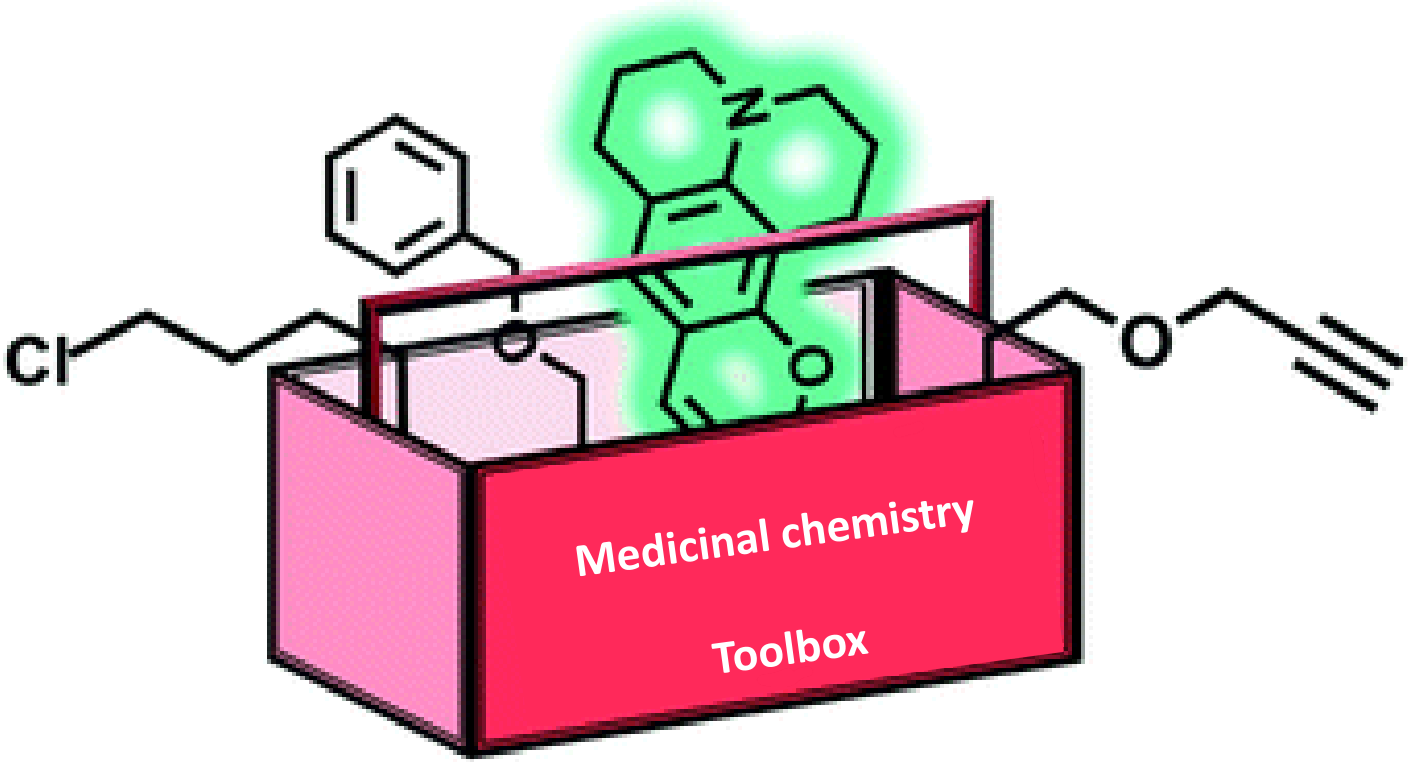
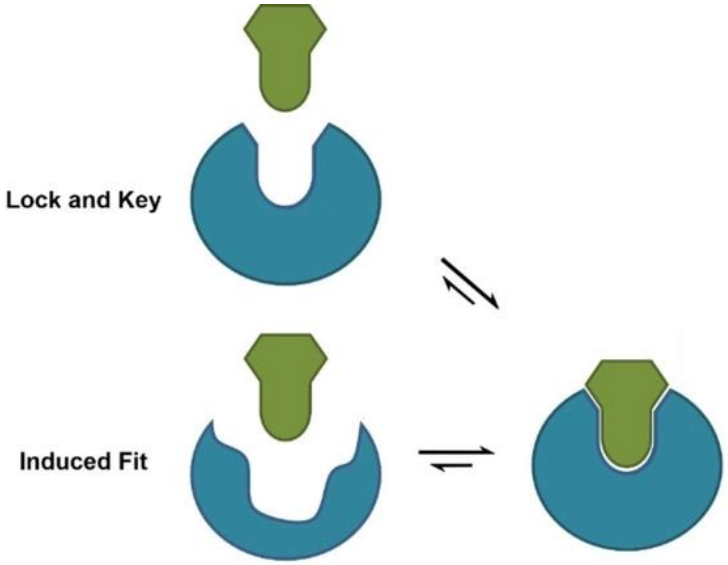
A Beginner's Guide to Medicinal Chemistry



