Medicinal Chemistry: An Overview

Course Outline

Lecture	Date	Topic
1	2015/12/17	General Aspects of Medicinal Chemistry
2	2016/01/07	General Biochemistry
3	2016/01/21	Principles of Chemical Synthesis
4	2016/02/04	Chemical Synthesis of Small and Complex Molecules
5	2016/02/18	Chemical Synthesis of Peptides
6	2016/04/07	Strategies for Discovering Lead Compounds
7	2016/04/17	Structure-Activity Relationships
8	2016/04/25	Spatial Organization, Receptor Mapping and Molecular Modeling
9	2016/05/02	Pharmacokinetic Properties
10	2016/05/09	Legal and Economic Aspects of Drug Development

Ligand Binding

The binding between a ligand and a protein is mediated by noncovalent interactions such as ion-ion, dipole-dipole, and ion-dipole forces, hydrophobicity, hydrogen bonding, and shape complementarity.

The binding affinity of a ligand under equilibrium conditions can be calculated by:

$\triangle G = -RT \ln K$ ($\triangle G = \triangle H - T\triangle S$; R = 8.13 J/mol/K)

Where $\triangle G$ = difference in free energy of the free and bound states

$\triangle H$ = difference in free enthalpy of the free and bound states

$\triangle S$ = difference in free entropy of the free and bound states

K = equilibrium constant

M = molar gas constant

T = temperature

Binding occurs only when $\triangle G$ = is negative; the more negative it is, the stronger is binding between the ligand and the receptor.

Factors Affecting Ligand Binding

Enthalpy-Versus Entropy-Driven Binding

Steric Constraints

Conformational Analysis

Steric Effects

Rigidity of Compounds and Bioavailability (F)

The lower the number of rotatable bonds in a molecule the higher the bioavailability of the compound.

