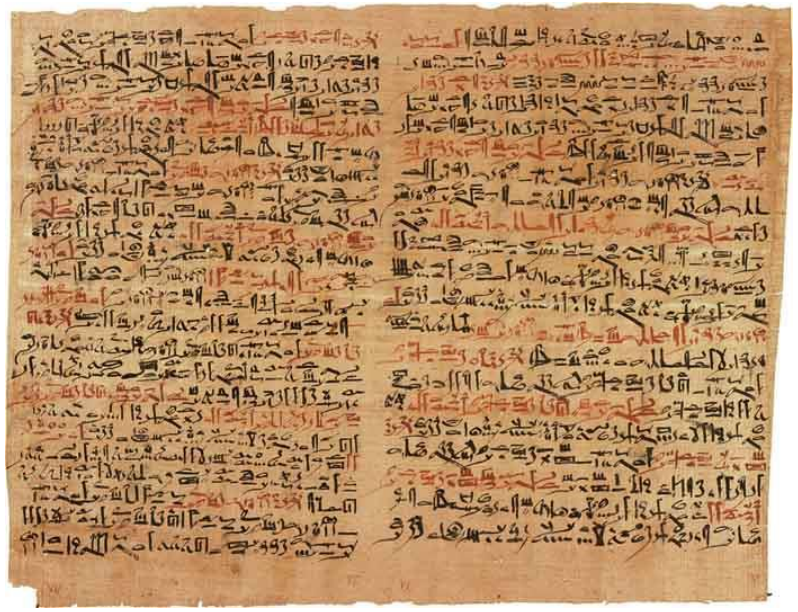
Thiorphan

Limitations of chelate therapy

- Chelating ligands more often or not produce undesirable symptoms like diarrhoea, skin rashes, vomiting tendency, irritations etc.
- It increases the concentration of toxic metal ions in kidneys, impairs kidney function
- Prolong chelation therapy may induce loss of essential trace metal ions
- In pregnancy, chelating agents may harm the embryo (congenital malformation)
- Sometimes chelating drug may induce undesirable translocation of metal complexes to enhance toxicity.

Metal in medical treatment

- Metals have been used in treatments since ancient times.
- The Ebers Papyrus from 1500BC is the first written account of the use of metals for treatment and describes the use of Cu to reduce inflammation and the use of Fe to treat anemia.
- The application of metals to medicine is a rapidly developing field and novel therapeutic and diagnostic metal complexes are now having an impact on medical practice.



Examples of metal-based drugs

Metal	Product name	Active compound	Medical usage
Li	Camcolit	Li_2CO_3	manic depression
Mg	Magnesia	MgO	laxative
Fe	Fenelmin	$Na_4Fe(II)(citrate)$	anemia
Co	Cobaltamin S	Vitamin B_{12}	supplement
Zn	Calamine	ZnO	skin ointment
Ba	Baridol	$BaSO_4$	X-ray contrast medium
Pt	Cisplatin	cis-$[Pt(NH_3)_2Cl_2]$	anticancer
Au	Auranofin	$Au(I)(PEt_3)$ (acetylthioglucose)	rheumatoid arthritis
Bi	De-Nol	$K_3[Bi(III)(citrate)_2]$	antiulcer

Metals/compounds with medicinal applications

Metal	Applications
Lithium	Treatment of bipolar disorders
Magnesium	Laxative, antacid, dietary supplement
Aluminium	Adjuvant, antacid, treatment of hyperphosphatemia and peptic ulcer disease
Calcium	Antacid
Chromium	Dietary (trace mineral) supplement
Manganese	MRI contrast agent
Iron	MRI contrast agent, dietary supplement
Cobalt	Treatment and diagnosis of pernicious anemia, dietary supplement
Nickel	Dietary (trace mineral) supplement
Copper	Treatment for Menke's disease, 64Cu PET - radio-imaging, intrauterine contraception
Zinc	Treatment of eczema, dietary supplement

Metals/compounds with medicinal applications continued

Metal	Applications
Gallium	67Ga - SPECT radio-imaging, 66/68Ga - PET radio-imaging
Arsenic	Treatment of leukemia
Selenium	Dietary (trace mineral) supplement
Rubidium	82Rb - PET radio-imaging
Strontium	Osteoporosis
Yttrium	90Y - therapeutic radionuclide, 86Y - PET radio
Zirconium	89Zr - PET radio-imaging
Molybdenum	Treatment for Wilson's
Technetium	99mTc - SPECT radio-imaging
Silver	Antimicrobial, Treatment of burns
Barium	Radiographic contrast medium

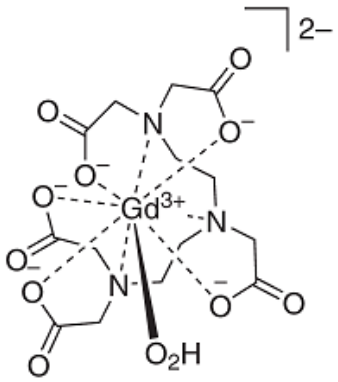
Metals/compounds with medicinal applications continued

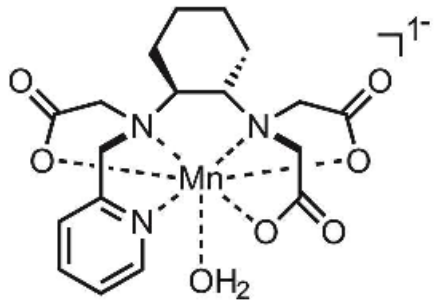
Metal	Applications
Lanthanum	Treatment of hyperphosphatemia
Cerium	Treatment of burns
Samarium	153Sm - therapeutic radionuclide
Gadolinium	MRI Contrast agent
Rhenium	188Re - therapeutic radionuclide
Gold	Antiarthritic
Bismuth	treatment of Antibacterial gastrointestinal

Metal and metal compounds in diagnosis

- Co-ordination complexes or specific metals has been in use in imaging ($BaSO_4$ in imaging gastro intestinal tract.
- Techniques like ultrasonography, computerized Tomography (CT) and magnetic resonance imaging (MRI) also involve different metal or metal compounds.
- B-10 isotope may be used in detecting tumour (neutron capture therapy).
- Metal compounds with radioactive nuclei (selective and should not damage the tissues) is extensively used for investigations like tumours, organs and other tissues.
- Some common nuclei that are used in diagnosis are Co-57, Ga-57, Tc-99 (most suitable), In-111, In-113, I-123, Yb-169, Hg-197, Tl-201 etc.
- The species $[Tc(CNR)_6]^+$ where R = t-butyl, CH_2COOBu^+ is used in hard imaging phosphonate. Tc-methylene diphosphonate complex is used in imaging bone malformities.

