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MPC103T Advanced Medicinal Chemistry, M.Pharm Semester 1

Unit 2: Prodrug Design and Analog Design

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2.1 The prodrug concept

A **prodrug** is a compound that is itself inactive, or much less active, and is converted in the body into the active drug. The idea is credited to Albert, who used the word in 1958, and to Harper, who framed drug latentiation: a drug is deliberately masked with a temporary group, the **promoiety**, chosen so that a chemical or enzymatic step in the body removes it at the right place and rate.

Prodrugs are designed against three classes of barrier:

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THE THREE BARRIERS A PRODRUG CAN CROSS
  Pharmaceutical barriers : poor solubility, instability, bad taste
        |
  Pharmacokinetic barriers: poor absorption, first pass loss,
        |                   short action, wrong distribution
  Pharmacodynamic barriers: toxicity at non-target sites,
                            no selectivity for the target tissue
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Classification by structure:

- **Carrier linked prodrugs:** the active drug is joined to a carrier group through a bond that the body breaks. Subtypes: **bipartite** (drug plus one carrier), **tripartite** (drug, linker and carrier, where the linker self-destructs after the first cleavage) and **mutual prodrugs** (two active drugs joined to each other, each the other's carrier).
- **Bioprecursors:** no carrier at all; the molecule itself is metabolically transformed into the active species, for example by oxidation, reduction or decarboxylation.

2.2 Carrier linked prodrugs and bioprecursors

Carrier linked examples. Enalapril is the ethyl ester of enalaprilat: the diacid enalaprilat inhibits the angiotensin converting enzyme well but is poorly absorbed, so one carboxyl group is masked as an ester, absorbed, and hydrolysed by liver esterases to the active diacid. Valaciclovir is the L-valyl ester of aciclovir: the amino acid ester is carried across the gut wall by a peptide transporter, then hydrolysed, giving several fold better oral delivery of aciclovir. Fosphenytoin is a phosphate ester prodrug of phenytoin that is freely water soluble for injection where phenytoin itself is not.

Bioprecursor examples. Levodopa crosses the blood brain barrier on an amino acid transporter and is decarboxylated to dopamine in the brain; dopamine itself cannot be given because it does not cross. Codeine is O-demethylated by CYP2D6 to morphine, which provides most of its analgesia, which is why CYP2D6 poor metabolisers get little effect and ultra rapid metabolisers are at risk of opioid toxicity. Cyclophosphamide is oxidised in the liver to an intermediate that breaks down to the cytotoxic phosphoramide mustard. Sulindac is reduced to its active sulfide.

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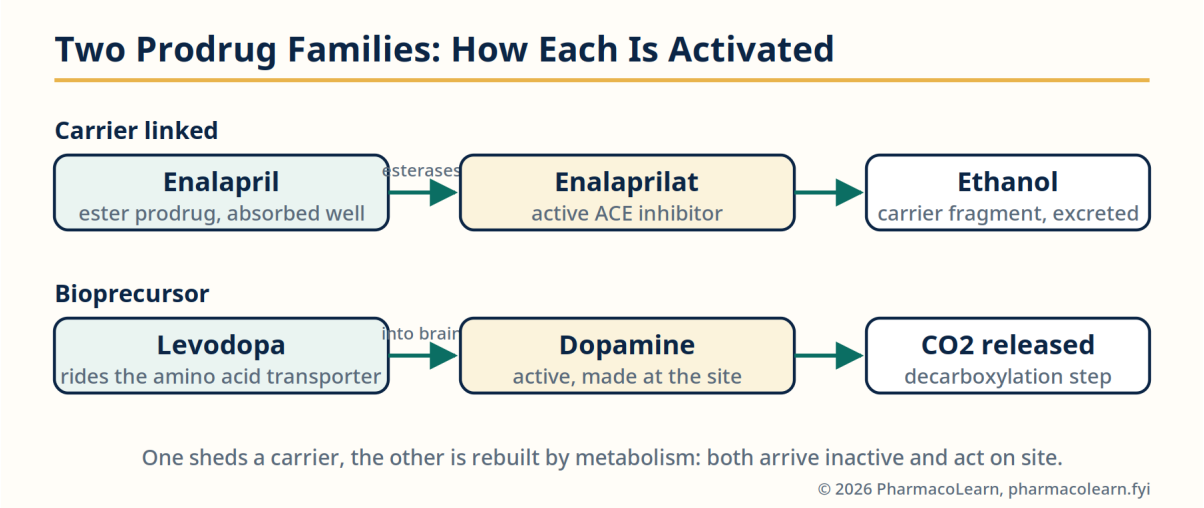

Figure: The two prodrug families. A carrier linked prodrug sheds a promoiety; a bioprecursor is itself rebuilt by metabolism into the active molecule.

