

Anti-cancer compounds / Antineoplastic Agents, chapter 38

Neoplasm: New and diseased form of tissue growth

Benign (godartet) neoplasm: Easy to separate from surrounding tissue,
no metastases

Malign (ondartet) neoplasm: Invassive to surrounding tissue
Metastases } **Cancer**

Metastase: Secondary tumors, different location
Malign cells separated from primary tumor
and spread by vascular- or lymph systh.

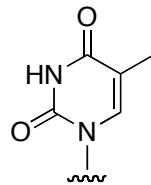
Terminology differents types of cancer confusing

Cancer Therapy

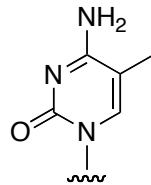
- Surgery
- Radiation
- Immunologican Therapy (interferons - Incr. prod. T-cells and B cells)
- Chemotherapy
 - Alkylolation Agents
 - Antimetabolites / Nucleoside Analogs
 - Antibiotics
 - Antimitotic Agents
 - Micellaneous Antineoplastic Agents
 - Hormonal Therapy

Alkylating Agents

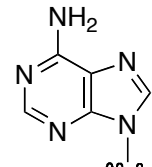
DNA Bases - Nucleophilic Centra



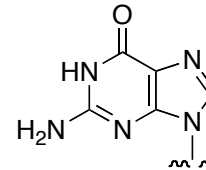
Thymin



Cytosin

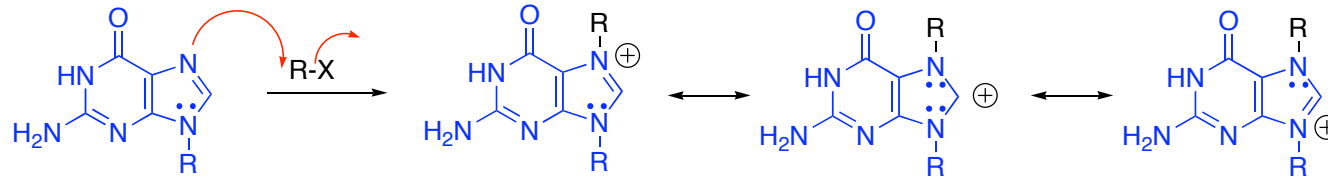