- MRI is based on NMR spectroscopy (paramagnetic metal ion changes the water-proton relaxation time around the tissue – distribution of metal ion in normal and abnormal tissue is different – provide means for diagnosis).
- Mn(II), Fe(III) and Gd(III) ions have been known to produce good proton relaxation enhancement in human. $[Gd(DTPA)(H_2O)]^{2-}$ has been successfully used in diagnosis of brain tumours. DTPA-diethylenetriamine pentaacetate ion.





$[Gd(DTPA)(H_2O)]^{2-}$

Co-ordination compounds as drug

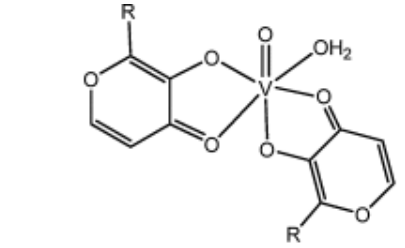
- Coordination compounds are extensively used as therapeutic agent (Au-arthritis, Cu-rheumatism and anti-inflammatories, Pt-anticancer agent).
- Efficiency of many organic drugs are also enhanced through metal binding (ibuprofen is more effective as its Zn-complex, anticancer drug bleomycin is activated as Fe(II) complex).

Lithium compounds as medicine

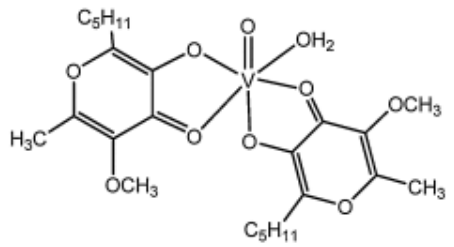
- Lithium carbonate is widely used in the treatment and prevention of manic depression (Li(II)).
- In the manic stage, neuronal communication becomes high. Lithium ion possibly binds to inositol phosphates reducing their degradation to inositol and thereby suppress neuronal communication.
- Lithium ion may also disturb neuro transmission by inhibiting the formation of the key signalling molecule adenosine monophosphate (AMP).

Vanadium compounds as medicine

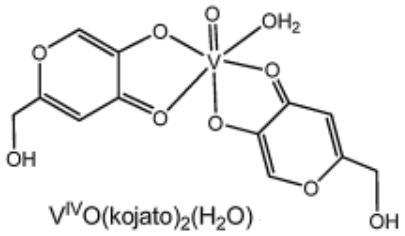
- V(IV) compounds have been reported to exhibit insulin like properties (toxicity prevents their use).
- (Dipicolinato) oxovanadate (V), $[VO_2dipic]^-$ is less toxic (adsorbed in acidic environment of stomach and intestine) is used orally in animals.
- Some Vanadium compound also known to have anticancer activity.



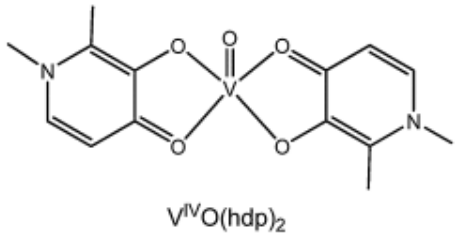
BMOV: R = CH_3 = $V^{IV}O(maltolato)_2(H_2O)$
BEOV: R = C_2H_5 = $V^{IV}O(ethylmaltolato)_2(H_2O)$



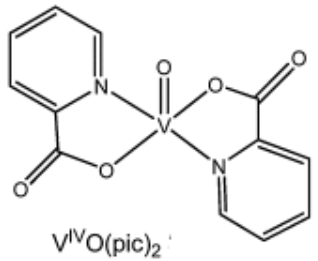
$V^{IV}O(allixinato)_2(H_2O)$ = $VO(alx)_2$



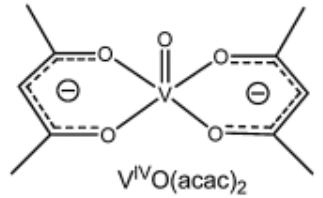
$V^{IV}O(kojato)_2(H_2O)$



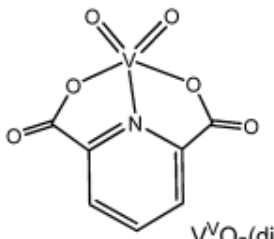
$V^{IV}O(hdp)_2$



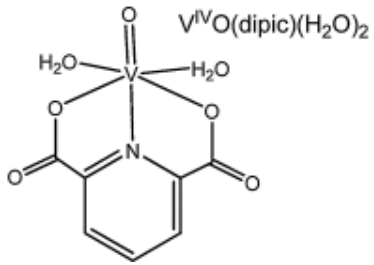
$V^{IV}O(pic)_2$



$V^{IV}O(acac)_2$



$V^{V}O_2(dipic)^-$



$V^{IV}O(dipic)(H_2O)_2$

Gold compounds in medicine

- Use of Gold in medicine (chrysotherapy) was initiated in 1929 by French physician Forestier.
- He used Au(I)thiolates for the treatment of rheumatoid arthritis.
- Up to 2% of the global population (120 million) are affected by rheumatoid arthritis (RA),

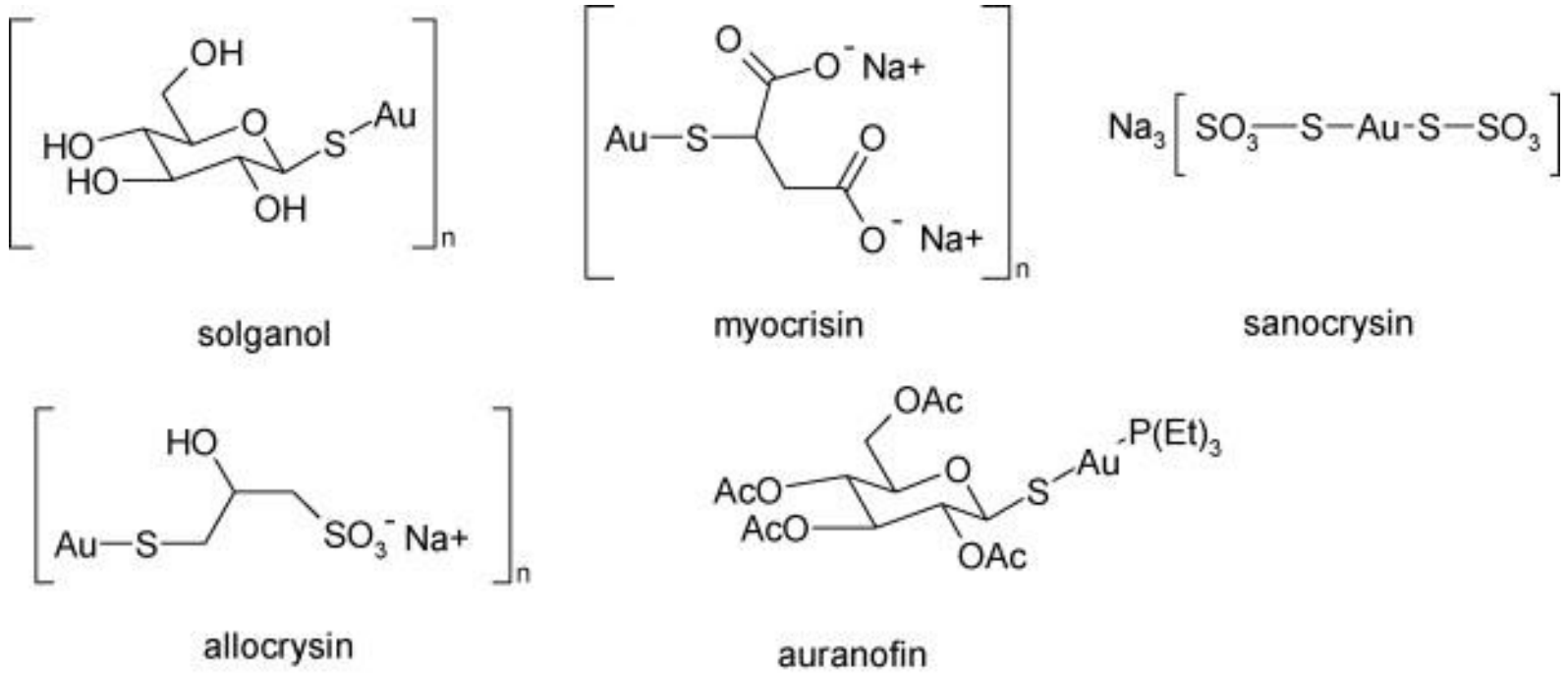
  - An inflammatory condition.

