BP501T · B.Pharm Semester V · Theory Notes

Biomedicinal Chemistry

Unit IV — Antineoplastic Agents

Unit IV (6 hours)

Pills & Python Notes

From-zero teaching standard: every technical term is defined before use.

Syllabus coverage: Unit IV (6 hours).

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CHAPTER 6: Antineoplastic Agents (Unit IV)

Subject: BP501T Biomedicinal Chemistry | **Unit:** IV | **Chapter 6 — Antineoplastic Agents Drugs covered (25):** Mechlorethamine, Cyclophosphamide, Melphalan, Chlorambucil, Busulfan, Thiotepa, Mercaptopurine*, Thioguanine, Fluorouracil, Floxuridine, Cytarabine, Methotrexate*, Azathioprine, Dactinomycin, Daunorubicin, Doxorubicin, Bleomycin, Etoposide, Vinblastine, Vincristine, Paclitaxel, Camptothecin, Cisplatin, Mitotane, Carboplatin (* = starred for synthesis)

6.1 Learning Objectives

After studying this chapter you will be able to:

1 Define neoplasm, cancer, metastasis, cytotoxic drug, and antimetabolite in simple words.

2 Explain in one paragraph why anticancer drugs damage normal dividing cells too (bone marrow, gut, hair).

3 Classify the 25 antineoplastic agents into their chemical classes with two examples each.

4 Describe the mechanism of action of each class: alkylating agents (nitrogen mustards, alkyl sulfonates, aziridines), antimetabolites (purine/pyrimidine analogues, antifolates), antitumor antibiotics (anthracyclines), plant alkaloids (vinca alkaloids, taxanes), topoisomerase inhibitors, and platinum compounds.

5 Draw/describe the chemical scaffold and key substituents of each drug and state the therapeutic uses of every drug listed.

6 Write the complete synthesis of Mercaptopurine and Methotrexate with starting materials, numbered steps, reagents, conditions, and named intermediates.

7 State the SAR rules of nitrogen mustards, antimetabolites, antifolates, anthracyclines, vinca alkaloids, taxanes, and platinum compounds.

8 Counsel a patient (as a pharmacist) on the safe handling, major toxicities, and rescue measures of these drugs (mesna, leucovorin, hydration, extravasation care).

6.2 Definitions

- **Neoplasm:** A "new growth" — a lump of cells growing in an uncontrolled way. From Greek *neo* (new) + *plasma* (formation). A tumour is a neoplasm you can often feel or see.
- **Cancer (malignant neoplasm):** A neoplasm whose cells not only grow uncontrollably but also **invade** nearby tissues and **spread** (metastasise) to distant organs. Benign tumours grow but do not invade or spread.
- **Metastasis:** The spread of cancer cells from the original tumour through blood or lymph to form new tumours in distant organs (e.g., breast cancer spreading to bone).
- **Antineoplastic agent:** A drug used against (*anti-*) new abnormal growth (*neoplastic*). The formal name for an anticancer/chemotherapy drug.

- **Cytotoxic:** "Cell-killing" (*cyto* = cell, *toxic* = poisonous). Most anticancer drugs are cytotoxic — they kill cells, preferably cancer cells.
- **Alkylation:** Attaching an **alkyl group** (a carbon chain fragment, e.g., $–CH_2CH_2–$) to a molecule — here, to DNA. Alkylating agents weld extra carbon pieces onto DNA so it cannot be read or copied.
- **Cross-link:** A chemical bridge joining two strands of DNA (or two parts of one strand) so the strands cannot separate during copying — like stapling two pages of a book together so you cannot turn them.
- **Antimetabolite:** A drug shaped almost exactly like a natural building block of the cell (a purine, pyrimidine, or folic acid) but with a small, deadly difference. The cell mistakes it for the real block, builds it into DNA/RNA or an enzyme, and the machinery jams. A "fake brick" in the wall.
- **Intercalation:** Slipping a flat drug molecule **between** the stacked base pairs of DNA, like sliding a playing card between the pages of a closed book — the book can no longer close or be read properly.
- **Prodrug:** A drug given in an inactive form that the body (usually the liver) converts into the active form.
- **Myelosuppression:** Suppression of the bone marrow — the factory that makes blood cells slows down, so white cells, red cells, and platelets fall. The commonest serious side effect of chemotherapy.
- **Vesicant:** A drug that causes severe blistering and tissue death if it leaks out of the vein into surrounding skin (**extravasation**). Anthracyclines and vinca alkaloids are vesicants.

6.3 Terminology Word Bank

Term	Meaning (in plain words)
Benign / Malignant	Benign = grows locally, does not spread (usually not life-threatening). Malignant = invades and spreads = cancer
Remission	The cancer has shrunk or disappeared on tests (not the same as "cured" — it can return)
Adjuvant therapy	Chemotherapy given **after** surgery to kill leftover invisible cells
Neoadjuvant therapy	Chemotherapy given **before** surgery to shrink the tumour first
Palliative	Treatment meant to relieve suffering, not to cure (used in advanced cancer)
Regimen	A fixed combination + schedule of anticancer drugs, e.g., CHOP, ABVD, MOPP
Nadir	The lowest point of blood counts after chemotherapy (usually 7–14 days), when infection risk is highest
Neutropenia	Dangerously low neutrophils (infection-fighting white cells)
Alopecia	Hair loss — because hair-follicle cells divide fast, chemotherapy hits them
Emetogenic	Likely to cause vomiting (cisplatin is the most emetogenic of all)
Cell-cycle specific	Drug kills only in a particular phase of the cell cycle (e.g., S or M phase)
Cell-cycle non-specific	Drug kills in any phase, including resting cells (alkylators, platinum drugs)

Term	Meaning (in plain words)
Thymineless death	Cell death caused by blocking thymine (T) supply — the cell tries to copy DNA without the letter T and dies
Rescue therapy	A second drug given to protect normal cells from the first drug (leucovorin after methotrexate; mesna with cyclophosphamide)
Cumulative toxicity	Damage that adds up with every dose over a lifetime (doxorubicin heart damage; bleomycin lung damage)
DPD / TPMT	Body enzymes that break down 5-fluorouracil (DPD) and mercaptopurine (TPMT) — patients lacking them suffer severe toxicity

6.4 Explanation — what is cancer, from absolute zero

Technical concept. Cancer is a disease of uncontrolled cell division caused by accumulated mutations in genes that control growth (oncogenes switched on, tumour-suppressor genes switched off). Malignant cells divide without normal stop signals, invade neighbouring tissue, and metastasise.

Simple explanation. Your body is made of about 30 trillion cells, and every day old cells die and new cells are born by division — one cell copies itself and splits into two. Normally there are strict traffic rules: divide only when told, stop when told, die when old. **Cancer is what happens when one cell's rulebook gets damaged** (its genes mutate): it starts dividing non-stop, ignores "stop" signals, refuses to die, and its daughters crawl into nearby areas and travel through blood to start new colonies (metastasis). One rebel cell becomes a lump (tumour) of millions of rebels.

Example. A normal skin cell divides only to replace a lost neighbour, then stops. A melanoma (skin cancer) cell divides again and again, piles up into a dark growing mole, and can send cells to the lungs. Chemotherapy targets exactly this property: **cells that divide fast die first** when their DNA-copying machinery is attacked.

Key takeaway. Cancer = broken growth rules endless division + invasion + spread. Anticancer drugs exploit the one thing cancer cells do most: divide rapidly.

6.5 Explanation — the cell cycle in 60 seconds (why these drugs work, and why they hurt)

Technical concept. A dividing cell passes through ordered phases: **G1** (growth) **S** (DNA synthesis — the genome is copied) **G2** (preparation) **M** (mitosis — the cell splits). Cells not dividing rest in **G0**. Drugs that attack DNA copying work best in S phase; drugs that attack the splitting machinery work in M phase; alkylators damage DNA in any phase.

Simple explanation. Imagine a photocopy shop that must (1) gather paper — G1, (2) photocopy the master document — S phase, (3) staple and sort — G2, (4) hand out two complete sets — M phase. Chemotherapy drugs are saboteurs placed at different counters: **antimetabolites** swap fake paper into the photocopier (S phase), **vinca alkaloids and taxanes** jam the paper-cutting/stapling machines (M phase), and **alkylating agents** pour glue on the master document itself (any phase). Normal fast-dividing cells — bone marrow (blood factory), gut lining, hair roots — use the same shop, so they get sabotaged too. That is why chemotherapy causes low blood counts, mouth sores/diarrhoea, and hair loss.

Example. Methotrexate starves the S-phase photocopier of ink (folate); vincristine breaks the M-phase delivery trucks (microtubules); cyclophosphamide glues the master DNA document shut in every phase.

Key takeaway. S-phase drugs (antimetabolites) and M-phase drugs (vinca, taxanes) are **cell-cycle specific** — they spare resting cells. Alkylators and platinum drugs are **cell-cycle non-specific** — they damage DNA whenever they meet it.

