

3.1 Traditional drug design: discovery before targets

For most of pharmaceutical history there was no target to design against. **Traditional drug design** found drugs by their effects in whole organisms, tissues or, later, crude biochemical tests, and understood their mechanisms afterwards, if at all. Its sources were the materia medica of traditional medicine, the dye and chemical industries, and chance. Its logic was phenotypic: a substance that relieved the observable disease sign was a lead, whatever it touched.

The method was far from barren. Morphine was isolated from opium, quinine from cinchona bark, and testing natural materials in patients and animals delivered much of the older pharmacopoeia. Penicillin arrived by famous serendipity, a contaminated plate noticed by an observant scientist, and the sulfonamides emerged from screening industrial dyes, the screening that revealed Prontosil. Traditional design's systematic weakness was the mirror of its strength: with no mechanism, optimization was blind chemistry around a scaffold, toxicity and inefficacy were discovered late, and whole classes of mechanism that whole animal tests cannot see were unreachable.

3.2 Methods followed in traditional drug design

The PCI syllabus asks for the methods of the traditional approach explicitly, and they form a coherent toolkit:

- **Random or phenotypic screening:** collections of natural products, plant extracts and synthetic compounds are tested in disease relevant whole animal or tissue models, and activity, not mechanism, selects the hits.
- **Serendipity and clinical observation:** unexpected effects noticed in the clinic are converted into new indications. The standard history is sildenafil, developed as a candidate for angina, whose observed side effect in trials redirected it to erectile dysfunction, a change of indication no screen would have requested.
- **Analogue synthesis around an existing drug (me too and me better design):** modifying a proven drug's structure to improve potency, duration, safety or patent position, learning from the predecessor's weaknesses. Much of the sulfonylurea, benzodiazepine and statin families grew this way.
- **Exploiting side effects and metabolites:** a drug's secondary action or its active metabolite becomes the starting point of a new programme, separating the wanted effect from the parent molecule.
- **Folk and ethnobotanical leads:** traditional remedies are tested and their active principles isolated and purified, the path of morphine, digoxin and, in the modern era, artemisinin.

Each method shares one property: the molecule is found before its target is known, and the target, sometimes, is only identified decades later. That inversion of the modern order is the cleanest definition of the traditional approach.

3.3 Rational drug design: the concept

Rational drug design inverts the traditional order. It begins from knowledge: of the disease mechanism, of the target's identity and ideally its structure, and of the chemistry of the interaction to be created or blocked.

The drug is then designed, on paper and on screen, to fit that knowledge, synthesized, and tested against predictions. Two classical programmes mark the transition and are the standard teaching examples.

Captopril was designed from a snake venom peptide that inhibited angiotensin converting enzyme and from the known active site chemistry of a related enzyme, carboxypeptidase A: a small molecule was drawn to present the same binding features, and it worked as drawn. **Cimetidine** was built by systematically modifying histamine itself, step by rational step, until agonism at the newly distinguished H₂ receptor had been converted into antagonism. In both, hypothesis preceded synthesis, which is the essence of the rational claim.

Rational design does not abolish empiricism; it relocates it. Screening still tests designs, and most designs still fail, but each failure now tests a stated hypothesis and returns usable information. The comparison the syllabus demands is summarized below.

Feature	Traditional drug design	Rational drug design
Starting point	Observed effect in organism or tissue	Knowledge of target and disease mechanism
Target known at start	Usually no; identified later or never	Yes; identification and validation precede chemistry
Role of screening	The discovery engine itself	A tool for testing designed or selected candidates
Optimization guided by	Activity and tolerability in whole systems	Structure, mechanism and quantitative relationships
Strength	Finds the unexpected; no assumptions about mechanism	Focused, information rich, reaches mechanisms invisible to whole animal tests
Weakness	Blind, slow, late toxicity, mechanism free	Fails completely if the target hypothesis is wrong; needs structures and assays traditional work did not

3.4 High throughput screening within rational design

HTS appears in this unit as well as Unit 2, and the double appearance is instructive. In the rational era, HTS is no longer random fishing: the target has been chosen and validated rationally, the assay designed against it deliberately, the library curated for drug likeness. The screen is empirical in execution and rational in architecture, and this hybrid is how most modern programmes begin. The examination distinction to retain is that HTS is a technique, usable by either philosophy, while rational design is a philosophy about the order of knowledge and experiment.