  - Progressive destruction of the articular cartilage lining the bone surfaces in joints.

  - Tissue damage results from action of lysosomal enzymes including collagenase and other proteases.

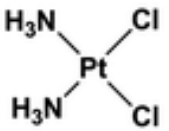
- Number of gold(I) thiolate drugs including sodium aurothiomalate (Myocrisin), aurothioglucose (Solganol), sodium aurothiopropanolsulfate (Allochrysine) and sodium aurothiosulfate (Sanochrysin).
- Myochrisin (sodium aurothiomalate), solganol (aurothioglucose) are now used as intramuscular injection curing arthritis.
- Auranofin is administered orally, binds to –SH and S-S units of proteins (blood serum albumin) – prolonged treatment is necessary.

- All of the clinically used gold(I) drugs have linear two coordinate geometry.
- The intramuscular administered drugs are oligomeric/polymeric in nature consisting of bridging thiolates between gold(I) ions (e.g., myocrisin)
- Auranofin, some Au-thiolate and Au-NHC drugs are also used as anticancer agents.

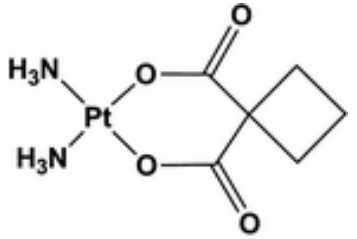


Platinum-based anticancer drug

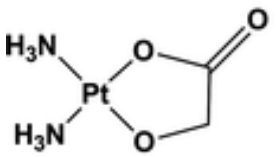
- cis-diamminedichloroplatinum (II) (cis-DDP or cis platin) is the best known example.
- It is an effective antitumor agent causing regression of both slow and fast moving tumours and also inhibitor of DNA synthesis.
- Effective against testicular cancer and active against ovarian, lung, bladder, neck and cervical cancers.
- It is administered as intravenous injection, usually given physiological saline electrolyte.
- But associated with kidney problem, nausea, vomiting as adverse side effect.



