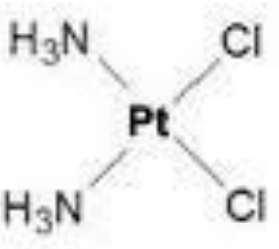
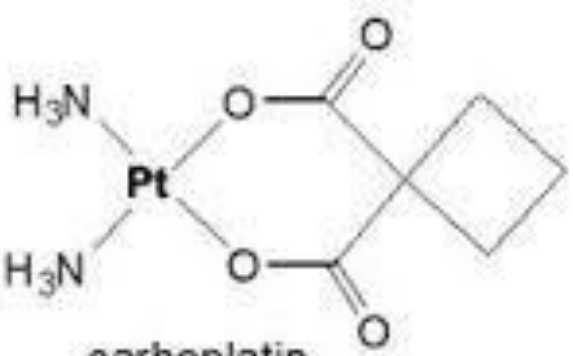
Anticancer Activity of Pt - complexes

The discovery of the powerful anticancer properties of Cis-platin (cis-diamine dichloro Pt (II), known as cis-DDP) by Rosenberg et al in the mid 1960 is a landmark in the discipline of anti metal complexes.

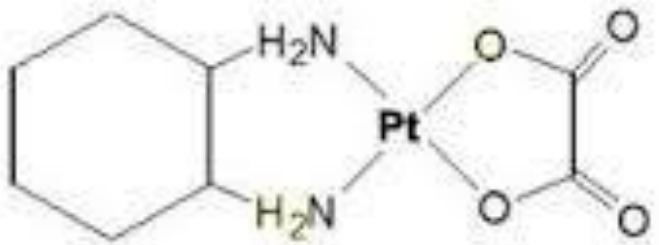
Several Pt-complexes like cis-$[Pt(NH_3)_2X_2]$, $[Pt(en)X_2]$ (X = Cl^-, Br^-, NO_2^-, etc); $[Pt(NH_3)_2X]$, [Pt(enX)], (X = malonate, oxalate) are now established to have anticancer properties. The NH_3 group may be replaced by different amines like CH_3NH_2, etc. Some important anticancer Pt(II) complexes are,



