Bioinorganic Chemistry

Metal ions in Biology

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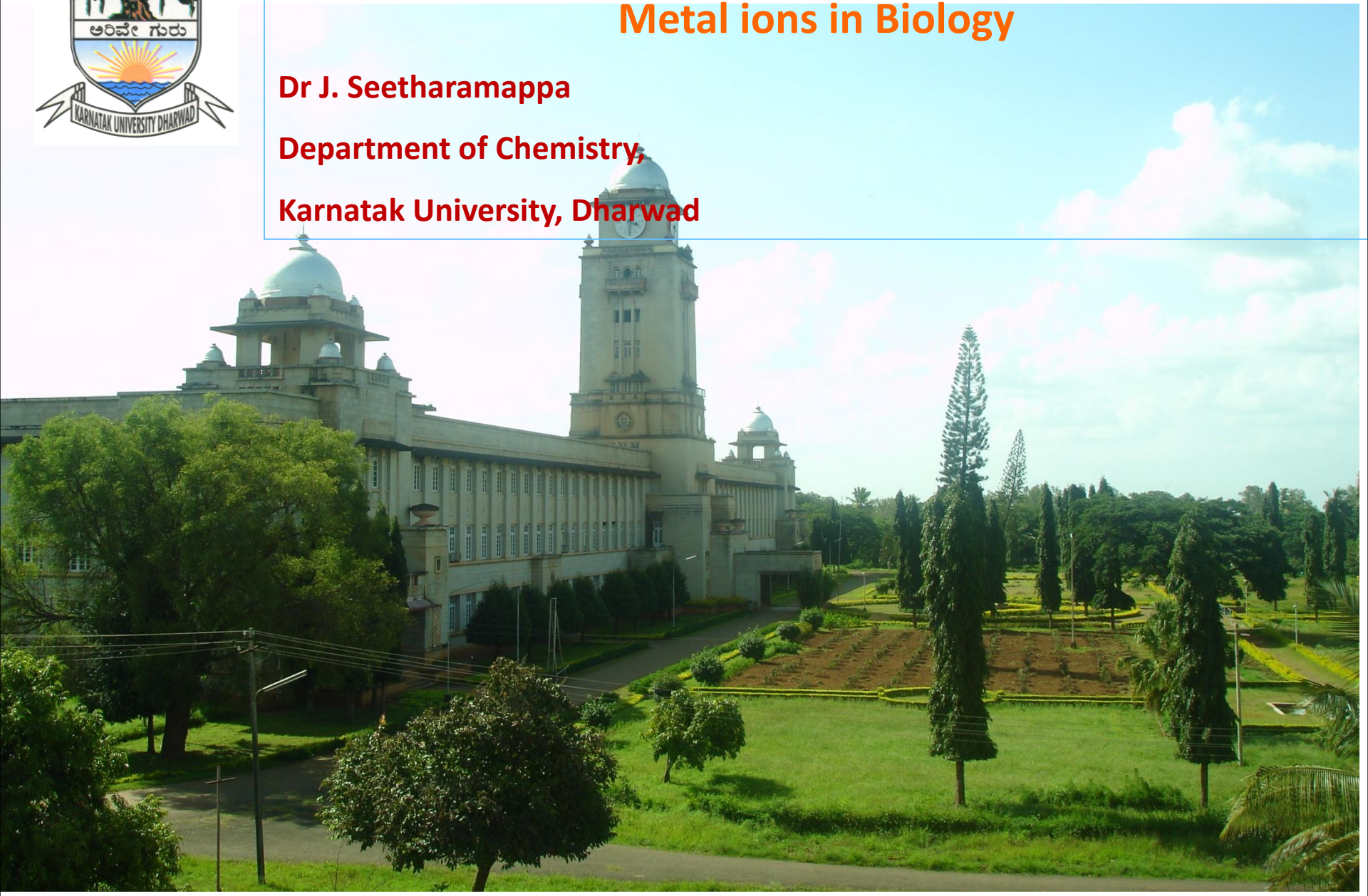


Bioinorganic Chemistry

Bioinorganic Chemistry is a leading discipline at the interface of chemistry and biology. It is also called as Inorganic Biochemistry.

It deals with the role of inorganic elements (other than C) in biological systems

Many critical processes including respiration, much of metabolism, nitrogen fixation, photosynthesis, development, nerve transmission, muscle contraction, signal transduction protection against toxic and mutagenic agents etc require metal ions.

Essential bulk and macro-elements: O, C, H, N, Ca, S, P, Na, K, Cl and Mg

Trace and Ultratrace Elements: Fe, Cu &, Zn, Mo, Co, Mn, Cr, Ni, V, Sn, B, Se, Si, F &I

3d-transition metal ions and their selected functions in biology

Metal ion	Function
Vanadium, Mo	Nitrogen Fixation
Chromium	Possible involvement in glucose tolerance
Manganese	Photosynthesis (water splitting enzyme)
Iron	O_2 transport & storage, electron transfer etc
Cobalt	Vitamin B_{12} (Group transfer & intramoleular rearrangement reactions)
Copper	O_2 transport, electron transfer
Zinc	Peptide hydrolysis, carbonic acid ionization

Why some metal ions are involved? -Rule of abundance, Rule of efficiency,

-Rule of basic fitness

Average Elemental Composition of a Human body

(Adult, 70 kg)

Element	Mass (g)
O	43000
C	16000
H	7000
N	1800
Ca	1200
P	780
S	140
K	125
Na	100
Cl	95
Mg	25
F	5.0(var.)
Fe	4.0
Zn	2.3
Si	1.0(var.)
I	0.015
Cu	0.07
Mn	0.012

Element	Mass (g)
Se	0.014
Mo	0.005
Ni	0.015
Cr	0.002(var.)
Co	0.002
Ti[a]	0.70
Rb[a]	0.68
Sr[a]	0.32
Br[a]	0.26
Ba[a]	0.02
Al[a]	0.06
Ce[a]	0.04
Li[a]	0.007
Cd[b]	0.02(var.)
Sn[b]	0.03
Pb[b]	0.12
As[b]	0.007(var.)
B[b]	0.018

[a]Not rated essential; [b]Essentiality uncertain.