2.3 Prodrugs of functional groups

The promoiety is chosen to fit the functional group being masked:

Functional group on the drug	Common prodrug forms	Cleavage
Carboxylic acid	Alkyl and aryl esters, (acyloxy)alkyl esters	Esterases
Alcohol or phenol	Esters, carbonates, carbamates, phosphate esters	Esterases, phosphatases
Amine	Amides, carbamates, imines (Schiff bases), N-Mannich bases	Amidase or hydrolysis
Carbonyl (ketone, aldehyde)	Oximes, imines, cyclic derivatives	Hydrolysis or oxidation
Phosphate or phosphonate on the drug	Aryl and acyloxyalkyl masking groups	Esterases, giving the charged parent for cell entry problems

Two practical rules follow. First, the masking bond must be stable enough to survive formulation and the stomach, yet labile enough to break in plasma, gut wall, liver or target tissue. Second, the promoiety itself must be safe: pivalate esters, for example, release pivalic acid, which is excreted as a carnitine conjugate and can lower body carnitine on prolonged use.

2.4 Prodrugs for patient acceptability

Some drugs fail simply because patients will not take them:

- **Taste:** chloramphenicol is intensely bitter; its palmitate ester is tasteless because it does not dissolve in saliva, and is hydrolysed in the gut to release the drug. This is the classical taste masked prodrug.
- **Pain and irritation on injection:** long chain esters and water soluble phosphate prodrugs reduce the irritation of insoluble or irritating drugs at the injection site.
- **Gastric irritation:** ester prodrugs of some acidic anti-inflammatory drugs were designed to pass the stomach intact and release the acid later, although in practice systemic prostaglandin inhibition still contributes to gastric damage, a useful warning that a prodrug cannot fix a mechanism based side effect.
- **Odour and formulation acceptability:** masking volatile or unstable groups improves handling and shelf presentation as well as compliance.

2.5 Prodrugs for solubility, absorption and distribution

Solubility. Adding an ionisable promoiety converts an insoluble drug into a salt forming, water soluble prodrug for parenteral use: chloramphenicol sodium succinate and fosphenytoin sodium are the standard examples. The prodrug dissolves, is injected, and hydrolysis releases a drug whose low solubility no longer matters because it is already in solution at low concentration in blood.

Absorption. Masking a polar group raises membrane permeability: enalapril (oral) versus enalaprilat (poorly absorbed) is the cleanest pair. Transporter targeting goes further: valaciclovir uses an amino acid ester to ride the intestinal peptide transporter PEPT1.

Distribution. Dipivefrin, the dipivalate ester of adrenaline, crosses the cornea far better than adrenaline itself and releases adrenaline inside the eye, giving the same effect at a fraction of the dose, with less systemic exposure. Levodopa is a distribution prodrug aimed at the blood brain barrier.

2.6 Site specific delivery and sustained action

Site specific delivery. Sulfasalazine carries 5-aminosalicylic acid (5-ASA) through the small intestine joined by an azo bond to sulfapyridine; colonic bacteria reduce the azo bond and release 5-ASA exactly where inflammatory bowel disease needs it, a prodrug switched on by the local microflora. Olsalazine joins two 5-ASA molecules the same way, removing the sulfapyridine carrier. The ADEPT concept (antibody directed enzyme prodrug therapy) generalises the idea: an enzyme is targeted to a tumour by an antibody, and a harmless prodrug given afterwards is converted to a cytotoxic drug only at the tumour.

Sustained action. Esterifying a drug with a long chain fatty acid makes an oily depot: fluphenazine decanoate and haloperidol decanoate release their antipsychotic slowly from an intramuscular oil depot over weeks, a prodrug answer to the compliance problem in chronic schizophrenia. Insulin analogs that precipitate or bind albumin after injection apply a related slow release logic at the protein level.