6.6 Classification of antineoplastic agents

Flowchart-style classification (memorise this tree):

```
ANTINEOPLASTIC AGENTS (25 drugs)
│
├── A. ALKYLATING AGENTS — weld alkyl groups onto DNA → cross-links (cell-cycle NON-specific)
│      ├── A1. Nitrogen mustards: Mechlorethamine, Cyclophosphamide, Melphalan, Chlorambucil
│      ├── A2. Alkyl sulfonates: Busulfan
│      └── A3. Aziridines (ethylenimines): Thiotepa
│
├── B. ANTIMETABOLITES — fake building blocks; jam DNA/RNA synthesis (S-phase specific)
│      ├── B1. Purine analogues: Mercaptopurine*, Thioguanine, Azathioprine (prodrug of 6-MP)
│      ├── B2. Pyrimidine analogues: Fluorouracil, Floxuridine, Cytarabine
│      └── B3. Antifolates: Methotrexate*
│
├── C. ANTITUMOUR ANTIBIOTICS — natural products that attack DNA directly
│      ├── C1. Anthracyclines (intercalate + block topoisomerase II): Dactinomycin*, Daunorubicin,
Doxorubicin
│      └── C2. Glycopeptide (cuts DNA with free radicals): Bleomycin
│
├── D. PLANT ALKALOIDS — attack microtubules (M-phase specific)
│      ├── D1. Vinca alkaloids (PREVENT microtubule assembly): Vinblastine, Vincristine
│      └── D2. Taxanes (PREVENT microtubule disassembly): Paclitaxel
│
├── E. TOPOISOMERASE INHIBITORS — trap the DNA-untangling enzymes
│      ├── E1. Topoisomerase II inhibitor: Etoposide
│      └── E2. Topoisomerase I inhibitor: Camptothecin (lead; clinical derivatives: irinotecan,
topotecan)
│
├── F. PLATINUM COMPOUNDS — platinum cross-links DNA like alkylators (NON-specific)
│         Cisplatin, Carboplatin
│
└── G. MISCELLANEOUS — Mitotane (adrenal-cortex destroyer)
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(*Dactinomycin is strictly an actinomycin antitumour antibiotic grouped here with the anthracyclines for teaching convenience;* = starred for synthesis in this chapter: Mercaptopurine, Methotrexate.)

6.7 Mechanisms of action — class by class

6.7a Alkylating agents — the DNA staplers (cell-cycle non-specific)

Technical concept. In the body, the $–CH_2CH_2Cl$ arms of a nitrogen mustard undergo intramolecular SN2 displacement: the nitrogen lone pair ejects chloride, forming a highly electrophilic **aziridinium ion** (a three-membered ring with positively charged nitrogen). The aziridinium carbon is attacked by the most nucleophilic site on DNA, the **N7 of guanine**. After the first alkylation, the second $–CH_2CH_2Cl$ arm forms a second aziridinium and alkylates a guanine on the **opposite strand** an **interstrand cross-link**. The two DNA strands can no longer separate, so replication and transcription halt apoptosis. Busulfan (alkyl sulfonate) works by SN2 displacement of methanesulfonate to give carbonium ions that alkylate guanines (mainly intrastrand cross-links). Thiotepa's three aziridine rings open in vivo (after conversion to TEPA) to alkylate DNA similarly.

Simple explanation. Think of DNA as a zipper. An alkylating agent is a drop of superglue with two sticky ends: one end sticks to the left side of the zipper (one guanine), the other end sticks to the right side (a guanine on the opposite strand). Now the zipper cannot open — the cell cannot unzip its DNA to copy it, so it dies. Nitrogen mustards first curl into a tiny charged ring (aziridinium) that is desperate to grab DNA; busulfan fires carbonium-ion "darts"; thiotepa opens its three little triangle rings and grabs DNA with each.

Example. Mechlorethamine's two $–CH_2CH_2Cl$ arms each become aziridinium rings; each ring is opened by a guanine N7 — first on one strand, then on the opposite strand — stapling the double helix shut. Cyclophosphamide does exactly the same, but only after the liver unwraps its "masked" mustard (phosphoramide mustard).

Key takeaway. Alkylators = electrophilic attack on guanine N7 → DNA cross-links → replication blocked → cell death in **any** cell-cycle phase. Price of non-specificity: heavy bone-marrow suppression and a small risk of second cancers years later.

6.7b Antimetabolites — the fake bricks (S-phase specific)

Technical concept. Antimetabolites are structural analogues of endogenous purines, pyrimidines, or folate. They enter cells via normal nutrient transporters and are enzymatically converted ("activated") into fraudulent nucleotides/cofactors that (i) **inhibit key enzymes** of nucleotide biosynthesis, or (ii) are **incorporated into DNA/RNA**, producing non-functional nucleic acids that trigger apoptosis. Because DNA is synthesised only in S phase, these drugs kill mainly S-phase cells.

- **Purine analogues** (mercaptopurine, thioguanine): activated by HGPRT to thio-IMP/thio-GMP, which inhibit *de novo* purine synthesis (PRPP amidotransferase) and are incorporated into DNA/RNA.
- **Pyrimidine analogues:** 5-fluorouracil → FdUMP, a suicide inhibitor of **thymidylate synthase** (blocks dUMP → dTMP, so no thymine → "thymineless death"); FUTP incorporates into RNA. Cytarabine → Ara-CTP, which **inhibits DNA polymerase** and terminates the growing DNA chain (the arabinose 2'-OH points the wrong way, jamming the polymerase).
- **Antifolates** (methotrexate): bind **dihydrofolate reductase (DHFR)** ~1,000× more tightly than folate, blocking regeneration of tetrahydrofolate (THF) → no one-carbon units for thymidylate and purine synthesis → S-phase death. **Leucovorin (folinic acid)** rescue supplies ready-made reduced folate to normal cells.

Simple explanation. To copy its DNA in S phase, the cell orders genuine bricks — A, T, G, C letters and folate "mortar." Antimetabolites are counterfeit bricks smuggled into the delivery: the wall gets built with fake letters that don't fit, or the mortar never arrives, and the whole construction collapses. Mercaptopurine/thioguanine are fake G/A letters; 5-FU removes the letter T from the alphabet; cytarabine is a brick with a wrongly-angled corner that jams the bricklaying machine; methotrexate steals the mortar-mixing machine (DHFR) so no mortar is made at all.

Example. 5-FU becomes FdUMP inside the cell and sits permanently in the active site of thymidylate synthase — the enzyme that makes thymine. No thymine → DNA copies come out with missing letters → the cell self-destructs. This is "thymineless death."

Key takeaway. Antimetabolites must first be **activated by the cell's own enzymes** (HGPRT, kinases) — that is why they are selective for dividing cells — and they kill in **S phase** by enzyme inhibition, fraudulent incorporation, or both.

6.7c Antitumour antibiotics — DNA intercalators and cutters

Technical concept. Anthracyclines (daunorubicin, doxorubicin) and **dactinomycin** are flat, multi-ring molecules that **intercalate** between DNA base pairs; their attached sugar/peptide portions anchor in the minor groove. The intercalated complex **traps topoisomerase II** in its DNA-cleaving state, so the enzyme cuts DNA but cannot re-seal it → double-strand breaks → apoptosis. Anthracyclines additionally generate free radicals (quinone redox cycling) that damage DNA and heart muscle. **Bleomycin** works differently: its metal-binding domain chelates Fe^{2+}, binds O_2, and generates radicals that directly **cleave the DNA sugar backbone** (single- and double-strand breaks), especially in G2/M.

Simple explanation. Dactinomycin, daunorubicin and doxorubicin slide like flat cards between the rungs of the DNA ladder and then handcuff the repairman (topoisomerase II) mid-job — he has cut the ladder but can never glue it back. Bleomycin is a pair of molecular scissors: it grabs an iron atom, breathes in oxygen, and snips the DNA backbone wherever it lands.

Example. Doxorubicin's four-ring anthraquinone chromophore slides between base pairs while its daunosamine sugar grips the minor groove; topoisomerase II is frozen on the broken DNA. The same quinone that kills cancer also redox-cycles in heart muscle — the reason for cumulative cardiotoxicity.

Key takeaway. Intercalation + topoisomerase-II trapping (anthracyclines, dactinomycin) or iron–oxygen DNA scission (bleomycin) irreparable DNA breaks. Anthracyclines are **vesicants** and cumulatively **cardiotoxic**; bleomycin is cumulatively **lung-toxic** (pulmonary fibrosis).

6.7d Plant alkaloids — microtubule saboteurs (M-phase specific)

Technical concept. During mitosis, the cell builds **microtubules** (tubulin polymers) into the spindle that pulls chromosomes apart. **Vinca alkaloids** (vinblastine, vincristine) bind tubulin dimers and **prevent polymerisation** — no spindle forms chromosomes cannot separate metaphase arrest. **Taxanes** (paclitaxel) do the exact opposite: they bind assembled microtubules and **prevent depolymerisation** — the spindle freezes rigid and cannot disassemble mitotic arrest. Both trap the cell in M phase apoptosis.

Simple explanation. To split, the cell must build temporary scaffolding (microtubules) to drag the two chromosome sets apart, then dismantle it. Vinca alkaloids **steal the scaffolding pipes** so nothing gets built; paclitaxel **welds the scaffolding permanently** so it can never be taken down. Either way the cell is stuck mid-split and dies. They are mirror-image saboteurs of the same machine.

Example. Vincristine binds tubulin so the mitotic spindle never assembles — under the microscope you see cells frozen in metaphase with scattered chromosomes. Paclitaxel-treated cells show thick, frozen microtubule bundles that never disassemble.

Key takeaway. Vinca = no assembly; taxane = no disassembly. Both = M-phase arrest. Because nerves also depend on microtubules for transport, vinca alkaloids (especially vincristine) cause **peripheral neuropathy**.

6.7e Topoisomerase inhibitors — trapping the untanglers

Technical concept. Topoisomerases relieve the twisting tension of DNA: topoisomerase I cuts **one** strand, lets it swivel, and re-seals it; topoisomerase II cuts **both** strands, passes another segment through, and re-seals. **Camptothecin** traps the topoisomerase I–DNA cleavage complex (single-strand breaks become lethal when a replication fork collides with them in S phase). **Etoposide** traps the topoisomerase II–DNA cleavage complex (double-strand breaks). Trapping = the enzyme cuts but cannot re-seal.

Simple explanation. DNA is a twisted telephone cord. Topoisomerases are technicians who snip the cord, untwist it, and tape it back. Camptothecin and etoposide handcuff the technician **after the snip but before the taping** — the cord stays cut. When the S-phase copying machine runs into the cut, the damage becomes fatal.

Example. Camptothecin's intact lactone E-ring is the handcuff — it wedges into the topoisomerase I–DNA complex. If the lactone ring opens (which happens at blood pH), the handcuff falls off and the drug goes inactive; that is why the lactone must be protected in drug design (irinotecan, topotecan).

Key takeaway. Topo I inhibitor (camptothecin) single-strand breaks, S-phase; Topo II inhibitor (etoposide) double-strand breaks. Both convert a repair enzyme into a DNA-damaging weapon.

6.7f Platinum compounds — the metal cross-linkers (cell-cycle non-specific)

Technical concept. Cisplatin, cis-[$Pt(NH_3)_2Cl_2$], is unreactive in blood (high chloride keeps the chlorides on). Inside the cell (low chloride), water displaces the chlorides (**aquation**) → positively charged diaquo species → attracted to DNA → binds **N7 of adjacent guanines** forming 1,2-**intrastrand** cross-links (both bonds on the same strand, unlike nitrogen mustards). The platinum bends the helix ~34°, the damage is recognised by repair proteins, and failed repair triggers apoptosis. **Carboplatin** carries a bidentate cyclobutanedicarboxylate leaving group instead of chlorides → aquates much more slowly → same DNA lesion, but less kidney/ear toxicity and more marrow suppression.