Source: Kaim, Schwederski & Klein, Bioinorganic Chemistry: Inorganic Chemistry of life, 2nd ed., 2013.

ABUNDANCE OF THE ELEMENTS ON EARTH SEA WATER AND HUMAN BODY

Composition of Earth's Crust		Composition of Seawater (in atom percent)		Composition of Human Body	
O	46.6%	H	66.2%	H	62.9%
Si	27.1	O	33.1	O	25.4
Al	8.1	Cl	0.33	C	9.5
Fe	5.0	Na	0.28	N	1.4
Ca	3.6	Mg	0.033	Ca	0.31
Na	2.8	S	0.017	P	0.22
K	2.6	Ca	0.006	Cl	0.03
Mg	2.1	K	0.006	K	0.06
Ti	0.46	C	0.0014	S	0.05
H	0.22	Br	0.0005	Na	0.03
C	0.03			Mg	0.01
All others ~ 1%		All others < 0.1%		All others < 0.1%	

Some Nobel Prize Winners in Bioinorganic Chemistry

For his researches on plant pigments, especially chlorophyll; Willstätter - 1915

1930 - Fischer; *Constitution of heme and chlorophyll and especially synthesis of heme.*

For his work on CO_2 assimilation plants; Calvin – 1961

Structures of hemoglobin and myoglobin;
1962 Perutz and Kendrew; 1962

1964 - Dorothy M. Hodgkin;
Protein Crystallography & Vitamin B_{12}.

Natural product synthesis including chlorophyll & later Vit B12; Woodward -1965

For determination of three-dimensional structure of a photosynthetic reaction centre (J. Deisenhofer, H. Michel and R. Huber) - 1988

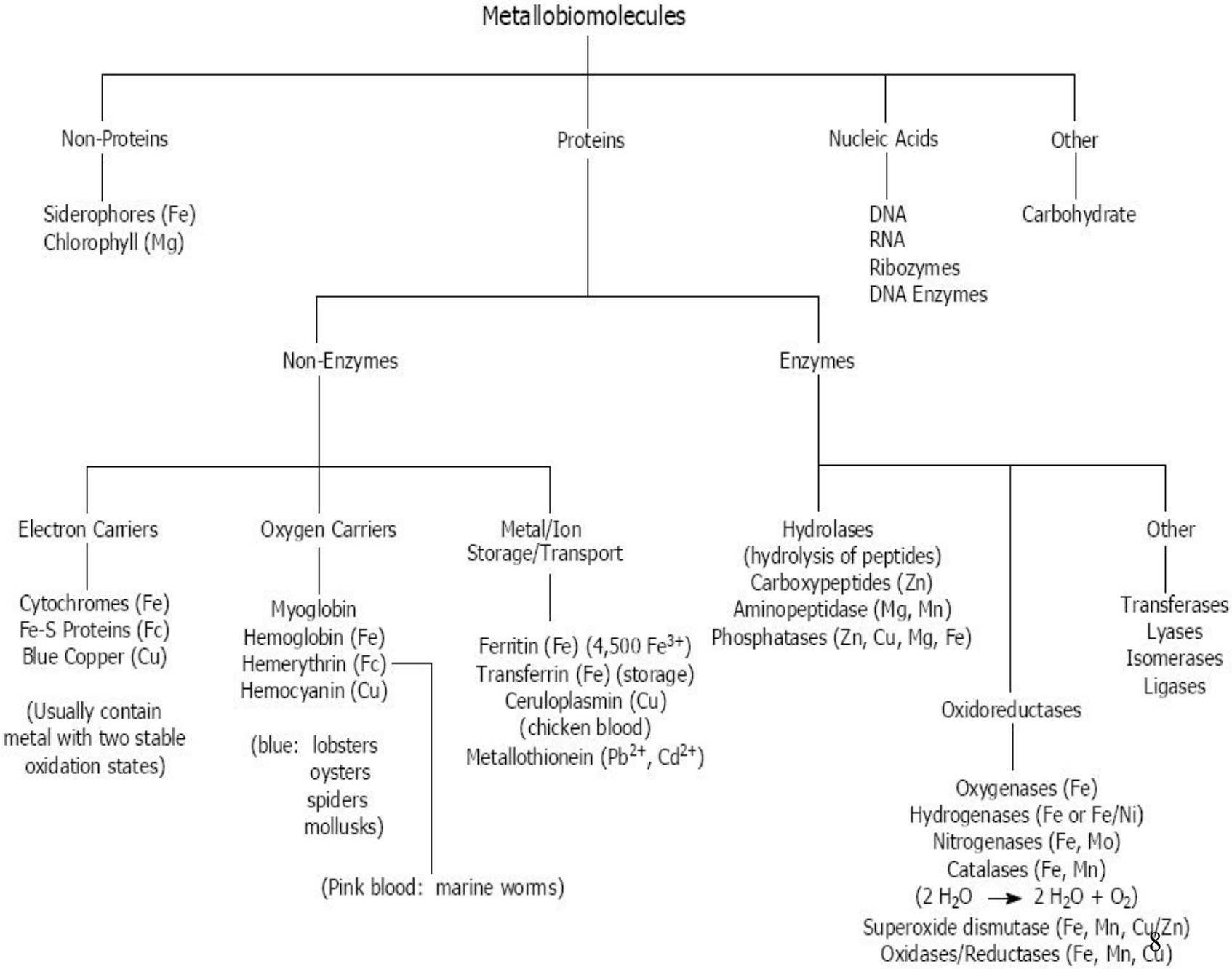
Deisenhaufer Michel Huber

- 1982: Aaron Klug(UK)-Development of crystallographic electron microscopy & his strl. Elucidation of biologically impt nucleic acids-protein complex.
- 1977: J.E.Walker, P.D.Boyer & Jens C Skou-Enzymatic mechanism underlying the synthesis of ATP&Discovery of ion-transporting enz Na-K ATPase.
- 2003: P.Agre & Roderick Mackinnon-Discovery of channels in cell membranes, discovery of water channels & ion channels in cells.
- Jacques Dubochet, Joachim Frank and Richard Henderson "for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution-2017
- **Osamu Shimomura, Martin Chalfie and Roger Y. Tsien** "for the discovery and development of the green fluorescent protein, GFP -2018