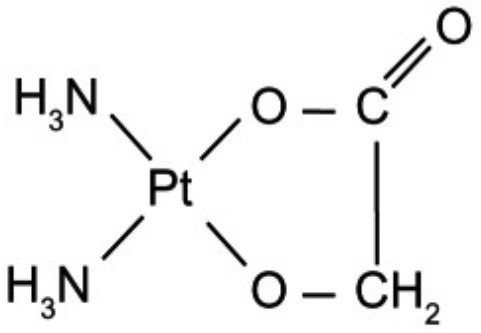
cisplatin



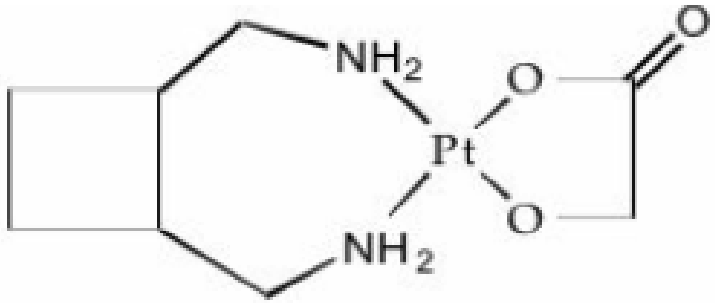
carboplatin



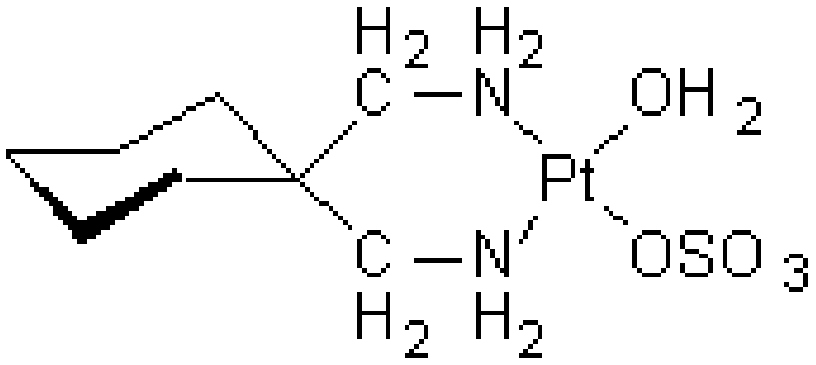
oxaliplatin



Nedaplatin



lobaplatin



Spiroplatin

It is interesting to note that though cis-platin is active, the trans-platin is inactive and toxic. Though cis-platin is quite effective for various types of cancers, it is specially effective for testicular and ovarian tumors. It is also used in the treatment of bronchogenic carcinoma, osteosarcoma, etc. In fact, cis-platin is one of the three most widely used anticancer drugs in the world.

From the knowledge of activity of the above mentioned neutral Cis-Pt (II) complexes, it has been concluded that:

(1) the compound should be neutral to allow its passive diffusion into the cells

(2) it should have cis configuration

(3) the non-leaving groups should [have poor trans-labilising power and they] should be amines.

Among the different neutral Pt(II) complexes, the two compounds Cis-platin and Carboplatin i.e., cis-diammine(1,1-cyclobutanedicarboxylato)Pt(II) have been approved worldwide for clinical use.

It may be noted that the anticancer activity is not only confined within the non-electrolytic Pt(II) complexes. The charge complexes called platinum pyrimidine blues, having structures, $Pt(NH_3)_2(pyrimidine)]X_n$ (where X = $CH_3CO_2^-$, Cl^-, etc) are known to have the therapeutic activity against some cancers. Some Pt (V) complexes like cis-$[Pt(NH_3)_2Cl_4]$, $[Pt(en)Cl_4]$ are also known to have anticancer activity.

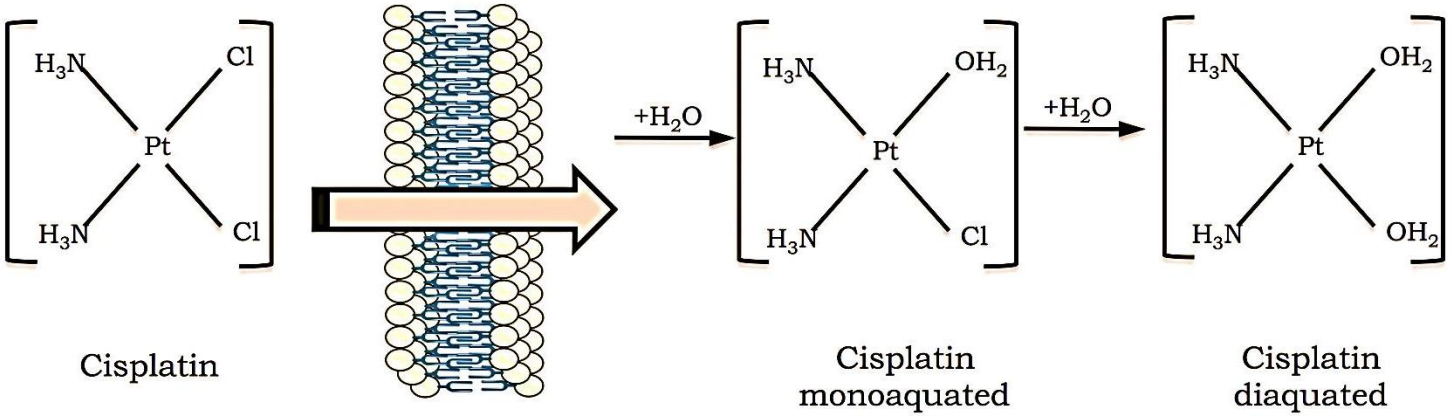
Mechanism

Cis-platin or *cis*-DDP is both thermodynamically and kinetically stable with respect to hydrolysis in blood.

