

Unit 1: Drug Discovery

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Advanced Medicinal Chemistry, subject code MPC103T, is a core Semester 1 subject of M.Pharm Pharmaceutical Chemistry. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. This subject is where organic chemistry meets biology. MPC102T taught how molecules are made; this subject teaches how molecules are designed to act on the body. Unit 1 sets out the modern drug discovery pipeline: how a disease target is identified and validated, where lead molecules come from, and how drugs interact with their main biological targets, the receptors, including the classical theories of drug receptor interaction and the difference between agonists and antagonists. Unit 2 covers the two great lead modification strategies: prodrug design, in which a temporary chemical group carries a drug past a pharmaceutical or pharmacokinetic barrier, and analog design, in which a lead is systematically varied by bioisosteric replacement, rigidification, ring changes and stereochemical design, together with the strategies used to combat drug resistance. Unit 3 applies the method of systematic study (classification, SAR, mechanism of action and synthesis) to eight major drug classes, from antihypertensives to antivirals, and closes with stereochemistry and drug action. Unit 4 is the rational design of enzyme inhibitors, built on enzyme kinetics. Unit 5 treats peptidomimetics, the art of making peptide like molecules that survive in the body, and the chemistry of the eicosanoids: prostaglandins, leukotrienes and thromboxanes. A student who completes this subject should be able to outline the stages of a drug discovery programme, propose a prodrug or analog strategy for a given problem, read the SAR of a drug class, and explain how a new generation inhibitor or peptidomimetic was designed.

1.1 Stages of drug discovery

Modern drug discovery is a funnel. Thousands of compounds enter at the top, and typically one reaches the market. The stages, in order, are:

- **Target identification and validation:** a biological molecule or pathway is chosen and evidence gathered that changing its activity will change the disease (Unit 1, section 1.3).
- **Hit discovery:** large numbers of compounds are screened against the target to find **hits**, compounds with measurable, reproducible activity.
- **Hit to lead:** hits are confirmed, checked for selectivity and obvious liabilities, and grouped into chemical series; the most promising series become **leads**.
- **Lead optimisation:** the lead is systematically modified (Unit 2) to improve potency, selectivity, solubility, metabolic stability and safety together. This is the home ground of medicinal chemistry.
- **Preclinical development:** the optimised candidate is tested in animals for pharmacokinetics and toxicology and a formulation is developed.
- **Clinical development and approval:** Phase I (safety in volunteers), Phase II (first efficacy in patients), Phase III (large confirmatory trials), then regulatory review, marketing, and Phase IV surveillance after launch.

The economics explain the funnel shape: most candidates fail, and they fail mostly for lack of efficacy or for toxicity, so every early test that removes a weak compound cheaply saves money later. A useful distinction is between the **lead**, a compound with proven activity and a workable structure but many faults, and the **drug candidate**, a compound in which those faults have been engineered out.

The Drug Discovery Pipeline



The funnel: numbers collapse at every stage, so weak compounds must leave early.

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Figure: The drug discovery funnel. Numbers fall steeply at every stage, which is why weak compounds must be removed as early and as cheaply as possible.

1.2 Lead discovery: where leads come from

A lead can come from many sources, and most marketed drugs trace back to one of a few classic routes:

- **Natural products and their derivatives:** morphine, the penicillins, lovastatin and paclitaxel all began as natural leads (their chemistry is the subject of MPC104T).
- **Screening of synthetic compound collections:** high throughput screening (HTS) tests hundreds of thousands of stored compounds against the target in automated assays. Fragment based screening tests very small molecules (fragments) at high concentration with sensitive biophysical methods and grows the best fragments into leads.
- **Existing drugs and their side effects:** many leads began as an observed side effect of a known drug; the sulfonamide antibacterials revealed hypoglycaemic sulfonylureas, and chlorpromazine grew out of work on antihistamines.
- **The endogenous ligand or substrate:** designing from the body's own messenger, as histamine guided the design of both H1 and H2 antagonists, and as angiotensin guided the ACE inhibitors.
- **Rational and structure based design:** when the three dimensional structure of the target is known, compounds can be designed to fit its binding site directly; this is developed in Unit 4 for enzymes.
- **Serendipity:** penicillin, librium (chlordiazepoxide) and sildenafil (developed for angina, redirected by an observed effect) all arrived partly by chance, although chance only helps a prepared screening programme.