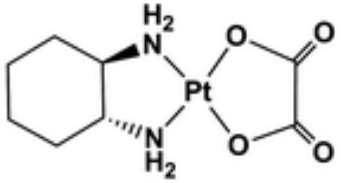
cisplatin



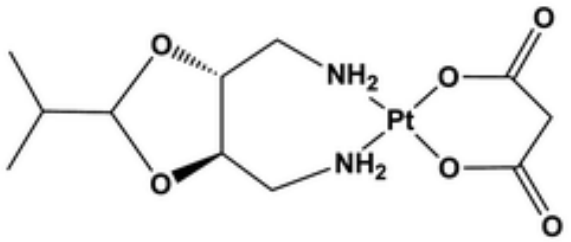
carboplatin



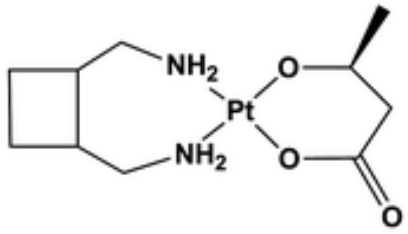
nedaplatin



oxaliplatin



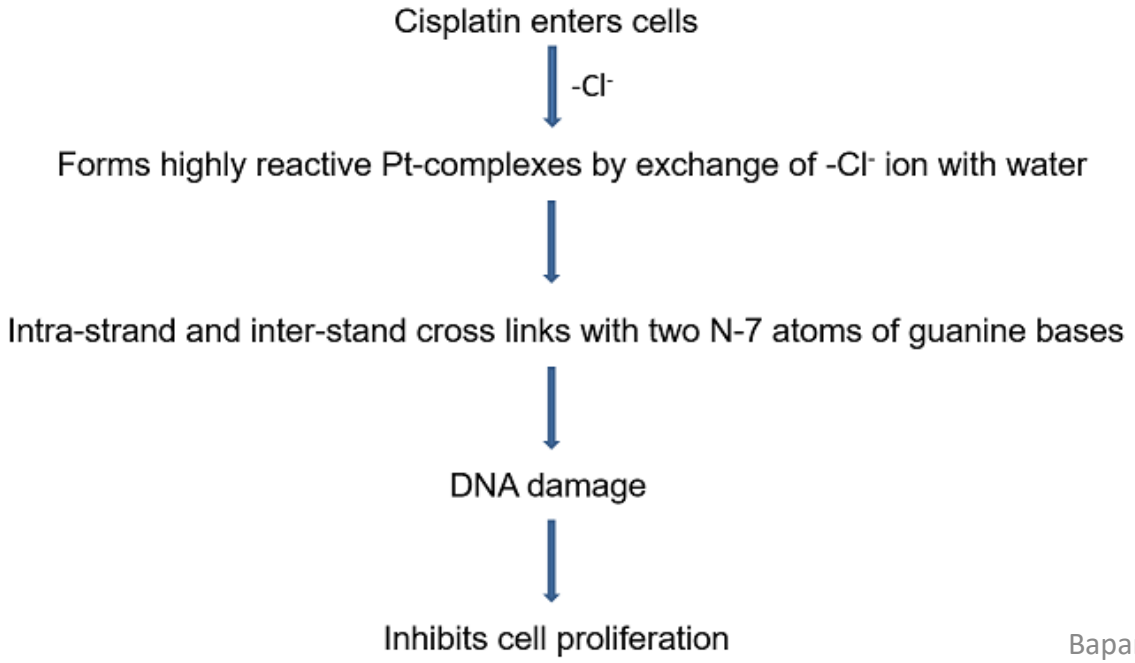
heptaplatin

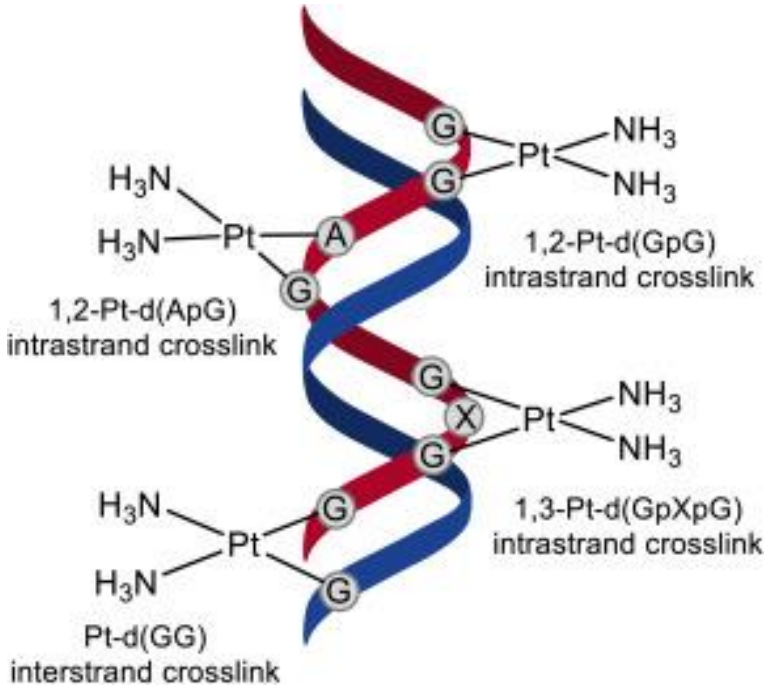


lobaplatin

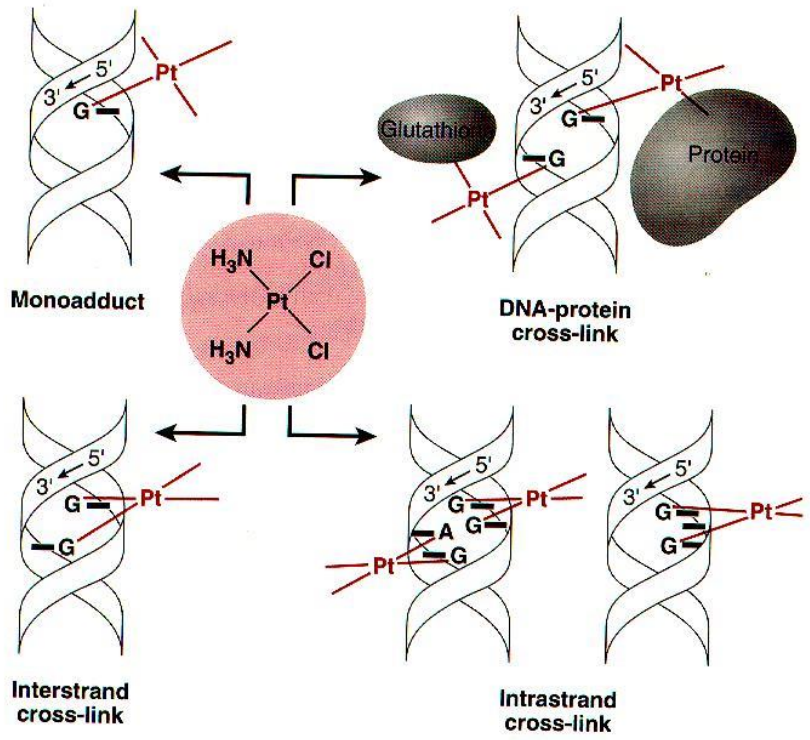
Mechanism

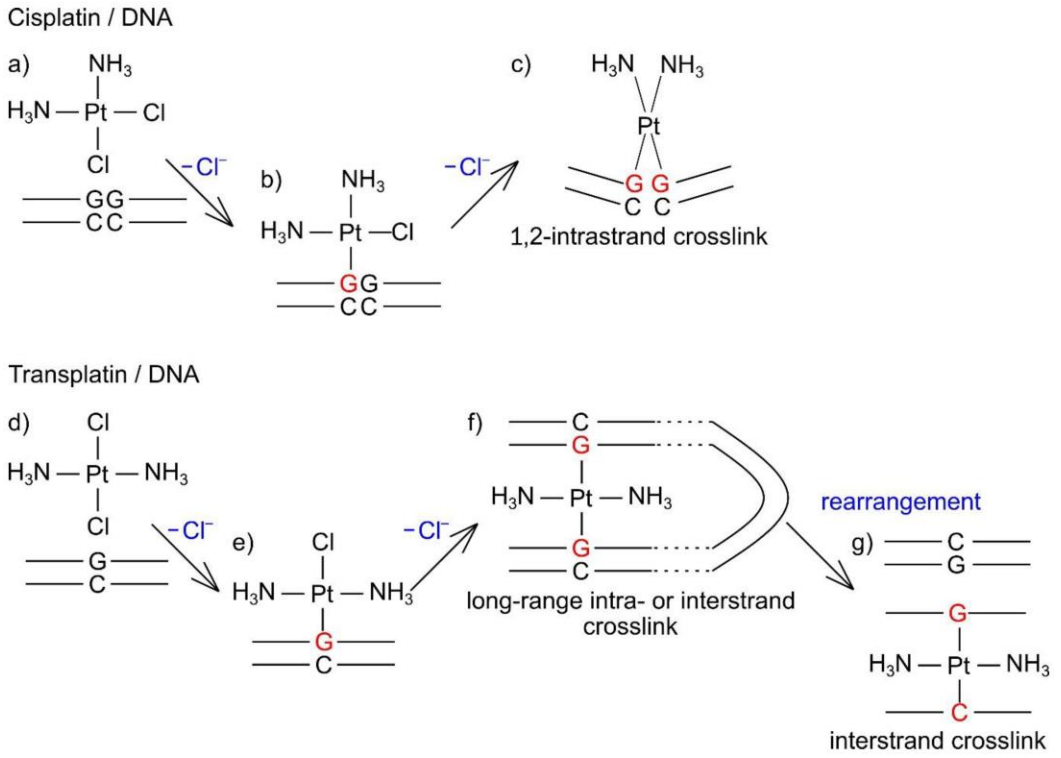
- Extracellular fluids have high Cl^- concentration and therefore hydrolysis of cis platin is suppressed.
- Inside the cell, the Cl^- concentration is low and hence cis platin hydrolyses to (exchange of Cl^- by water) diaqua complex $[Pt(NH_3)_2(OH_2)_2]^{2+}$, which reacts with the N-atoms (N-7) of the guanine (major) and adenine (lesser extent) bases, to produce either intra- (more important) or inter- stand cis-$Pt(NH_3)_2$ bridges viz. dinucleotide complex $[Pt(NH_3)_2\{d(pGpG)\}]$ with adjacent guanine bases.
- The result is a kink in the DNA helix, with angles upto 34^o (prohibits self replication).