Adenine

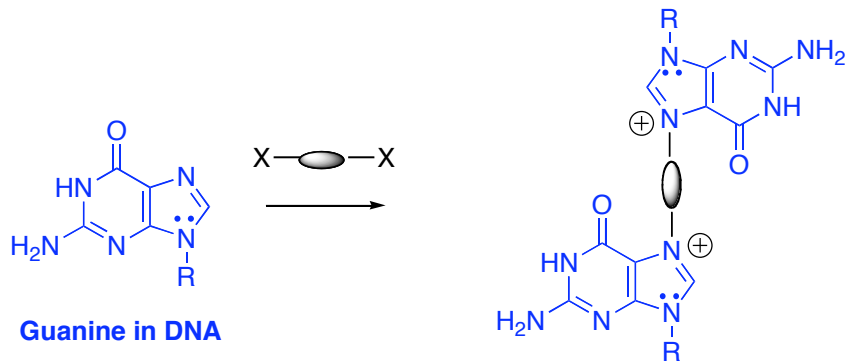


Guanine

Also O in phosphate
may be alkylated



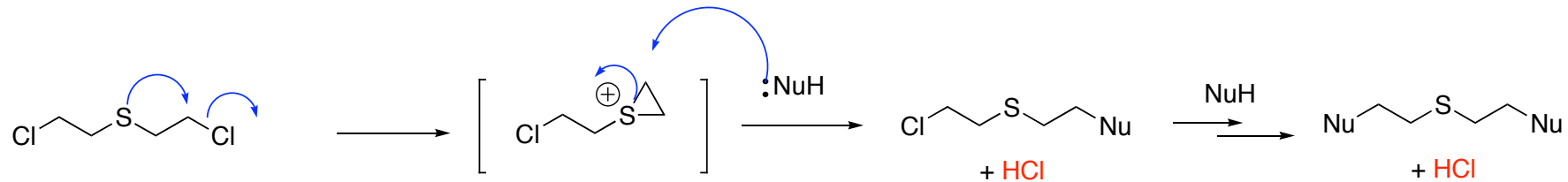
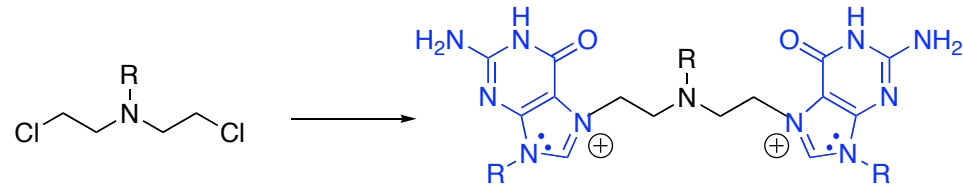
Guanine in DNA



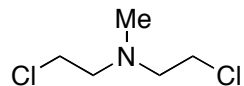
Guanine in DNA

Alkylating Agents

- 1) Nitrogen mustards
- 2) Other alkylation agents
- 3) Pt-complexes



Sulfur mustard
Mustard gas
Yprite
Worlds war I (1917)
Impurity smell like mustard / garlic

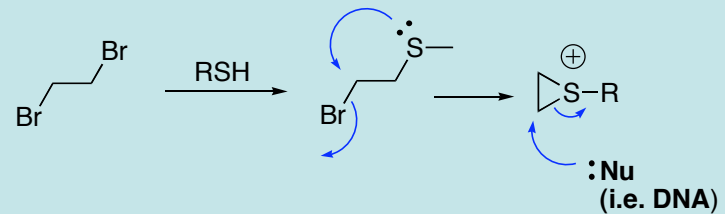


Mechlorethamine
FDA 1949

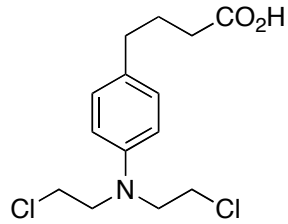
Rel. selective tox. to lymphoid tissue
(Hodkins disease, Lymphomas)

More water sol.

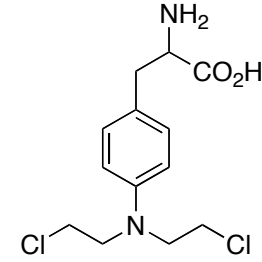
Metabolism of alkyl halides Phase II conjug. glutathion



Tox. to rapid proliferating cells (short time for DNA repair)



Chlorambucil
Leukeran®,



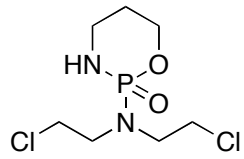
Melfalan
Alkeran®,



Aryl decrease reactivity

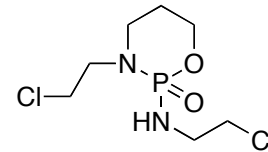
L-isomer

Active transport mech (L-AA)