3.5 Structure based drug design

Structure based drug design (SBDD) is the rational method that designs from the three dimensional structure of the target, obtained by X-ray crystallography or NMR (Unit 2) or by a validated model. Knowing the binding site's shape, its hydrogen bond donors and acceptors, its hydrophobic surfaces and its charged residues, the designer either builds a molecule to complement them (de novo design, Unit 4) or selects and modifies existing molecules by docking them in the site computationally. The working cycle is iterative: structure of target with lead bound, design a change, synthesize, test, new structure. The HIV protease inhibitors are the canonical success of the method: the viral enzyme's structure was solved early, its symmetric active site was unlike any human protease, and inhibitors were designed against the structure to clinical effect. SBDD's precondition is written into its name: without a structure, or a model of homology modelling quality, there is nothing to base the design on, and the programme must fall back on the ligand based methods.

3.6 Pharmacophore based (ligand based) design

When several compounds are known to act on a target but the target's structure is unknown, the common pattern among the actives themselves becomes the design guide. A **pharmacophore** is that pattern: the spatial arrangement of chemical features, hydrogen bond donors and acceptors, hydrophobic groups, aromatic rings, charged centres, that a molecule must present to bind. **Pharmacophore based design** builds this model from the active molecules (mapping is treated fully in section 3.8), then uses it to design new molecules that present the same features on different skeletons, and to screen databases for them. Because it needs no protein structure, it was historically the first rational method available for most targets, and it remains the method of choice when the target is a membrane protein whose structure resists experiment. Its weakness is shared with all inference from examples: the model explains the compounds it was built from, and unusual new chemistry may bind in ways the feature pattern never imagined.

3.7 Virtual screening: the concept and the cascade

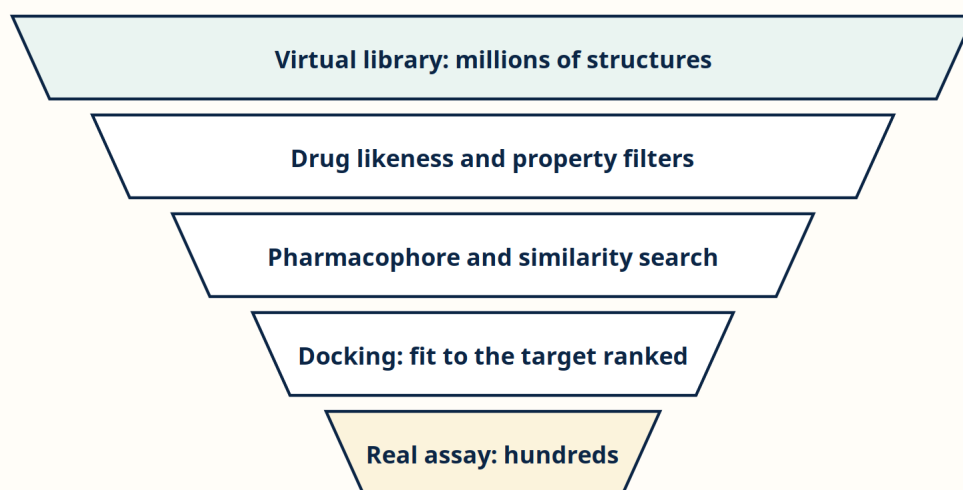
Virtual screening is the in silico counterpart of HTS: a large collection of compounds, existing only as computed structures, is passed through a sequence of computational filters of increasing cost and sophistication, and the survivors, a few hundred at most, are purchased or synthesized and tested in the real assay. A typical cascade runs:

THE VIRTUAL SCREENING CASCADE

```
Virtual library (millions of structures)
|
v
Drug likeness and property filters remove the hopeless
|
v
Pharmacophore search or similarity search selects the plausible
|
v
Docking ranks the survivors by predicted fit to the target
|
v
Human inspection: chemistry sense, diversity, no artefacts
|
v
A few hundred compounds -> real assay -> real hits
```

Each stage discards most of what reaches it, exactly as a physical screen's funnel does, but at computing prices. The result is judged by **enrichment**: a virtual screen returning actives at many times the random rate has done its job, even though most selections still fail in the assay. Virtual screening complements rather than replaces HTS: it reaches chemical space no physical collection contains, but its rankings carry model error everywhere, which the assay alone corrects.

The Virtual Screening Cascade



Each stage discards most of what reaches it, at computing prices.

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Figure: The virtual screening cascade. Each computational stage discards most of what reaches it, so the expensive real assay is spent on hundreds, not millions.