$$F = Fa \times Fg \times Fh$$

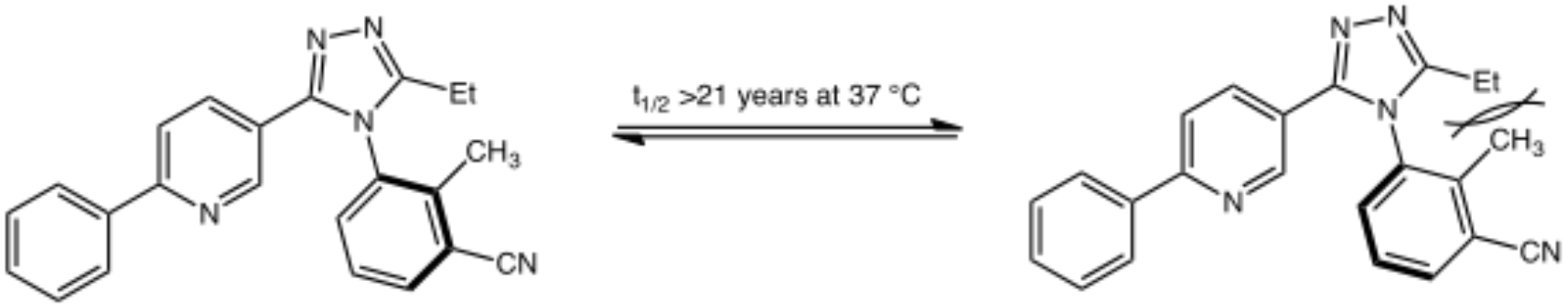
Fa = fraction absorbed

Fg = fraction escaping first-pass elimination

Fh = fraction escaping hepatic elimination

Examples of Potent Conformationally-Restricted Compounds

Glycine transporter 1 (GlyT1) inhibitors showing atropisomerism

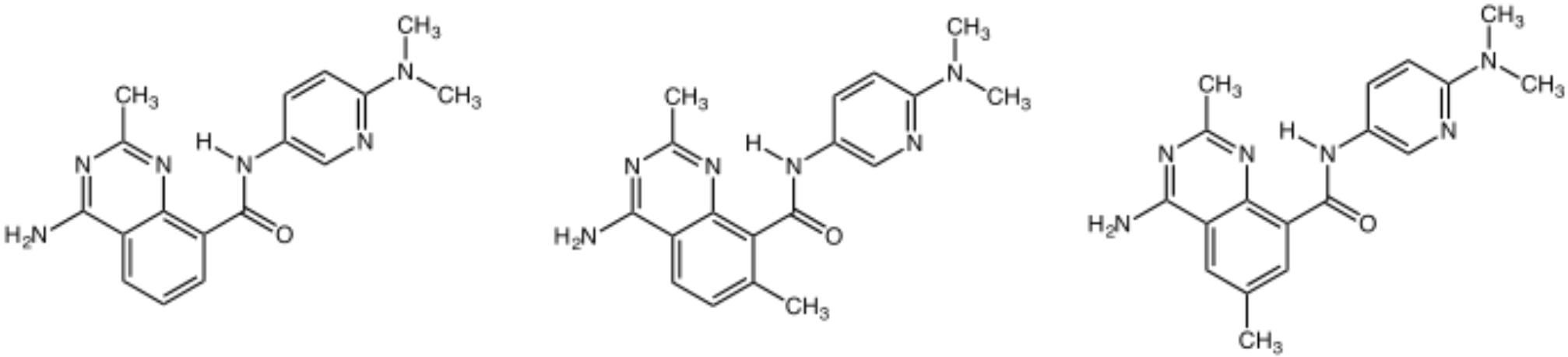


rGlyT1 IC_{50} = 0.064 μM
rGlyT2 IC_{50} > 30 μM
(selectivity > 469:1)

rGlyT1 IC_{50} = 20 μM
rGlyT2 IC_{50} > 30 μM
(selectivity > 1.5:1)

Sugane *et al. J. Med. Chem.* **2013**, *56*, 5744–5756.

Effect of methyl group on conformation of phosphatidylinositol-3-kinase (PI3K) inhibitors



PI3Kα Ki = 54 nM

PI3Kα Ki: no inhibition at 100 nM

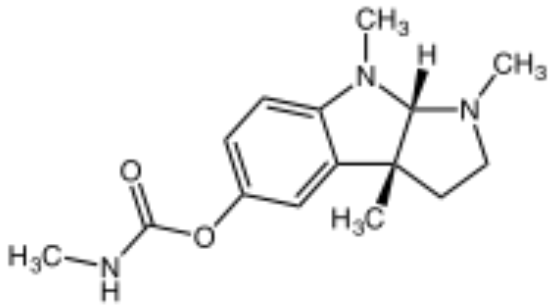
PI3Kα Ki = 12 nM

Liu *et al. Bioorg. Med. Chem. Lett.* **2011**, *21*, 1270–1274.

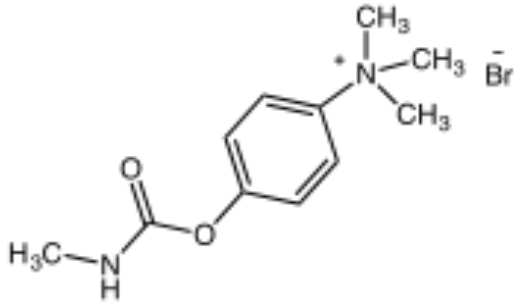
Initial Considerations in Structural-Activity Relationships

Depending on the structure (size and complexity) of the lead compound, the medicinal chemist will decide to either use a disjunctive, analogical, or conjunctive approach.

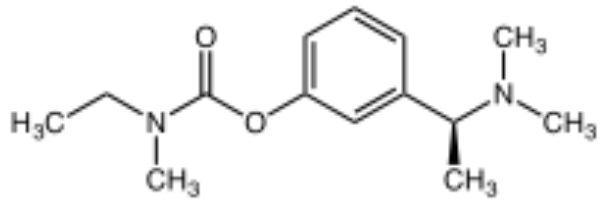
Disjunctive approach: simplification of the lead.