Prof. A. HAMZE

1. Target-Ligand Interactions



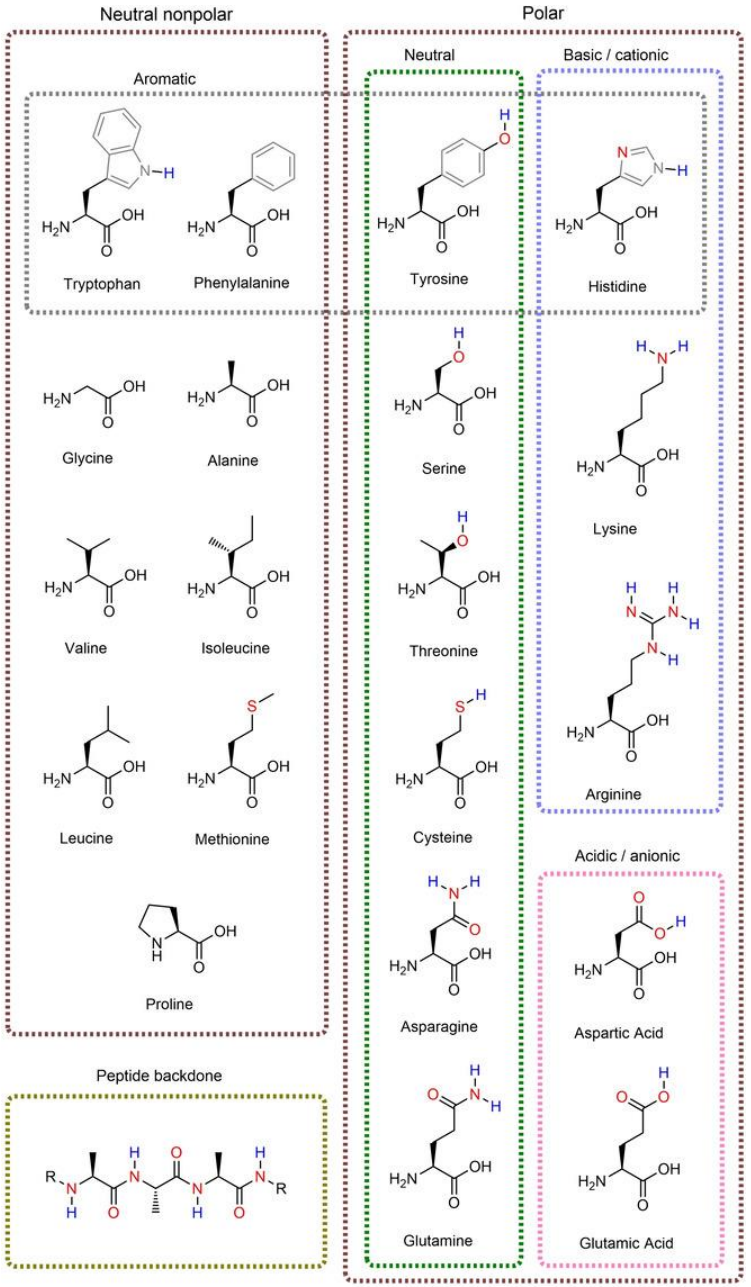
Four major categories of amino acids:,

- Non-polar neutral
- Polar neutral
- Polar acidic
- Polar basic

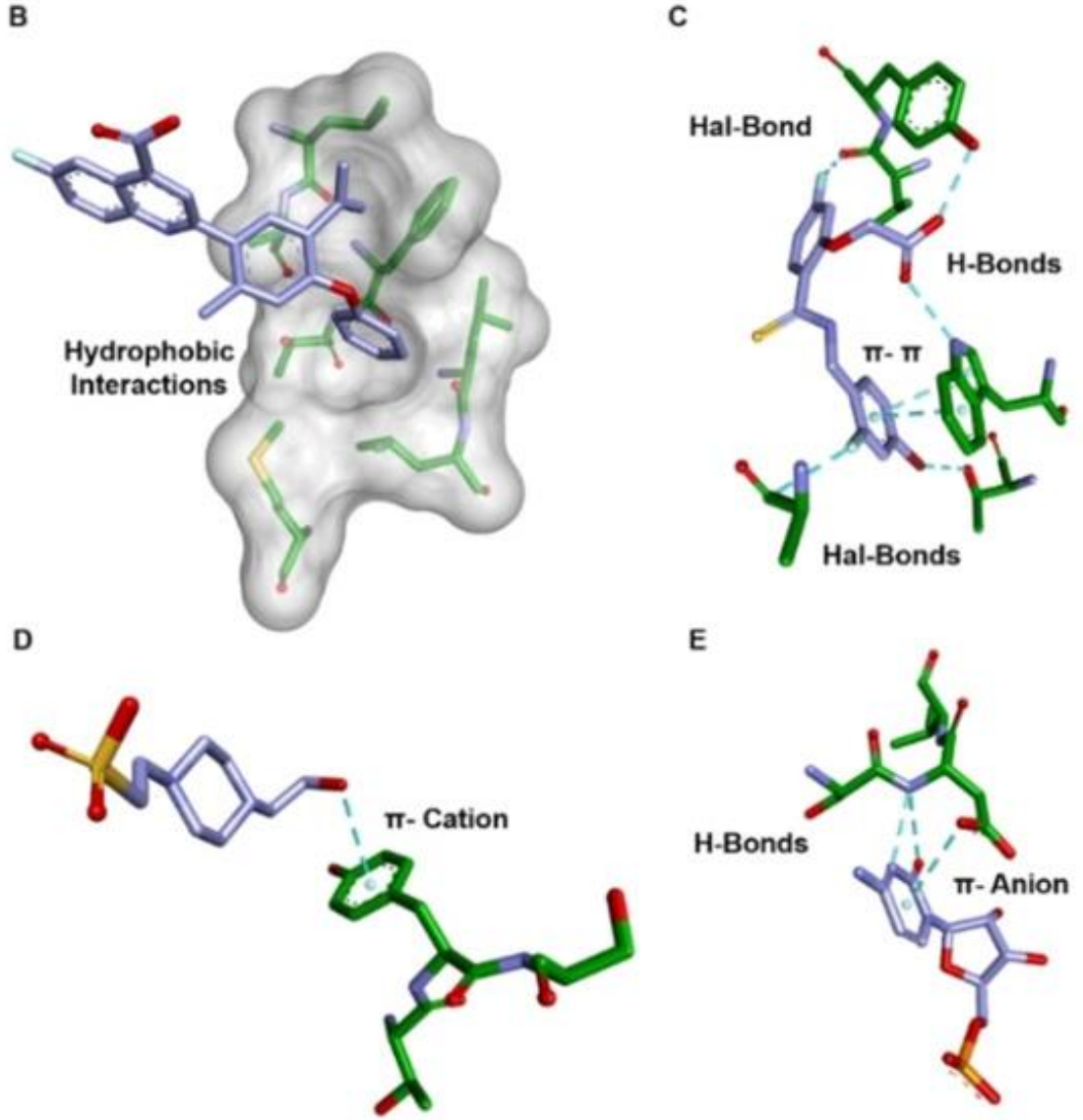
The heteroatoms (highlighted in red) and their attached hydrogens (highlighted in blue) can respectively act as acceptors and donors of hydrogen bonds.

Under neutral conditions, basic residues will be cationic, while acidic residues will be anionic.

The non-substituted heteroatoms of polar amino acids have the potential to react as nucleophiles under favorable conditions.

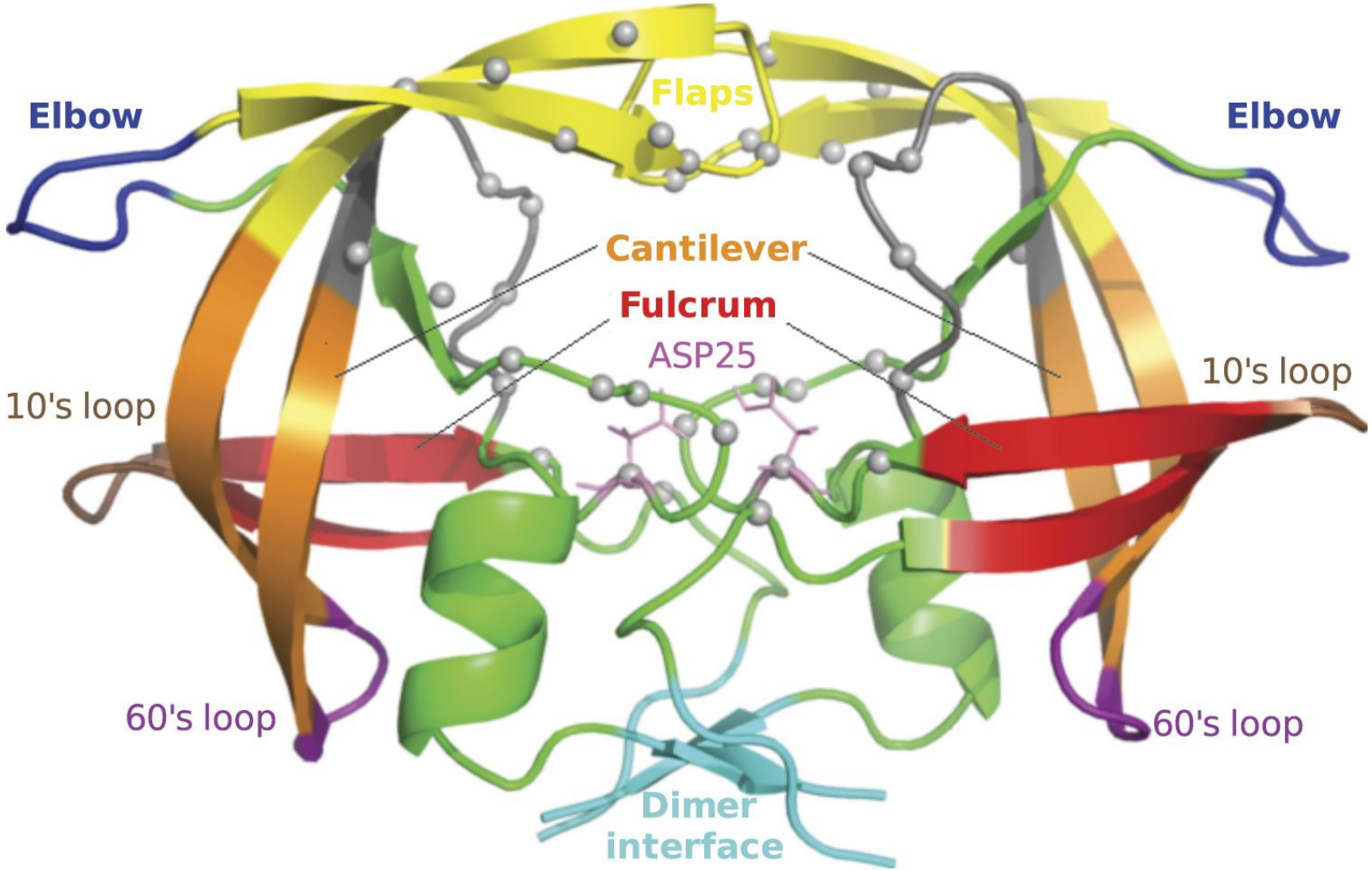


1. Target-Ligand Interactions



B)–E) Examples of common interactions, between targets and ligands highlighting the diversity in possible inter- and intramolecular interactions