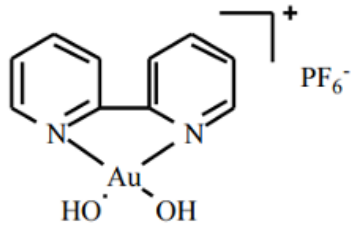
- The interaction of cis-platin would interfere with the process of DNA replication and thereby synthesis of messenger RNA by prohibiting the base pairing (DNA perturbation).
- The isomer, trans-platin has no such activity. It cannot form crosslink between adjacent guanine bases within the same strand (intra-strand bridge) due to steric reasons. It is labile and undergoes rapid, non specific nucleophilic substitution before reaching the target.



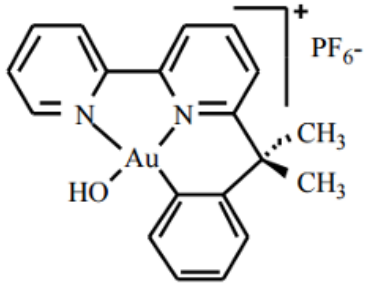


Non platinum anticancer drug

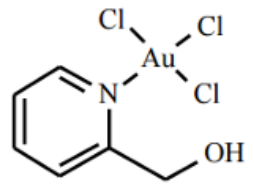
- The primary goal is to find Pt-resistance anticancer or antitumor drug.
- The secondary goal is that activity of non platinum antitumor drug should be associated with severe toxicity like Pt-drugs.
- The different toxicity may be attributed to their different co-ordination geometry, binding preference, ligand exchange rates and hence different mechanism of action and different biological properties.
- Radiometals aside, arsenic is the only other metal whose compounds are approved for the treatment of cancer. A crude solution of As_2O_3 and trace amounts of mercury, as a potential treatment for acute promyelocytic leukemia.



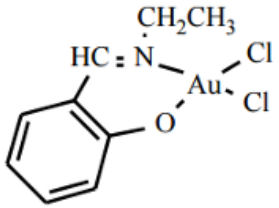
[Au(bipy)(OH)$_2$][PF$_6$]



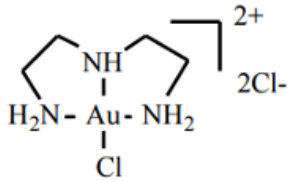
[Au(bipy-H)(OH)](PF$_6$)



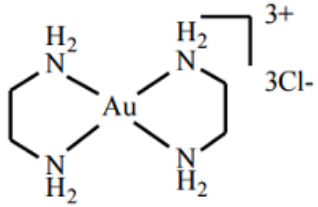
AuCl$_3$(Hpm)



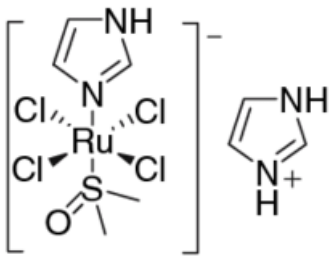
AuCl$_2$(esal)



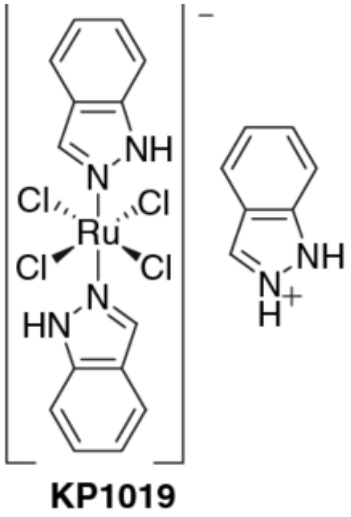
[AuCl(dien)]Cl$_2$



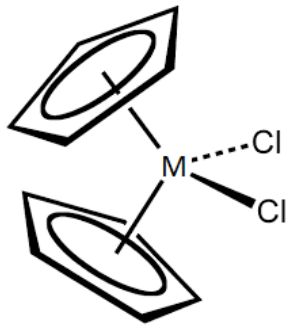
Au(en)$_2$]Cl$_3$



NAMI-A



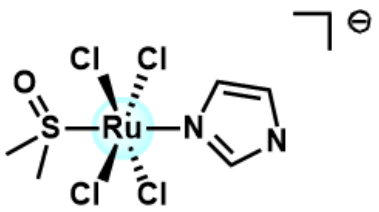
KP1019



M = Ti (Cl may be Br), V, Mo, Nb

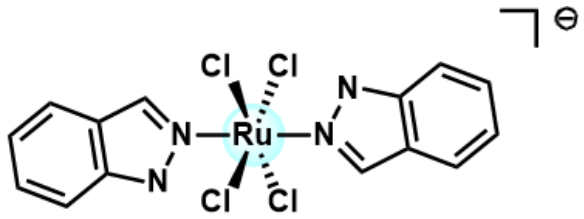
Ru-based drugs

- In recent years, ruthenium-based molecules have emerged as promising antitumor and antimetastatic agents.
- Ruthenium compounds are usually less toxic and no cross resistant than platinum counterparts, therefore better tolerated *in vivo*.
- In animal models, ruthenium compounds are effective in the treatment of cancer types which cannot be treated by platinum compounds, most probably due to a different mode of action.



NAMI-A

- **NAMI-A** and **KP1019** are two potential ruthenium drugs in phase II clinical trials.
- Former strongly inhibits metastasis without effects on the primary tumor & latter induces apoptosis in colorectal tumor in which cisplatin is inactive, via intrinsic mitochondria apoptosis pathway.