Simple explanation. Cisplatin is a Trojan horse: quiet in the bloodstream, but once inside the cell it drops its two chloride "disguises," grabs the nearest guanines with its platinum hands, and staples two neighbouring rungs of the **same** DNA strand together, kinking the ladder. The cell's repair crew sees the kink, tries to fix it, fails, and orders the cell to die. Carboplatin is the same horse with heavier disguises — it unmasks slowly, so it is gentler on kidneys but hits the marrow harder.

Example. The **cis** geometry is everything: cisplatin's two reactive positions sit side by side so they can grip two adjacent guanines; **trans**platin (reactive groups opposite) cannot form the 1,2-intrastrand link and is inactive against cancer — a classic exam trap.

Key takeaway. Platinum drugs = aquation → intrastrand GpG cross-link → helix kink → apoptosis. Cisplatin: nephrotoxic, ototoxic, highly emetogenic (needs heavy hydration). Carboplatin: dosed by kidney function (Calvert formula, target AUC), marrow is the limit.

6.7g Mitotane — the adrenal destroyer

Technical concept. Mitotane (o,p'-DDD), a DDT analogue, is selectively taken up by and toxic to **adrenocortical cells** — it damages their mitochondria and blocks steroid synthesis enzymes (cholesterol side-chain cleavage, 11β-hydroxylase). The adrenal cortex atrophies.

Simple explanation. Mitotane is a poison with a postcode: it travels everywhere but only detonates inside the adrenal cortex, the small gland cap on each kidney that makes cortisol. Useful when that gland itself turns cancerous (adrenocortical carcinoma) or overproduces cortisol (Cushing syndrome).

Example. In adrenocortical carcinoma — a rare cancer of the cortisol-making gland — mitotane both shrinks the tumour and lowers the dangerous excess cortisol.

Key takeaway. Mitotane = selective adrenolytic (adrenal-cortex killer). Expect adrenal insufficiency — patients need steroid replacement and monitoring.

6.8 Master table — all 25 drugs at a glance

#	Drug	Chemical class	Key structure (scaffold + substituents)	Main uses
1	Mechlorethamine	Nitrogen mustard (aliphatic)	$CH_3–N(–CH_2CH_2Cl)_2$: tiny tertiary amine with methyl + two 2-chloroethyl arms	Hodgkin lymphoma (MOPP regimen), NHL; topical for cutaneous T-cell lymphoma
2	Cyclophosphamide	Nitrogen mustard (masked/prodrug, oxazaphosphorine)	Six-membered O–P(=O)–N ring; P carries $–N(–CH_2CH_2Cl)_2$	Leukemias, lymphomas (CHOP), breast, ovarian, myeloma, neuroblastoma; immunosuppression (lupus nephritis, GPA, transplant)

#	Drug	Chemical class	Key structure (scaffold + substituents)	Main uses
3	Melphalan	Nitrogen mustard (aromatic, amino-acid carrier)	p-[bis(2-chloroethyl)amino]-L-phenylalanine: mustard on phenyl ring of phenylalanine	Multiple myeloma, ovarian cancer; high-dose transplant conditioning
4	Chlorambucil	Nitrogen mustard (aromatic)	p-[bis(2-chloroethyl)amino]phenyl–butyric acid: mustard on phenyl + 4-carbon acid side chain	CLL, indolent NHL, Waldenström macroglobulinemia
5	Busulfan	Alkyl sulfonate	$CH_3SO_3–(CH_2)_4–OSO_3CH_3$: 4-carbon chain with methanesulfonate ester at each end	CML; conditioning before stem-cell transplant
6	Thiotepa	Aziridine (ethylenimine)	$(CH_2CH_2N)_3P=S$: P=S core with three aziridine (3-membered N) rings	Bladder cancer (intravesical), breast/ovarian, malignant effusions; conditioning
7	Mercaptopurine*	Purine antimetabolite	Purine ring with –SH at C6 (6-mercaptopurine)	ALL maintenance, AML; (also IBD — gastroenterology use)
8	Thioguanine	Purine antimetabolite	Purine with $–NH_2$ at C2 and –SH at C6 (2-amino-6-mercaptopurine)	AML, ALL
9	Fluorouracil (5-FU)	Pyrimidine antimetabolite	Uracil with –F at C5 (5-fluorouracil)	Colorectal, breast, GI, pancreatic cancers; topical: actinic keratosis, superficial basal cell carcinoma
10	Floxuridine (FUDR)	Pyrimidine antimetabolite (nucleoside)	5-FU base + 2'-deoxyribose sugar (5-fluoro-2'-deoxyuridine)	Hepatic arterial infusion for colorectal liver metastases
11	Cytarabine (Ara-C)	Pyrimidine antimetabolite (nucleoside)	Cytosine + arabinose sugar (2'-OH "up")	AML induction/consolidation ("7+3"), ALL, CML blast crisis; intrathecal for CNS leukemia
12	Methotrexate*	Antifolate antimetabolite	Pteridine ring (4-NH_2, N10–CH_3) + p-aminobenzoyl + glutamate tail	ALL, NHL, osteosarcoma, choriocarcinoma, breast; low-dose: RA, psoriasis, ectopic pregnancy
13	Azathioprine	Purine antimetabolite (prodrug)	6-MP with S-linked 1-methyl-4-nitroimidazole at C6	Transplant rejection prophylaxis, RA, Crohn's/ulcerative colitis, autoimmune hepatitis
14	Dactinomycin	Antitumour antibiotic (actinomycin)	Phenoxazinone chromophore + two cyclic pentapeptide lactone rings	Wilms tumour, rhabdomyosarcoma, Ewing sarcoma, gestational trophoblastic neoplasia

#	Drug	Chemical class	Key structure (scaffold + substituents)	Main uses
15	Daunorubicin	Anthracycline antibiotic	Tetracyclic quinone aglycone + daunosamine sugar at C7; –$COCH_3$ side chain	AML, ALL
16	Doxorubicin	Anthracycline antibiotic	Same as daunorubicin but –$COCH_2OH$ (14-hydroxy) side chain	Breast, lymphomas, sarcomas, bladder, thyroid, Wilms — broadest spectrum ("red devil")
17	Bleomycin	Glycopeptide antibiotic	Bithiazole DNA-binding tail + Fe-binding domain + disaccharide	Testicular (BEP), Hodgkin (ABVD), squamous cell head/neck/cervix
18	Etoposide	Topoisomerase II inhibitor (podophyllotoxin derivative)	Epipodophyllotoxin + β-D-glucose at C4; 4'-demethyl on pendant aryl	Testicular, small-cell lung cancer, lymphomas
19	Vinblastine	Vinca alkaloid (dimeric)	Catharanthine + vindoline halves joined C–C; N–CH_3 on vindoline half	Hodgkin (ABVD), testicular, Kaposi sarcoma, breast
20	Vincristine	Vinca alkaloid (dimeric)	Same dimer but N–CHO (formyl) instead of N–CH_3	ALL (children), Wilms, neuroblastoma, rhabdomyosarcoma; IV ONLY — fatal intrathecally
21	Paclitaxel	Taxane (diterpene)	Taxane 6-12-6 tricyclic core + oxetane ring + C13 N-benzoyl phenylisoserine side chain	Ovarian, breast, NSCLC, Kaposi sarcoma
22	Camptothecin	Topoisomerase I inhibitor (quinoline alkaloid)	Pentacyclic: quinoline + pyrroloquinoline + α-hydroxy lactone E-ring (20S)	Lead compound only (too toxic); derivatives irinotecan (colorectal), topotecan (ovarian, SCLC) used clinically
23	Cisplatin	Platinum compound	Square-planar Pt(II): cis-[$Pt(NH_3)_2Cl_2$]	Testicular, ovarian, bladder, head & neck, lung, cervical
24	Carboplatin	Platinum compound	cis-[$Pt(NH_3)_2$(CBDCA)]: cyclobutane-1,1-dicarboxylate chelate replaces chlorides	Ovarian, lung, head & neck (less kidney/ear toxicity than cisplatin)
25	Mitotane	Miscellaneous (DDT analogue)	o,p'-DDD: $Cl_2CH–CH(aryl)_2$ with o-chloro + p-chloro phenyl rings	Adrenocortical carcinoma; Cushing syndrome

6.9 Drug-by-drug profiles — structure and uses

A. Alkylating agents

1. Mechlorethamine (nitrogen mustard, HN2)

- **Chemical classification:** Aliphatic nitrogen mustard — the prototype alkylator.
- **Structure:** The smallest possible mustard: a central tertiary nitrogen carrying one methyl group and two 2-chloroethyl arms — $CH_3–N(–CH_2–CH_2–Cl)_2$. No ring, no carrier — the naked, highly reactive warhead.
- **Uses:** Hodgkin lymphoma as part of the **MOPP** regimen (Mechlorethamine, Oncovin/vincristine, Procarbazine, Prednisone); non-Hodgkin lymphomas; topical chlormethine gel for cutaneous T-cell lymphoma (mycosis fungoides). It is a severe **vesicant** — given IV with great care.
- **Key takeaway.** The original "chemical warfare chemotherapy" drug: tiny, violently reactive, IV only.

2. Cyclophosphamide

- **Chemical classification:** Cyclic phosphoramide nitrogen mustard — a **prodrug** (oxazaphosphorine).
- **Structure:** A six-membered ring containing O–P(=O)–N (1,3,2-oxazaphosphorinane). The phosphorus carries the masked mustard: $–N(–CH_2CH_2Cl)_2$. The ring "hides" the reactive nitrogen so it survives the bloodstream.
- **Activation:** Liver CYP450 hydroxylates C4 4-hydroxycyclophosphamide aldophosphamide splits into **phosphoramide mustard** (the true alkylator) + **acrolein** (toxic to bladder haemorrhagic cystitis; prevented by **mesna** + hydration).
- **Uses:** Very broad — leukemias, lymphomas (CHOP regimen), breast and ovarian cancers, multiple myeloma, neuroblastoma; plus immunosuppression: lupus nephritis, granulomatosis with polyangiitis (Wegener), organ transplant. Less local vesicant damage than mechlorethamine because activation happens in the liver, not the vein.
- **Key takeaway.** A smart bomb: harmless in the vein, armed by the liver; always pair with mesna + fluids to protect the bladder.

3. Melphalan (L-PAM)

- **Chemical classification:** Aromatic nitrogen mustard with an amino-acid carrier.
- **Structure:** L-phenylalanine whose phenyl ring carries, at the para position, the $–N(–CH_2CH_2Cl)_2$ mustard group. The amino-acid part (with $–NH_2$ and –COOH) is recognised by amino-acid transporters, smuggling the mustard into cells.
- **Uses: Multiple myeloma** (its signature use), ovarian cancer; high-dose melphalan with autologous stem-cell rescue is standard conditioning for myeloma transplant.
- **Key takeaway.** A Trojan horse: cancer cells hungry for amino acids swallow their own poison.

4. Chlorambucil

- **Chemical classification:** Aromatic nitrogen mustard (phenylbutyric acid derivative).
- **Structure:** A phenyl ring with the mustard $–N(–CH_2CH_2Cl)_2$ at the para position and a four-carbon butyric acid side chain ($–CH_2CH_2CH_2COOH$) at the opposite side. The aromatic ring donates electrons less readily than an aliphatic amine, so it reacts **slowly** — gentler, orally active.
- **Uses: Chronic lymphocytic leukemia (CLL)** — its classic indication; indolent (slow-growing) non-Hodgkin lymphomas; Waldenström macroglobulinemia. Valued because it can be taken as tablets at home.

- **Key takeaway.** The "slow and steady" mustard: aromatic = less reactive = oral, better tolerated, ideal for chronic leukemias.

5. Busulfan

- **Chemical classification:** Alkyl sulfonate (bifunctional alkylator, not a mustard).
- **Structure:** A straight 4-carbon chain (butane) with a methanesulfonate ester (–O–SO_2–CH_3) at each end: CH_3SO_2–O–$(CH_2)_4$–O–SO_2CH_3. The sulfonates are excellent leaving groups for SN2 attack, generating carbonium ions.
- **Uses: Chronic myeloid leukemia (CML)** — selectively wipes out granulocytic (myeloid) cells; myeloablative conditioning before allogeneic stem-cell transplant ("busulfan + cyclophosphamide" regimen).
- **Key takeaway.** The marrow-selective alkylator: two sulfonate "handles" that the cell's nucleophiles grab, with special appetite for myeloid cells.

6. Thiotepa

- **Chemical classification:** Aziridine (ethylenimine) alkylator — a thiophosphoramide.
- **Structure:** A central P=S (thiophosphoryl) with **three aziridine rings** attached — each aziridine is a strained three-membered ring with one nitrogen (like a tiny triangle). In the body it converts to TEPA, whose opened rings alkylate DNA.
- **Uses:** Bladder cancer by **intravesical instillation** (drug put directly into the bladder through a catheter); breast and ovarian cancers; malignant pleural/peritoneal effusions; conditioning regimens. Crosses into the CNS.
- **Key takeaway.** Three spring-loaded nitrogen triangles on a phosphorus hub — instilled straight into the bladder where it works locally.

B. Antimetabolites

**7. Mercaptopurine (6-MP) — starred: full synthesis in §6.10*

- **Chemical classification:** Purine antimetabolite (thiopurine).
- **Structure:** A **purine** scaffold — a six-membered pyrimidine ring fused to a five-membered imidazole ring — with a thiol (–SH) at carbon-6 instead of the –OH of hypoxanthine. Numbering: N1–C2–N3–C4–C5 bridge, N7–C8–N9 in the imidazole; the –SH sits at C6.
- **Activation:** HGPRT converts it to thioinosinic acid (tIMP), which (a) inhibits PRPP amidotransferase (first step of *de novo* purine synthesis) and (b) becomes thioguanine nucleotides incorporated into DNA/RNA. Patients with low **TPMT/NUDT15** enzyme activity suffer life-threatening myelosuppression — test before dosing.