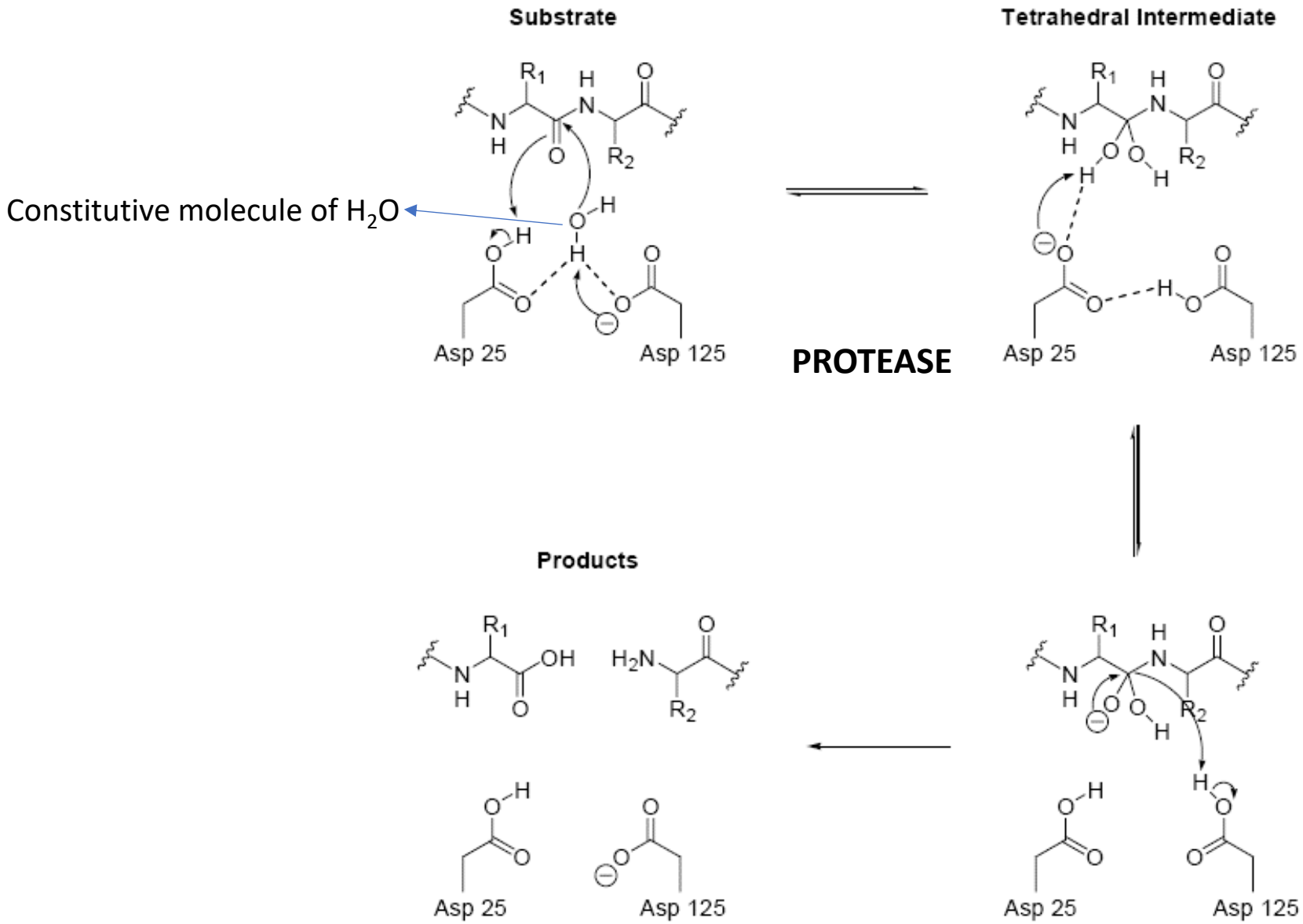
2. Rational Design : PROTEASE INHIBITORS (PI)



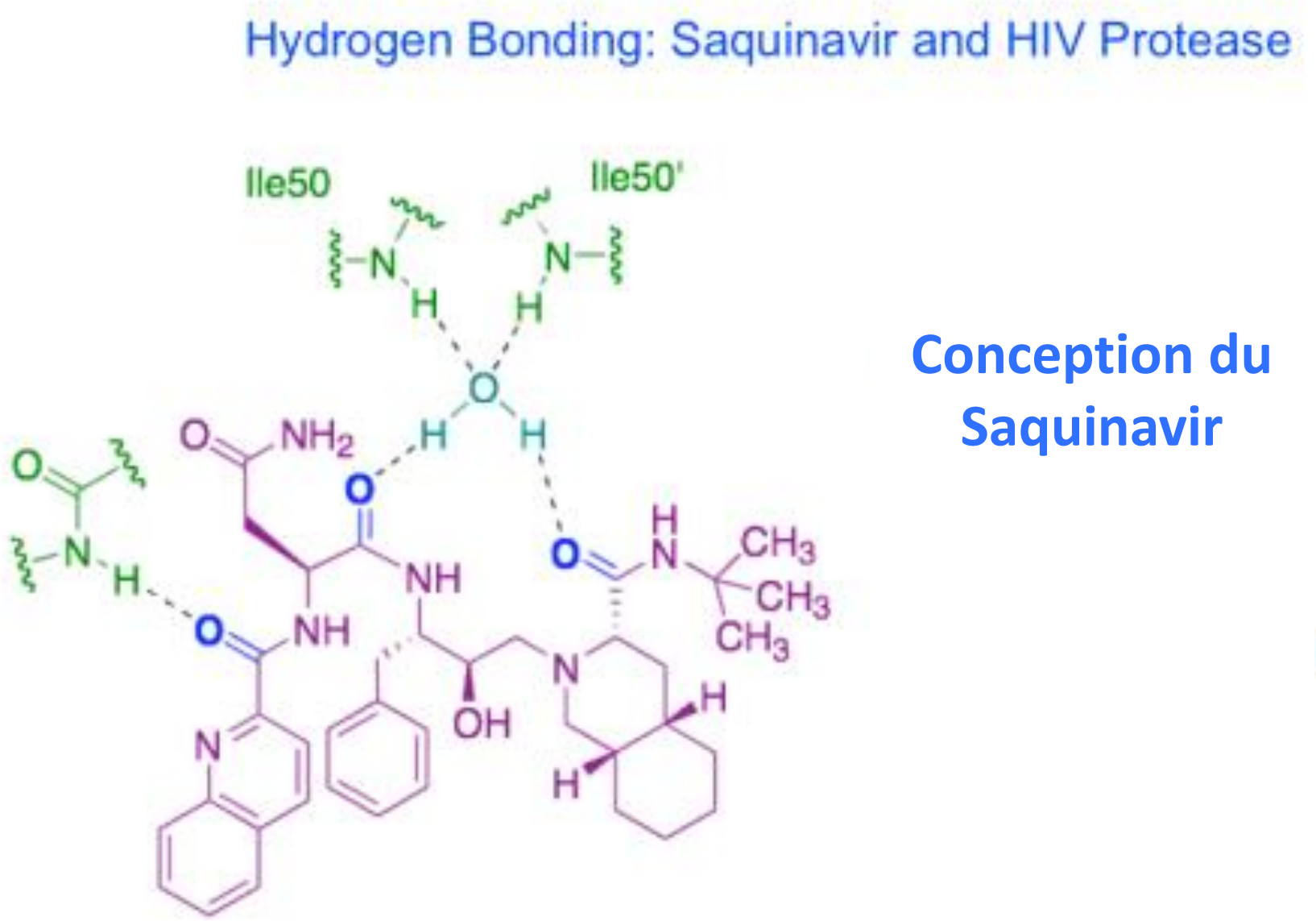
☞ Crystal structure has been known since 1989: rational design of new inhibitors is possible.

PIs: mimic the transition state of the Phe-Pro bond.

2. Rational Design : PROTEASE INHIBITORS (PI)



2. Rational Design : PROTEASE INHIBITORS (PI)

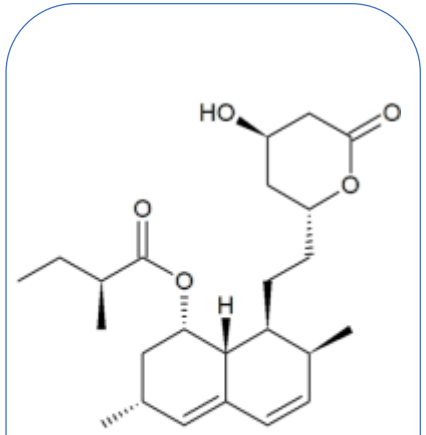


Conception du Saquinavir

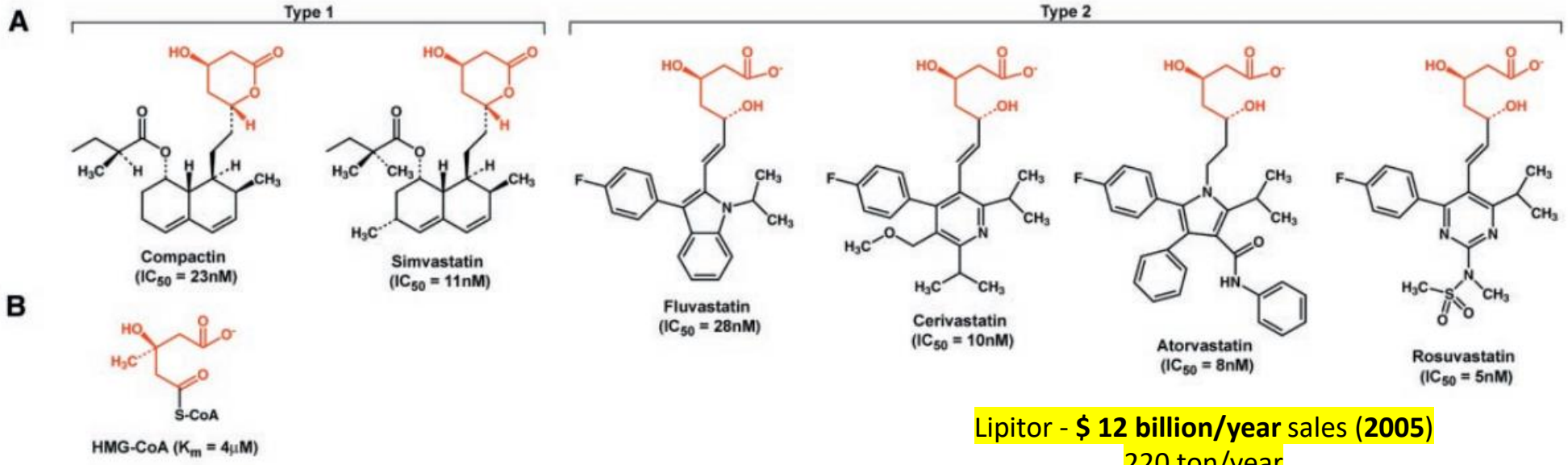
3. Structure-Activity Relationships (SAR)

Statins

- ☑ They reduce cholesterol in blood and are used for hyperlipidemia treatment.
- ☑ This class of drugs resulted in many blockbusters.