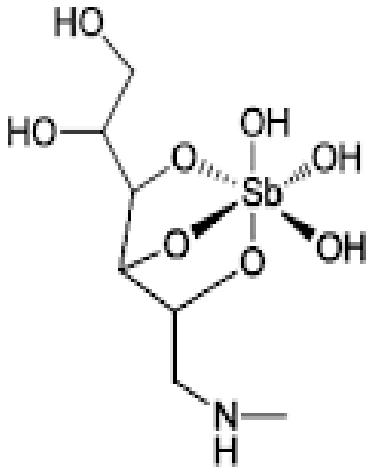
KP1019

Anti-infective – Ag as medicine

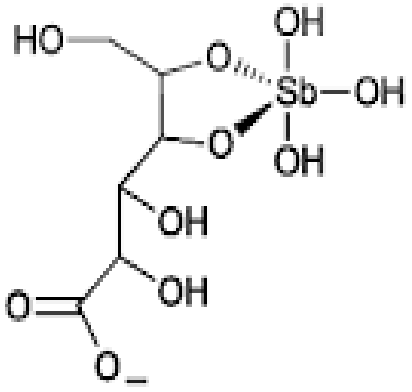
- Ag is commonly used in the treatment for burns and wounds, venereal diseases, abscesses, removal of granulation tissue and newborn conjunctivitis, the majority of which rely on the antibacterial action of Ag(I) ions.
- A dilute preparation of $AgNO_3$ (0.5%) (1960s) was used in treatment for burns based on its anti-bacterial action against a range of pathogens such as *S. aureus.*
- Silver sulfadiazine cream (Silvadene, Silvazine 1970s), containing 1% Ag(I) and a sulfonamide antibacterial drug, came into use as a broad spectrum antibacterial agent for burns treatment.
- $AgNO_3$ is widely used for cauterization in the treatment of epistaxis (nose bleed) in children and is the recommended first line medical treatment for cauterization of cutaneous pyogenic granulomas.
- AgNP wound dressing for use on burns and ulcers.
- AgNP impregnated polyurethane ventricular catheter for neurosurgical use

Antimony Agents

- Sb was first used to treat leishmaniasis in Brazil in the form of Tartar 65 Emetic (Potassium antimony tartrate)
- The drug which contained Sb(III) increased survival rates despite its toxicity and later succeeded less toxic Sb(V) drugs with improved therapeutic and toxicity profiles such as stibamine, stibosan and neostibosan in 1920s
- Sb(III) targets Zn-finger binding domains responsible for regulatory functions like DNA recognition, RNA packaging, protein folding and assembly, transcriptional activation, cell differentiation, growth and apoptosis.



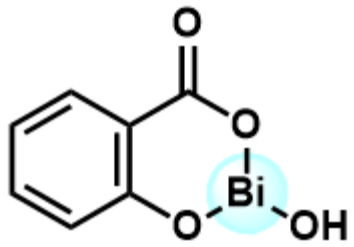
Meglumine antimoniate



Sodium stibogluconate

Bi-based drugs

- Bismuth is a highly acidic metal ion and may allow it to block Ca^{2+} channels and to disrupt the cell walls of bacteria.
- These are also active against the bacterium *Helicobacter pylori* which is associated with the mucus layer of ulcers and cancers
- Bismuth drugs are used to treat occasional upset stomach, heartburn, and nausea. It is also used to treat diarrhea
- **Bismuth subsalicylate** is a drug used to treat temporary discomforts of the stomach and gastrointestinal tract. Commonly known as pink bismuth, it is the active ingredient in popular medications such as Pepto-Bismol



Bismuth subsalicylate

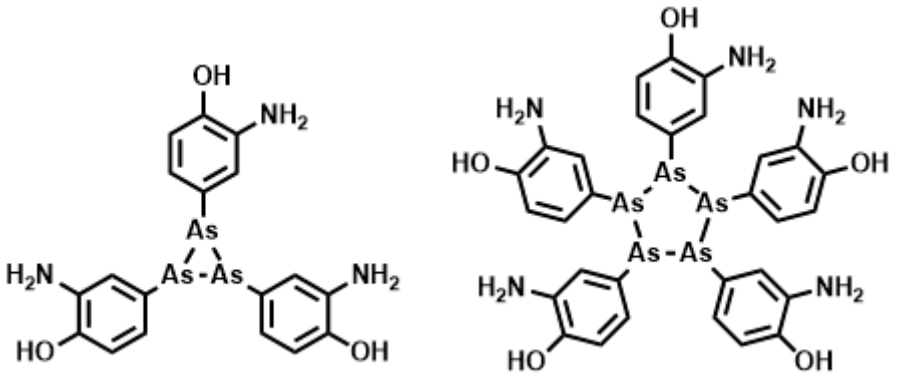
Al-based drugs

- In addition to Bi, Al-compounds play a role as adjunctive treatments for H. Pylori infection given its association with treatments for peptic ulcer disease.
- Al containing drugs, as antacids, antisecretory medication and mucosal protecting agents, are therefore known to help manage acute and chronic gastroduodenal ulcerations and contribute to ulcer healing.
- $Al(OH)_3$ containing antacids for example are known to adsorb heat shock proteins, cytotoxin VacA and urease, all of which are implicated in H. pylori associated ulceration.

As-based drugs

Salvarsan

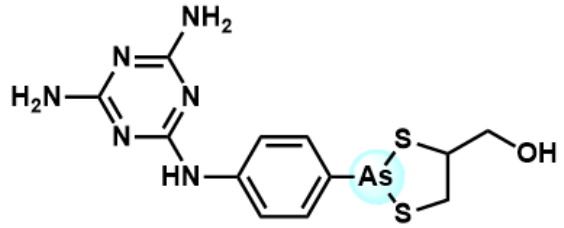
- **Salvarsan,** the first chemotherapeutic compound introduced in 1910 as the effective treatment for syphilis.
- Risk of side effects, used until 1943 when penicillin became available.



Trimer-pentamer mixture

Melarsoprol

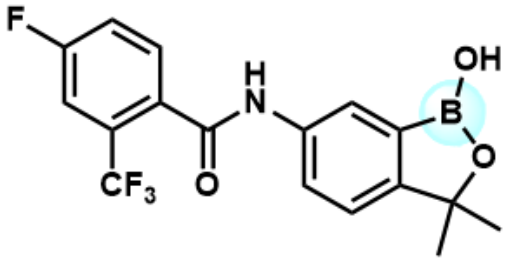
- **Melarsoprol** is widely used in the treatment of late-stage human African trypanosomiasis (sleeping sickness, a parasitic disease).
- 48,000 people died of it in 2008
- Melarsoprol is toxic to humans, causing severe brain disease in some cases.



Melarsoprol
(Injection drug)

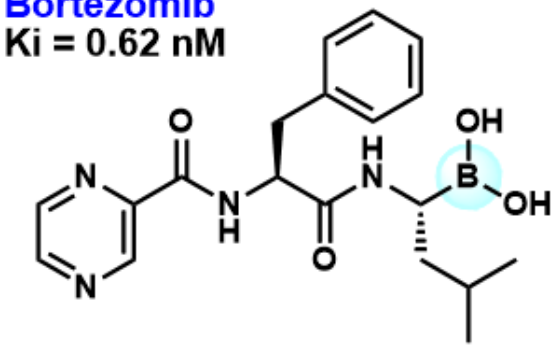
B-based drugs

- Boric acid has antiseptic, antifungal and antiviral properties and for this reasons is applied as a water clarifier in swimming pool water treatment and eye antiseptics.
- Benzoxaboroles were developed by Anacor as oral treatment for human African trypanosomiasis (sleeping sickness). SCYX-7158 was shown to be safe and exhibited excellent *in vivo* PK and *in vivo* efficacy
- **Bortezomib** is the first-in-class proteasome inhibitor for the treatment of multiple myeloma (a plasma cell cancer) approved in the US in 2003.