2.7 Rationale and practical considerations of prodrug design

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PRODRUG DESIGN DECISION SEQUENCE
  Name the barrier precisely        (solubility? absorption? site?)
        |
  Choose the group to mask          (which functional group, which
        |                            promoiety fits it?)
  Check the cleavage step           (which enzyme or pH, where, how
        |                            fast relative to the journey?)
  Check the promoiety               (inactive, non toxic, excreted)
        |
  Test stability vs activation      (shelf stable, body labile)
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The ideal prodrug is chemically stable in the bottle, converts quantitatively and predictably at the intended site, produces an inert promoiety, and does not create a new problem while solving the old one. Practical failures come from conversion that is too fast (the prodrug behaves like the drug, barrier unsolved), too slow (drug levels never reached), or dependent on an enzyme that varies between patients, as codeine depends on CYP2D6.

2.8 Combating drug resistance

Drug resistance is the inherited ability of a microbe or a cancer cell to survive a drug concentration that previously killed it. Its main mechanisms:

Mechanism	Bacterial example	Cancer example
Target modified so the drug binds poorly	Altered penicillin binding proteins in MRSA	Mutated BCR-ABL gatekeeper (T315I) resisting imatinib
Drug destroyed or modified	Beta-lactamases hydrolyse penicillins	Enzyme induction and detoxification in tumour cells
Drug pumped out (efflux)	Tetracycline efflux pumps	P-glycoprotein (MDR1) expelling many anticancer drugs
Drug kept out (reduced uptake)	Porin loss in Gram negative bacteria	Reduced folate carrier loss resisting methotrexate
Bypass of the blocked step	Alternative folate routes	Alternative signalling pathways bypass a blocked kinase

Genetic principles. Resistance genes arise by mutation and, decisively in bacteria, spread by horizontal gene transfer: plasmids carrying resistance genes pass between bacteria by conjugation, and transformation and transduction move genes as well. Selection does the rest: every course of antibiotic kills the susceptible and leaves the resistant. In cancer, resistance arises from the genetic instability of the tumour, which generates resistant subclones that treatment then selects.

Strategies in antibiotics: combine a drug with an inhibitor of the resistance enzyme (amoxicillin with clavulanic acid, a suicide inhibitor of beta-lactamases, Unit 4); use combinations that require two independent resistance events at once (tuberculosis therapy); design analogs that the resistance enzyme handles poorly (later generation cephalosporins); and reduce selection pressure by correct dosing and duration.

Strategies in anticancer therapy: combination chemotherapy with non cross resistant drugs (the logic of regimens such as CHOP); next generation inhibitors designed against the resistant mutant itself (osimertinib was designed for the T790M mutant EGFR that resists first generation inhibitors); and attacking the efflux or bypass mechanism, although P-glycoprotein inhibitors have so far disappointed in the clinic because the pump also protects normal tissues.