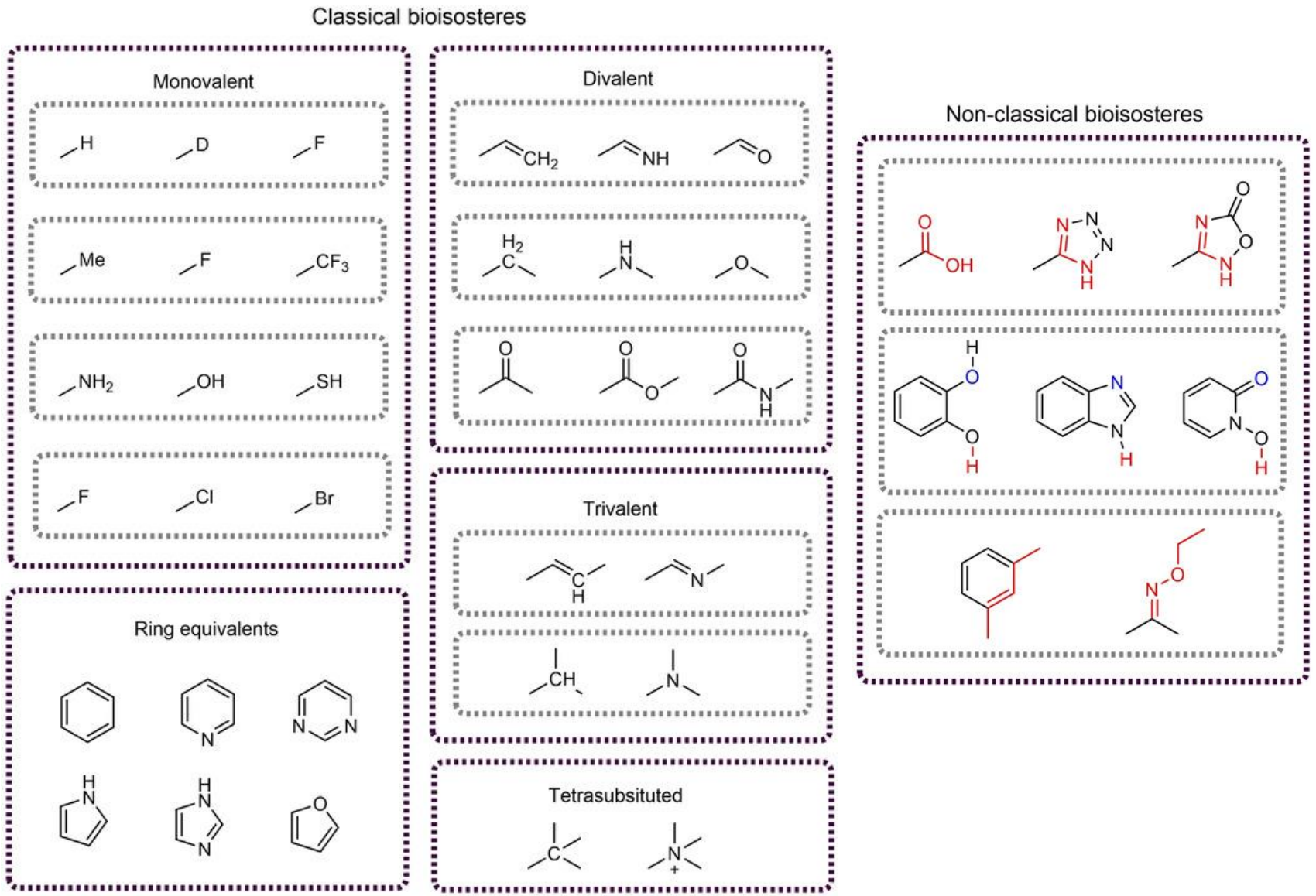
Mevastatin
natural product



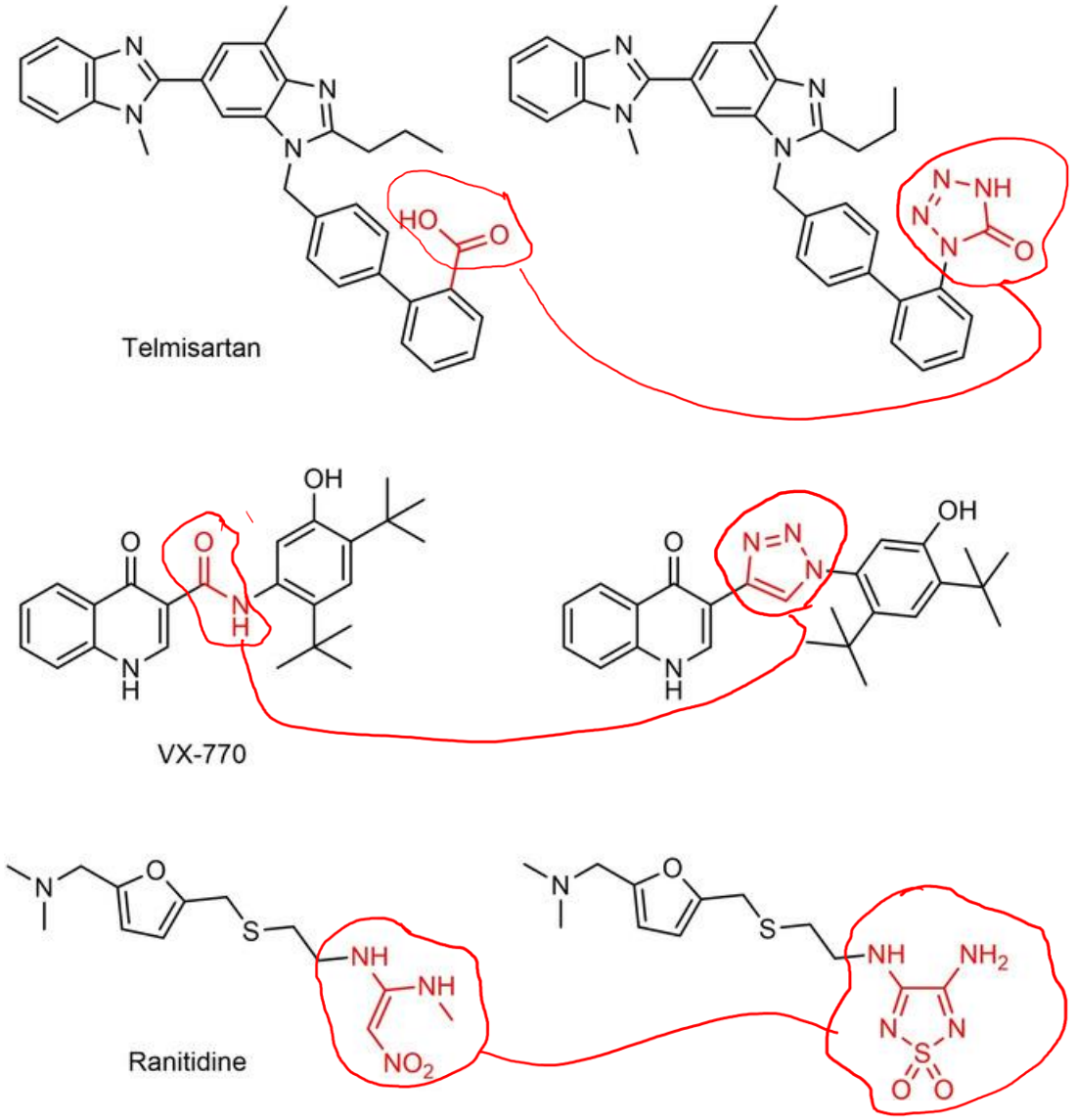
Lipitor - **$ 12 billion/year** sales (**2005**)
220 ton/year

4. Bioisosterism

- Bioisosteres are chemical groups that have similar physicochemical properties.
- Bioisosteric replacement can be used as a tool to modify physicochemical properties, metabolic profiles, and toxicity.
- It also allows for the simplification of the molecule to solve synthesis problems.