Functions of Metal Ions in biological systems

--- STRUCTURAL AND FUNCTIONAL

- **<u>As Charge carriers</u>: Ex Na, K (Charge carrier, osmotic balance, acid-base balance of the body, nerve impulses, enzyme activators**
- **<u>Structural, triggers</u>: Ex Ca-Str. stabilization, charge carrier, PO_4^{3-} transfer, trigger reactions, muscle contraction, blood clotting**
- **Mg-Str.in hydrolases, isomerases, PO_4^{3-} transfer, trigger reactions**
- **Zn-Str.in zinc fingers, gene regulation, anhydrases, dehydrogenases**
- **Mn-Str. In oxidases, photosynthesis**
- **<u>Electron transfer:</u> Fe-Electron transfer in N2 fixation by nitrogenases, electron transfer in oxidases, electron transfer in Fe-S proteins**
- **Cu-Electron tranfer in Type I blue copper proteins**
- **<u>DioxygenTransport:</u> Fe-transfer in Hb, Mb, Hr (in marine invertibrates-worms)**
- **Cu-Type II copper oxidases, hydroxylases, Type III copper hydroxylases, Hc (in mollusks & arthropods)**
- **<u>Enzyme catalysts</u>: Cu-Type II copper oxidases, Ni-Hydrogenases,Mo-N2 fixation, oxo transfer in oxidases, Co-alkyl group transfer, Zn-reqd. for 300 enz, in str.formn, hydrolytic enz-alkaline phosphatase, carboxy peptidase, alcohol dehydrogenase etc**
- **Fe-Cyt P-450, catalase, peroxidase, vit B12 co-enzyme**
- **<u>Metal ion storage & transport:</u> Siderophores-bacterial/fungal iron transport, Transferrin-vertebrate iron transport, Ferritin-vertibrate iron storage, Ceruloplasmin-Cu transport inmammalian blood plasma**

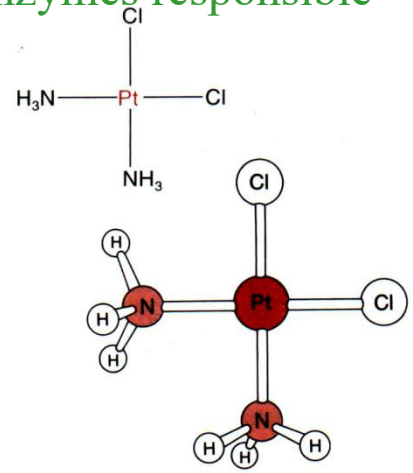

Metallobiomolecules
Non-Proteins
Siderophores (Fe)
Chlorophyll (Mg)
Proteins
Nucleic Acids
DNA
RNA
Ribozymes
DNA Enzymes
Other
Carbohydrate
Non-Enzymes
Enzymes
Electron Carriers
Cytochromes (Fe)
Fe-S Proteins (Fc)
Blue Copper (Cu)
(Usually contain metal with two stable oxidation states)
Oxygen Carriers
Myoglobin
Hemoglobin (Fe)
Hemerythrin (Fc)
Hemocyanin (Cu)
(blue: lobsters oysters spiders mollusks)
(Pink blood: marine worms)
Metal/Ion Storage/Transport
Ferritin (Fe) (4,500 Fe^{3+})
Transferrin (Fe) (storage)
Ceruloplasmin (Cu)
(chicken blood)
Metallothionein (Pb^{2+}, Cd^{2+})
Hydrolases
(hydrolysis of peptides)
Carboxypeptides (Zn)
Aminopeptidase (Mg, Mn)
Phosphatases (Zn, Cu, Mg, Fe)
Oxidoreductases
Oxygenases (Fe)
Hydrogenases (Fe or Fe/Ni)
Nitrogenases (Fe, Mo)
Catalases (Fe, Mn)
($2\,H_2O \rightarrow 2\,H_2O + O_2$)
Superoxide dismutase (Fe, Mn, Cu/Zn)
Oxidases/Reductases (Fe, Mn, Cu)
Other
Transferases
Lyases
Isomerases
Ligases

Inorganic Compounds in Medicine

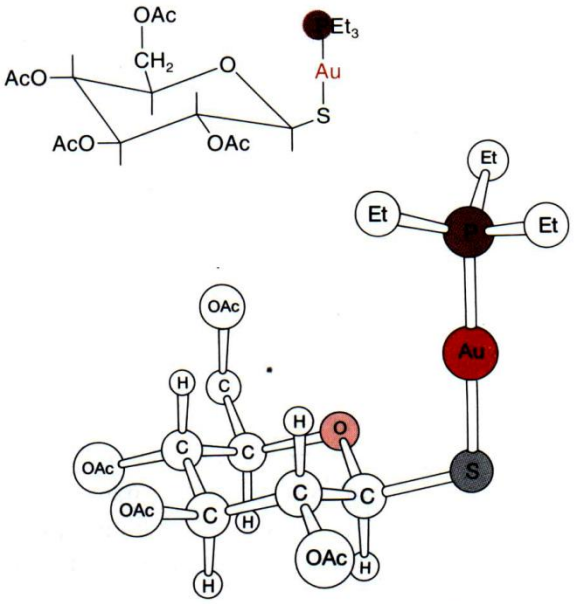
Anticancer drugs-Cis-Platin,Oxaliplatin, carboplatin, iproplatin, nedaplatin etc

V(IV) insulin mimetic agents:$VO(acac)_2$, $VO(Me/Et\ –acac)_2$

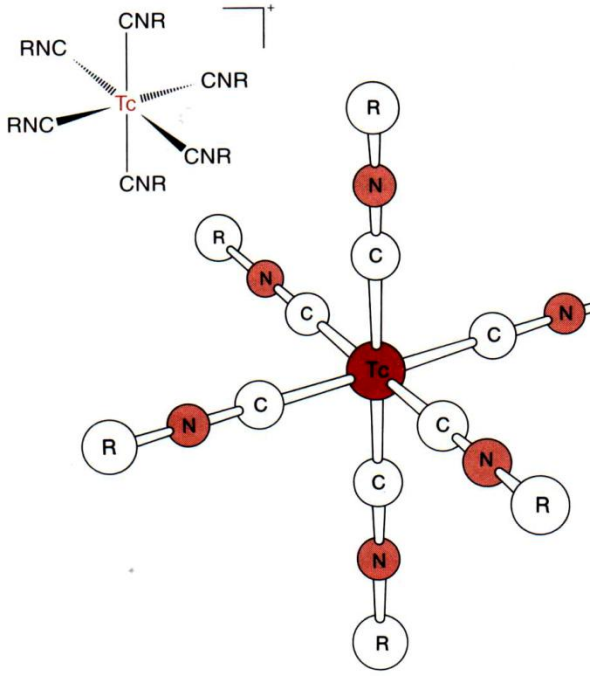
Gold compounds: Myocrysin, Sanocrysin, Solganol, auranofin, (aurosomes-hydrolytic enzymes responsible