- **Uses: Acute lymphoblastic leukemia (ALL)** maintenance therapy (with methotrexate — the classic pair); acute myeloid leukemia; outside oncology, inflammatory bowel disease (Crohn's, ulcerative colitis).
- **Key takeaway.** A fake hypoxanthine: the cell activates its own poison via HGPRT; check TPMT status first.

8. Thioguanine (6-TG)

- **Chemical classification:** Purine antimetabolite (thiopurine).
- **Structure:** Purine with **–NH_2 at C2 and –SH at C6** — i.e., guanine in which the C6 carbonyl oxygen is replaced by sulphur (2-amino-6-mercaptopurine). One extra amino group distinguishes it from mercaptopurine.
- **Uses: Acute myeloid leukemia (AML)** — its mainstay; acute lymphoblastic leukemia. Converted by HGPRT to 6-thio-GMP and built into DNA/RNA.
- **Key takeaway.** Mercaptopurine's close sibling with an extra C2 amino group — the AML thiopurine.

9. Fluorouracil (5-FU)

- **Chemical classification:** Pyrimidine antimetabolite (fluorinated uracil).
- **Structure:** A **uracil** ring (pyrimidine-2,4-dione) with a **fluorine atom at C5** — the only change from natural uracil, but a lethal one: fluorine's size mimics hydrogen, yet it cannot be removed by thymidylate synthase.
- **Mechanism recap:** FdUMP irreversibly inhibits **thymidylate synthase** (no dTMP thymineless death); FUTP incorporates into RNA; FdUTP incorporates into DNA. Broken down by **DPD** — DPD-deficient patients risk fatal toxicity.
- **Uses: Colorectal cancer** (with leucovorin — the FOLFOX/FOLFIRI regimens), breast, gastric, pancreatic, head & neck cancers; **topical cream** for actinic keratosis and superficial basal cell carcinoma.
- **Key takeaway.** One fluorine atom turns harmless uracil into a thymine-starving weapon; DPD testing saves lives.

10. Floxuridine (FUDR)

- **Chemical classification:** Pyrimidine antimetabolite — the **deoxyribonucleoside** of 5-FU.
- **Structure:** 5-fluorouracil base linked at N1 to a **2'-deoxyribose** sugar (β-D configuration) — i.e., 5-fluoro-2'-deoxyuridine. It is one enzymatic step closer to the active FdUMP than 5-FU.
- **Uses:** Given by **continuous hepatic arterial infusion** for **liver metastases of colorectal cancer** — the liver extracts it on first pass, giving high local dose with lower systemic exposure.
- **Key takeaway.** 5-FU wearing a sugar coat, pumped straight into the liver artery to ambush liver metastases.

11. Cytarabine (Ara-C)

- **Chemical classification:** Pyrimidine antimetabolite (nucleoside analogue).
- **Structure: Cytosine** base attached to **arabinose** instead of deoxyribose — the only difference is the 2'-OH points **up** (in deoxyribose there is no 2'-OH at all). That one wrongly-angled –OH is the whole trick.
- **Mechanism recap:** Phosphorylated to Ara-CTP **inhibits DNA polymerase** and gets incorporated into the growing DNA chain, where the misplaced 2'-OH stalls elongation (**chain termination**).
- **Uses:** Backbone of **AML** treatment — "7+3" (7 days cytarabine + 3 days daunorubicin) induction; ALL; CML blast crisis; **intrathecal** injection for meningeal leukemia (it crosses into CSF).

- **Key takeaway.** A cytosine brick with its sugar corner bent the wrong way — the polymerase chokes on it mid-chain.

**12. Methotrexate (MTX) — starred: full synthesis in §6.11*

- **Chemical classification:** Antifolate antimetabolite (folic acid analogue).
- **Structure:** Three parts: (i) a **pteridine** ring (pyrimidine fused to pyrazine) carrying **$-NH_2$ at C4** (where folate has =O) — the single most important change; (ii) an **N10-methyl** bridge ($-N(CH_3)-$) linking to (iii) **p-aminobenzoyl-glutamate** tail (benzene ring + glutamic acid with two –COOH groups). Full name: 4-amino-10-methylpteroylglutamic acid.
- **Mechanism recap:** Binds **DHFR ~1,000× tighter** than dihydrofolate → tetrahydrofolate not regenerated → no thymidylate, no purines → S-phase death. Inside cells it is **polyglutamated** (extra glutamates added), which traps it inside for prolonged action. **Leucovorin (folinic acid)** rescue bypasses the block in normal cells.
- **Uses:** ALL, non-Hodgkin lymphomas, **osteosarcoma** (high-dose with leucovorin rescue), choriocarcinoma, breast cancer; low-dose non-cancer uses: **rheumatoid arthritis, psoriasis** (weekly dosing), ectopic pregnancy.
- **Key takeaway.** Folic acid's evil twin: one $-NH_2$ and one $-CH_3$ turn a vitamin into a DHFR super-glue; leucovorin is the antidote key.

13. Azathioprine

- **Chemical classification:** Purine antimetabolite — a **prodrug of 6-mercaptopurine**.
- **Structure:** Mercaptopurine's C6 sulphur linked to a **1-methyl-4-nitroimidazol-5-yl** group — i.e., 6-[(1-methyl-4-nitroimidazol-5-yl)thio]purine. Glutathione in blood/tissues cleaves the C–S bond, releasing free 6-MP.
- **Uses:** Primarily an **immunosuppressant**, not a cancer drug: prevention of **kidney transplant rejection**, rheumatoid arthritis, Crohn's disease and ulcerative colitis, autoimmune hepatitis.
- **Key takeaway.** Mercaptopurine in a slow-release disguise — cleaved to 6-MP wherever glutathione meets it; the transplant surgeon's thiopurine.

C. Antitumour antibiotics

14. Dactinomycin (actinomycin D)

- **Chemical classification:** Actinomycin antitumour antibiotic (chromopeptide).
- **Structure:** A flat red **phenoxazinone** chromophore (three fused rings containing N and O) with **two identical cyclic pentapeptide lactone** rings attached at positions 1 and 9. Each peptide ring: L-threonine–D-valine–L-proline–sarcosine–L-N-methylvaline, closed by a lactone (ester) bond.
- **Mechanism:** The phenoxazinone **intercalates** between G–C base pairs while the two peptide rings lie in the DNA minor groove → **blocks RNA polymerase** → transcription stops → cell death. (Grouped here with anthracyclines for teaching; strictly an actinomycin.)
- **Uses: Wilms tumour** (children's kidney cancer), **rhabdomyosarcoma**, Ewing sarcoma, **gestational trophoblastic neoplasia** (choriocarcinoma), testicular cancer. A strong vesicant.

- **Key takeaway.** A flat red dye with two peptide lassos: slides into DNA and strangles RNA synthesis — a childhood-cancer specialist.

15. Daunorubicin (daunomycin)

- **Chemical classification:** Anthracycline antitumour antibiotic.
- **Structure: Aglycone (daunomycinone):** four linearly fused rings (A–B–C–D) with a **quinone** in rings B/C (the redox-active heart); ring A carries a **–$COCH_3$ (acetyl)** side chain at C9 and –OH groups. **Sugar: daunosamine** (a 3-amino-2,3,6-trideoxy sugar) attached at C7 — essential for DNA binding.
- **Mechanism:** Intercalation + **topoisomerase II trapping** → double-strand breaks; quinone generates free radicals.
- **Uses: Acute myeloid leukemia (AML)** and **acute lymphoblastic leukemia (ALL)** — the "3" in "7+3" induction with cytarabine.
- **Key takeaway.** The leukemia anthracycline: four-ring intercalator + amino-sugar anchor + acetyl side chain.

16. Doxorubicin (adriamycin)

- **Chemical classification:** Anthracycline antitumour antibiotic — **14-hydroxydaunorubicin**.
- **Structure:** Identical to daunorubicin except the side chain is **–$COCH_2OH$** (a primary alcohol) instead of –$COCH_3$. That single –OH broadens the anticancer spectrum dramatically.
- **Mechanism:** Same as daunorubicin (intercalation + topo II trap + free radicals). The radicals also injure heart muscle → **cumulative, dose-related cardiomyopathy** (lifetime limit; dexrazoxane is the rescue chelator).
- **Uses:** The broadest-spectrum single agent here: **breast cancer, lymphomas** (CHOP, ABVD), **sarcomas**, bladder, thyroid, Wilms tumour, neuroblastoma. Nicknamed the **"red devil"** — it colours urine red (warn patients so they don't panic).
- **Key takeaway.** Daunorubicin + one –OH = the red devil: widest use, red urine, and a lifetime heart-dose budget.

17. Bleomycin

- **Chemical classification:** Glycopeptide antitumour antibiotic (from *Streptomyces verticillus*).
- **Structure:** Three functional domains in one complex molecule: (i) a **bithiazole** tail that binds DNA; (ii) a metal-binding region (pyrimidine–imidazole) that chelates **Fe^{2+}**; (iii) a **disaccharide** (sugar) moiety affecting uptake. No intercalation — it sits in the groove and cuts.
- **Mechanism:** Fe(II)–bleomycin + O_2 → activated complex → free radicals abstract hydrogen from DNA's deoxyribose → **strand scission** (single- and double-strand breaks), mainly in G2/M.
- **Uses: Testicular cancer** (BEP: bleomycin, etoposide, cisplatin — curative even when spread), **Hodgkin lymphoma** (ABVD), squamous cell carcinomas of head/neck and cervix. **Dose-limiting toxicity: pulmonary fibrosis** — lungs lack the inactivating enzyme bleomycin hydrolase, so damage accumulates; test doses and lung monitoring are routine.
- **Key takeaway.** Molecular scissors needing iron + oxygen; brilliant against testicular cancer and Hodgkin — but the lungs keep the score, so watch breathing and cap the lifetime dose.

D. Plant alkaloids

18. Vinblastine

- **Chemical classification:** Vinca alkaloid — **dimeric indole alkaloid** from *Catharanthus roseus* (periwinkle; *sadabahar*).
- **Structure:** Two complex halves joined by a single C–C bond: **catharanthine** (upper, iboga-type half) + **vindoline** (lower, aspidosperma-type half carrying an **N–CH_3** methyl on its indoline nitrogen). Huge, intricate, stereochemistry-rich molecule.
- **Mechanism:** Binds tubulin **blocks microtubule polymerisation** no mitotic spindle metaphase arrest (M-phase).
- **Uses: Hodgkin lymphoma** (ABVD), testicular cancer, Kaposi sarcoma, breast cancer, choriocarcinoma. Main toxicity: **myelosuppression** (marrow is its weak spot).
- **Key takeaway.** The periwinkle dimer that steals the spindle's building blocks — marrow-toxic more than nerve-toxic.

19. Vincristine (Oncovin)

- **Chemical classification:** Vinca alkaloid — dimeric indole alkaloid, sister of vinblastine.
- **Structure:** Identical dimer (catharanthine + vindoline), except the vindoline nitrogen carries **–CHO (formyl)** instead of –CH_3. One substituent changes the whole toxicity profile.
- **Mechanism:** Same as vinblastine (blocks tubulin polymerisation metaphase arrest).
- **Uses: Childhood ALL** (backbone of paediatric regimens), **Wilms tumour, neuroblastoma, rhabdomyosarcoma**, Hodgkin and non-Hodgkin lymphomas (MOPP, CHOP — the "O" is Oncovin). **NEUROTOXIC, minimally myelosuppressive** — the mirror image of vinblastine. **IV use only — intrathecal injection is fatal** (syringes must be labelled "FOR IV USE ONLY — FATAL IF GIVEN INTRATHECALLY").
- **Key takeaway.** Vinblastine's formyl twin: trades marrow toxicity for nerve toxicity; a paediatric-leukemia hero that must never enter the spinal canal.

20. Paclitaxel

- **Chemical classification:** Taxane — **diterpene** alkaloid-like natural product from yew trees (*Taxus*).
- **Structure:** A rigid **taxane core**: fused 6–12–6 tricyclic system plus a four-membered **oxetane** ring; the activity-critical **C13 side chain** is an ester of **N-benzoyl-3-phenylisoserine** (with essential 2'-OH and 3'-benzamido groups). Originally from Pacific yew bark; now semisynthesised from 10-deacetylbaccatin III of *Taxus baccata* needles.
- **Mechanism:** Binds assembled microtubules and **prevents depolymerisation** — freezes the spindle mitotic arrest (M-phase). The exact opposite of vinca alkaloids.
- **Uses: Ovarian, breast, non-small-cell lung cancers**, Kaposi sarcoma. Needs premedication (hypersensitivity to the cremophor vehicle) and causes neuropathy and myelosuppression.
- **Key takeaway.** The yew-tree diterpene that welds the spindle shut — vinca's mirror image, a giant of breast and ovarian cancer therapy.