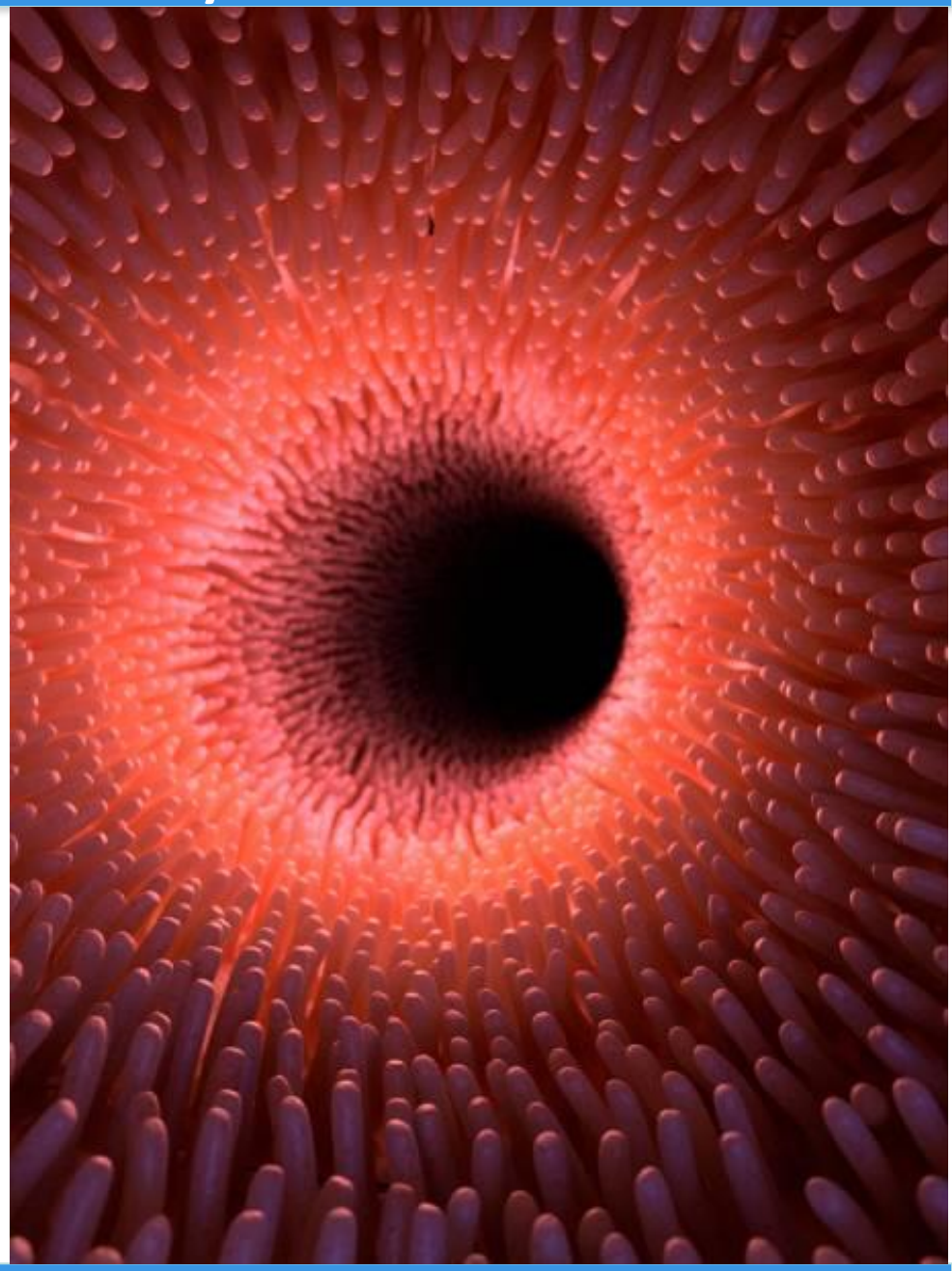
4. Bioisosterism: examples



5. Property-Based Design

a. Physicochemical and pharmacokinetic properties.

- The physicochemical properties of compounds, including solubility, and lipophilicity, have a significant effect on the development of a new drug.
- ***In vitro,*** *these properties can affect the reproducibility of biological assays.*
- ***In vivo,*** *they have a fundamental influence on pharmacokinetic properties, duration of action, and toxicity.*
- **Poor water solubility**, as well as **low membrane permeability**, are most frequently cited as reasons for the low bioavailability of drugs.



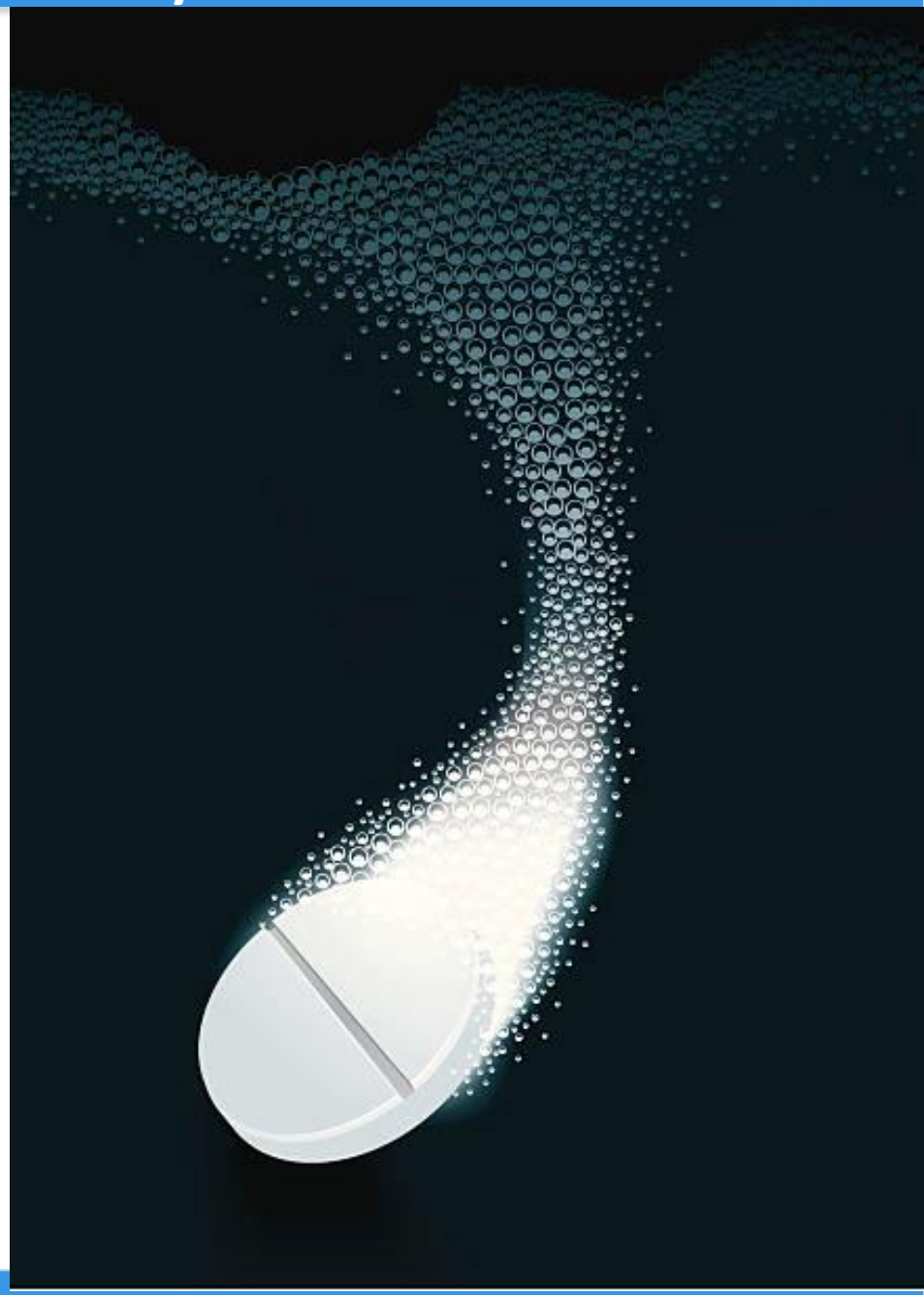
5. Property-Based Design

b. Hydrophilicity, hydrophobicity, and solubility.

A commonly used strategy to improve the solubility of a molecule is to increase hydrophilicity by introducing polar functional groups.

