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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.

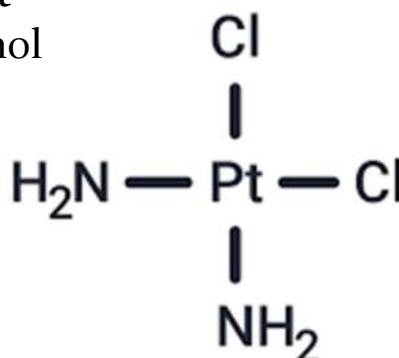


## Cisplatin

- 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.

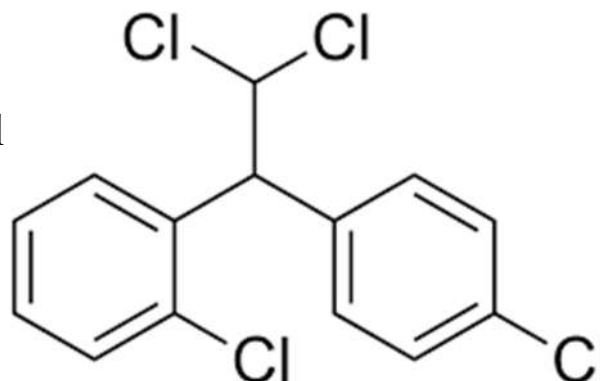
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## Mitotane

- 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  $11\beta$ -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 ( $\text{AlCl}_3$ ) → 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.

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