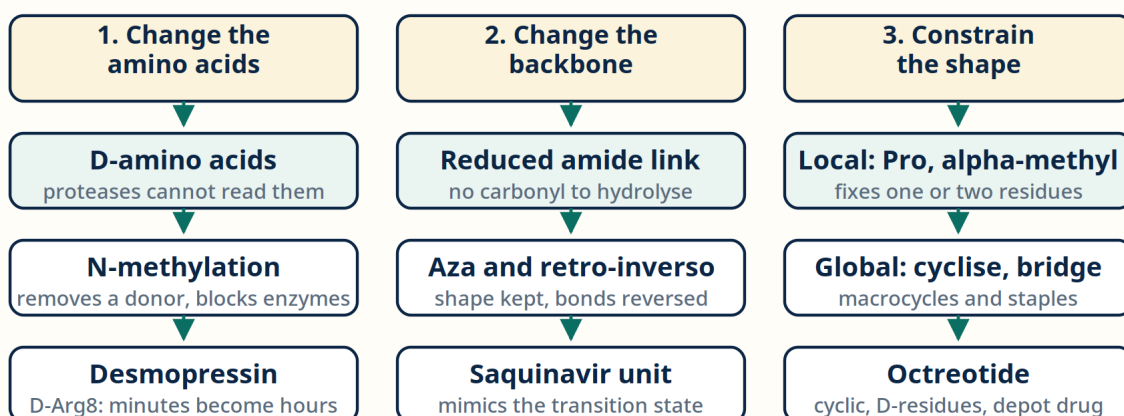


5.1 Why peptides make difficult drugs

Peptides are attractive starting points because biology uses them as precise signals (hormones, neurotransmitters), so a peptide lead often arrives with potency and selectivity built in. As drugs they are poor: digestive and plasma proteases hydrolyse their amide bonds within minutes; their size and hydrogen bonding surface keep them out of membranes, so oral absorption is negligible; kidneys clear them quickly; and many are expensive to make. A **peptidomimetic** is a molecule designed to reproduce the peptide's active shape and side chain display on a scaffold the body cannot digest so easily. The design strategies of this unit answer the three faults in order: stop the enzymes, improve the journey, keep the shape.

5.2 Peptidomimetics: concept and therapeutic value

Three Families of Peptidomimetic Design



Most successful peptidomimetics combine all three families of moves.

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Figure: Three families of moves turn a fragile peptide into a drug-like molecule. Most successful peptidomimetics combine all three.

The therapeutic value is concrete: peptidomimetics have delivered renin and HIV protease inhibitor chemistry, thrombin inhibitors, and the whole class of constrained peptide drugs. Desmopressin, a deaminated arginine vasopressin analog with a D-amino acid, lasts hours where vasopressin lasts minutes. Octreotide, a cyclic octapeptide analog of somatostatin with D-amino acids and a reduced terminal alcohol, turned a two minute hormone signal into a monthly depot drug. Neither is a small molecule; both are peptides rebuilt by the strategies below until they behaved like drugs.

5.3 Design by manipulation of the amino acids

PEPTIDE OPTIMISATION LOOP

Replace one residue at a time (alanine scan finds which side chains the target actually reads)
|
Protect the cleavage sites those assays reveal
|
Re-test activity, stability and solubility together
|
Repeat: every gain in stability must not cost the shape

- **D-amino acids:** proteases are built for L-amino acids; a D-residue at or near the cleavage site is not recognised, and it also bends the chain differently, which can help or must be compensated. Desmopressin's D-Arg8 is the model case.
- **N-methylation:** methylating a backbone nitrogen removes a hydrogen bond donor, blocks protease binding and can improve membrane passage; cyclosporine is extensively N-methylated by nature.
- **Unnatural amino acids:** residues outside the coded twenty add side chains no protease expects and new interactions with the target; alpha-methyl amino acids also restrict local conformation (section 5.5).
- **Side chain surgery:** shortening, lengthening or capping side chains, and replacing a charged terminus, tunes potency and stability independently of the backbone.

5.4 Design by modification of the peptide backbone

The amide bond is both the protease target and a strong hydrogen bonding unit, so backbone isosteres trade one property against the other:

Backbone change	What it does	Cost to watch
Reduced amide, -CH ₂ -NH- in place of -CO-NH-	Not hydrolysed by proteases; keeps chain length	Loses the carbonyl hydrogen bond acceptor; the amine is basic and may be protonated
Ketomethylene, -CO-CH ₂ -	Keeps the carbonyl, removes the nitrogen	Loses the NH donor
Aza-peptide (nitrogen replaces the alpha carbon)	Resists proteolysis, biases conformation	Changes side chain presentation geometry
Depsipeptide (ester replaces one amide)	Alters solubility and conformation; found in natural products	The ester is itself hydrolysable, but by different enzymes
Retro-inverso (reversed sequence of D-amino acids)	Side chains keep roughly the original display while every amide is reversed	End groups need correction; not a perfect mirror of binding
Alkene or alkane isostere for the amide	Fully non hydrolysable link	Removes both hydrogen bonding partners of that bond

The transition state analogs of Unit 4 (the hydroxyethylene unit in saquinavir) are this table in action: one backbone unit of a peptide substrate was replaced by a non cleavable mimic of the reaction's high point, and a drug resulted.