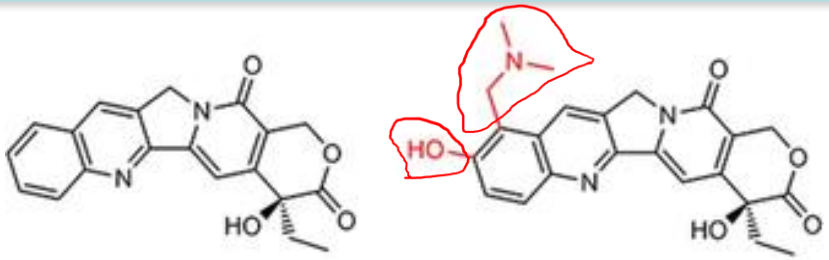
However, care must be taken to ensure that the positions of these structural modifications do not disrupt key target interactions.

An alternative strategy is to reduce molecular planarity and symmetry, thereby disrupting crystalline packing and reducing the energy barrier to dissolution.



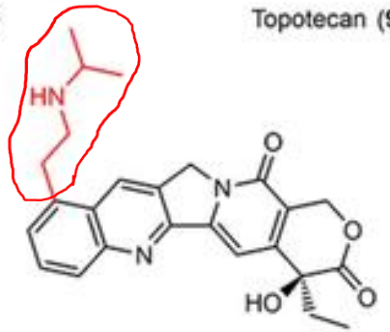
b. Hydrophilicity, hydrophobicity, and solubility.

Case study: Introduction of polar functional groups.



Camptothecin (**95**, a natural inhibitor of topoisomerase) has excellent broad-spectrum anticancer activity.

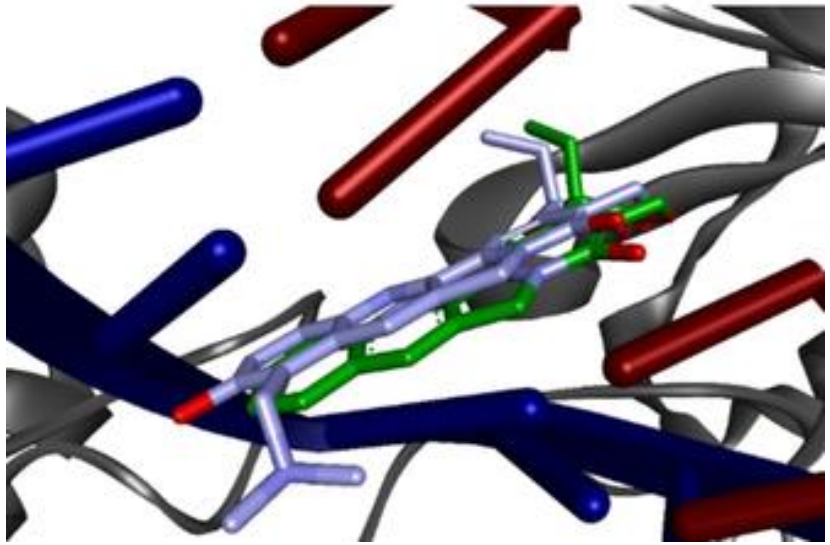
However, despite the start of clinical trials, its development and approval as an anticancer agent were hindered by its low aqueous solubility.



Introduction of ionizable groups into the scaffold.

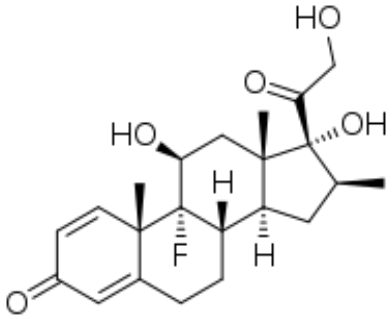
The new agents (**96**, **97**) had improved solubility without disturbing the binding of the camptothecin pharmacophore to its active site.

Improved solubility→
clinical development→
→ approved for use in many cancers.



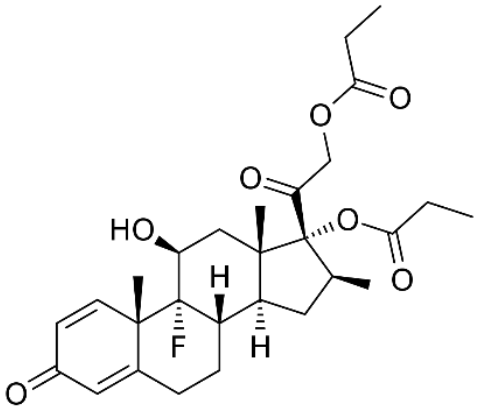
Overlay of the binding positions of camptothecin (green, PDB ID: 1T8I) and topotecan (lilac, PDB ID: 1 K4T) at the active site of the topoisomerase–DNA complex.

c) Lipophilicity - dermal passage.



Betaméthasone

Oral corticosteroids.



Betamethasone dipropionate

Topical corticosteroids

Esterification of the alcohol groups of betamethasone makes the molecule more lipophilic, which facilitates membrane penetration (skin).

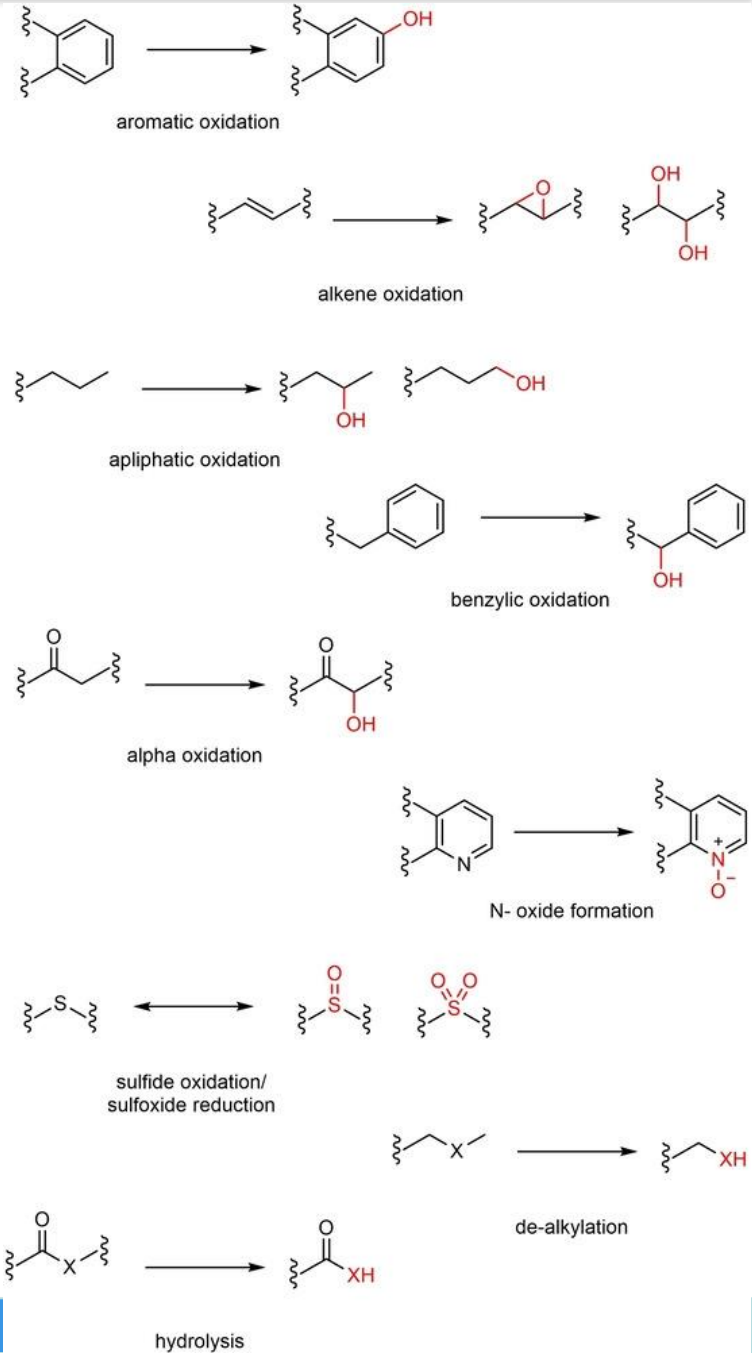
Indications: Dermatitis; eczema...

6. Metabolism and elimination.

The speed and extent of metabolic transformations are influenced by the electronic environment of the functional group in question.

Important metabolic transformations occur through the action of enzymes such as esterases, amidases, and dehydrogenases. However, the cytochrome P450 oxidative enzyme superfamily is responsible for the majority of phase 1 metabolic transformations of marketed drugs.