E. Topoisomerase inhibitors

21. Etoposide

- **Chemical classification: Epipodophyllotoxin** — semisynthetic derivative of podophyllotoxin (from *Podophyllum* resin).
- **Structure:** The four-ring podophyllotoxin lignan lactone, modified at C4 with a **β-D-glucopyranoside** (sugar) in the β configuration, and **4'-demethylated** on the pendant trimethoxyphenyl ring (now a 4'-hydroxy-3',5'-dimethoxyphenyl). The sugar makes it water-soluble enough for IV use.
- **Mechanism: Topoisomerase II poison** — traps the enzyme–DNA cleavage complex double-strand breaks.
- **Uses: Testicular cancer** (BEP), **small-cell lung cancer**, lymphomas, AML, choriocarcinoma.
- **Key takeaway.** A sugared podophyllotoxin that handcuffs topoisomerase II mid-cut — a testicular and small-cell-lung workhorse.

22. Camptothecin

- **Chemical classification: Quinoline alkaloid** topoisomerase I inhibitor (from *Camptotheca acuminata*; Indian source: *Nothapodytes nimmoniana* of the Western Ghats).
- **Structure: Pentacyclic**: quinoline rings A–B fused to a pyrroloquinoline C–D system, ending in the E-ring — an **α-hydroxy-δ-lactone** with a 20(S)-hydroxy and 20-ethyl group. The **intact lactone** is essential; at blood pH it opens to an inactive carboxylate.
- **Mechanism: Topoisomerase I poison** — traps the single-strand cleavage complex; replication forks colliding with the trapped complex in S phase create lethal breaks.
- **Uses:** Camptothecin itself is **too toxic for clinical use** — it is the **lead compound** for **irinotecan** (colorectal cancer) and **topotecan** (ovarian, small-cell lung cancers), which are the drugs actually prescribed.
- **Key takeaway.** The too-poisonous parent: its lactone handcuffs topo I, and its safer children (irinotecan, topotecan) do the clinical work.

F. Platinum compounds

23. Cisplatin

- **Chemical classification:** Inorganic platinum coordination complex — Pt(II).
- **Structure: Square-planar** platinum with two **chloride** leaving groups and two **ammine (NH_3)** ligands in **cis** positions: cis-[$Pt(NH_3)_2Cl_2$]. Small, simple, symmetrical — geometry is destiny.
- **Mechanism recap:** Intracellular **aquation** (Cl^- H_2O) binds N7 of **adjacent guanines** 1,2-**intrastrand** cross-link helix kink apoptosis.
- **Uses: Testicular** (curative with etoposide/bleomycin), **ovarian, bladder, head & neck, lung, cervical** cancers. Toxicities: **nephrotoxicity** (needs aggressive IV hydration + mannitol), **ototoxicity** (hearing loss), peripheral neuropathy, and the **most emetogenic** chemotherapy known (needs triple antiemetics).
- **Key takeaway.** The cis geometry is non-negotiable (transplatin is inactive); cures testicular cancer but demands hydration, hearing checks, and heavy antiemetics.

24. Carboplatin

- **Chemical classification:** Second-generation platinum coordination complex — Pt(II).
- **Structure:** Same cis-diammine platinum core, but the two chlorides are replaced by one bidentate **cyclobutane-1,1-dicarboxylate (CBDCA)** chelating ligand — a four-membered carbon ring with two $–COO^-$ arms gripping the platinum.
- **Mechanism:** Identical DNA lesion (intrastrand GpG cross-link) but **much slower aquation** gentler, slower-reacting cisplatin.
- **Uses: Ovarian, lung, head & neck** cancers — where cisplatin's kidney/ear toxicity is unacceptable. **Dosed by the Calvert formula** (dose = target AUC × [GFR + 25]) because kidney function controls exposure; **myelosuppression** (thrombocytopenia) is dose-limiting.
- **Key takeaway.** Cisplatin with stabilisers: the CBDCA chelate slows activation kinder to kidneys and ears, harder on platelets; dose by AUC, not body surface.

G. Miscellaneous

25. Mitotane (o,p'-DDD)

- **Chemical classification:** Chlorinated hydrocarbon — a **DDT analogue**.
- **Structure:** An ethane backbone: C1 carries two chlorines ($–CHCl_2$… precisely 1,1-dichloro), C2 carries an **ortho-chlorophenyl** and a **para-chlorophenyl** ring — 1,1-dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)ethane. Looks like the insecticide DDT, aimed at the adrenal gland instead of insects.
- **Mechanism:** Selectively destroys **adrenocortical cells** (mitochondrial damage + blockade of cortisol-synthesis enzymes).
- **Uses: Adrenocortical carcinoma** (rare adrenal-gland cancer); **Cushing syndrome** (cortisol excess) to suppress steroid output. Patients need glucocorticoid replacement and drug-level monitoring (narrow therapeutic window, very long half-life stored in fat).
- **Key takeaway.** A DDT cousin with an adrenal postcode — kills the cortisol factory; replace the steroids it wipes out.

6.10 Synthesis of Mercaptopurine* (starred)

Technical concept. 6-Mercaptopurine is made from the natural purine **hypoxanthine** in three operations: (1) replace the C6 carbonyl oxygen with chlorine (chlorination with $POCl_3$), (2) displace that chlorine with thiourea (nucleophilic aromatic substitution at C6) to give an isothiouronium salt, (3) hydrolyse the salt with base to liberate the free –SH.

Step 1 — Chlorination: hypoxanthine 6-chloropurine.

- **Starting material:** Hypoxanthine (6-hydroxypurine, exists mainly as the C6=O keto tautomer) — the natural purine base.
- **Reagents and conditions: Phosphorus oxychloride ($POCl_3$)**, with heating (reflux). (A little N,N-dimethylaniline is classically added as an acid scavenger/catalyst.)

- **Reaction:** The C6 carbonyl oxygen is replaced by chlorine (nucleophilic substitution via a chlorophosphate intermediate): C6=O C6–Cl.
- **Intermediate/product of step 1: 6-Chloropurine** — purine ring with –Cl at C6, a good leaving group for the next step.

Step 2 — Thiation via thiourea: 6-chloropurine isothiouronium salt.

- **Starting material:** 6-Chloropurine (from Step 1).
- **Reagents and conditions: Thiourea (NH_2–CS–NH_2)** in refluxing **ethanol**.
- **Reaction:** Nucleophilic aromatic substitution — the sulphur of thiourea attacks C6, displacing chloride.
- **Intermediate/product of step 2: S-(Purin-6-yl)isothiouronium chloride** — the purine C6 now joined through sulphur to a –S–C(=NH_2^+)–NH_2 amidinium group (isolated as its hydrochloride salt).

Step 3 — Hydrolysis: isothiouronium salt 6-mercaptopurine.

- **Starting material:** S-(Purin-6-yl)isothiouronium chloride (from Step 2).
- **Reagents and conditions: Aqueous sodium hydroxide (NaOH)**, gentle warming, then acidification (dilute HCl) to precipitate the product.
- **Reaction:** Base hydrolyses the isothiouronium group: –S–C(=NH)NH_2 + H_2O –SH + urea.
- **Final product: 6-Mercaptopurine** — purine with a free thiol (–SH) at C6 (exists partly as the thione tautomer, C6=S with H on N1).

Simple explanation. Start with hypoxanthine, a natural purine. Boil it with $POCl_3$ and the oxygen at position 6 is swapped for chlorine (6-chloropurine) — like replacing a door handle with one that comes off easily. Then reflux with thiourea: the sulphur grabs position 6 and kicks out the chlorine, forming a temporary "sulphur-plus-urea" handle (isothiouronium salt). Finally, mild base chops the urea part off, leaving a free –SH — mercaptopurine. Three steps: chlorinate, attach sulphur via thiourea, cut loose with base.

Example of the balanced change: Hypoxanthine ($C_5H_4N_4O$) —O +Cl 6-chloropurine ($C_5H_3ClN_4$); + thiourea (CH_4N_2S) –HCl isothiouronium salt; + H_2O –urea 6-mercaptopurine ($C_5H_4N_4S$).

Key takeaway. Hypoxanthine —($POCl_3$, heat) 6-chloropurine —(thiourea, EtOH reflux) isothiouronium salt —(aq. NaOH, then acidify) 6-mercaptopurine. Chlorinate substitute with thiourea hydrolyse.

6.11 Synthesis of Methotrexate* (starred)

Technical concept. Methotrexate is assembled in four operations: (1) **build the pteridine ring** by double condensation of 2,4,5,6-tetraaminopyrimidine with 1,2-dibromopropionaldehyde 2,4-diamino-6-methylpteridine; (2) **brominate the 6-methyl group** 6-bromomethylpteridine; (3) **alkylate** the protected tail — diethyl N-[p-(methylamino)benzoyl]-L-glutamate — whose secondary amine displaces the bromide, installing the N10-methyl bridge; (4) **hydrolyse the ethyl esters** free methotrexate.

Step 1 — Pteridine ring formation: tetraaminopyrimidine + dibromopropionaldehyde 2,4-diamino-6-methylpteridine.

- **Starting materials: 2,4,5,6-Tetraaminopyrimidine** (used as its sulphate salt) + **1,2-dibromopropionaldehyde** ($BrCH_2$–CHBr–CHO).

- **Reagents and conditions: Sodium acetate** (buffer) in aqueous ethanol, with heating.
- **Reaction:** Double condensation — the vicinal 5,6-diamino groups of the pyrimidine attack the aldehyde carbon and displace both bromines, closing the **pyrazine ring** fused to the pyrimidine = the **pteridine** bicyclic system, with a methyl group at position 6 (from the aldehyde's carbon skeleton).
- **Intermediate/product of step 1: 2,4-Diamino-6-methylpteridine** — the complete pteridine core with $–NH_2$ at C2 and C4 and $–CH_3$ at C6.

Step 2 — Side-chain bromination: 6-methyl 6-bromomethyl.

- **Starting material:** 2,4-Diamino-6-methylpteridine (from Step 1).
- **Reagents and conditions: Bromine (Br_2)** in **glacial acetic acid**, controlled temperature.
- **Reaction:** Selective bromination of the activated 6-methyl group (benzylic-type position next to the electron-deficient pteridine ring): $–CH_3$ $–CH_2Br$.
- **Intermediate/product of step 2: 2,4-Diamino-6-(bromomethyl)pteridine** — now carrying an excellent SN2 leaving group on the side chain.

Step 3 — Alkylation with the tail: installing the N10-methyl bridge.

- **Starting materials:** 2,4-Diamino-6-(bromomethyl)pteridine (from Step 2) + **diethyl N-[p-(methylamino)benzoyl]-L-glutamate** (the "tail": p-$CH_3NH–C_6H_4–CO–NH–CH(COOH)–CH_2CH_2COOH$ with both glutamate carboxyls protected as ethyl esters).
- **Reagents and conditions:** Heating in a polar solvent (the secondary aromatic amine acts as nucleophile; no extra base strictly required, mild base may be used to mop up HBr).
- **Reaction:** SN2 — the tail's secondary amine nitrogen ($–NHCH_3$) attacks the bromomethyl carbon, displacing bromide forms the **N10–CH_2** bond with the methyl already on nitrogen = the **N10-methyl bridge** of methotrexate.
- **Intermediate/product of step 3: Methotrexate diethyl ester** — full methotrexate skeleton with the glutamate carboxyls still masked as –COOEt groups.

Step 4 — Ester hydrolysis: diester free diacid.

- **Starting material:** Methotrexate diethyl ester (from Step 3).
- **Reagents and conditions: Dilute aqueous sodium hydroxide (NaOH)** at room temperature, then **acidification** (dilute HCl) to precipitate.
- **Reaction:** Saponification of both ethyl esters: 2 × (–COOEt $–COO^-$ –COOH on acidification).
- **Final product: Methotrexate** — 4-amino-10-methylpteroylglutamic acid, with the free glutamate diacid tail.

Simple explanation. Build the drug like a three-piece puzzle. **Piece 1 (the head):** take a pyrimidine loaded with four amino groups and cook it with a dibromo-aldehyde — the two neighbouring amines zip up with the aldehyde to close a second ring, giving the pteridine "head" with a methyl flag at position 6. **Piece 2:** brominate that methyl flag so it becomes a good handle ($–CH_2Br$). **Piece 3 (the tail):** take p-(methylamino)benzoic acid already stitched to glutamic acid whose acids are temporarily capped as ethyl esters; its nitrogen grabs the $–CH_2Br$ handle, clicking head to tail with the N10-methyl in place.

Finally, wash off the ester caps with dilute NaOH and acid — free methotrexate.

Example of the sequence in one line: Tetraaminopyrimidine —($BrCH_2CHBrCHO$, NaOAc, heat) 2,4-diamino-6-methylpteridine —(Br_2, AcOH) 6-bromomethylpteridine —(EtO_2C-tail-$NHCH_3$, heat) methotrexate diethyl ester —(NaOH, then H^+) methotrexate.