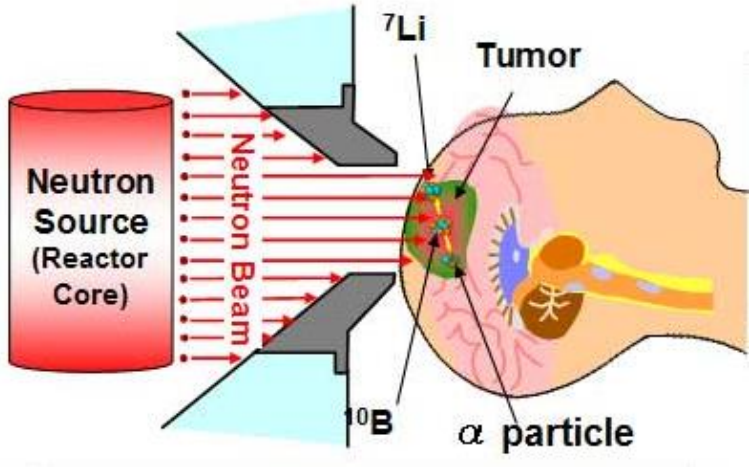
SCYX-7158
(Phase I)

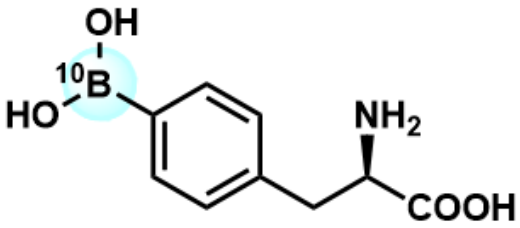
Bortezomib
Ki = 0.62 nM



Boron neutron capture therapy (BNCT)

- **BNCT** is a combination of treatment with boron and low energy neutrons. Radiotherapy using neutrons can get rid of glioblastoma cells.
- The boron molecules give off radiation within the brain tumor cells when the external neutron radiation hits them.





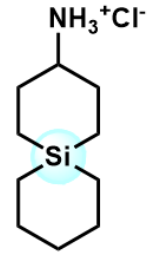
p-Boronphenylalanine

1. ^{10}B compound which accumulates in the cancer cell is injected in a patient
2. The neutron beam is irradiated to the lesion
3. The cancer cells are selectively destroyed using a-particles which are generated by the ^{10}B

Si-based drugs

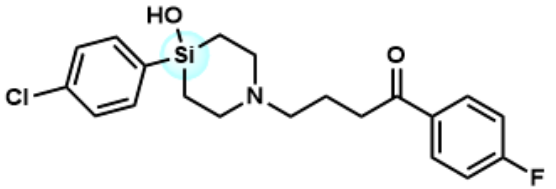
- Silicones (silicon containing polymers) are used in the applications requiring high biocompatibility such as bandages, breast implants and contact lenses.

- In the influenza A virus M2 proton channel inhibitor, hydrophobicity is known to play a critical role in improving the antiviral potency. The larger size and increased lipophilicity of silicon can provide a better hydrophobic contact between the inhibitor and the channel.



Silaspirane amine

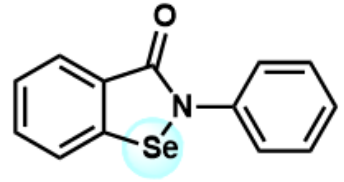
- A clinically useful antipsychotic drug, **haloperidol** is associated with a problematic metabolic pathway. The sila-analogs show a higher potency and selectivity than haloperidol and avoid the formation of a toxic metabolite.



Se-based drugs

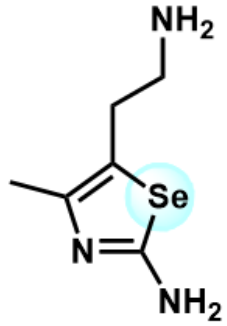
- Se-deficiency is associated with a number of serious or chronic diseases like cancer, diabetes, AIDS & tuberculosis.

- **Ebselen** is a mimic of the antioxidant enzymes glutathione peroxidase (GPx), which is a potent scavenger of hydrogen peroxide as well as hydroperoxides. It is being investigated as a possible treatment for stroke, tinnitus and manic depression.



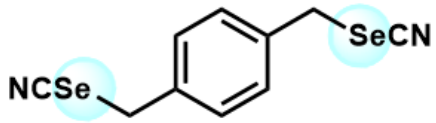
Ebselen
(Phase III)

- **Amselamine**, which is the seleno analog of amthamine, behave as a histamine H_2-agonist with a higher potency than histamine and amthamine. Moreover amselamine exerts hardly any activity for histamine H_1 and H_3-receptors, which make it selective for the H_2-receptor.



Amselamine

- **p-XSC** exerts chemo-preventive activity for carcinogenesis in colon, lung, liver, intestine and oral tissues.

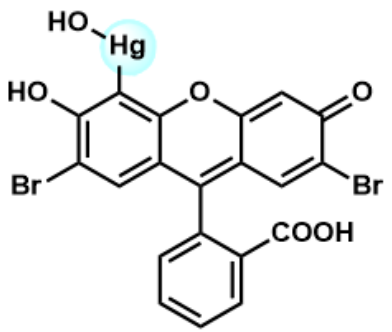


p-XSC
1,4-phenylenebis(methylene) selenocyanate

Hg-based drugs

- In China, Hg use was thought to prolong life, heal fractures, and maintain generally good health, although it is now known that exposure to mercury leads to serious adverse health effects.
- Today, the use of mercury in medicine has greatly declined in all respects, especially in developed countries.