In blood the concentration of Cl^- is sufficiently high (~ 0.1 M) to prevent the hydrolysis of *cis*-DDP *Cis*-DDP enters through the cell membrane by passive diffusion

In cytoplasm Cl^- concentration is low (~ 0.04 M) and hydrolysis is possible

The mechanism of action of cisplatin is mediated by the interaction of cisplatin with DNA in order to for DNA adducts. The principle of action involves exerting its cytotoxicity upon cancer cells through the formation of DNA adducts that include mono-, inter, and intrastrand cisplatin DNA cross-links



Cis-platin becomes activated once it enters the cell. In the cytoplasm the chloride atoms on *cis*-platin are displaced by water molecules.

Cis-platin, under low intracellular chloride ion concentrations, has been shown to hydrolyze into variously charged reactive species including [*cis*-$(NH_3)_2Pt(OH_2)(HO)]^+$ and diaquated [*cis*-$(NH_3)_2Pt(OH_2)_2]^{2+}$ forms

This hydrolyzed product is a potent electrophile that can react with any nucleophile, including the sulfhydryl groups on proteins and nitrogen donor atoms on nucleic acids.

Cis-platin binds to the N7 reactive center on purine residues and as such can cause deoxyribonucleic acid (DNA) damage in cancer cells, blocking cell division and resulting in apoptotic cell death.

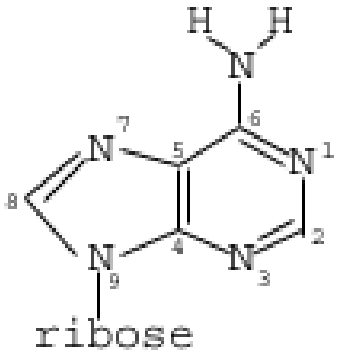
Apoptosis is a controlled type of cell death which is energy-dependent leading to cell shrinkage, chromatin condensation, membrane budding, phosphatidylserine externalization

The 1,2-intrastrand cross-links of purine bases with cisplatin are the most notable among the changes in DNA. These include the 1,2-intrastrand d(GpG) adducts 1,2-intrastrand d(ApG) adducts representing about 90% and 10% of adducts, respectively.

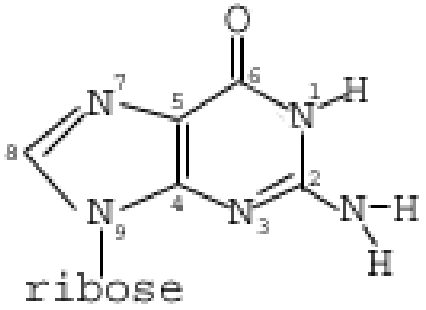
1,3-intrastrand d(GpXpG) adducts and other adducts such as inter-strand crosslinks and nonfunctional adducts have been reported to contribute to cisplatin's toxicity.

The intrastrand adducts, ApG and GpG in particular, are responsible for the cytotoxic effects of cisplatin and account for 85–90% of the bound platinum. These adducts block DNA replication and transcription.