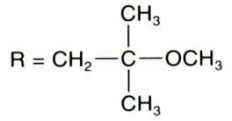
Cisplatin, an anticancer drug



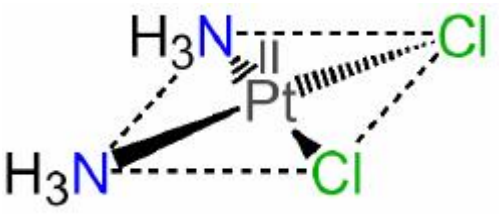
Auranofin, an oral rheumatoid arthritis drug



Cardiolyte, a heart imaging agent

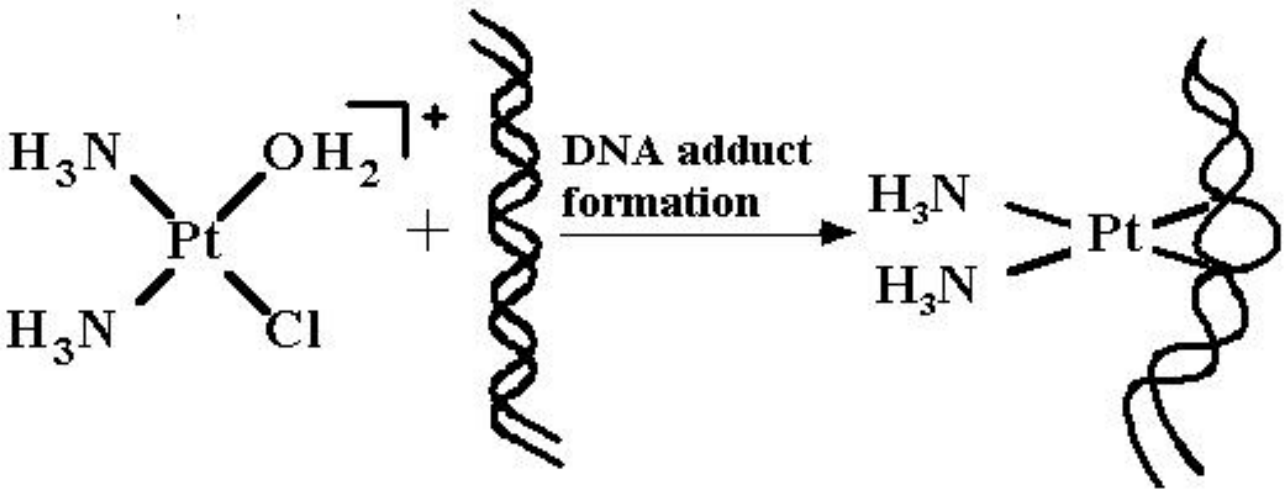


Cisplatin: An anticancer agent (Rosenberg-1964)

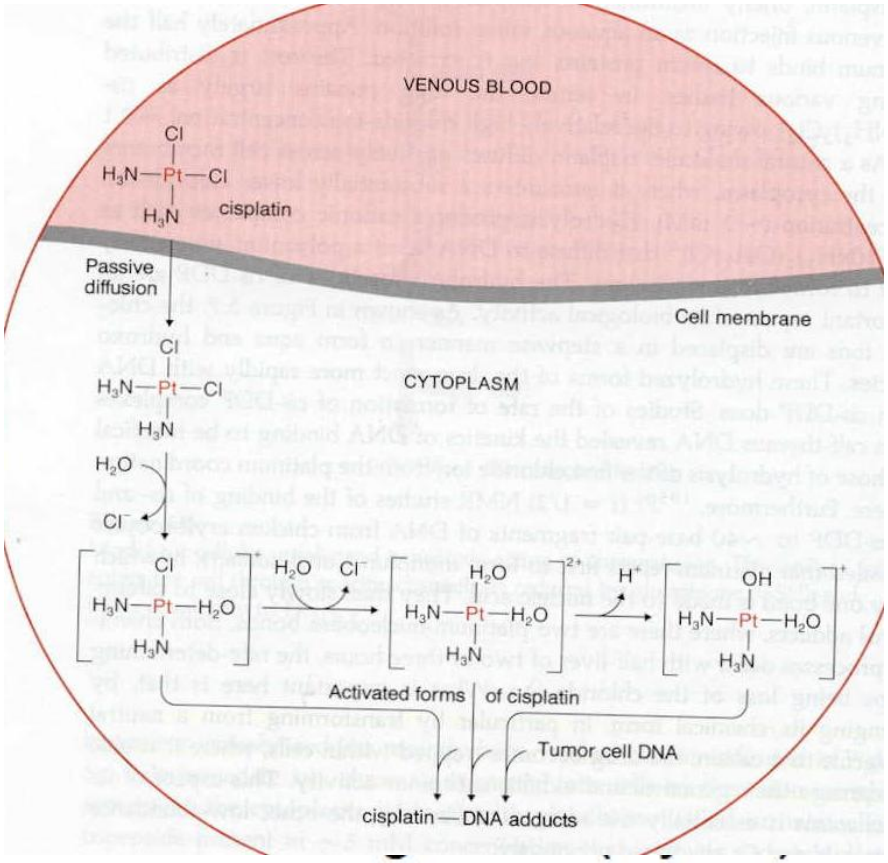


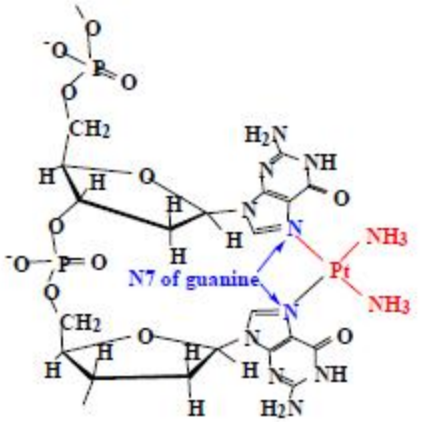
Used for treatment of testicular, ovarian, lung, and head and neck cancers