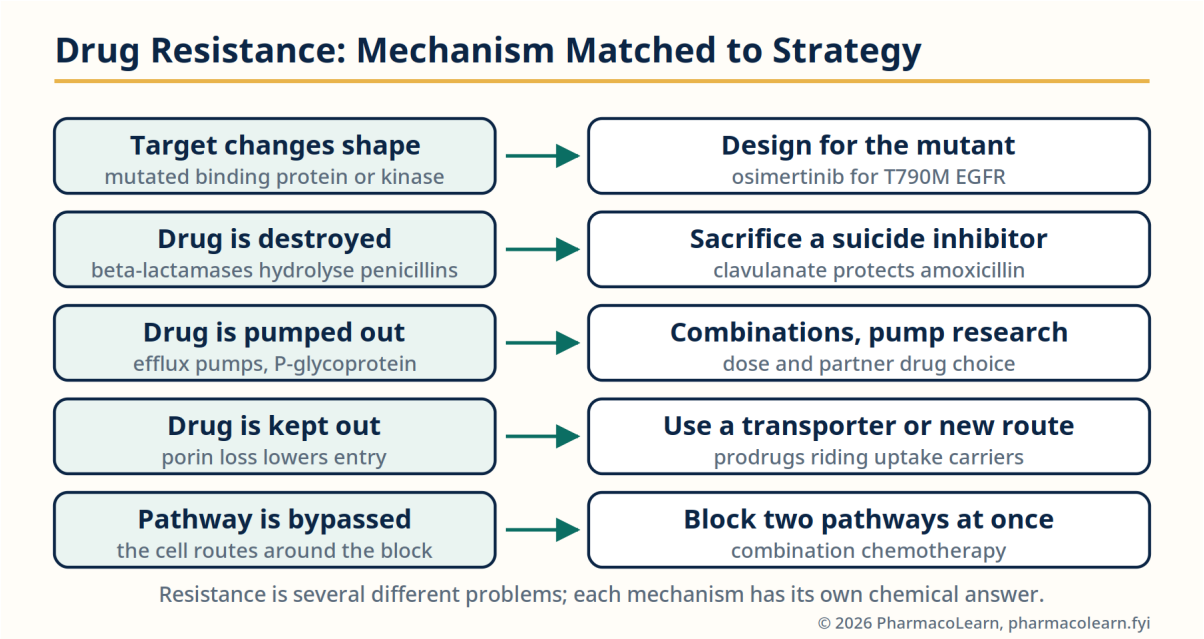

Figure: Resistance is a set of distinct mechanisms, and each has its own chemical answer. One drug rarely answers two mechanisms at once, which is why combinations work.

2.9 Analog design: modifying a lead molecule

Analog design (lead modification) is the systematic structural variation of a lead to improve the properties the lead lacks: potency, selectivity, duration, solubility, safety. The medicinal chemist works around a **pharmacophore**, the arrangement of features (hydrogen bond donors and acceptors, charged groups, hydrophobic regions, at defined distances) that the target recognises, and varies everything else one change at a time so that the effect of each change can be read. The strategies in the rest of this unit are the working tools: bioisosteric replacement (2.10), and the structural variations of 2.11.

2.10 Bioisosteric replacement strategies

A **bioisostere** is a group that can replace another group in a molecule with a similar biological result, because the target reads the two as alike in the property that matters (size, charge, hydrogen bonding, electron distribution), while other properties such as stability or solubility improve.

Classical bioisosteres come from the old isosterism rules, atoms and groups with the same number of valence electrons (Grimm's hydride displacement law) or similar size and shape (Erlenmeyer's ring equivalents):

Classical replacement	Examples
-CH3, -NH2, -OH, -SH (one row of the hydride series)	Swapping along the series changes acidity and hydrogen bonding in small steps
-CH= exchanged for -N= in a ring	Pyridine for benzene in a ring system
Ring equivalents	Benzene, thiophene, furan and pyridine rings exchanged for one another
Halogen for hydrogen or CF3	Fluorine for hydrogen (similar size, very different electronics)
-O-, -S-, -NH-, -CH2- in a chain	Linker exchanges that change bond angles and metabolism

Non-classical bioisosteres do not look alike on paper but present the same key interaction: the **tetrazole ring for a carboxylic acid** is the famous case, since both are acidic and anionic at body pH, but the tetrazole is more lipophilic and resists glucuronidation; replacing the acid of an early angiotensin antagonist lead with tetrazole produced losartan. Others: the **cyanoguanidine group for thiourea** in cimetidine (section 3.5), sulfonamide and carboxamide exchanges, and replacing an ester with a 1,2,4-oxadiazole or other ring that keeps the geometry but refuses hydrolysis.