5.5 Conformational constraints, local and global

A flexible peptide pays an entropy penalty when it folds into its bound shape, and presents many shapes to proteases. Constraining it pre-pays that cost:

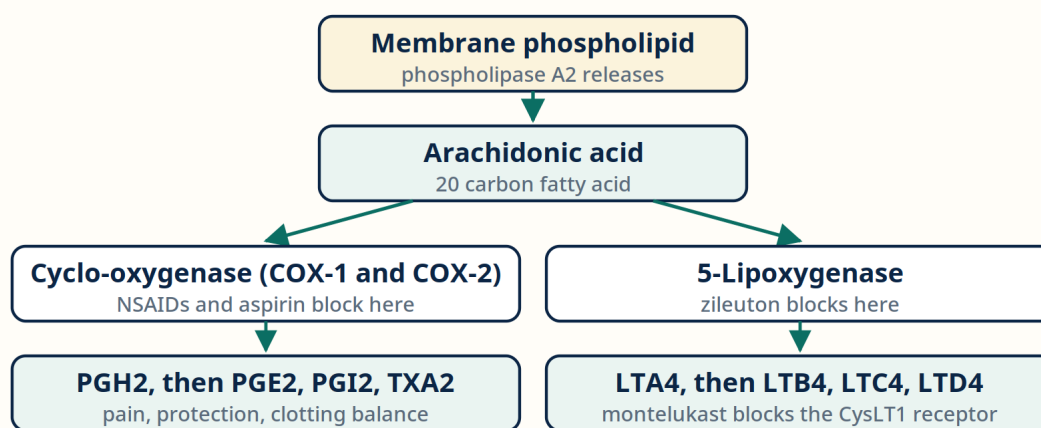
- **Local constraints** act on one or two residues: proline and its analogs fix the preceding bond angle; alpha-methyl and other alpha, alpha-disubstituted amino acids narrow the allowed shapes; a D-amino acid in a turn position stabilises beta turns.

- **Global constraints** tie distant parts of the molecule together: **macrocyclisation** head to tail or side chain to side chain (cyclosporine is a natural macrocycle, and its ring is a large part of why it is orally available at all); **disulfide bridges** (oxytocin and insulin use them, although disulfides can be reduced in the body and are sometimes replaced by carbon or thioether bridges); lactam bridges between lysine and acidic side chains; and hydrocarbon **staples** that brace an alpha helix in peptide inhibitors of protein interactions.
- **The balance to strike:** constraint helps only when the locked shape is the active shape; locking the wrong conformation is worse than flexibility, which is why constraint follows structure determination of the bound peptide, not guesswork.

5.6 Chemistry of prostaglandins

The eicosanoids are local hormones made from **arachidonic acid**, a 20 carbon polyunsaturated fatty acid released from membrane phospholipids by phospholipase A2. Two enzyme families then compete for it:

The Arachidonic Acid Cascade and Its Block Points



One fatty acid, two branches: anti-inflammatory therapy is a choice of block point.

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Figure: One fatty acid, two great branches. Most anti-inflammatory pharmacology is a choice of where to block this diagram.

Prostaglandin structure and chemistry. Prostaglandins are 20 carbon fatty acids carrying a five membered ring: the letter (E, F, D, I and others) names the ring's oxygen pattern, the subscript counts the double bonds. The cyclo-oxygenase pathway first builds the endoperoxide PGH₂, the shared parent, which tissue specific enzymes convert to PGE₂ (pain sensitisation, fever, gastric protection), PGF₂α (uterine and luteal actions, and intraocular pressure control), PGD₂, prostacyclin PGI₂ and thromboxane A₂ (next sections).

Prostaglandin drugs. Natural prostaglandins are destroyed in minutes by 15-hydroxyprostaglandin dehydrogenase; analog design (Unit 2 methods) fixed that: **misoprostol** is a PGE₁ analog with a methyl ester and a moved hydroxyl group that resists the dehydrogenase, used for gastric protection and in obstetrics; **latanoprost** is a PGF₂α analog given as an isopropyl ester prodrug eye drop for glaucoma. Carboprost (a 15-methyl PGF₂α) resists oxidation at the 15 position, the literal weak point, because the added methyl group blocks the enzyme that starts prostaglandin destruction.

5.7 Leukotrienes

The 5-lipoxygenase branch converts arachidonic acid to the unstable epoxide LTA₄, the parent of the leukotrienes. LTB₄ is a powerful neutrophil attractant. The **cysteinyl leukotrienes** LTC₄, LTD₄ and LTE₄

carry amino acid derived substituents (the peptide part is what cysteinyl means here), are released from mast cells and eosinophils, and are the substances once called slow reacting substance of anaphylaxis (SRS-A): potent bronchoconstrictors and drivers of mucus secretion and vascular leak in asthma.

