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MEDICINAL CHEMISTRY - II

UNIT 1

TOPIC :

- **Miscellaneous : Cisplatin, Mitotane.**



Miscellaneous

- Miscellaneous antineoplastic agents are a group of anticancer drugs that do not fit neatly into standard chemotherapy categories such as alkylating agents, antimetabolites, plant products, or antibiotics.
- These agents often have unique mechanisms of action or target specific pathways in cancer cells, making them useful in specialized or combination therapies.

Example

- Cisplatin,
- Mitotane.

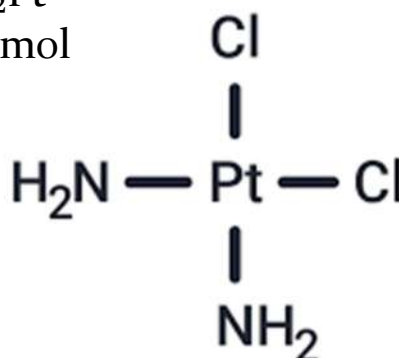


Cisplatin

- Cisplatin is a **platinum-based chemotherapeutic agent** used widely in **solid tumors**.
- Discovered in 1965, it is one of the first metal-containing anticancer drugs.
- Administered **intravenously**, it has poor oral bioavailability.
- Used in **testicular cancer, ovarian cancer, bladder cancer, lung cancer, and head & neck cancers**.

Chemical Structure

- **IUPAC Name:** cis-Diamminedichloroplatinum(II)
- **Molecular Formula:** $\text{Cl}_2\text{H}_6\text{N}_2\text{Pt}$
- **Molecular Weight:** 300.05 g/mol
- **Chemical Structure**



Mechanism of Action

- **Activation:**
 - Chloride ligands are replaced by **water molecules (aquation)** inside the cell → forms reactive **platinum complex**.
- **DNA Binding:**
 - Cisplatin forms **covalent bonds with purine bases (mainly guanine)** → causes **DNA cross-linking** (intra- and inter-strand).
- **Inhibition of DNA Replication & Transcription:**
 - Cross-links distort DNA helix → blocks DNA replication and transcription.
- **Cell Cycle Effect:**
 - **Non-phase specific**, affects both dividing and non-dividing cells.
- **Cytotoxicity:**
 - Leads to **apoptosis** due to DNA damage and failed repair.

Synthesis of Cisplatin

1. Starting Material:

- Potassium tetrachloroplatinate(II) $[K_2PtCl_4]$

2. Reaction with Ammonia:

- $K_2PtCl_4 + NH_3 \rightarrow [Pt(NH_3)_2Cl_2]$ (cisplatin)

3. Purification:

- Precipitation and crystallization to obtain **clinically pure cisplatin**.

Uses

1. Solid tumors:

- Testicular cancer, ovarian cancer, bladder cancer, lung cancer, head and neck cancers.

2. Combination therapy:

- Often used in regimens like **BEP (Bleomycin, Etoposide, Cisplatin)** for testicular cancer.

3. Side Effects:

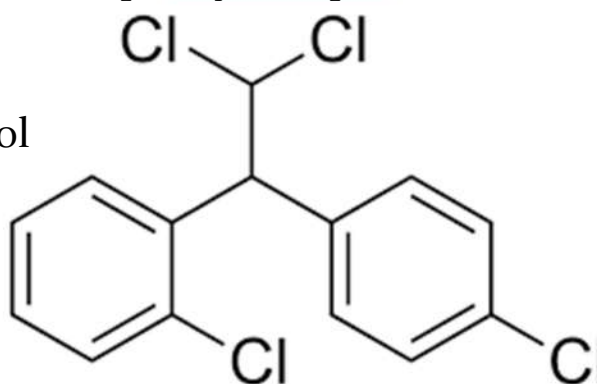
- Nephrotoxicity (dose-limiting), ototoxicity, peripheral neuropathy, nausea, vomiting, myelosuppression, and electrolyte disturbances.

Mitotane

- Mitotane is a **synthetic derivative of the insecticide DDT** and classified as an **adrenolytic and cytotoxic agent**.
- Primarily used in the treatment of **adrenocortical carcinoma (ACC)** and for **Cushing's syndrome** secondary to adrenal carcinoma.
- Administered **orally**, it has **poor water solubility** and requires **high-fat meals** for absorption.
- Selectively **destroys adrenal cortex cells** and inhibits **steroidogenesis**.

Chemical Structure

- **IUPAC Name:** 1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane
- **Molecular Formula:** $C_{14}H_9Cl_3$
- **Molecular Weight:** 256.48 g/mol
- **Chemical Structure**



Mechanism of Action

- **Adrenolytic Effect:**
 - Mitotane selectively accumulates in the **zona fasciculata and zona reticularis** of adrenal cortex.
 - Causes **necrosis of adrenal cortical cells**, reducing cortisol production.
- **Inhibition of Steroidogenesis:**
 - Inhibits **11 β -hydroxylase** and **cholesterol side-chain cleavage enzyme** → reduces cortisol and aldosterone synthesis.
- **Cytotoxic Effect:**
 - Induces **apoptosis in adrenal cortical cells** → used in adrenocortical carcinoma.
- **Pharmacokinetics:**
 - Lipophilic → accumulates in **adipose tissue**, with **slow onset** and **long half-life (~18–159 days)**.

Synthesis of Mitotane

1. Starting Materials:

- o-Chlorobenzyl chloride and p-chlorobenzyl chloride

2. Reaction:

- Friedel-Crafts alkylation using **aluminum chloride (AlCl_3)** → forms **dichlorodiphenylethane derivative**

3. Purification:

- Crystallization to obtain **pharmaceutical-grade mitotane**

Uses

1. Adrenocortical carcinoma (ACC):

- First-line therapy for **inoperable or metastatic ACC**.

2. Cushing's syndrome:

- Secondary therapy in **adrenal carcinoma-induced hypercortisolism**.

3. Side Effects:

- Gastrointestinal disturbances (nausea, vomiting, diarrhea), lethargy, dizziness, rash, hepatic toxicity, neurological symptoms (confusion, ataxia), and adrenal insufficiency.