Purines

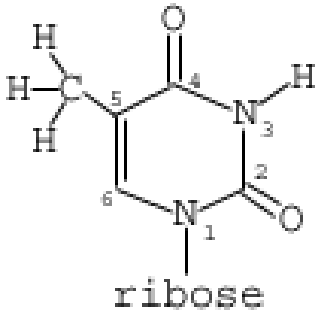


adenosine

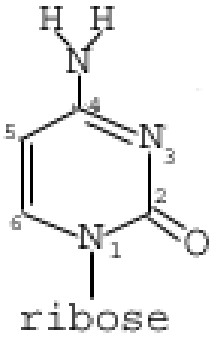


guanine

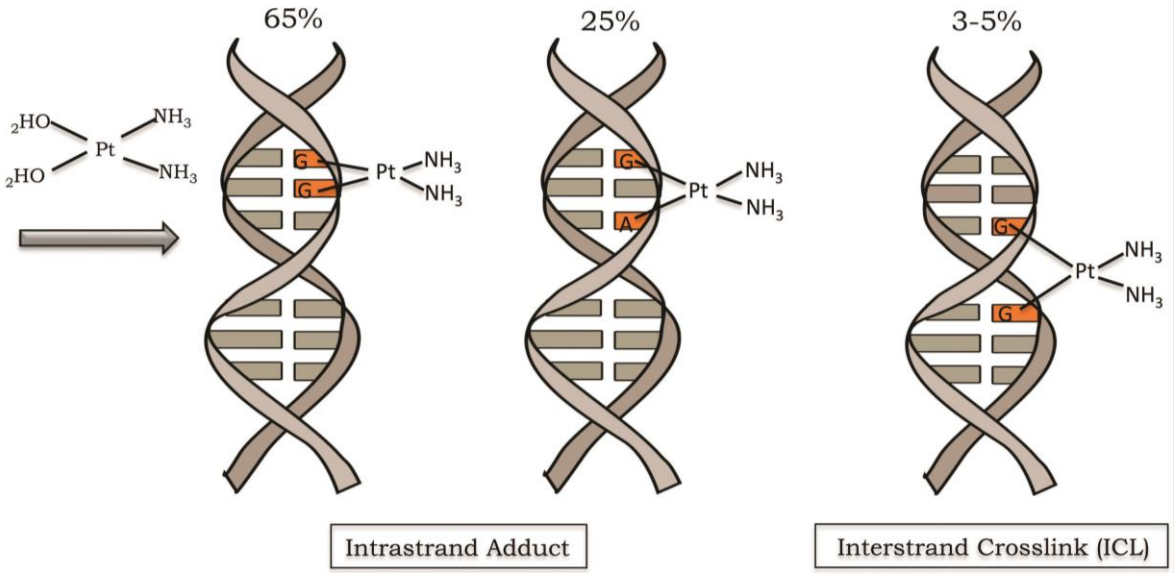
Pyrimidines

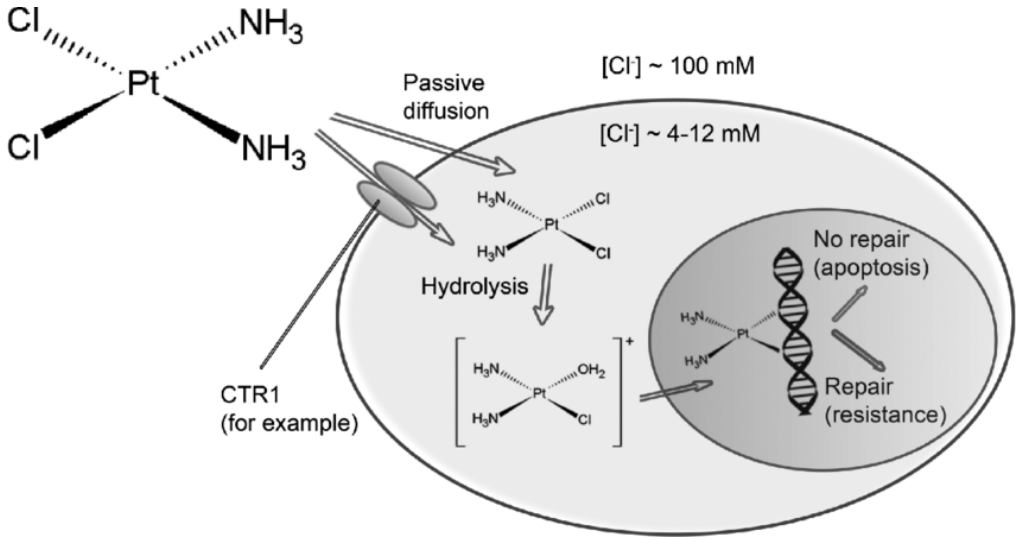


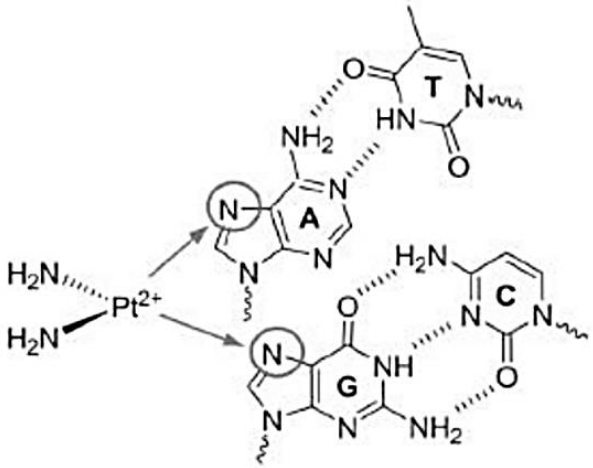
thymine

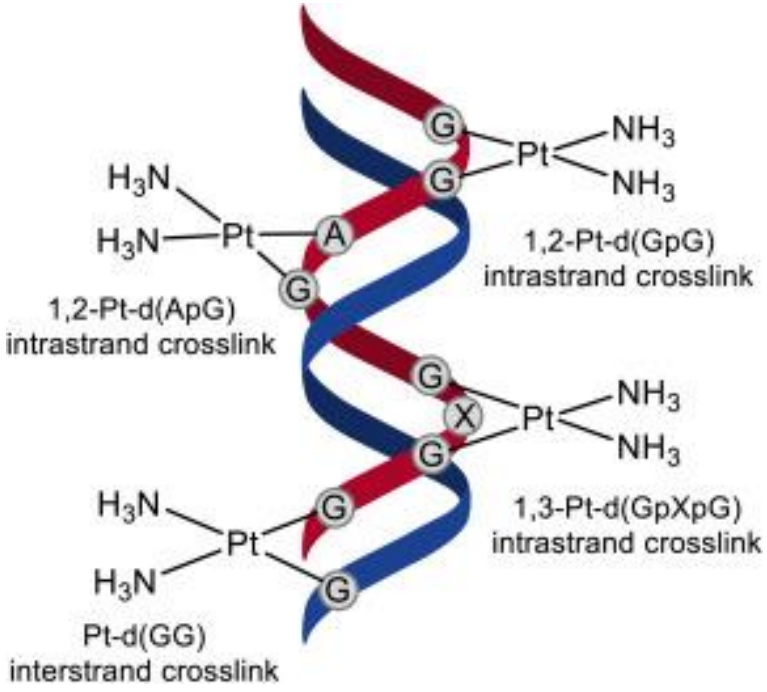


cytosine




Cl
NH3
Pt
Cl
NH3
Passive
diffusion
[Cl-] ~ 100 mM
[Cl-] ~ 4-12 mM
Hydrolysis
No repair
(apoptosis)
Repair
(resistance)
CTR1
(for example)


H2N
H2N
Pt2+
NH2
T
HN
O
A
C
G
NH
NH2


G
G
Pt
NH3
NH3
H3N
H3N
Pt
A
G
1,2-Pt-d(GpG)
intrastrand crosslink
1,2-Pt-d(ApG)
intrastrand crosslink
G
X
G
Pt
NH3
NH3
1,3-Pt-d(GpXpG)
intrastrand crosslink
H3N
H3N
Pt
G
G
Pt-d(GG)
interstrand crosslink

Trans-platin is kinetically more labile (due to trans effect) and undergoes rapid and non-specific binding.

Trans-platin, is known to be biologically inactive because of the diversity of qualitative and quantitative DNA adducts that it forms compared with cisplatin

Toxic effects of Anticancer Pt-complexes

Pt is not biologically involved and the living system does not have any efficient mechanism to cope with the toxic effects pf Pt-complexes. Pt (II) being soft can interact like other heavy metals with the soft and border tissue sites (e.g. –SH, -$NH_{2,}$ etc.) of different enzymes. However, the toxicity largely depends on the nature of amine and acid ligands present in the Pt (II) complex.

Radioisotopes as therapeutic and in diagnostic

Metal complexes having radioactive nuclei find many applications in medicine, such as tumor, organ and tissue imaging. Early detection of cancer, e.g., by selective uptake and imaging of the tumor using a radioactive metal complex can facilitate surgical removal or chemotherapeutic treatment before the disease reaches an advanced stage. Ideally, radioisotopes used for diagnostic purposes should be short lived, emit high energy γ photons and emit no α or β particles.