Whichever the source, a hit becomes a lead only after confirmation: the activity must repeat in a fresh sample of verified identity and purity, show a sensible dose response, and not be an assay artifact (some compounds interfere with assays themselves, for example by aggregating or by reacting with assay reagents).

1.3 Drug targets: identification, validation and diversity

A **drug target** is the biological molecule whose activity the drug changes to produce its therapeutic effect. Target identification draws on genomics and disease biology (genes linked to disease by mutation or expression studies), on pathway analysis, and on the targets of drugs that already work in the disease.

Target validation asks whether the target deserves a full discovery programme. The evidence, in increasing strength:

TARGET VALIDATION SEQUENCE	
Genetic evidence	: disease linked to the gene or pathway
Expression evidence	: target present in the diseased tissue
Tool compound or genetic knockdown	: changing the target in cells changes the disease relevant behaviour
Animal model evidence	: changing the target helps in vivo
Human evidence	: human genetics or an existing drug acting on the target works in patients

The human evidence line is the strongest: the cholesterol target HMG-CoA reductase was validated by the statins themselves, and targets supported by human genetic evidence succeed in the clinic at a clearly higher rate than targets without it.

Diversity of drug targets. Most marketed drugs act on a small set of target classes:

Target class	Share of drug action (approx.)	Examples of drug and target
Receptors (mostly GPCRs)	Largest single class	Propranolol at beta adrenoceptors, morphine at opioid receptors
Enzymes	Second largest class	Statins at HMG-CoA reductase, methotrexate at dihydrofolate reductase
Ion channels	Smaller but important	Amlodipine at L-type calcium channels, phenytoin at sodium channels
Transporters (carriers)	Smaller	Fluoxetine at the serotonin transporter, omeprazole at the proton pump (an ATPase)
Nucleic acids and structural proteins	Smallest	Alkylating agents and intercalators on DNA, colchicine on tubulin

The diversity point the syllabus makes is that the druggable genome is much larger than the few hundred targets of current drugs, and new target classes (protein protein interactions, RNA targets) keep opening as techniques improve.

1.4 Receptors: the major biological drug target

A **receptor** is a protein that recognises an endogenous chemical messenger (a neurotransmitter, hormone or local mediator) and converts that recognition into a cellular response. Receptors are classified into four superfamilies by structure and signalling mechanism:

Superfamily	Structure	Signalling	Response speed	Examples
Ligand gated ion channels	Multi subunit membrane protein with a central pore	Ion flow across the membrane	Milliseconds	Nicotinic acetylcholine receptor, GABA-A receptor

Superfamily	Structure	Signalling	Response speed	Examples
G protein coupled receptors (GPCRs)	Single protein, seven transmembrane helices	G proteins, then second messengers (cAMP, IP3, DAG) or ion channels	Seconds	Adrenoceptors, histamine, dopamine, opioid receptors
Kinase linked receptors	Single transmembrane protein with intracellular enzyme (kinase) activity	Phosphorylation cascades	Minutes to hours	Insulin receptor, growth factor receptors
Nuclear receptors	Intracellular (cytoplasmic or nuclear) protein	Direct control of gene transcription	Hours	Steroid, thyroid hormone and vitamin D receptors

Binding and activation. A drug binds to a receptor at a defined **binding site**, usually the site used by the endogenous agonist (the orthosteric site) or a separate regulatory site (an allosteric site). Binding alone is not enough: the receptor must also change shape and signal. Section 1.5 separates these two properties, affinity and efficacy.