Key takeaway. Four steps: (1) close the pteridine ring, (2) brominate the 6-methyl handle, (3) SN2-click the N-methylated benzoyl-glutamate tail, (4) deprotect the esters. The N10-methyl and C4-amino are what make it a DHFR super-binder instead of a vitamin.

6.12 SAR — rule tables

How to read SAR: each rule states which part of the molecule is essential, what happens if you change it, and a drug example. Learn the bolded phrases.

SAR Table 1 — Nitrogen mustards (mechlorethamine, cyclophosphamide, melphalan, chlorambucil)

#	Rule	Explanation	Example
1	The **bis(2-chloroethyl)amino** group is the pharmacophore — both $–CH_2CH_2Cl$ arms are needed	One arm gives only mono-alkylation (weak); two arms give the lethal cross-link	All four mustards carry $–N(–CH_2CH_2Cl)_2$
2	**Electron-donating groups on nitrogen speed up** aziridinium formation more reactive, more toxic	Aliphatic nitrogen (mechlorethamine) donates strongly violently reactive vesicant, IV only	Mechlorethamine >> chlorambucil in reactivity
3	**Aromatic mustards are slower and more selective** — the ring withdraws electron density from N	Slower aziridinium formation survives to reach tumour, oral activity, better tolerated	Chlorambucil, melphalan (oral, chronic leukemias)
4	**Masking the nitrogen** (as in cyclophosphamide's phosphoramide) creates a prodrug	Inert in blood; liver unmasks it less vein/tissue damage at injection site	Cyclophosphamide needs hepatic activation
5	A **carrier group** can target the mustard to cancer cells	Amino-acid carrier uptake by amino-acid transporters	Melphalan's phenylalanine carrier

SAR Table 2 — Purine antimetabolites (mercaptopurine, thioguanine, azathioprine)

#	Rule	Explanation	Example
1	The **6-thio (–SH) group is essential** — it is what makes the base "fake"	Replacing C6=O of hypoxanthine/guanine with C6–SH creates the fraudulent base	6-MP, 6-TG
2	The drug must be a **substrate for HGPRT** — no activation, no activity	HGPRT adds the sugar-phosphate, making thio-IMP/thio-GMP	Resistance arises via HGPRT deficiency
3	**C2 substituent tunes the base**: H (mercaptopurine) vs NH_2 (thioguanine)	Both work; the 2-amino mimics guanine more closely	Thioguanine = 2-amino-6-mercaptopurine
4	**Masking the 6-S** gives a prodrug	S-linked bulky group cleaved in vivo to release 6-MP	Azathioprine (S-imidazole mask)

SAR Table 3 — Pyrimidine antimetabolites (fluorouracil, floxuridine, cytarabine)

#	Rule	Explanation	Example
1	**5-Fluoro on uracil is essential** for thymidylate-synthase inhibition	F mimics H in size but cannot be abstracted FdUMP irreversibly blocks TS	5-FU; removing F gives inactive uracil
2	The **nucleoside form** (base + sugar) is one step closer to the active nucleotide	Floxuridine FdUMP more directly than 5-FU	Floxuridine for hepatic infusion
3	**Arabinose sugar (2'-OH "up")** makes cytarabine a chain terminator	The misplaced –OH stalls DNA polymerase after incorporation	Cytarabine vs cytidine (normal sugar = normal brick)
4	Resistance to **cytidine deaminase** matters	Enzymes that deaminate cytosine analogues inactivate them; structural tweaks prolong action	Ara-C's sugar also slows deamination

SAR Table 4 — Antifolates (methotrexate)

#	Rule	Explanation	Example
1	**4-Amino (instead of 4-oxo)** is the key change — converts folate into a DHFR blocker	The $-NH_2$ binds DHFR ~1,000× tighter than folate's =O	Methotrexate vs folic acid
2	**N10-methyl** increases DHFR affinity and prevents metabolism as a vitamin	The methyl blocks the site folate enzymes would act on	Aminopterin (no N10-methyl) is even more toxic
3	The **glutamate tail** is needed for cellular retention via polyglutamation	Extra glutamates added inside the cell trap the drug for days	Removing the tail drug leaks out, activity lost
4	The **pteridine ring** must stay intact	It mimics the pterin of folate in the DHFR active site	Ring-opened analogues are inactive

SAR Table 5 — Anthracyclines (daunorubicin, doxorubicin) and dactinomycin

#	Rule	Explanation	Example
1	The **flat tetracyclic quinone chromophore** is essential for intercalation	Four fused rings slide between base pairs; quinone also redox-cycles (radicals)	Both anthracyclines; the quinone also causes cardiotoxicity
2	The **daunosamine sugar at C7** is essential for DNA binding	The amino sugar anchors in the minor groove; removing it kills activity	Aglycones alone are nearly inactive
3	**C13/C14 side chain tunes spectrum**: $-COCH_3$ (daunorubicin) vs $-COCH_2OH$ (doxorubicin)	One extra –OH dramatically broadens anticancer activity	Doxorubicin = 14-hydroxydaunorubicin
4	For dactinomycin: the **phenoxazinone + two peptide rings** are all required	Chromophore intercalates; peptides grip the minor groove	Either half alone is inactive

SAR Table 6 — Vinca alkaloids and taxanes

#	Rule	Explanation	Example
1	The **dimeric (bis-indole) structure is essential** — neither half works alone	Catharanthine + vindoline joined by one C–C bond	Monomeric halves are inactive
2	**N-substituent on the vindoline half controls toxicity**: N–CH_3 (vinblastine) vs N–CHO (vincristine)	Formyl neurotoxic, marrow-sparing; methyl myelosuppressive, less neurotoxic	Vincristine vs vinblastine
3	For taxanes: the **C13 side chain (N-benzoyl phenylisoserine)** is essential	2'-OH and 3'-benzamido groups are critical contact points	Removing the side chain (baccatin III) inactive
4	The **oxetane ring** of paclitaxel is required for activity	Ring-opened taxanes lose microtubule binding	Part of the rigid core pharmacophore

SAR Table 7 — Platinum compounds and topoisomerase inhibitors

#	Rule	Explanation	Example
1	**cis geometry is essential** — trans isomers are inactive	Only cis leaving groups can form the 1,2-intrastrand GpG cross-link	Cisplatin active; transplatin inactive (classic trap)
2	**Leaving group controls toxicity**: Cl^- (fast) vs CBDCA chelate (slow)	Fast aquation kidney/ear damage; slow aquation marrow suppression	Cisplatin vs carboplatin
3	The **ammine ligands stay bound** — they are the non-leaving groups	They position the Pt and H-bond to DNA	Both drugs keep 2 × NH_3
4	Camptothecin: the **E-ring lactone must be closed**	Opened carboxylate form cannot trap topoisomerase I	Lactone stabilisation is a design goal (irinotecan, topotecan)
5	Etoposide: the **4β-glucoside and 4'-demethylation** convert podophyllotoxin (a spindle poison) into a topo II poison	Small changes switch the target from tubulin to topoisomerase II	Podophyllotoxin vs etoposide

6.13 Diagrams (describe textually so they can be drawn)

Diagram 1 — Nitrogen mustard activation: from mustard to cross-link (draw left to right). Draw mechlorethamine as N with –CH_3 and two –CH_2CH_2Cl arms. Arrow 1 (label "N lone pair ejects Cl^-, intramolecular SN2"): draw the three-membered aziridinium ring (N^+ with two CH_2 groups). Arrow 2 (label "Guanine N7 of DNA attacks the ring carbon"): draw the ring opened, with –CH_2CH_2–N^+– now bonded to a guanine base (label "DNA strand 1 alkylated"). Arrow 3 (label "Second arm repeats on the opposite strand"): draw a bridge –CH_2CH_2– connecting guanine (strand 1) to guanine (strand 2). Caption: "Two arms, two aziridinium rings, one interstrand cross-link — the zipper is stapled shut."

Diagram 2 — Antimetabolite "fake brick" concept (draw a wall). Draw a brick wall labelled "DNA under construction in S phase." Show genuine bricks labelled A, T, G, C being laid by a bricklayer labelled "DNA polymerase." Now show counterfeit bricks: one labelled "6-MP (fake G/A)" with a small skull, one labelled "FdUMP (no T available — thymidylate synthase blocked)" with the T-brick crossed out, one labelled "Ara-C (bent corner brick)" jamming the bricklayer's trowel, and a mortar mixer labelled "DHFR" padlocked by a brick labelled "Methotrexate." Caption: "Fake bricks, missing letters, a jammed trowel, and a locked mortar mixer — S-phase sabotage."

Diagram 3 — Microtubule: vinca vs taxane (draw a cell in M phase). Left panel: draw short tubulin pieces (small rods) scattered, labelled "Vinblastine/vincristine steal tubulin — spindle never built." Draw chromosomes scattered with no spindle, label "Metaphase arrest." Right panel: draw a thick, rigid spindle of fused rods that cannot come apart, labelled "Paclitaxel welds microtubules — spindle never dismantled." Same end label: "Metaphase arrest apoptosis." Caption: "Mirror-image saboteurs: no assembly (vinca) vs no disassembly (taxane)."

Diagram 4 — Cisplatin intrastrand cross-link (draw a DNA ladder segment). Draw two vertical rails (sugar-phosphate backbones) with three rungs (base pairs); label the middle two rungs on the left rail "G" and "G" (adjacent guanines, N7 atoms facing the major groove). Draw a small square labelled "Pt" with two short lines to the two guanine N7 atoms, both on the SAME rail; label "1,2-intrastrand GpG cross-link." Draw the ladder bent ~34° at that point with an arrow labelled "Helix kink repair fails apoptosis." Add a note: "transplatin (Cl atoms opposite) cannot bridge two neighbours — inactive."

Diagram 5 — Anthracycline intercalation + topoisomerase II trap (draw a ladder). Draw a DNA ladder; slide a flat four-ring card between two rungs, label "Doxorubicin chromophore intercalated"; attach a small pentagon labelled "daunosamine sugar" sitting in the groove. Draw a scissor-like figure labelled "Topoisomerase II" cutting both rails; draw a handcuff linking the drug card to the scissors, label "Enzyme trapped AFTER cutting, BEFORE re-sealing double-strand break." Caption: "Intercalate, then handcuff the repairman mid-cut."

Diagram 6 — Mercaptopurine synthesis scheme (draw three boxes with arrows). Box 1: "Hypoxanthine (purine C6=O)" —arrow labelled "$POCl_3$, heat" Box 2: "6-Chloropurine (C6–Cl)" —arrow labelled "Thiourea, EtOH, reflux" Box 3: "Isothiouronium salt" —arrow labelled "aq. NaOH, then H^+" Box 4: "6-Mercaptopurine (C6–SH)."

Diagram 7 — Methotrexate synthesis scheme (draw four boxes with arrows). Box 1: "2,4,5,6-Tetraaminopyrimidine + $BrCH_2CHBrCHO$" —arrow labelled "NaOAc, heat (double condensation)" Box 2: "2,4-Diamino-6-methylpteridine" —arrow labelled "Br_2, AcOH" Box 3: "6-Bromomethylpteridine" —arrow labelled "tail-$NHCH_3$ (SN2)" Box 4: "Methotrexate diethyl ester" —arrow labelled "NaOH, then H^+" Box 5: "Methotrexate."

6.14 Flowcharts

Flowchart 1 — Choosing the class from the target (draw as a decision tree). "Where does the drug strike?" "DNA itself, any phase Alkylators (mustards, busulfan, thiotepa) or Platinum (cis/carboplatin)" "DNA building blocks, S phase Antimetabolites (purine/pyrimidine analogues, methotrexate)" "DNA + topoisomerase trap Anthracyclines/dactinomycin (topo II), Etoposide (topo II), Camptothecin (topo I)" "DNA cutting via radicals Bleomycin" "Spindle/microtubules, M phase Vinca (no assembly), Paclitaxel (no disassembly)" "Adrenal cortex only Mitotane."

Flowchart 2 — Cyclophosphamide activation and rescue. "Cyclophosphamide (inert prodrug)" —(liver CYP450) "4-Hydroxycyclophosphamide" "Aldophosphamide" splits into "Phosphoramide mustard (kills cancer AND marrow)" + "Acrolein (burns the bladder)". Rescue branch: "Mesna (in blood/urine) + IV hydration" "binds acrolein harmless" "No haemorrhagic cystitis."

Flowchart 3 — Methotrexate action and leucovorin rescue. "Methotrexate" "binds DHFR 1,000× tighter than folate" "No tetrahydrofolate" "No thymidylate + no purines" "S-phase death (cancer AND marrow/gut)." Rescue branch: "Leucovorin (folinic acid = ready-made reduced folate)" "bypasses DHFR block" "Normal cells rescued (given after high-dose MTX)."

Flowchart 4 — Cell-cycle specificity map. "G1 S G2 M back to G1": mark "S phase: antimetabolites (6-MP, 6-TG, 5-FU, floxuridine, Ara-C, MTX), camptothecin"; mark "M phase: vinca alkaloids, paclitaxel";

mark "G2/M: bleomycin"; mark "ALL phases (non-specific): alkylators, cisplatin, carboplatin, anthracyclines, dactinomycin." Side note: "Specific drugs spare resting (G0) normal cells; non-specific drugs do not."