Diagnostic radiopharmaceuticals

- **Isotope must emit high energy particle such as γ-ray**
- **Emitted particle must have high penetrating power**
- **Isotope must have short half-life, preferably few hours**

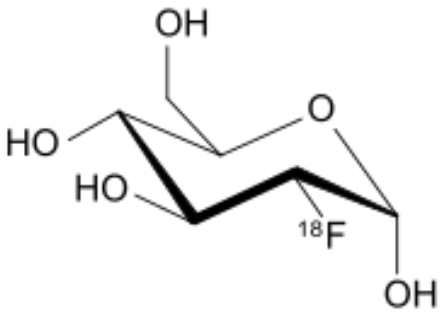
Therapeutic radiopharmaceuticals

- **Isotope preferably emit low energy particle**
- **Emitted particle must have low penetrating power**
- **Isotope must have high half-life, few days to few years**

Radionuclides most commonly employed in diagnostic nuclear medicine

Radionuclide	$t_{½}$	Energy (KeV)
^{57}Co	271d	836
^{67}Ga	78h	1,001
^{99m}Tc	6h	140
^{111}In	67h	172, 247
^{113m}In	104m	392
^{123}I	13h	1,230
^{169}Yb	32d	207
^{197}Hg	64h	159
^{201}Tl	72h	135, 167

Positron emission tomography (PET scan): Positron emission tomography (PET) is a nuclear medicine, functional imaging technique that is used to observe metabolic processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. The biologically active molecule chosen for PET is fludeoxyglucose (FDG), an analogue of glucose, the concentrations of tracer imaged will indicate tissue metabolic activity as it corresponds to the regional glucose uptake. One of the main differences between PET scans and other imaging tests like CT scan or magnetic resonance imaging (MRI) is that the PET scan reveals the cellular level metabolic changes occurring in an organ or tissue. This is important and unique because disease processes often begin with functional changes at the cellular level. A PET scan can often detect these very early changes whereas a CT or MRI detect changes a little later as the disease begins to cause changes in the structure of organs or tissues.



Fludeoxyglucose (^{18}F) also commonly called fluorodeoxyglucose (^{18}F-FDG) is a radiopharmaceutical used in the medical imaging modality positron emission tomography (PET). Chemically, it is 2-deoxy-2-(18F)fluoro-D-glucose, a glucose analog, with the positron-emitting radionuclide fluorine-18 substituted for the normal hydroxyl group at the C-2 position in the glucose molecule. The labeled ^{18}F-FDG compound has a relatively short shelf life which is dominated by the physical decay of ^{18}F with a half-life of 109.8 minutes, or slightly less than 2 hours. It decays by positron emission 97% of the time and electron capture 3% of the time. PET tracers emit positrons that annihilate with electrons up to a few millimeters away, causing two gamma photons to be emitted in opposite directions. A PET scanner detects these emissions "coincident" in time, which provides more radiation event localization information.

^{18}F-FDG, as a glucose analog, is taken up by high-glucose-using cells such as brain, brown adipocytes, kidney, and cancer cells, where phosphorylation prevents the glucose from being released again from the cell, once it has been absorbed. The 2-hydroxyl group (—OH) in normal glucose is needed for further glycolysis (metabolism of glucose by splitting it), but ^{18}F-FDG is missing this 2-hydroxyl. Thus, in common with its sister molecule 2-deoxy-D-glucose, FDG cannot be further metabolized in cells. The ^{18}F-FDG-6-phosphate formed when 18F-FDG enters the cell thus cannot move out of the cell before radioactive decay. As a result, the distribution of ^{18}F-FDG is a good reflection of the distribution of glucose uptake and phosphorylation by cells in the body.

After ^{18}F-FDG decays radioactively, however, its 2-fluorine is converted to $^{18}O^{-}$, and after picking up a proton H+ from a hydronium ion in its aqueous environment, the molecule becomes glucose-6-phosphate labeled with harmless nonradioactive "heavy oxygen" in the hydroxyl at the C-2 position. The new presence of a 2-hydroxyl now allows it to be metabolized normally in the same way as ordinary glucose, producing non-radioactive end-products.

- Cancer
- heart problems
- brain disorders
- problems with the central nervous system