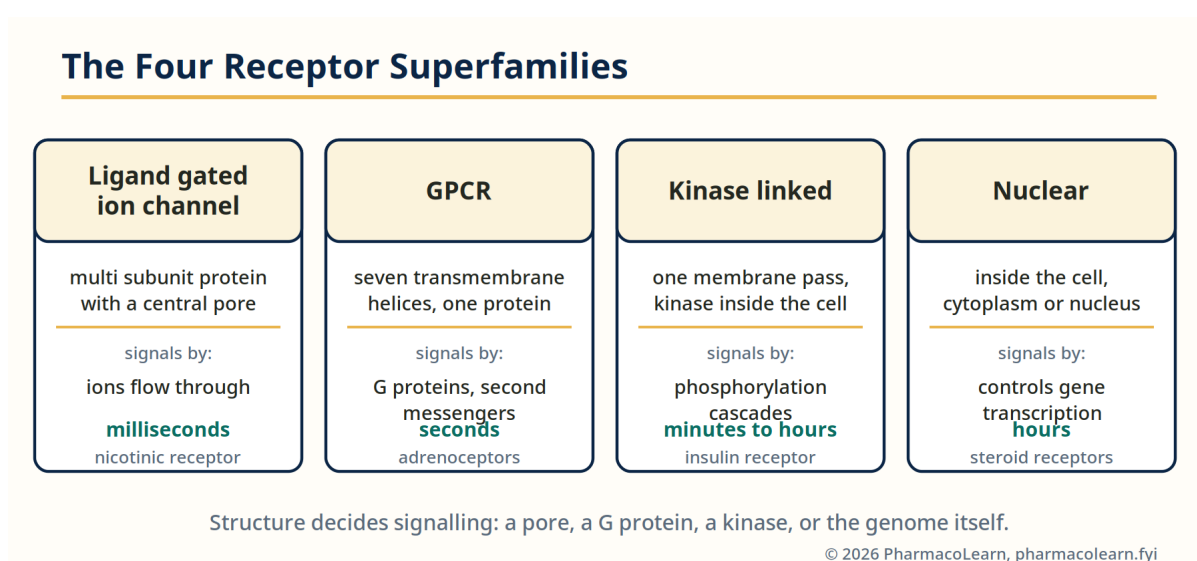


Figure: The four receptor superfamilies. Structure decides signalling: a pore, a G protein, a kinase, or the genome itself.

1.5 Drug receptor interactions: binding forces, affinity and efficacy

Drug receptor binding is held together by the same non-covalent forces that hold any molecular complex together, acting together over the surface of the binding site:

- **Ionic (electrostatic) interactions:** between oppositely charged groups, for example a protonated amine of the drug and a carboxylate of the receptor. Strong, and often the first anchor point.
- **Hydrogen bonds:** directional, moderate strength; donors and acceptors must be correctly positioned, which is one source of selectivity.
- **Van der Waals forces:** weak individually, but summed over a well fitting surface they contribute greatly; fit must be close, since the force falls off very steeply with distance.
- **Hydrophobic interactions:** non-polar surfaces of drug and pocket exclude water and associate; a major driver of binding for lipophilic drugs.
- **Covalent bonds:** rare in receptor binding, common in enzyme inhibition (Unit 4); usually irreversible.

Two independent properties describe what a bound drug does:

- **Affinity** is how tightly the drug binds, measured by the equilibrium dissociation constant K_d (or its negative log, pK_d). Low K_d means high affinity.
- **Efficacy (intrinsic activity)** is the ability of the bound drug to activate the receptor and produce a response. It is a property of the drug receptor complex, not of binding strength.

A drug can therefore have high affinity and no efficacy: it occupies the site, activates nothing, and blocks the agonist. That combination is exactly an antagonist (section 1.7).

1.6 Theories of drug receptor interaction

The classical theories were attempts to connect binding with response mathematically:

Theory	Core idea	What it explains	Limitation or extension
Occupancy theory (Clark)	Response is proportional to the fraction of receptors occupied	Graded dose response, the basis of K_d and E_{max} thinking	Cannot explain partial agonists, which occupy fully but respond partially
Rate theory (Paton)	Response depends on the rate of drug receptor encounters, not occupancy	Why some agonists act briefly; dissociation rate matters	Hard to test directly; largely of historical interest
Induced fit theory (Koshland)	Binding changes the shape of the receptor; the fit is induced, not preformed	Activation as a conformational event; applies to enzymes too	Extended by later conformational models
Two state (allosteric) model	Receptors exist in equilibrium between inactive (R) and active (R*) states; agonists stabilise R*, antagonists bind both equally, inverse agonists stabilise R	Partial agonism, constitutive activity and inverse agonism in one scheme	The working modern framework

The **Easson-Stedman hypothesis** belongs in this section for stereochemistry: a chiral drug needs at least three points of attachment to a receptor to distinguish its enantiomers, because two points can be matched by either mirror image. Unit 3 returns to this with case studies.