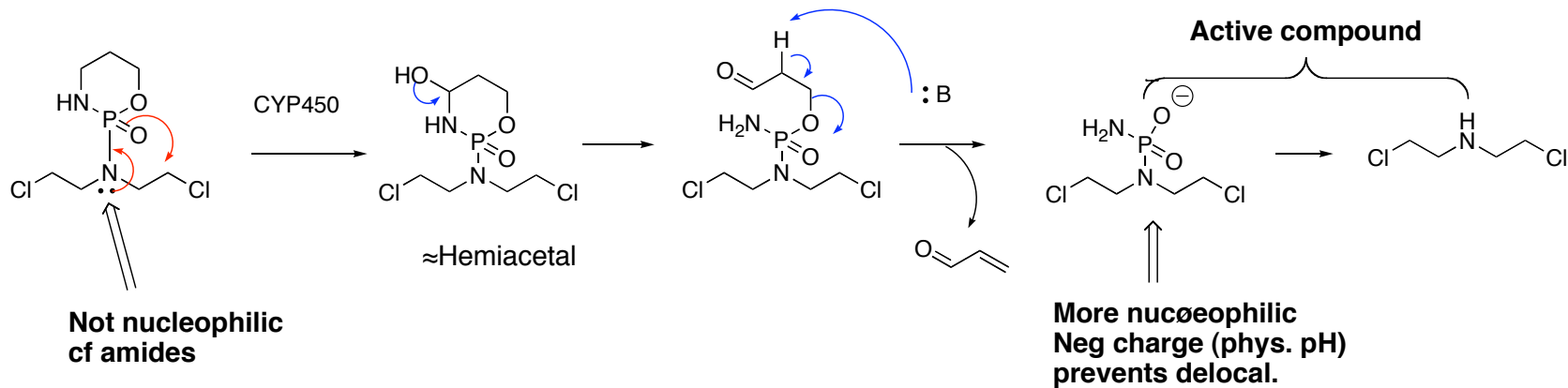
Cyclophosphamide
Sendoxan®

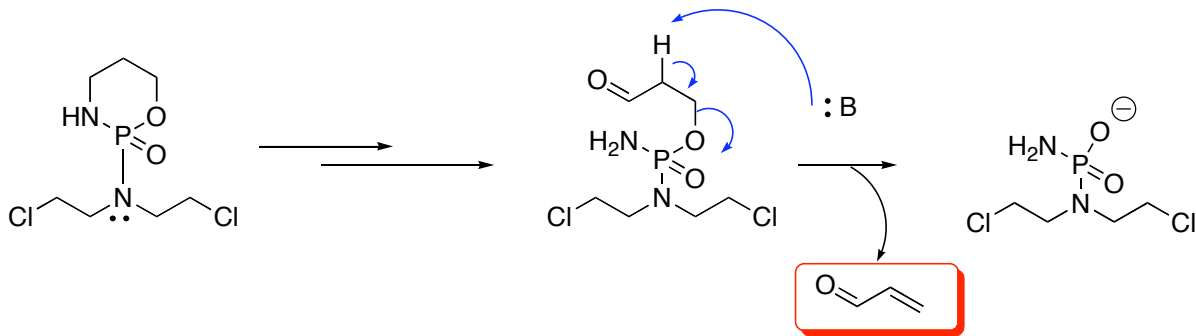
Pro-drug



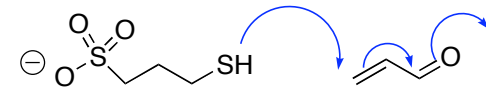
Ifosfamide
Holoxan®

Pro-drug





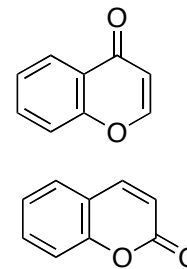
MESNA Co-admin.



Activation by CYP450 (CYP3A4); enzyme inducing drugs may increase activity



CYP3A4 inhibitors



**Flavenoid / coumarine der
see p 225**

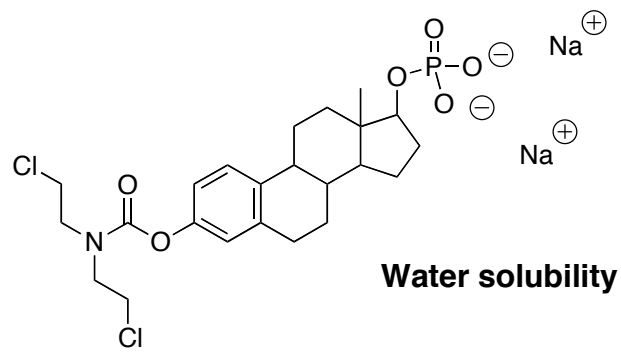


Decrease activation of cyclophosphamide

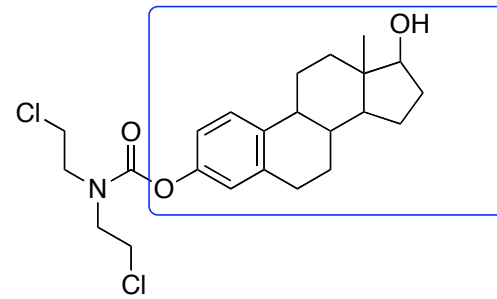
Estramustine phosphate

Estracyt®

Pro-drug



1) Oral absorb
2) Fast metabol.