It diffuses into cells, aquates, and attacks cellular targets, DNA, RNA and proteins

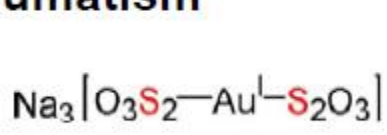


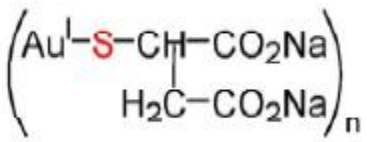
Pt(II): Cisplatin(*cis*-[$Pt(NH_3)_2Cl_2$]), chemotherapy (inhibition of cell division, not cell growth)

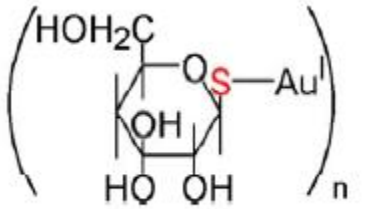




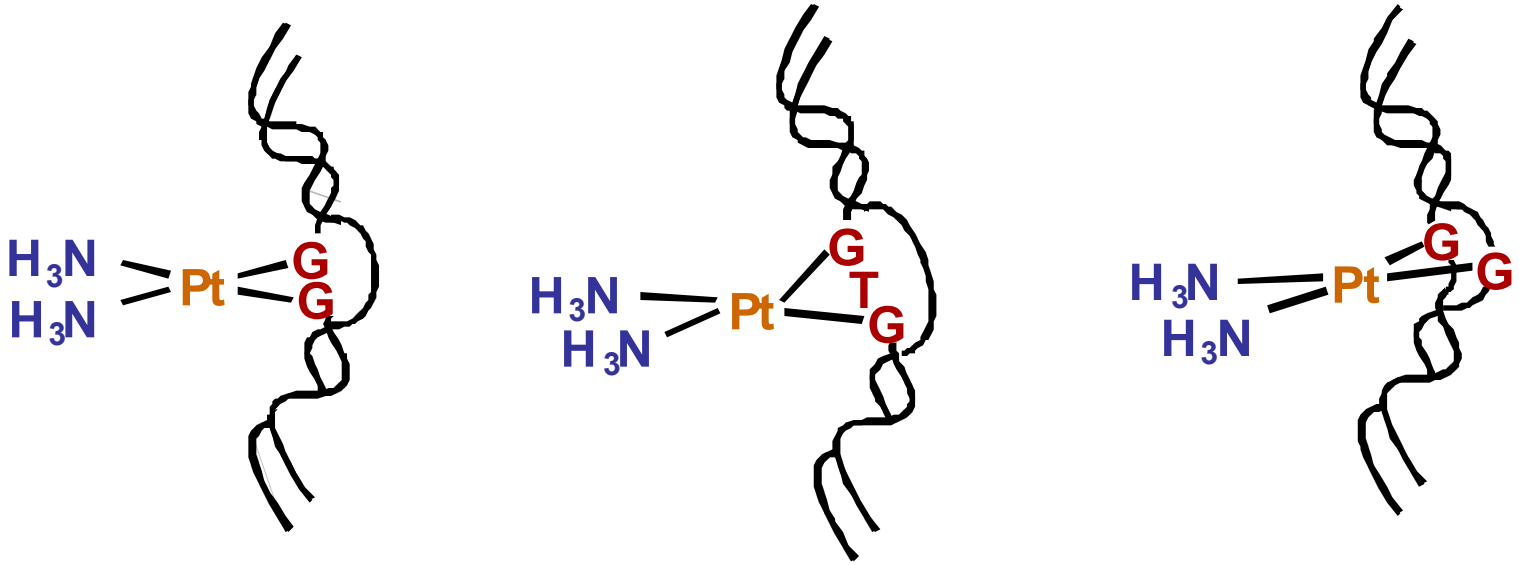
- **Au(I): Rheumatism**







Cisplatin -DNA Adducts



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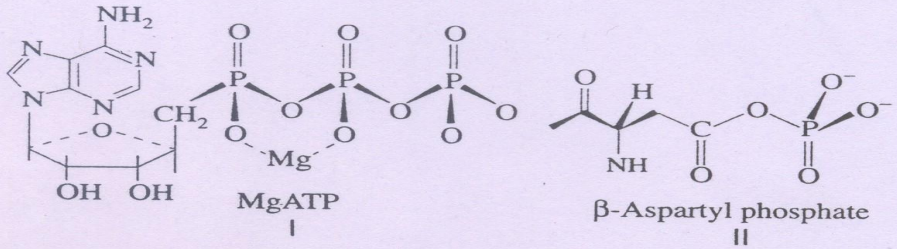
Active Transport

- Active transport is the pumping of molecules or ions through a membrane **against** their concentration gradient. It requires:
- a transmembrane protein (usually a complex of them) called a transporter
- The source of this energy is **ATP**.
- The energy of ATP may be used directly or indirectly.
- **Direct Active Transport.** Some transporters bind ATP directly and use the energy of its hydrolysis (30.5 kJ/mol) to drive active transport.
- **Indirect Active Transport.** Other transporters use the energy already stored in the gradient of a directly-pumped **ion**. Direct active transport of the ion establishes a concentration gradient. When this is relieved by facilitated diffusion, the energy released can be harnessed to the pumping of some other ion or molecule.