3.8 Drug likeness screening

The cheapest filter in the cascade is **drug likeness screening**: the removal, before any target specific test, of compounds whose general properties make them unlikely ever to become acceptable oral drugs. Its famous codification is Lipinski's **rule of five**, distilled from the properties of marketed oral drugs: poor absorption or permeation becomes more likely when a compound has molecular weight above 500, calculated log P above 5, more than 5 hydrogen bond donors, or more than 10 hydrogen bond acceptors. A related refinement adds limits on rotatable bonds (flexibility) and polar surface area, which govern the same permeability behaviour.

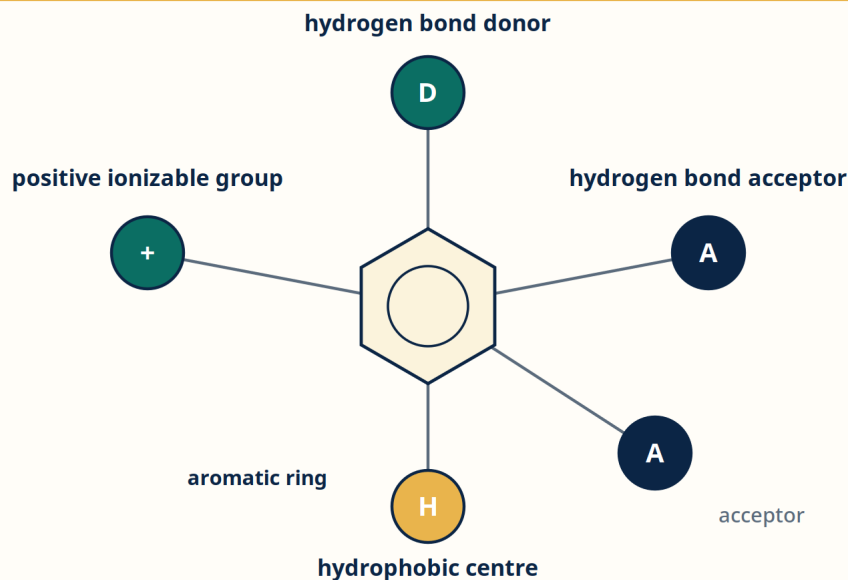
The rules are used as flags, not laws, and the examination nuance matters. They describe a statistical tendency of oral small molecules, not a definition of a drug: many successful medicines violate a rule, especially natural products and drugs for non oral routes or transporter carried drugs, and rigid enforcement would have deleted them. In screening practice a single violation warns, two violations argue strongly against a lead series, and properties are rechecked at every optimization step, because medicinal chemistry has a known tendency to buy potency with size and lipophilicity until the rule of five debt comes due.

3.9 Pharmacophore mapping

Pharmacophore mapping is the disciplined construction of the pharmacophore model of section 3.6. The steps are: assemble a training set of active compounds, ideally spanning a range of potencies and chemotypes; generate, for each, the set of conformations it can realistically adopt; identify the chemical **features** each molecule offers (hydrogen bond donor, hydrogen bond acceptor, hydrophobic centre, aromatic ring, positively or negatively ionizable group); and then search for an arrangement of features, with distances and angles between them, that some accessible conformation of every active can present simultaneously. Features shared by all actives and absent in inactives are weighted most; the finished model is a three dimensional query: a map of what a binder must look like, drawn in features rather than atoms.

Two refinements complete the practical method. **Exclusion volumes** mark space that inactive compounds occupy and actives avoid, modelling the walls of the binding site without any protein structure. And the model is validated like a QSAR: it must retrieve known actives from a database seeded with inactives, and fail to retrieve the inactives, before it is trusted to screen.

Pharmacophore Features of a Binding Molecule



A pharmacophore: features a binder must present together, in the right geometry.

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Figure: The features of a pharmacophore: a donor, acceptors, a hydrophobic centre, an ionizable group and an aromatic ring, held in the geometry the target demands.

3.10 Pharmacophore based screening

Pharmacophore based screening runs the validated pharmacophore as a three dimensional search query against databases of computed compound conformations. Every database molecule whose conformers can present the required features, within tolerance, in the required geometry is returned as a candidate hit. The method's distinctive prize is **scaffold hopping**: because the query is written in features, not atoms, it retrieves molecules whose skeletons differ completely from every training compound while presenting the same binding pattern. A programme trapped in a patented or toxic chemotype can thereby jump to fresh chemistry without losing the binding logic, something neither similarity searching, which stays near known matter, nor analogue synthesis can do. Retrieved hits are then filtered for drug likeness, docked if a structure exists, and tested, entering the ordinary hit to lead gauntlet of section 2.6.

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