Drugs of this branch: **montelukast** and **zafirlukast** block the CysLT1 receptor and are taken orally for asthma prophylaxis; **zileuton** inhibits 5-lipoxygenase itself, cutting off production of all leukotrienes at the branch point, at the price of liver monitoring. The comparison is a clean design contrast: block the factory, or block the receptor that reads its main product.

5.8 Thromboxanes and the prostacyclin balance

Platelets convert PGH₂ to **thromboxane A₂ (TXA₂)**, a potent platelet aggregator and vasoconstrictor with a half life of about 30 seconds before it hydrolyses to the inactive TXB₂. Blood vessel endothelium converts the same PGH₂ to **prostacyclin (PGI₂)**, which opposes TXA₂ point for point: it inhibits platelet aggregation and dilates vessels. Haemostasis reads the balance between them.

Low dose aspirin exploits the asymmetry of the two systems: it irreversibly acetylates platelet COX (section 3.6), the anucleate platelet cannot make new enzyme, so TXA₂ production stays off for the platelet's life, while nucleated endothelial cells resynthesising COX restore PGI₂. The same balance explains the rofecoxib lesson of section 3.6: blocking COX-2 alone suppresses endothelial PGI₂ while leaving platelet COX-1 and TXA₂ intact, tipping the scale towards clotting.

Frequently Asked Questions

Q: What is the difference between a hit, a lead and a drug candidate? A hit is a compound with confirmed, reproducible activity against the target in a screening assay. A lead is a hit series judged worth optimising: it has real potency, a workable structure and no fatal liability. A drug candidate is the optimised end product of lead optimisation, good enough in potency, selectivity, pharmacokinetics and early safety to enter preclinical and then clinical development.

Q: Why is target validation done before screening begins? Because screening and optimisation are the expensive stages. Validation gathers genetic, expression, tool compound, animal and ideally human evidence that changing the target's activity changes the disease, so the programme spends its chemistry budget on a target that can actually deliver a medicine. Targets with human genetic support succeed in the clinic at a notably higher rate.

Q: What separates affinity from efficacy at a receptor? Affinity is how tightly a drug binds, measured by K_d. Efficacy is what the bound drug does, whether it activates the receptor. A full agonist has both, an antagonist has affinity with zero efficacy, and a partial agonist has affinity with submaximal efficacy, which is why a partial agonist can also antagonise a full agonist.

Q: How do carrier linked prodrugs and bioprecursors differ? Give one example of each. A carrier linked prodrug joins the drug to a removable promoiety: enalapril is the ethyl ester that esterases convert to enalaprilat. A bioprecursor has no carrier and is itself metabolically rebuilt into the active drug: levodopa is transported into the brain and decarboxylated to dopamine.

Q: Tetrazole in losartan is called a non-classical bioisostere of a carboxylic acid. Why does the exchange work? Both groups are acidic and exist as anions at body pH, with a similar spread of negative charge, so the AT₁ receptor reads them alike. The tetrazole is more lipophilic and is not cleared by glucuronidation the way the acid was, so duration and exposure improve while binding is retained: the definition of a successful bioisosteric replacement.

Q: How does clavulanic acid combat beta-lactam resistance? Clavulanic acid is itself a weak antibacterial but an excellent suicide substrate for bacterial beta-lactamases: the enzyme processes it into a species that permanently disables the enzyme. Given with amoxicillin, it sacrifices itself to the resistance enzyme so the antibiotic survives to reach its penicillin binding protein targets.

Q: What does SAR mean, and how is it established? Structure activity relationship: the pattern connecting structural features of a series of analogs to their biological activity. It is established by varying one feature at a time around a lead, synthesising and testing the series, and reading which groups are essential (removing them kills activity), which are tolerated, and which improve potency or properties. Every class study in Unit 3 is presented as classification, mechanism, SAR and synthesis in that order.

Q: Why would a drug be sold as a single enantiomer instead of the racemate? Because enantiomers can differ at every pharmacokinetic and pharmacodynamic stage: levofloxacin carries almost all the antibacterial activity of ofloxacin, levocetirizine is the active half of cetirizine, and D-penicillamine avoids the toxicity of its mirror image. A single enantiomer is justified when it is genuinely more active, cleaner or safer, as in those cases, not merely when it is patentably newer.

Q: Competitive and non-competitive inhibition look different on a Lineweaver-Burk plot. How? A competitive inhibitor raises apparent K_m and leaves V_{max} unchanged, so the lines for different inhibitor concentrations meet on the $1/v$ axis. A non-competitive inhibitor lowers V_{max} and leaves K_m unchanged, so the lines meet on the $1/[S]$ axis. Uncompetitive inhibition lowers both and gives parallel lines.

Q: What three design moves turn a peptide into a peptidomimetic drug? Manipulate the amino acids (D-residues, N-methylation, unnatural side chains) to defeat proteases; modify the backbone (reduced amide, ketomethylene, aza and other isosteres) so the cleavable bonds disappear while the shape is kept; and constrain the conformation, locally with proline or alpha-methyl residues or globally by cyclisation and bridges, so the molecule is pre-organised into its active shape. Desmopressin and octreotide combine all three.

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