Direct Active Transport

- **The Na^+/K^+ ATP_{ase}(a tetramer, has two each of α &βunits)**
- The cytosol of animal cells contains a concentration of potassium ions (K^+) as much as 20 times higher than that in the extracellular fluid. Conversely, the extracellular fluid contains a concentration of sodium ions (Na^+) as much as 10 times greater than that within the cell. K^+ is reqd. in the cell for glucose metabolism, protein synthesis, activation of some enzymes.
- These concentration gradients are established by the active transport of both ions. And, in fact, the same transporter, called the Na^+/K^+ ATPase, does both jobs. It uses the energy from the hydrolysis of ATP to
- actively transport 3 Na^+ ions out of the cell
- pump 2 K^+ ions into the cell
- A specific membrane protein (*sodium-potassium pump*) *pumps* sodium out of cells and potassium into cells against a concentration gradient in a manner stoichiometrically balanced as follows:
- $3Na^+$ (intracell) + $2K^+$ (extracell) + ATP → $3Na^+$ (extracell) + $2K^+$ (intracell) + ADP + Pi



Using these clues, the following mechanism was proposed :

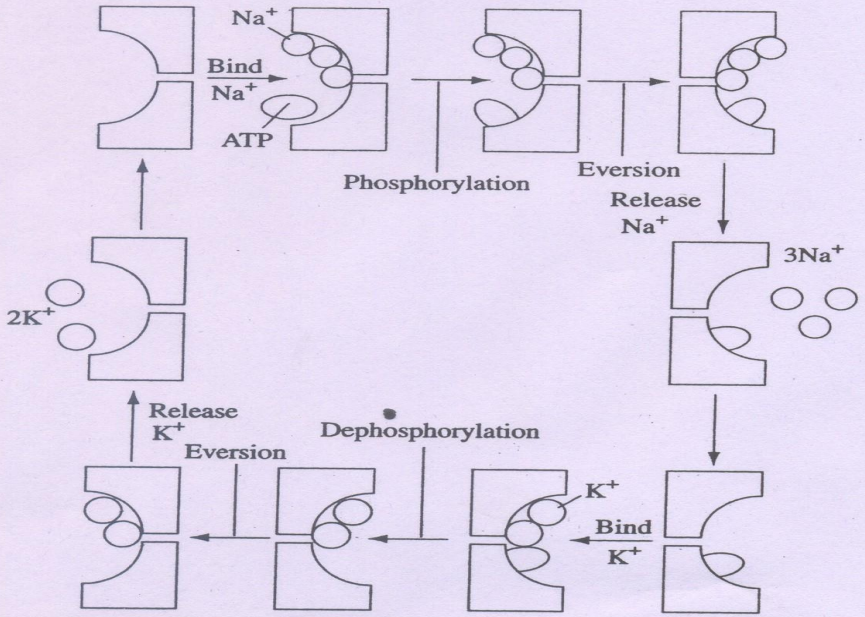


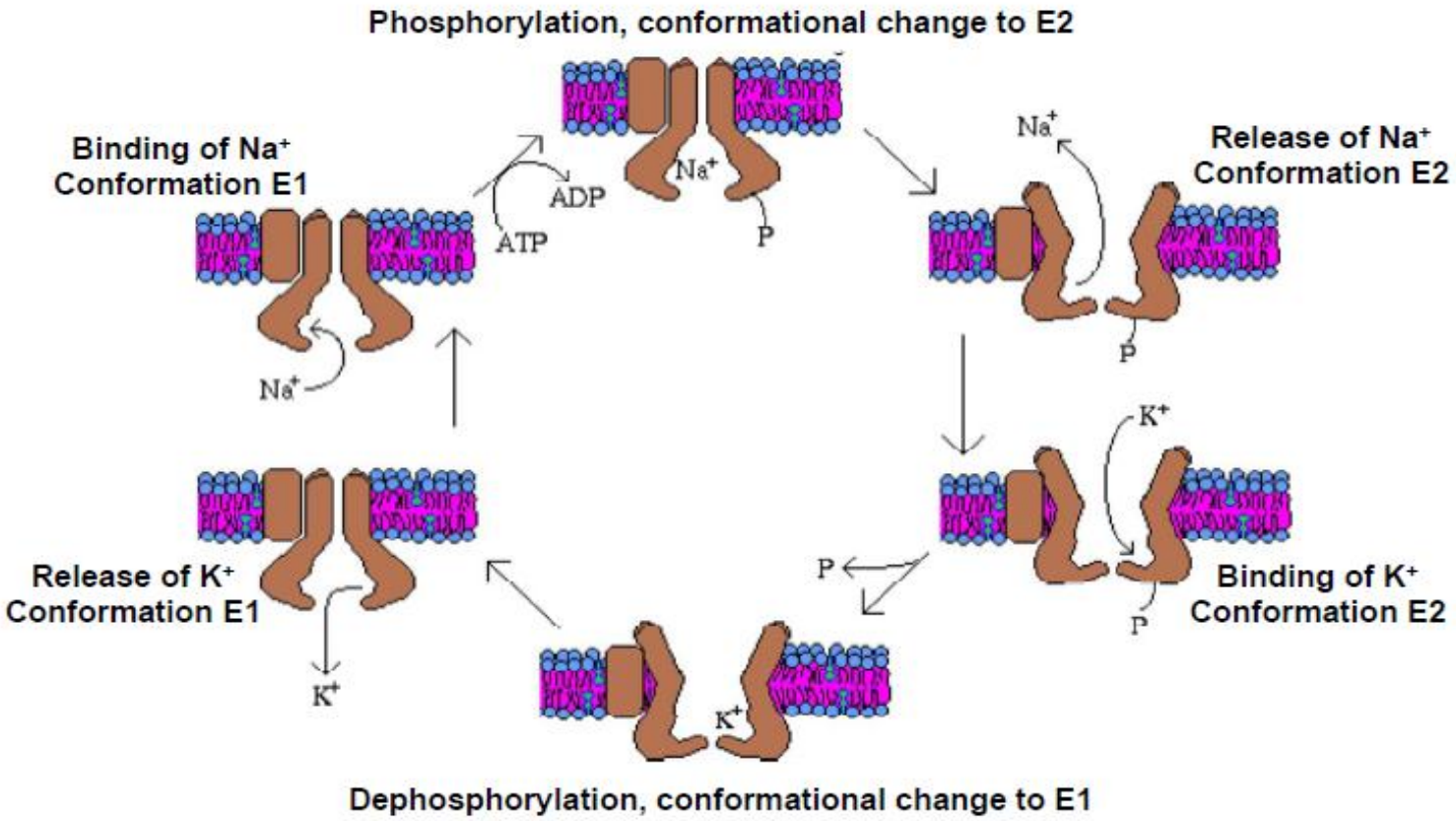
Fig. : A schematic diagram of the mechanism of sodium pumping showing the role of eversion of the enzyme which transfers ions between the inside and outside of the cells.