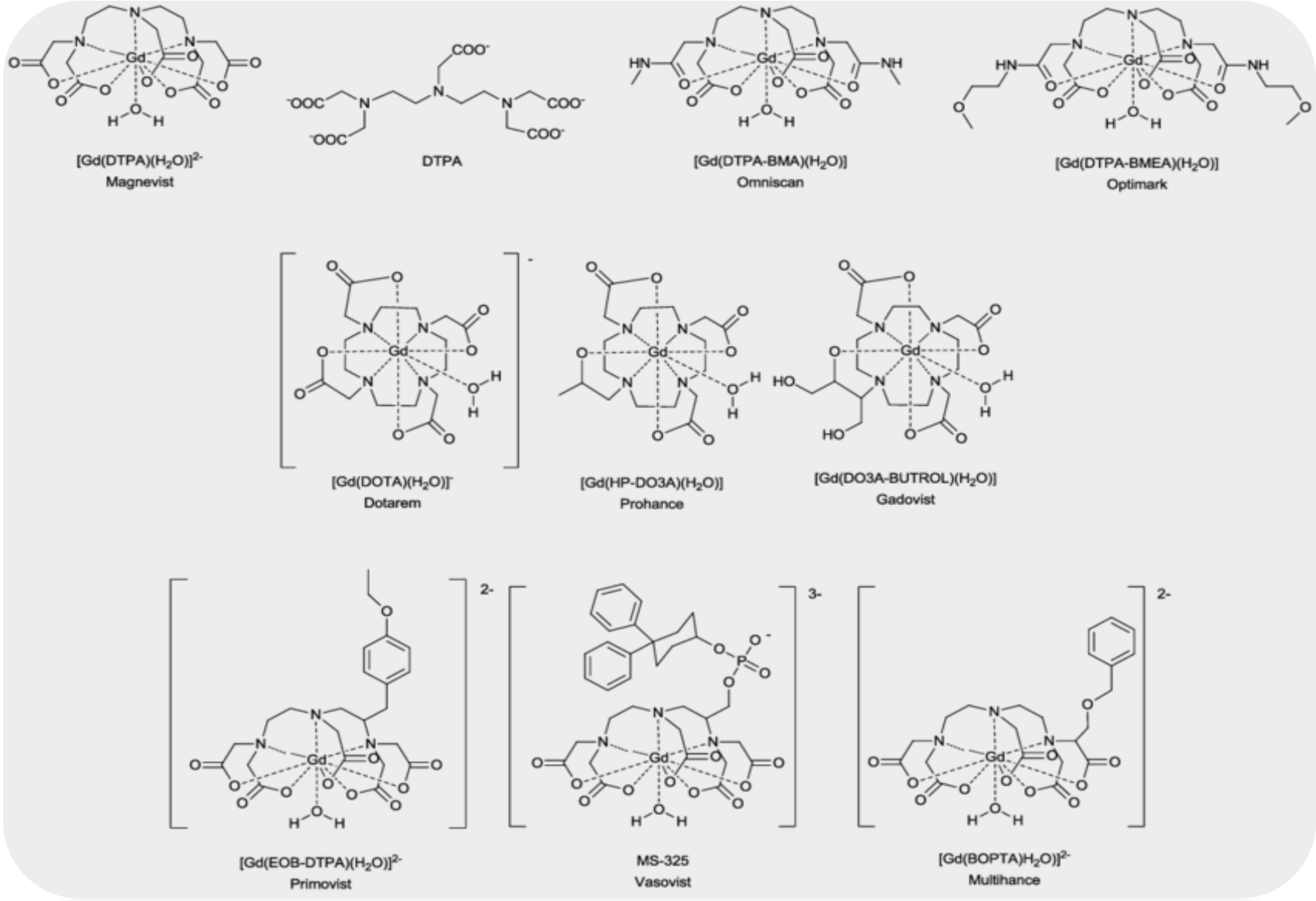
- **Merbromin** is a topical antiseptic drug discovered in 1918. This chemical soon became popular among parents and physicians for everyday antiseptic uses. It is readily available in most countries, but because of its mercury content, it is no longer sold in the US, Germany and France.
- It is still an important antiseptic, particularly in developing nations, due to its "unbelievably low cost".



Merbromin

MRI Contrast Agents

- MRI is an invaluable non invasive diagnostic tool, which provides high resolution and 3-dimensional images of internal physiological structures.
- MRI employs nuclear magnetic resonance (NMR) to image hydrogen protons in free water and organic molecules such as lipids and proteins inside the body.
- Metal complexes can enhance MR images by shortening the T_1 and T_2 relaxation times of water molecules that encounter the complexes.

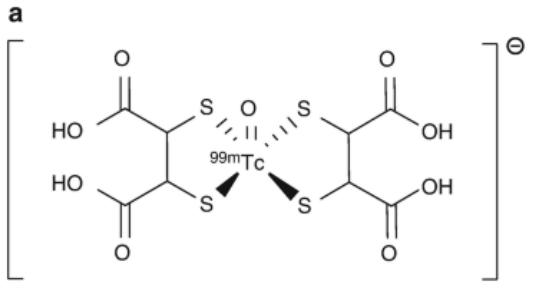


Structures of commercial MRI contrast agents and DTPA ligand

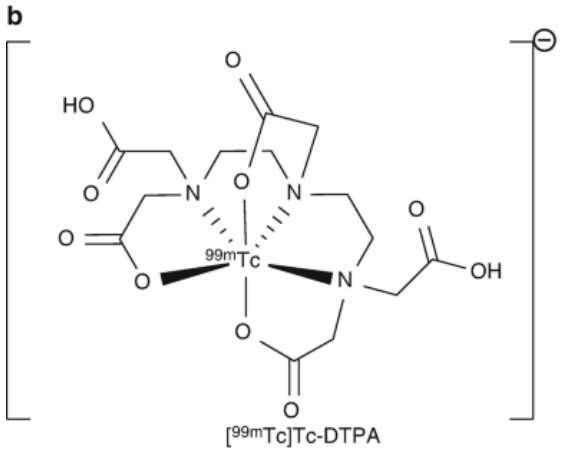
Radiotherapeutic and Radio diagnostic Agents

- Radiopharmaceuticals provide a valuable source of ionizing radiation and have important clinical applications in the diagnosis and treatment of various diseases. Metallic nuclides or radiometals, also play an important role.
- Radio diagnostic imaging is a non-invasive procedure where radiopharmaceuticals are introduced in to the human body at suitably low concentrations, with a view to locating a potential disease, assessing a pre-existing disease or monitoring the effects of treatment
- Diagnostic radiometals emit suitably energized γ rays
- There are two primary diagnostic modalities in clinical use viz. positron emission tomography (PET) and single photon emission computed tomography (SPECT).
- In PET a positron emitter, for example gallium-68, is administered
- In contrast for SPECT a γ emitting radiopharmaceutical is administered and γ emissions from the radioisotope are collected by a γ camera, providing vital information regarding the source of the rays.
- Nearly 80% of all clinically-used radiopharmaceuticals are technetium-based

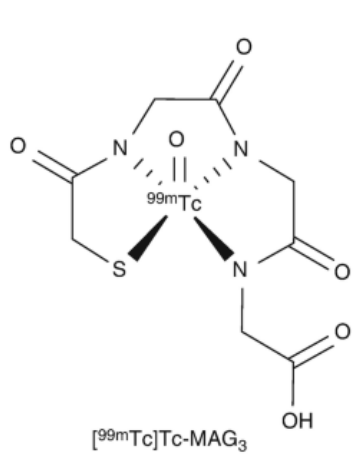
Radiometal	Half-Life (hours)	Decay Mode (% branching mode)	Applications
Tc	6.01	Isomeric transition (99.99)	SPECT
In	67.39	Electron capture (100)	SPECT
Ga	78.28	Electron capture (100)	SPECT
	12.70	Electron capture	PET
Zr	78.41	Electron capture	PET



[99mTc]Tc-DMSA



[99mTc]Tc-DTPA



[99mTc]Tc-MAG3

Selected 99mTc essential radiopharmaceuticals