6.15 Infographic concept box

ANTINEOPLASTIC AGENTS AT A GLANCE The enemy: Cells that divide without rules. Every drug here attacks dividing cells — which is also why marrow, gut, and hair suffer. **Six weapons, six targets: Staple the DNA** — alkylators (mustards, busulfan, thiotepa) & platinum drugs cross-link guanines; work in ANY phase. **Smuggle fake bricks** — antimetabolites (6-MP, 6-TG, 5-FU, Ara-C, MTX) jam S-phase DNA building; must be activated by the cell itself. **Handcuff the repairman** — anthracyclines & etoposide trap topoisomerase II; camptothecin traps topo I. **Cut the DNA** — bleomycin's iron–oxygen scissors. **Wreck the spindle** — vinca (no assembly) vs paclitaxel (no disassembly); M-phase arrest. **Burn one gland** — mitotane destroys only the adrenal cortex. **Name tricks:** "-mustine" is not here, but **mustards** = mechlorethamine, cyclophosphamide, melphalan, chlorambucil; **"vin-"** = vinca (vinblastine, vincristine); **"platin"** = platinum (cisplatin, carboplatin); **purine fakes** = mercaptopurine, thioguanine, azathioprine. **Rescue kit (exam favourite):** Mesna + hydration cyclophosphamide (acrolein bladder); Leucovorin methotrexate (DHFR block); Dexrazoxane doxorubicin extravasation/cardiac iron; Hydration + mannitol cisplatin (kidney). **Star syntheses:** 6-MP = hypoxanthine ($POCl_3$) 6-chloropurine (thiourea) isothiouronium (NaOH) 6-MP. Methotrexate = tetraaminopyrimidine + dibromopropionaldehyde (NaOAc) 6-methylpteridine (Br_2) 6-bromomethyl (tail-$NHCH_3$) diester (NaOH) MTX. **Never forget:** Vincristine IV ONLY (intrathecal = fatal) • Doxorubicin red urine + lifetime heart budget • Bleomycin lifetime lung budget • Cisplatin = hydration + hearing checks • TPMT before thiopurines, DPD before 5-FU.

6.16 Worked examples

Example 1 — Spot the mustard. Which of these is a nitrogen mustard: busulfan, chlorambucil, cisplatin? Chlorambucil — it carries the $–N(–CH_2CH_2Cl)_2$ group on an aromatic ring. Busulfan is an alkyl sulfonate (no nitrogen mustard group); cisplatin is a platinum complex (no carbon arms at all).

Example 2 — Prodrug spotting. Which of these needs liver activation: mechlorethamine, cyclophosphamide, melphalan? Cyclophosphamide — its mustard nitrogen is masked inside the oxazaphosphorine ring and CYP450 must hydroxylate it first. Mechlorethamine and melphalan are already reactive.

Example 3 — Rescue matching. A patient on high-dose methotrexate is prescribed leucovorin 24 hours later. Why? Methotrexate blocks DHFR, starving ALL cells of reduced folate. Leucovorin (folinic acid) supplies ready-made reduced folate that bypasses DHFR — normal marrow and gut cells recover, while the tumour (already lethally damaged) does not. This is "leucovorin rescue."

Example 4 — Geometry matters. Why is transplatin inactive while cisplatin cures testicular cancer? The anticancer lesion is a 1,2-intrastrand cross-link between two ADJACENT guanines — only possible when the two leaving groups sit side by side (cis). In transplatin they point opposite, so it cannot bridge neighbours.

Example 5 — One substituent, opposite toxicity. Vinblastine ($N–CH_3$) dose limited by myelosuppression; vincristine (N–CHO) dose limited by neurotoxicity (neuropathy, constipation, jaw pain) with little marrow suppression. Same dimer, one substituent, swapped toxicity — a favourite exam comparison.

6.17 Analogies (quick reference)

1. **Alkylators as superglue on a zipper.** DNA is a zipper; the mustard glues both sides together — it can never open again.
2. **Antimetabolites as counterfeit bricks.** The cell builds its DNA wall with fake letters; the wall collapses mid-construction.
3. **Methotrexate as a padlock on the mortar mixer.** DHFR is the mixer making folate-mortar; methotrexate padlocks it, and leucovorin is the spare key given only to normal cells.
4. **Anthracyclines as a card slid into a book + handcuffed librarian.** The flat drug slides between pages (intercalation) and handcuffs topoisomerase II after it cuts but before it tapes.
5. **Vinca vs taxane as scaffolding thieves vs welders.** Vinca steals the pipes so the spindle is never built; paclitaxel welds the finished scaffolding so it can never come down.
6. **Cisplatin as a Trojan horse.** Quiet in blood (high chloride), drops its disguise inside the cell (low chloride), then staples neighbouring guanines.
7. **Bleomycin as scissors needing iron + air.** It grabs iron, breathes oxygen, and snips DNA — but the lungs have no sheath (no hydrolase), so they get cut too.
8. **Mitotane as a poison with a postcode.** Travels everywhere, detonates only in the adrenal cortex.

6.18 Pharmacy relevance

- **Cytotoxic handling is non-negotiable:** prepare in a biological safety cabinet, wear double gloves, gown, eye protection; use closed-system transfer devices; cytotoxic spill kits on the ward; dispose as biomedical waste (yellow bags/incineration) — never down the sink.
- **Vesicant extravasation:** anthracyclines, dactinomycin, vinca alkaloids, mechlorethamine are vesicants — verify blood return before and during infusion; if extravasation occurs, stop infusion, aspirate, elevate limb, apply cold (anthracyclines) and notify immediately; dexrazoxane is the antidote for anthracycline extravasation.
- **"FOR IV USE ONLY — FATAL IF GIVEN INTRATHECALLY":** vincristine (and vinblastine) syringes must carry this warning and never be dispensed in a syringe that fits a spinal needle — intrathecal vinca is uniformly fatal. Dispense in a minibag, never a syringe, where possible.
- **Mesna + hydration with cyclophosphamide/ifosfamide:** counsel patients to drink plenty of fluids and void frequently; haemorrhagic cystitis (blood in urine) must be reported the same day.
- **Leucovorin rescue:** after high-dose methotrexate, leucovorin doses are timed by MTX blood levels — a pharmacist verifies the nomogram timing; delayed rescue = rescue failure.
- **Cisplatin hydration protocol:** pre- and post-hydration with mannitol/furosemide diuresis is mandatory; check creatinine, magnesium, and hearing (audiometry) before each cycle.
- **Doxorubicin counselling:** warn about **red urine** for 1–2 days (harmless), total lifetime dose tracking (cardiomyopathy risk), and baseline + periodic echocardiograms.
- **Bleomycin:** counsel to report new cough, breathlessness, or chest pain immediately (pulmonary fibrosis); lifetime dose is capped; avoid high-flow oxygen where possible.
- **Pharmacogenetic checks:** TPMT/NUDT15 before mercaptopurine/azathioprine; DPD before 5-FU/capecitabine — flag the test on the prescription.

- **Antiemetic premedication:** cisplatin needs triple therapy (5-HT_3 antagonist + NK_1 antagonist + dexamethasone) BEFORE the infusion, not after vomiting starts.
- **Alopecia and fertility:** warn about hair loss (reversible), and discuss sperm/egg preservation before alkylator or platinum therapy — alkylators can cause permanent infertility.
- **Oral agents at home (chlorambucil, mercaptopurine, methotrexate weekly, capecitabine):** counsel on exact weekly (not daily!) methotrexate dosing — daily MTX instead of weekly has killed patients; use a calendar/checkbox.

6.19 India context

- **Sadabahar in the backyard:** vinblastine and vincristine come from *Catharanthus roseus* (periwinkle, *sadabahar*) — a common Indian garden plant. India is a major global producer of these vinca alkaloids, which keeps their cost low for Indian patients.
- **Western Ghats camptothecin:** the topoisomerase-I lead camptothecin is sourced in India from *Nothapodytes nimmoniana* (a Western Ghats tree) — Indian research groups work on sustainable semisynthesis of irinotecan/topotecan from it.
- **Generics capital:** Indian companies (Cipla, Sun Pharma, Dr. Reddy's, Intas, Zydus, Natco) manufacture affordable generic cyclophosphamide, methotrexate, 5-FU, cisplatin, carboplatin, paclitaxel, and doxorubicin — the reason CHOP, ABVD, and BEP regimens are deliverable at Indian price points.
- **Where treatment happens:** Tata Memorial Centre (Mumbai), AIIMS (New Delhi), Kidwai (Bengaluru), RCC Thiruvananthapuram, and the National Cancer Grid network; **Ayushman Bharat PM-JAY** and state schemes (e.g., Maharashtra's MJPJAY) cover many chemotherapy regimens; **Jan Aushadhi** stores stock low-cost cytotoxics.
- **Pharmacist's ground reality:** most Indian oncology pharmacists compound cytotoxics in day-care biosafety cabinets, track cumulative doxorubicin/bleomycin doses on paper cards, and counsel in regional languages about red urine, hair loss, and the weekly-methotrexate rule — small counselling steps that prevent big tragedies.
- **Exam tip for Indian universities:** PCI/RGUHS-style questions love "write the synthesis of methotrexate," "SAR of alkylating agents," "why is vincristine never given intrathecally," and "mesna/leucovorin rescue" — all covered above.

6.20 Key points

1 Antineoplastic = against new abnormal growth; cancer = uncontrolled division + invasion + metastasis.

2 Chemotherapy hits all fast-dividing cells — marrow (low counts), gut (mucositis/diarrhoea), hair (alopecia).

3 Cell-cycle specific: antimetabolites (S), vinca/taxanes (M), bleomycin (G2/M), camptothecin (S), etoposide (S/G2). Non-specific: alkylators, platinum drugs, anthracyclines.

4 Nitrogen mustards: $-N(-CH_2CH_2Cl)_2$ → aziridinium ion → guanine-N7 alkylation → interstrand cross-link.

5 Four mustards: mechlorethamine (prototype, vesicant, MOPP), cyclophosphamide (prodrug, liver-activated, mesna needed), melphalan (phenylalanine carrier, myeloma), chlorambucil (aromatic, slow, oral, CLL).

6 Busulfan = alkyl sulfonate, marrow/myeloid selective, CML + transplant conditioning. Thiotepa = triple aziridine on P=S, bladder instillation.

7 Purine fakes: mercaptopurine* and thioguanine (HGPRT-activated; check TPMT); azathioprine = 6-MP prodrug (transplant/IBD/RA).

8 Pyrimidine fakes: 5-FU → FdUMP blocks thymidylate synthase (thymineless death; check DPD); floxuridine = hepatic infusion; cytarabine = arabinose sugar → DNA polymerase jam + chain termination (AML "7+3").

9 Methotrexate* = folate with 4-NH_2 + N10-CH_3 → DHFR super-blocker; polyglutamated for retention; leucovorin rescue; uses from ALL to rheumatoid arthritis.

10 Anthracyclines: intercalation + topo II trap; daunorubicin (AML/ALL), doxorubicin (broadest, red devil, cardiotoxic — lifetime dose); dactinomycin (phenoxazinone + 2 peptide rings, Wilms/rhabdomyosarcoma).

11 Bleomycin = Fe^{2+}/O_2 DNA scissors; testicular + Hodgkin; pulmonary fibrosis is dose-limiting.

12 Vinca (vinblastine, vincristine): block microtubule assembly → M arrest; vincristine = neurotoxic, IV ONLY. Paclitaxel: blocks disassembly → M arrest (mirror image).

13 Etoposide = topo II poison; camptothecin = topo I poison (lead only; irinotecan/topotecan used).

14 Cisplatin: cis-[$Pt(NH_3)_2Cl_2$] → aquation → intrastrand GpG cross-link → kink; nephro/oto/emeto-toxic, needs hydration. Carboplatin: CBDCA chelate, slower, marrow-limited, dosed by AUC (Calvert).

15 Mitotane = DDT analogue, destroys adrenal cortex; adrenocortical carcinoma.

16 Star syntheses: 6-MP (hypoxanthine → $POCl_3$ → thiourea → NaOH); methotrexate (tetraaminopyrimidine + dibromopropionaldehyde → Br_2 → tail alkylation → NaOH).

6.21 Common confusions

1 **Vinblastine vs vincristine** — same dimer, one substituent different (N–CH_3 vs N–CHO); toxicities are swapped: vinBLASTine BLASTS the marrow (myelosuppression); vincristine attacks nerves (neurotoxicity, minimal marrow effect).

2 **Interstrand vs intrastrand cross-link** — nitrogen mustards bridge two OPPOSITE strands (interstrand); cisplatin bridges two neighbouring guanines on the SAME strand (intrastrand). Both block replication; the geometry differs.