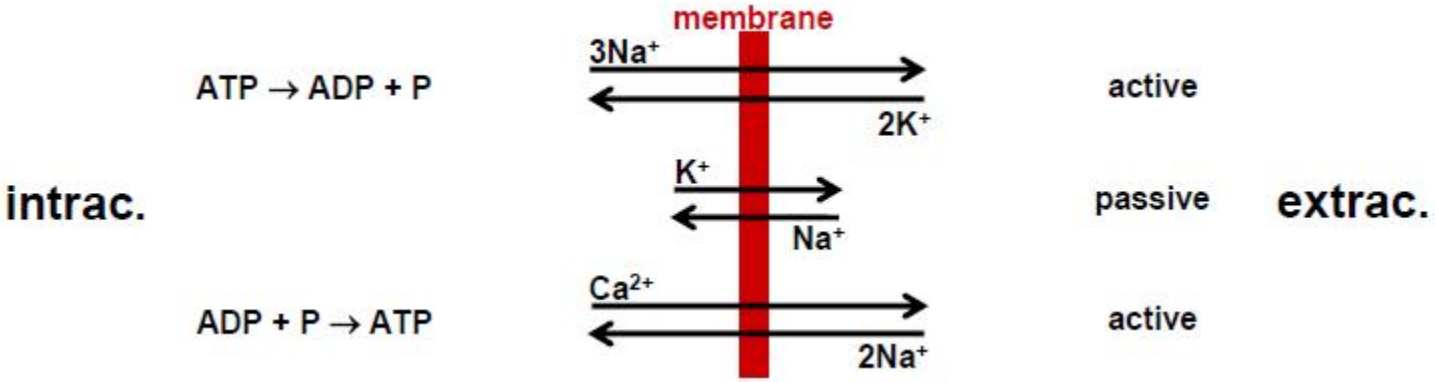
Q. 8. Match the following metals in I with the appropriate biomolecule in II.

I	II
(A) Zn	(i) Phosphotransferase
(B) Cu	(ii) Peroxidase
(C) Fe	(iii) Carboxypeptidase

- The ATPase is phosphorylated at an aspartase site only in the presence of Na^+ and Mg^{+2} ions.
- The phosphorylated product is hydrolysed if K^+ ions are present.
- Enzyme undergoes conformational change when it is phosphorylated or dephosphorylated

Na^+/K^+/MgATPase: Flip-Flop-mechanism



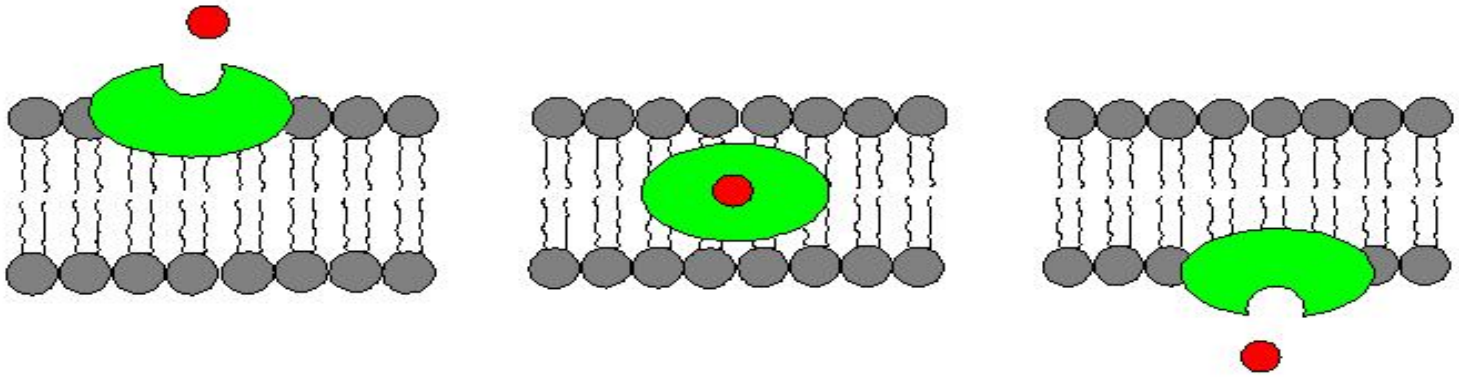


- It helps establish a net charge across the plasma membrane with the interior of the cell being negatively charged with respect to the exterior. This resting potential prepares nerve and muscle cells for the propagation of action potentials leading to nerve impulses and muscle contraction.
- The accumulation of sodium ions outside of the cell draws water out of the cell and thus enables it to maintain osmotic balance (otherwise it would swell and burst from the inward diffusion of water).
- The gradient of sodium ions is harnessed to provide the energy to run several types of indirect pumps.
- The crucial roles of the Na^+/K^+ ATPase are reflected in the fact that almost one-third of all the energy generated by the mitochondria in animal cells is used just to run this pump

Calcium--Muscle Contraction

- Muscle Cells
  - *Sarcoplasmic Reticulum(SR)*: muscle cell organelle
  - Ca^{2+}-ATPase pumps Ca^{2+} into SR to concentrations up to 0.03 M
  - Inside SR, Ca^{2+} is bound by Calsequestrin, a 40,000 dalton protein (50 Ca^{2+} per molecule)
  - Hormone induced stimulation of ion channels releases Ca^{2+} from the SR into the muscle cell causing contraction.