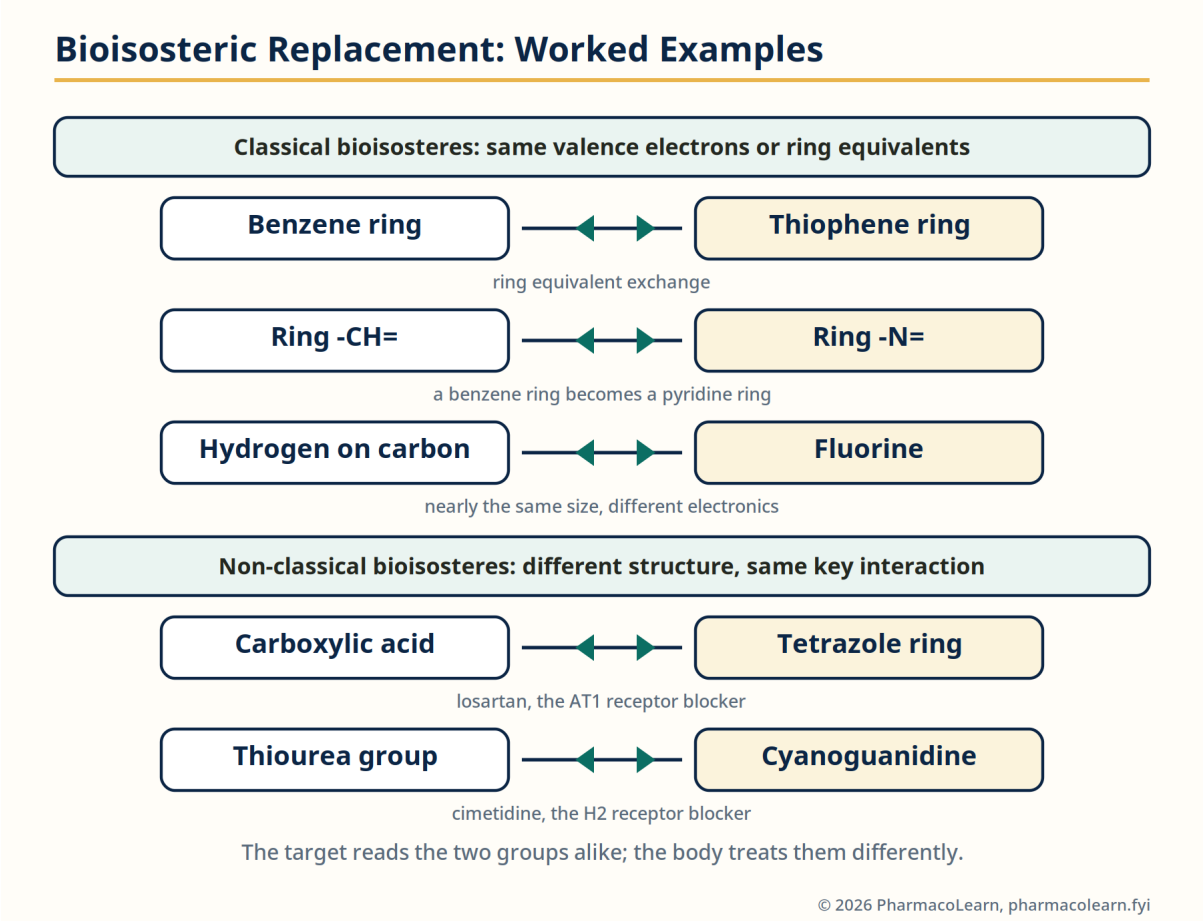

Figure: Bioisosteres keep the interaction the target reads and change the properties the body imposes: stability, solubility, duration.

2.11 Other analog design strategies

- **Rigid analogs (conformational restriction):** locking a flexible lead into the shape it adopts at the target removes the entropic cost of folding on binding and often raises potency and selectivity; it also tests the active conformation. Ring closure and added double bonds are the usual tools.
- **Alteration of chain branching:** adding or moving a methyl branch changes fit and blocks or exposes metabolic sites; branching near a functional group also slows hydrolysis by steric shielding.
- **Changes in ring size:** expanding or contracting a ring repositions every substituent on it; a six membered ring lead may become a better five or seven membered analog.
- **Ring position isomers:** moving a substituent around a ring (ortho, meta, para) scans the geometry of the pocket at almost no synthetic cost and is one of the first scans in any program.
- **Design of stereoisomers and geometric isomers:** making and testing each enantiomer separately (Unit 3), and locking cis or trans geometry, as in the stilbene framework where the trans isomer diethylstilbestrol carries the oestrogenic activity.
- **Fragments of a lead molecule (molecular dissection):** cutting a complex lead down to the smallest fragment that keeps activity. Morphine dissected stepwise gave the simpler pethidine: the anilinopiperidine fragment retained analgesia and was far easier to make and vary.
- **Variation in interatomic distance (homologation):** lengthening or shortening the chain between two key groups finds the distance the target prefers. The antipsychotic phenothiazines need three carbons between ring nitrogen and side chain nitrogen; two carbons gives a different (antihistaminic) profile, a classical distance lesson.