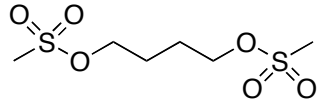
Estradiol
Carry to cells with
estrogenic receptors

Estrogenic (Anti-androgenic) effect prostate cancer
Cleaved to active alkylating agent?

Alkylating Agents

- 1) Nitrogen mustards
- 2) Other alkylation agents
- 3) Pt-complexes

Busulfan

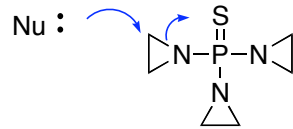


Not reg. N

Mono or dialkylation

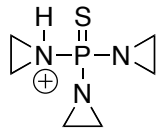
Better leav. gr, not 3-embered ring intermed
cf dimethyl sulfate

Thiotepa



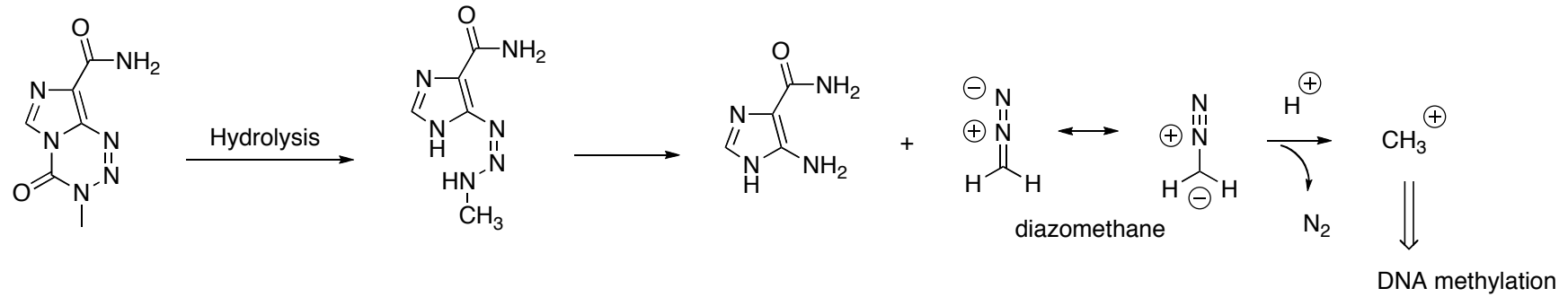
Not reg. N

Even more reactive at low pH



Temozolomide

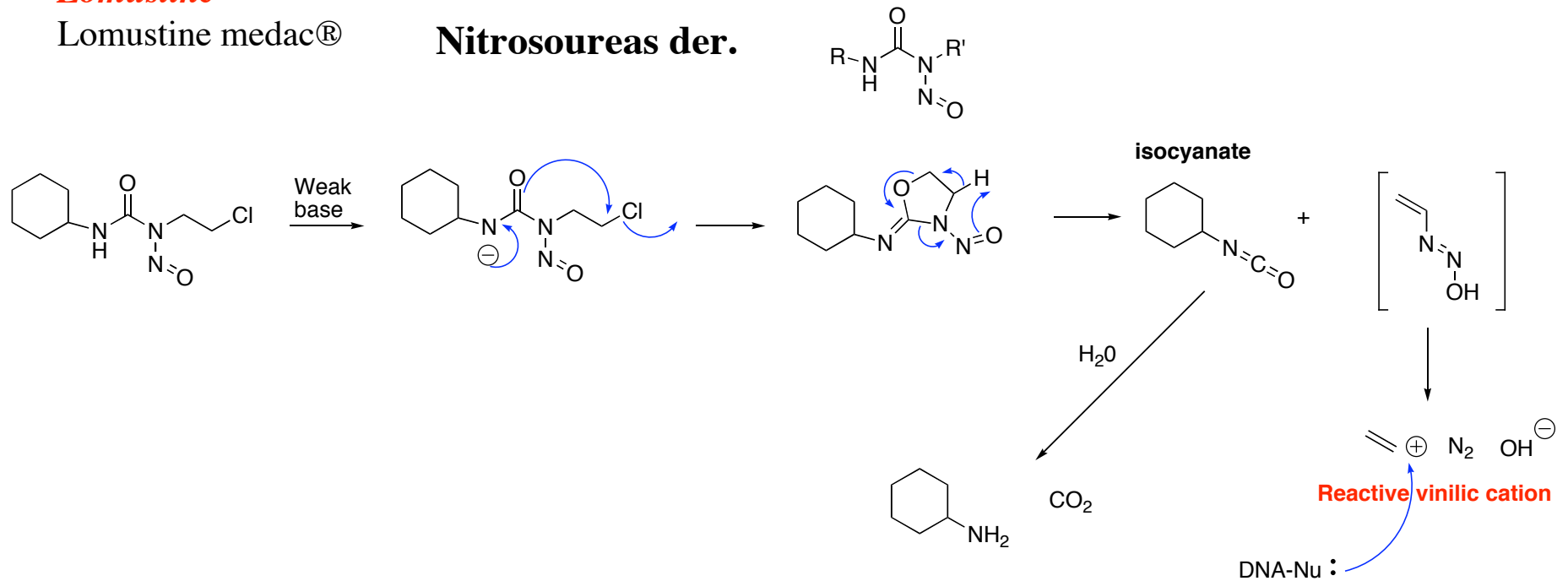
Temodal®



Lomustine

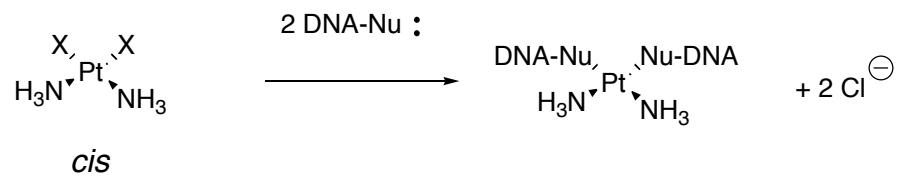
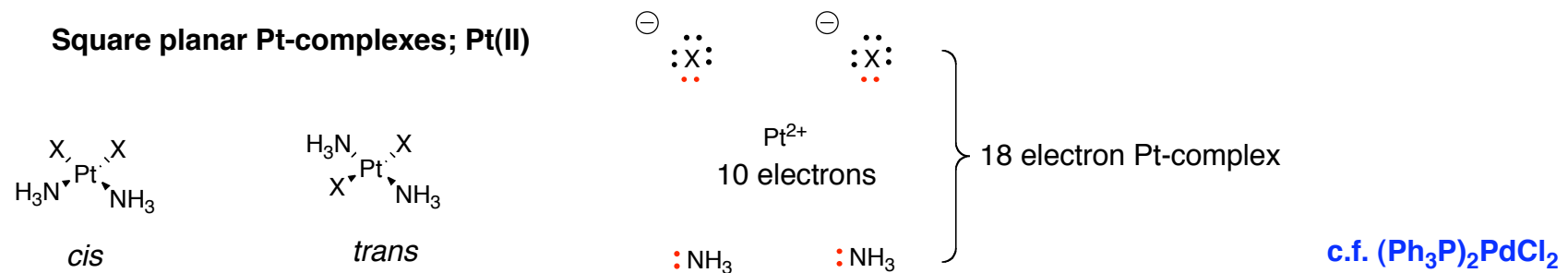
Lomustine medac®

Nitrosoureas der.