- ***Ionophores are hydrophobic molecules* (synthesized by microorganisms) *that selectively***
- bind to a given metal ion and increase its cell permeability. The inner part of ionophores is made up of polar groups forming a tetra- or octahedral geometry that fits and encloses a specific ion. Ionophores shield the charge of the ion to be transported, enabling it to penetrate the hydrophobic interior of the lipid bilayer.
- There are two broad classifications of ionophores.
- Small molecules (ion carriers) that bind to a particular ion, shielding its charge from the surrounding environment, and thus facilitating its crossing of the hydrophobic interior of the lipid membrane. Ex: Valinomycin, Enniatin B, Nonactin
- Channel formers that introduce a hydrophilic pore into the membrane, allowing ions to pass through while avoiding contact with the membrane's hydrophobic interior. Ex: Gramicidin A, F.30 Alamethicin

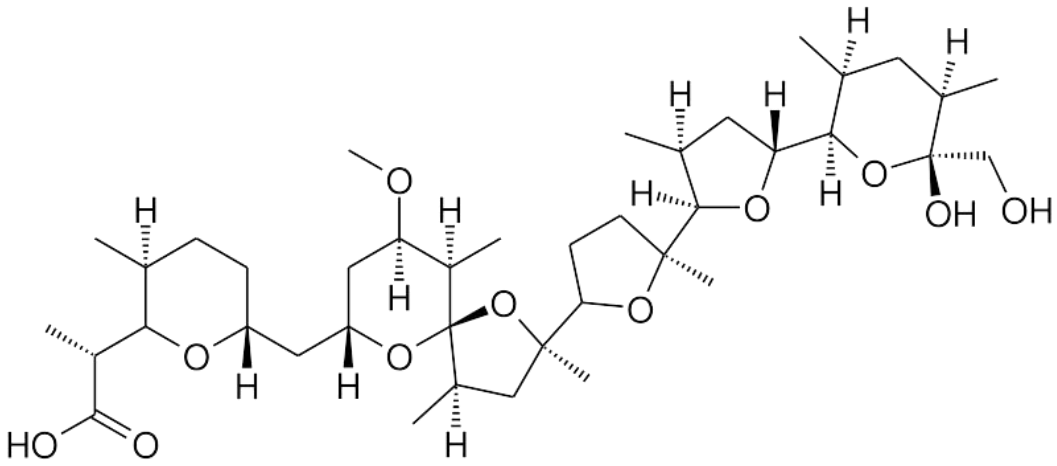


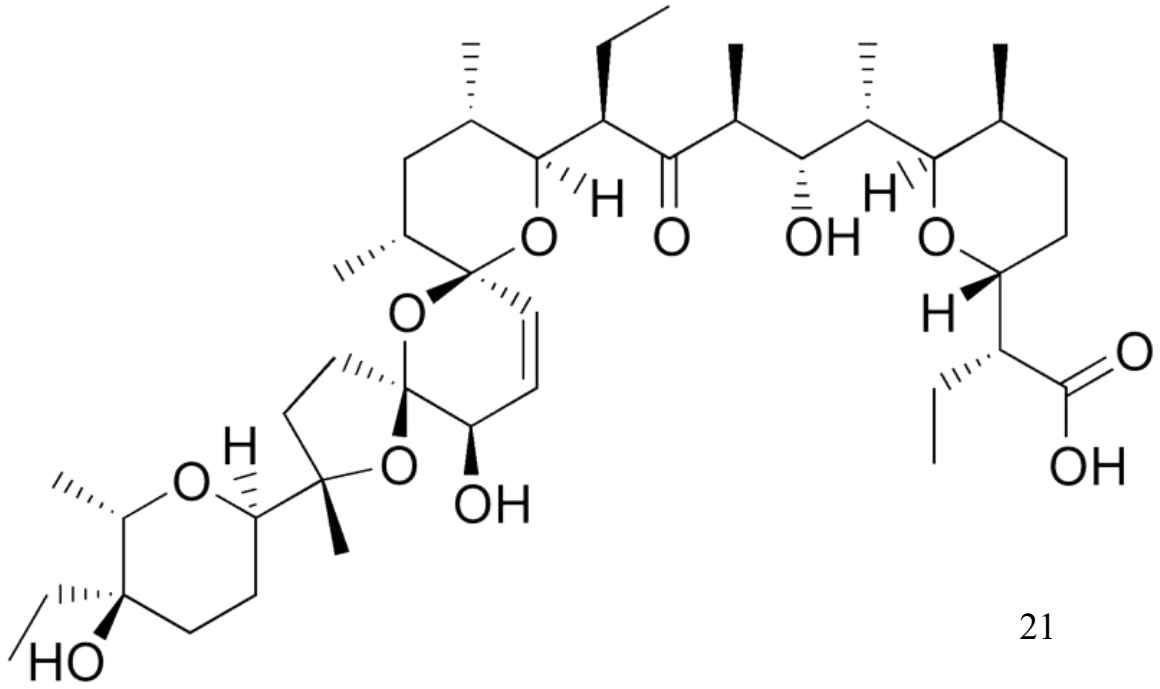
- Ionophores disrupt transmembrane ion concentration gradients, required for the proper functioning and survival of microorganisms, and thus have antibiotic properties. They are produced naturally by certain microbes and act as a defense against competing microbes.
- In laboratory research, ionophores are used to increase the permeability of biological membranes to certain ions. Additionally, some ionophores are used as antibiotics and/or as growth enhancing feed additives for certain feed animals such as cattle (see monensin).

Representative ionophores (with the ion(s) they act upon):

- 2,4-Dinitrophenol (H^+)
- Beauvericin (Ca^{2+}, Ba^{2+})
- Calixarene
- Calcimycine (A23187)
- Carbonyl cyanide *m*-chlorophenyl hydrazone
- Crown ether
- FCCP or Carbonyl cyanide-*p*-trifluoromethoxyphenylhydrazone (H^+)
- Gramicidin A (H^+, Na^+, K^+)
- Ionomycin (Ca^{2+})
- Alkaloids
- Monensin (Na^+, H^+)
- Nigericin (K^+, H^+, Pb^{2+})
- Nonactin (Ammonium ionophore I)
- Nystatin
- Proton ionophore II (4-Nonadecylpyridine)
- Proton ionophore III (*N*,*N*-Dioctadecylmethylamine)
- Salinomycin (K^+)
- Valinomycin (K^+)

Nigericin is an antibiotic derived from *Streptomyces hygroscopicus.* Nigericin acts as an H^+, K^+, Pb^{2+} ionophore. Most commonly it is an antiporter of H^+ and K^+.





Salinomycin

Valinomycin is a dodecadepsipeptide, that is made of twelve alternating amino acids and esters to form a macrocyclic molecule. Valinomycin is obtained from the cells of several *Streptomyces* strains, one of them "*S. tsusimaensis*". It is a member of the group of natural neutral ionophores because it doesn't have a residual charge.