Transformations métaboliques de phase 1

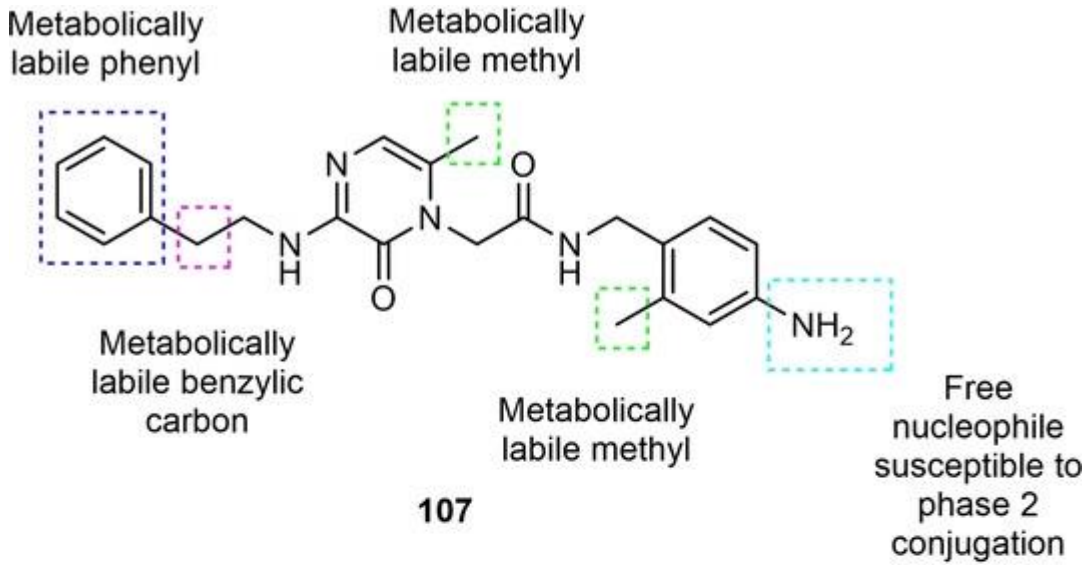


6. Metabolism and elimination.

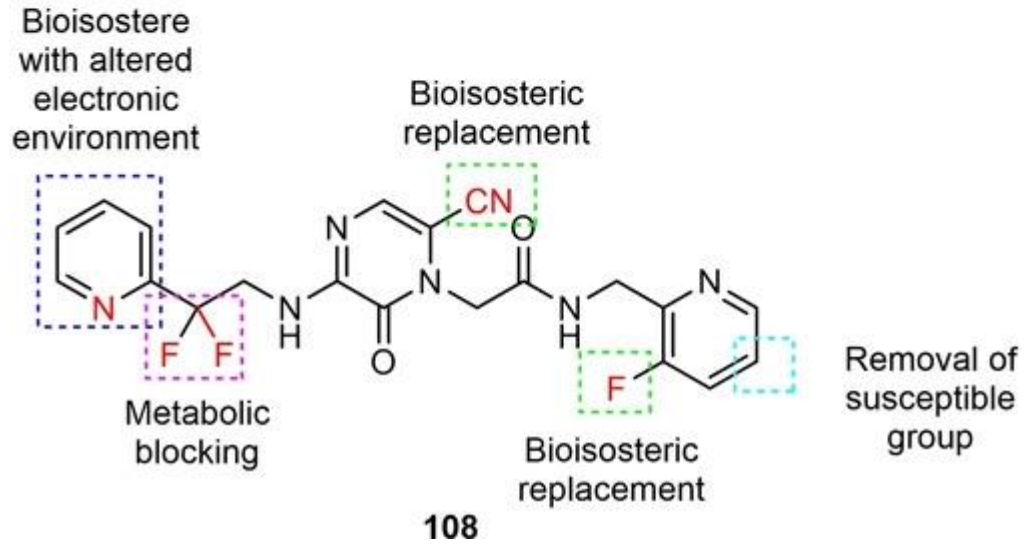
Compound **107** has many functionalities that are sensitive to phase 1 or 2 metabolisms.

Compound **108** underwent substantial bioisosteric replacement to reduce the labile nature of these regions. This includes:

Elimination of labile groups
Blocking of labile sites
Introduction of electron-attracting groups, which hinder metabolic oxidation.

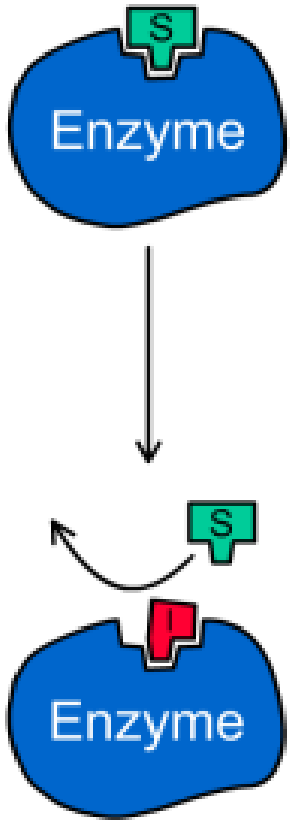


107



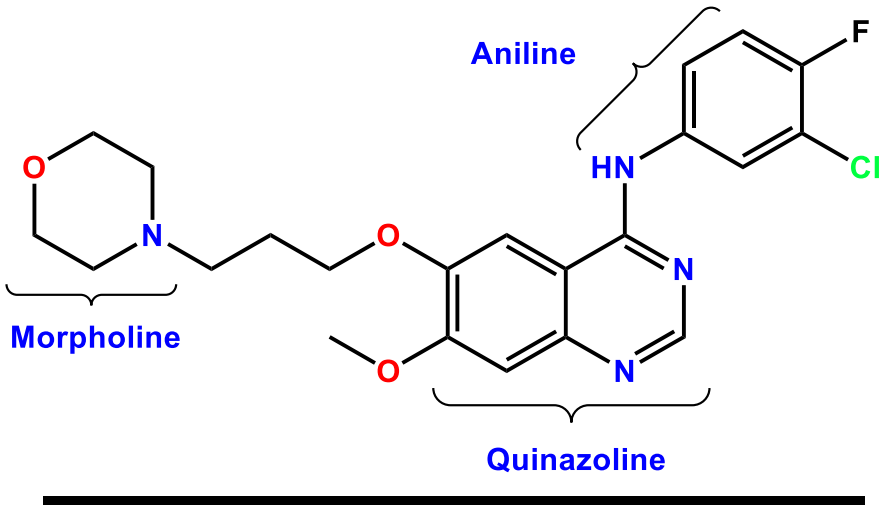
108

7. Covalent inhibitors



The first generation of small molecule inhibitors of EGFR were reversible, binding to the ATP binding site in a conventional manner (for example, gefitinib and erlotinib).

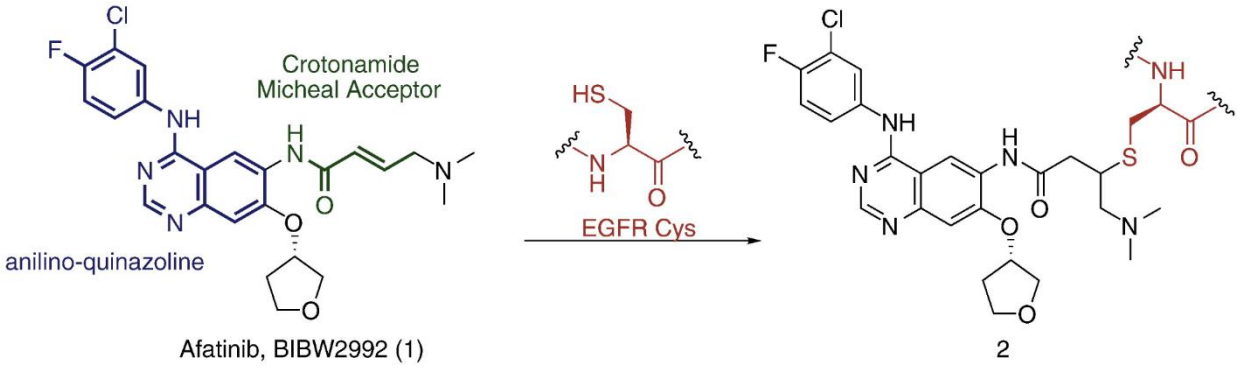
However, resistance to these inhibitors often occurs via a T790M mutation, which increases the affinity of EGFR for ATP.



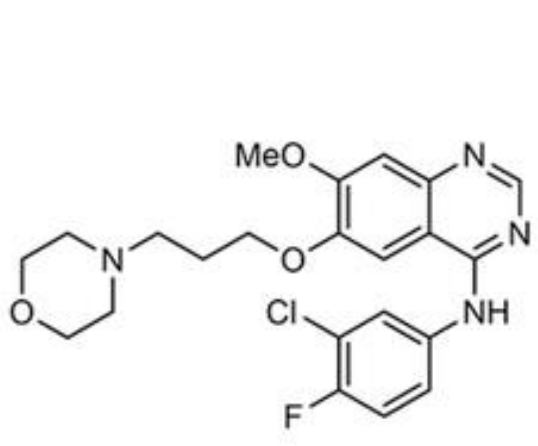
7. Covalent inhibitors

- **Covalent inhibitors (e.g., Afatinib)** are small molecules with an **electrophilic functionality (warhead)** that reacts with a nucleophilic amino acid residue present on the target biomacromolecule, forming a new covalent bond and inhibiting enzymatic activity.