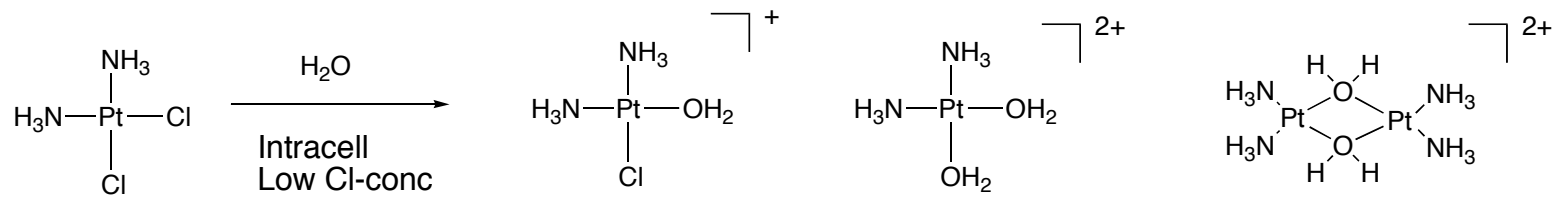


Alkylating Agents

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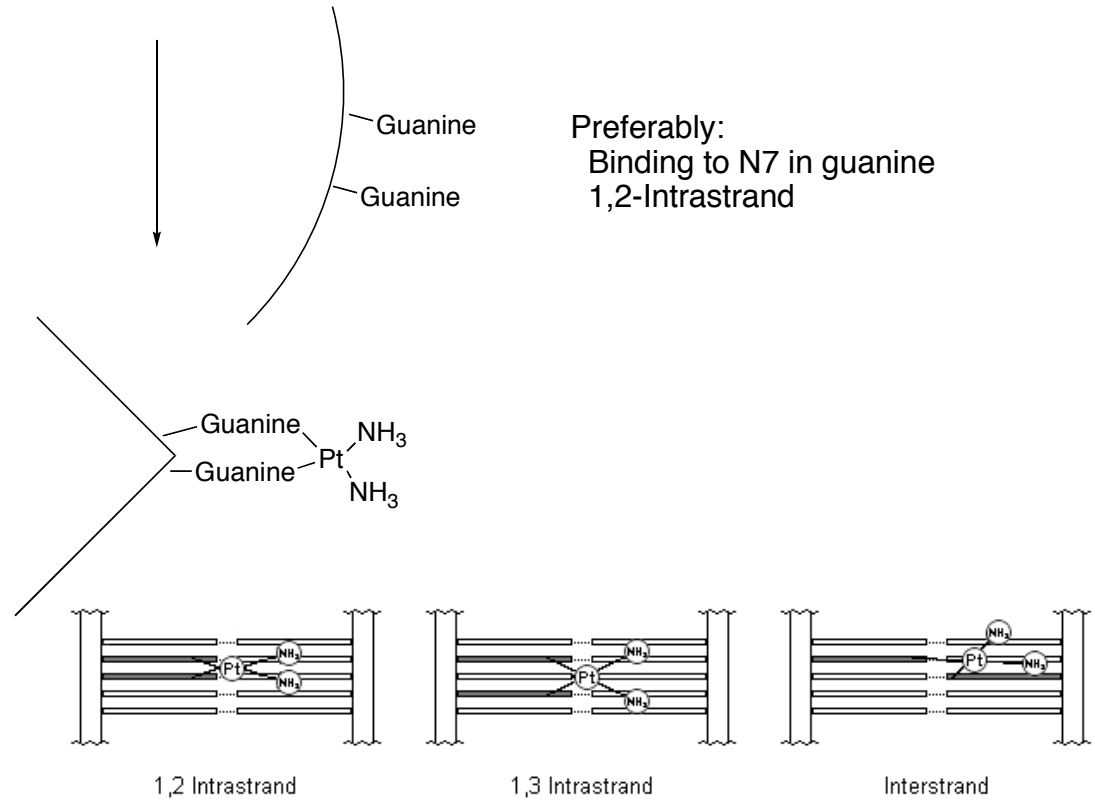
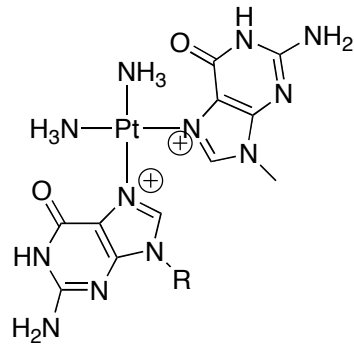
(Complexes with trans isomers are more readily recognized and repaired)



Pt(II) [as Pd(II)] electrophilic
Nucleophilic subst.

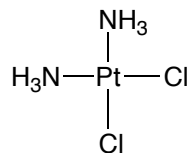
Most probably

Preferably:
Binding to N7 in guanine
1,2-Intrastrand



Cisplatin

Platinol® Platistin®



Carboplatin

Carboplatin® Carbosin® Paraplatin®

More stabile comp. (reacts less readily with water)