3 **Cyclophosphamide is a prodrug; mechlorethamine is not** — cyclophosphamide needs liver CYP450 activation; mechlorethamine reacts instantly (hence vesicant, IV only).

4 **Methotrexate is a vitamin lookalike, not a vitamin** — folic acid has 4-oxo; methotrexate has 4-amino + N10-methyl, which is exactly why it blocks DHFR instead of feeding it.

5 **Leucovorin is not "more folate to feed cancer"** — it is reduced folate that bypasses the DHFR block, given AFTER high-dose MTX to rescue normal cells.

6 **Etoposide (topo II) vs camptothecin (topo I)** — both "trap the untangler," but topo I cuts one strand, topo II cuts both; camptothecin itself is not used clinically (too toxic) — its derivatives are.

7 **Cisplatin vs carboplatin toxicity** — cisplatin: kidneys, ears, vomiting; carboplatin: platelets/marrow. Same DNA lesion, different leaving group, different price paid.

8 **Azathioprine is not mainly a cancer drug** — it is a 6-MP prodrug used as an immunosuppressant (transplant, RA, IBD).

9 **Dactinomycin is not an anthracycline** — it is an actinomycin (phenoxazinone + peptide rings); grouped with anthracyclines here only because both intercalate.

10 **Red urine after doxorubicin is expected** — it is the drug's colour, not bleeding; but blood in urine on cyclophosphamide (acrolein cystitis) is an emergency.

6.22 Common mistakes (exam hall errors)

1 Writing "transplatin" as active — only the **cis** isomer forms the 1,2-intrastrand cross-link; transplatin is inactive.

2 Saying alkylators are "S-phase specific" — they are **cell-cycle non-specific** (attack DNA in any phase).

3 Forgetting that antimetabolites need **activation** (HGPRT, kinases) — the drug given is not the drug that acts.

4 Mixing up vinca and taxane: vinca **prevents assembly**, taxane **prevents disassembly** — writing it backwards loses the mark.

5 Prescribing vincristine intrathecally in a case study — it is **fatal**; always write "IV only, labelled."

6 Writing methotrexate dosing as "daily" in RA — it is **weekly**; daily dosing is a classic fatal error.

7 Omitting **mesna** with cyclophosphamide or **leucovorin** after high-dose methotrexate in regimen questions.

8 Calling camptothecin a routine clinical drug — it is the **lead**; irinotecan and topotecan are the clinical agents.

9 Confusing thymineless death (5-FU) with DHFR blockade (methotrexate) — both starve thymine, but at different enzymes.

10 Listing cardiotoxicity under bleomycin — bleomycin's cumulative organ is the **lung**; the **heart** belongs to doxorubicin.

6.23 Mnemonics

1 **Mustards — "Me-Cy-Mel-Chlor":** "**Me**et **Cy**nical **Mel** at the **Chlor**ine factory" Mechlorethamine, Cyclophosphamide, Melphalan, Chlorambucil.

2 **Vinca toxicity swap:** "vinBLASTine BLASTS the Bone marrow; vinCRIStine CRIes the nerves" (neurotoxicity).

3 **Rescue pairs:** "**M**esna **M**ops **M**ustard's **M**ess (cyclophosphamide–acrolein)"; "**L**eucovorin **L**ifts the **M**TX **L**ock (DHFR)."

4 **Platinum toxicities:** "**CIS**platin hits **KIS**neys (nephro), **E**ars (oto), **S**tomach (emesis)"; "**CARBO**platin **CAR**ries marrow suppression (platelets)."

5 **Anthracycline trio:** "**D**auno for **D**own-in-the-marrow leukemias (AML/ALL); **D**oxo **D**oes everything (broadest) but **D**amages the heart; **D**actino for **D**eveloping children (Wilms, rhabdomyosarcoma)."

6 **Antimetabolite fakes:** "**F**luorouracil **F**akes uracil; **M**ercaptopurine **M**imics hypoxanthine; **C**ytarabine **C**opies cytosine wrongly; **M**ethotrexate **M**asquerades as folate."

7 **Topo trappers:** "**C**amptothecin **C**uffs topo **I** (one strand); **E**toposide **E**nsnares topo **II** (two strands)."

8 **Synthesis hooks:** "6-MP: **P**$POCl_3$ **P**uts on **C**hlorine, **T**hiourea **T**acks on **S**ulphur, **B**ase **B**reaks it free." / "MTX: **C**lose the ring, **B**rominate the methyl, **C**lick the tail, **C**lear the esters."

6.24 Exam summary

- **Big picture:** 25 drugs in 7 groups — alkylators (6: 4 mustards + busulfan + thiotepa), antimetabolites (7: 6-MP, *6-TG, 5-FU, FUDR, Ara-C, MTX*, azathioprine), antitumour antibiotics (4: dactinomycin, daunorubicin, doxorubicin, bleomycin), vinca alkaloids (2), taxane (1: paclitaxel), topoisomerase inhibitors (2: etoposide, camptothecin), platinums (2), miscellaneous (1: mitotane).
- **Mechanism one-liners:** mustards → aziridinium → interstrand cross-link; busulfan → carbonium ions; thiotepa → aziridine ring opening; thiopurines → HGPRT → fake nucleotides; 5-FU → FdUMP → thymidylate synthase block; Ara-C → Ara-CTP → DNA polymerase jam; MTX → DHFR block; anthracyclines/dactinomycin → intercalation + topo II trap; bleomycin → Fe/O_2 DNA scission; vinca → no microtubule assembly; paclitaxel → no disassembly; etoposide → topo II trap; camptothecin → topo I trap; platinums → intrastrand GpG cross-link; mitotane → adrenal cortex destruction.
- **Structures to practise drawing:** mechlorethamine, cyclophosphamide's oxazaphosphorine ring, 6-MP vs thioguanine (C2 difference), 5-FU, cytarabine's arabinose, methotrexate's three parts, cisplatin square-planar cis geometry, carboplatin's CBDCA chelate, mitotane.
- **Two syntheses:** mercaptopurine (3 steps) and methotrexate (4 steps) — reagents, conditions, intermediates named.
- **Rescue/monitoring triad for every answer:** mesna–cyclophosphamide, leucovorin–MTX, hydration–cisplatin, TPMT–thiopurines, DPD–5-FU, lifetime dose–doxorubicin (heart)/bleomycin (lung), vincristine IV only.

6.25 One-minute revision

Cancer = rule-breaking division. **Staple DNA:** mustards (aziridinium → interstrand link), busulfan, thiotepa, platinums (intrastrand kink — cis only!). **Fake bricks (S phase):** 6-MP/6-TG (HGPRT, TPMT check), azathioprine (6-MP prodrug), 5-FU (TS block, DPD check), floxuridine (liver infusion), Ara-C (polymerase jam, AML 7+3), MTX (DHFR block, leucovorin rescue). **Intercalate + trap:** daunorubicin (leukemias), doxorubicin (broadest, red devil, heart budget), dactinomycin (kids' tumours), bleomycin (iron scissors, lung budget). **Spindle (M phase):** vinca = no assembly (vinblastinemarrow, vincristinenerves, IV ONLY), paclitaxel = no disassembly. **Topo traps:** etoposide (II), camptothecin (I, lead only). **Mitotane:** adrenal killer. Syntheses: 6-MP = $POCl_3$ → thiourea → NaOH; MTX = close pteridine → brominate → click tail → deprotect.

6.26 Exam questions

Short-answer questions

1 Define antineoplastic agent, alkylation, cross-link, and antimetabolite with one example each.

2 Classify the 25 antineoplastic agents chemically with two examples per class.

3 Explain the aziridinium-ion mechanism of nitrogen mustards with a labelled scheme.

4 Why is cyclophosphamide called a prodrug? Name its active metabolite and its bladder-toxic metabolite, with the rescue agent.

5 Distinguish vinblastine from vincristine on structure and dose-limiting toxicity.

6 Write the scaffold + key substituents of (a) mercaptopurine, (b) fluorouracil, (c) cisplatin, (d) methotrexate.

7 Why is the cis geometry essential for cisplatin's activity?

8 Name the rescue agents for methotrexate and cyclophosphamide toxicity and explain how each works.

9 Give two uses each of bleomycin, paclitaxel, and mitotane.

10 Why must vincristine never be given intrathecally?

Long-answer questions

1 Classify alkylating agents. Discuss the chemistry of nitrogen mustards (aziridinium mechanism), giving the structures and uses of mechlorethamine, cyclophosphamide, melphalan, and chlorambucil. Add SAR rules of nitrogen mustards.

2 Write the complete synthesis of methotrexate starting from 2,4,5,6-tetraaminopyrimidine, naming all reagents, intermediates, and conditions. Explain its mechanism as an antifolate and the role of leucovorin rescue.

3 Write the complete synthesis of 6-mercaptopurine from hypoxanthine with reagents, conditions, and intermediates. Describe its activation, mechanism of action, and uses.

4 Describe the mechanisms of action of (a) anthracyclines, (b) vinca alkaloids vs taxanes, (c) platinum compounds, with one structure and two uses for each class representative.

MCQs (answers at the end)

1 The reactive intermediate of nitrogen mustards is:

a) Carbonium ion b) Aziridinium ion c) Nitrenium ion d) Free radical

1 Cyclophosphamide is activated in the:

a) Kidney b) Liver c) Lung d) Gut wall

1 The urotoxic metabolite of cyclophosphamide is:

a) Phosphoramide mustard b) Acrolein c) Aldophosphamide d) 4-Hydroxycyclophosphamide

1 Mercaptopurine is activated by:

a) DPD b) TPMT c) HGPRT d) DHFR

1 5-Fluorouracil kills cells by inhibiting:

a) DHFR b) DNA polymerase c) Thymidylate synthase d) Topoisomerase II

1 The sugar in cytarabine is:

a) Deoxyribose b) Ribose c) Arabinose d) Glucose

1 Methotrexate differs from folic acid by:

a) 4-amino + N10-methyl b) 2-chloro c) 6-thio d) 5-fluoro

1 The rescue agent for high-dose methotrexate is:

a) Mesna b) Leucovorin c) Dexrazoxane d) Amifostine

1 Vincristine differs from vinblastine by:

a) N–CHO instead of N–CH_3 b) Extra sugar c) Lactone ring d) Platinum atom

1 The dose-limiting toxicity of bleomycin is:

a) Cardiomyopathy b) Pulmonary fibrosis c) Nephrotoxicity d) Ototoxicity

1 Which statement about cisplatin is TRUE?

a) It forms interstrand cross-links b) Transplatin is equally active c) It forms 1,2-intrastrand GpG cross-links d) It needs no hydration

1 Camptothecin inhibits:

a) Topoisomerase I b) Topoisomerase II c) DHFR d) Tubulin polymerisation

Answers: 1-b, 2-b, 3-b, 4-c, 5-c, 6-c, 7-a, 8-b, 9-a, 10-b, 11-c, 12-a

Viva questions (with answers)

1 **Q: What does "antineoplastic" literally mean?**

A: Anti (against) + neo (new) + plastic (growth/formation) — a drug acting against new abnormal growth.

1 **Q: Why does chemotherapy cause hair loss and low blood counts?**

A: Hair follicles, gut lining, and bone marrow divide rapidly like cancer cells, so cytotoxic drugs hit them too.

1 **Q: Name the intermediate after $POCl_3$ treatment of hypoxanthine in 6-MP synthesis.**

A: 6-Chloropurine.

1 **Q: What is the key ring-closing step in methotrexate synthesis?**

A: Double condensation of 2,4,5,6-tetraaminopyrimidine with 1,2-dibromopropionaldehyde to form the pteridine (pyrazine) ring.

1 **Q: Vincristine is ordered intrathecally by mistake — what do you do?**

A: Stop immediately and escalate — intrathecal vinca alkaloids are fatal; they must only ever be given IV, in labelled minibags.

1 **Q: A patient on doxorubicin reports red urine. Emergency?**

A: No — expected harmless discolouration from the drug's red colour for 1–2 days; reassure and document.

1 **Q: Why check TPMT before mercaptopurine?**

A: TPMT breaks down thiopurines; deficient patients accumulate toxic metabolites life-threatening myelosuppression.

1 **Q: How does mesna protect the bladder during cyclophosphamide therapy?**

A: Mesna's thiol binds acrolein (the urotoxic metabolite) in urine, forming a harmless conjugate.

Application-based questions

1 A 7-year-old with ALL is prescribed vincristine, but the ward sends an intrathecal syringe labelled "vincristine" from the pharmacy. As the pharmacist, what went wrong and what system fix do you implement?

2 A patient on high-dose methotrexate for osteosarcoma misses the scheduled leucovorin dose at 24 hours. Explain the pharmacological consequence and your immediate action.

3 A 62-year-old on cisplatin develops rising creatinine and tinnitus after cycle 2. Identify the toxicities, the monitoring that should have occurred, and whether carboplatin could be considered — with reasons.

4 A woman starting doxorubicin asks why her urine may turn red and whether she needs an ECG. Counsel her, covering the red urine, cumulative cardiotoxicity, and lifetime dose tracking.

6.27 References

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