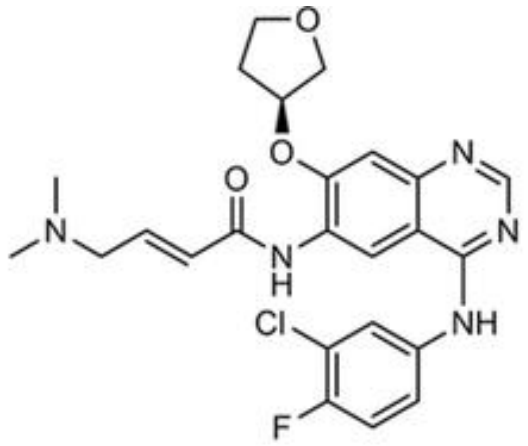
- Reactivity between thiols and Michael acceptors containing an α, β-unsaturated carbonyl group, particularly acrylamides or crotonamides.



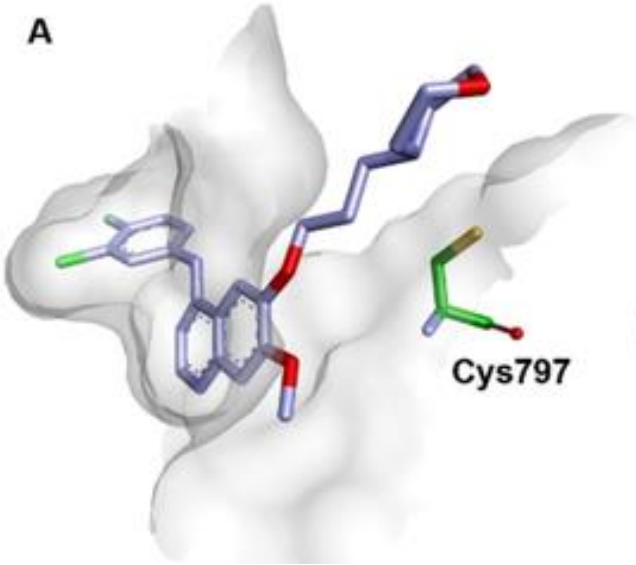
Afatinib, BIBW2992 (1) 2

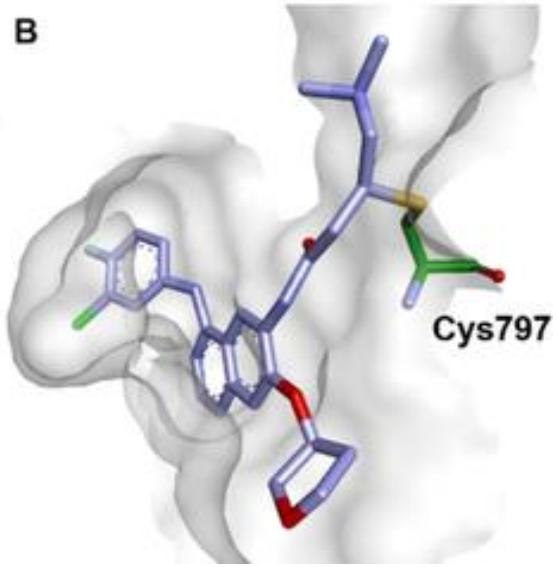


Gefitinib (**122**)



Afatinib (**123**)





8. Activity and chirality.

Chirality plays an important role in the activity of many drugs.
The interaction of a chiral drug with a chiral target can lead to different pharmacological effects between enantiomers. For example, one enantiomer may be responsible for the desired therapeutic effect, while the other enantiomer may contribute to adverse effects or have no effect at all.

Therefore, it is important to determine the pharmacological activity of each enantiomer and to develop methods for the separation and production of individual enantiomers or enantiomeric mixtures with specific ratios of enantiomers, depending on their pharmacological activity. This field is known as chiral drug development or enantioselective drug synthesis.

Important terms to know

Eutomers: Enantiomers with the highest affinity for the target.

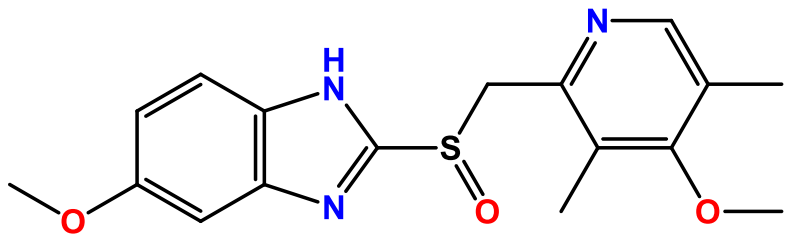
Distomers: Enantiomers with the lowest affinity for the target.

Eudismic ratio = IC_{50} of eutomer / IC_{50} of distomer.

8. Activity and chirality.

Chiral switch: to switch from an old racemic drug to a pure enantiomer.

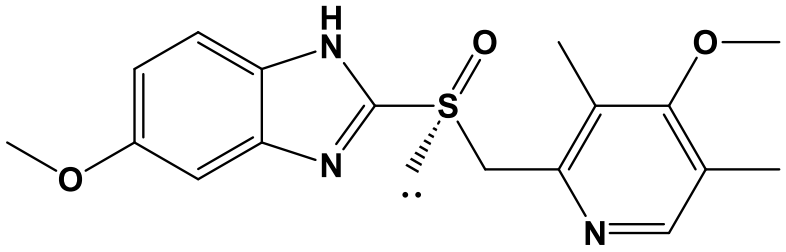
Example: Omeprazole -> Esomeprazole (the (*S*)-enantiomer of omeprazole).



omeprazole
= racémate

Omeprazole = Racemate in which both *R* and *S* enantiomers are active.
The bioavailability of the *S* enantiomer is approximately 1.5 times greater than that of the racemate and 4 times greater than that of the *R* enantiomer.

A dose of 20 mg of esomeprazole is equivalent to slightly more than 30 mg of omeprazole.

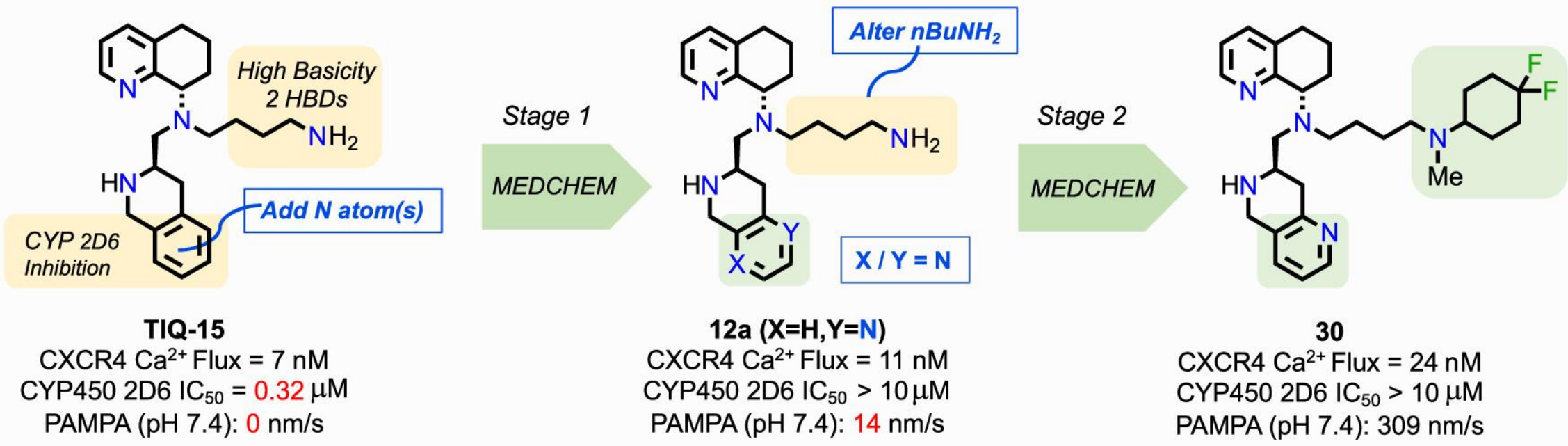


Esomeprazole

9. ADMET Optimization

Journal of Medicinal Chemistry
pubs.acs.org/jmc Article

Synthesis and Evaluation of Novel Tetrahydronaphthyridine CXCR4 Antagonists with Improved Drug-like Profiles



TIQ-15
CXCR4 Ca^{2+} Flux = 7 nM
CYP450 2D6 IC_{50} = 0.32 µM
PAMPA (pH 7.4): 0 nm/s

12a (X=H,Y=N)
CXCR4 Ca^{2+} Flux = 11 nM
CYP450 2D6 IC_{50} > 10 µM
PAMPA (pH 7.4): 14 nm/s

30
CXCR4 Ca^{2+} Flux = 24 nM
CYP450 2D6 IC_{50} > 10 µM
PAMPA (pH 7.4): 309 nm/s