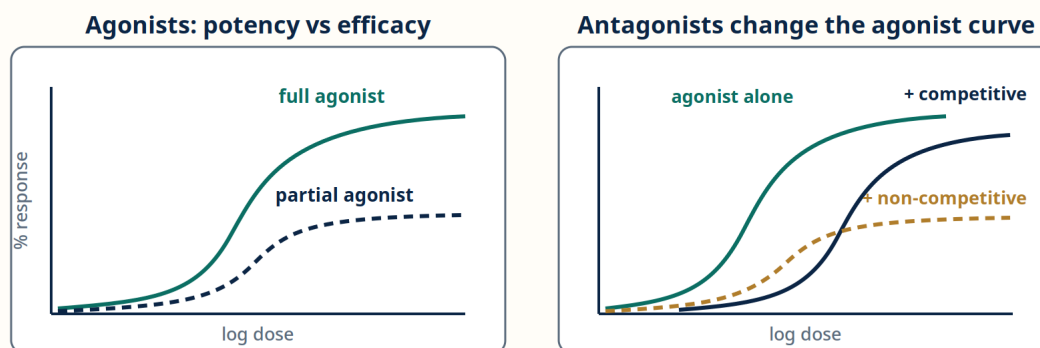
1.7 Agonists, antagonists and dose response

Response is plotted against the logarithm of dose or concentration, giving the sigmoidal **log dose response curve**. Two numbers are read from it: **EC₅₀**, the concentration giving half the maximal response (a measure of potency), and **E_{max}**, the maximal response the drug can produce (a measure of efficacy in that system).

- **Full agonist:** high efficacy, reaches the system maximum. Adrenaline at beta receptors is the physiological example.
- **Partial agonist:** lower efficacy; even at full occupancy its E_{max} stays below the system maximum, and it antagonises a full agonist when both are present. Pindolol at beta adrenoceptors and aripiprazole at dopamine D₂ receptors are standard examples.
- **Competitive antagonist:** binds the agonist site reversibly without activating; the agonist curve shifts to the right in parallel, with E_{max} unchanged, and the block is surmountable by more agonist. Naloxone at opioid receptors is the classic example. The dose ratio it produces underlies the Schild analysis and the pA_2 measure of antagonist affinity.
- **Non-competitive antagonist:** binds a separate site, or irreversibly, and reduces E_{max} ; the curve is depressed, not just shifted, and more agonist cannot restore the maximum. Phenoxybenzamine at alpha adrenoceptors (covalent, irreversible) is the textbook case.

- **Inverse agonist:** reduces the basal (constitutive) activity of a receptor that signals without any agonist; predicted by the two state model and real for several GPCRs, for example rimonabant at cannabinoid CB1 receptors.

Dose Response: Agonists and Antagonists



Parallel shift right: surmountable. Depressed maximum: not surmountable.

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Figure: Reading a log dose response curve. A parallel shift right means competitive antagonism; a depressed maximum means the block cannot be surmounted.

1.8 Artificial enzymes

An **artificial enzyme** (enzyme mimic) is a synthetic molecule designed to do what an enzyme does: bind a substrate selectively and catalyse its reaction. The syllabus includes them because they are drug target chemistry viewed from the other side, and because several are used as tools and scavenger drugs:

- **Cyclodextrins:** ring shaped sugars with a hydrophobic cavity that binds guest molecules; used mainly as solubilising hosts, and in one case as a drug itself, sugammadex, which encapsulates the neuromuscular blocker rocuronium and reverses it.
- **Catalytic antibodies (abzymes):** antibodies raised against a transition state analog of a reaction bind the transition state and can accelerate the reaction; proof that binding energy alone can produce catalysis.
- **Molecularly imprinted polymers:** a polymer is formed around a template molecule; removing the template leaves a shaped cavity with selective binding, used in separations and sensing.
- **Synthetic hosts and metallomimics:** macrocycles and metal complexes designed to reproduce one step of an enzyme's chemistry, for example superoxide dismutase mimics that remove reactive oxygen species.

Artificial enzymes rarely match natural enzymes in rate, but they are robust, designable, and they teach the central lesson of this unit: selective binding, correctly arranged, is the foundation of all drug action.

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