Physostigmine (an acetylcholine esterase inhibitor)

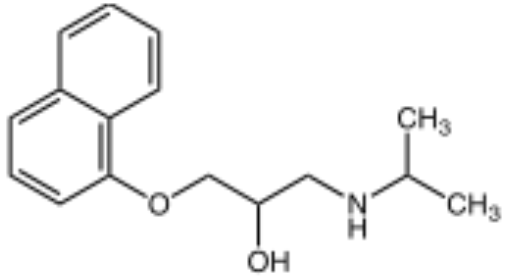


Neostigmine

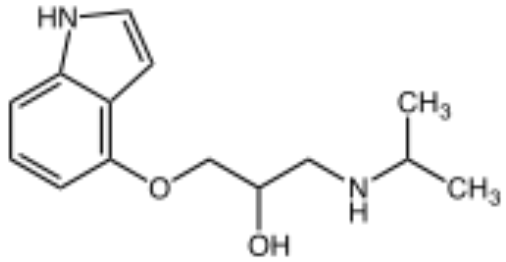


Rivastigmine

Analogical approach: same level of complexity as the lead.

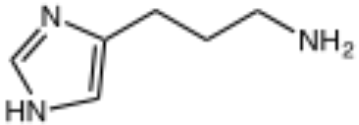


Propranolol (a beta-blocker use for treating angina and hypertension)

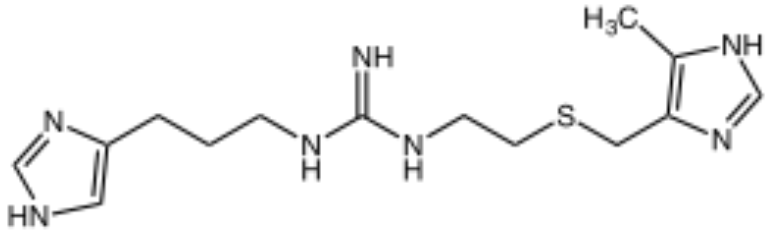


Pindolol

Conjuctive approach: extra functional groups are attached to the lead.



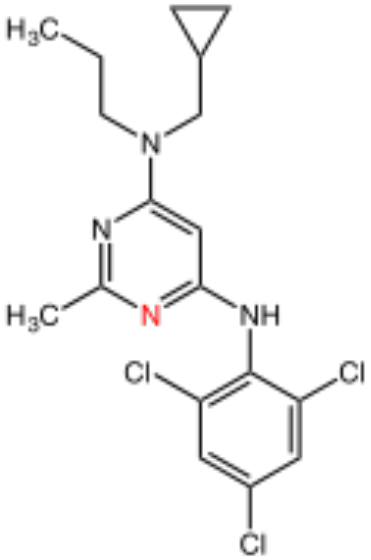
Histamine (a neurotransmitter involve in the immune response)



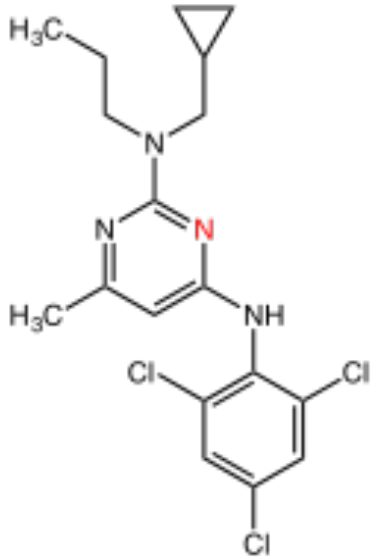
Impromidine

Information About the Target

If there is experimental or non-experimental information on the 3D structure of the target, computer assisted drug design (CADD) can be used to eliminate compounds that lack the required geometry for target binding. However, CADD has limitations.



K_i = 30 nM



K_i > 10 000 nM

Unexpectedly, repositioning of a nitrogen atom in the diazine ring resulted in no binding to the corticotropin-releasing factor (CRF)

Chen *et al. J. Med. Chem.* **1996**, *39*, 4358–4360.

For a novel target, the medicinal chemist can only proceed by designing compounds that are elicit both desired and undesired activities.

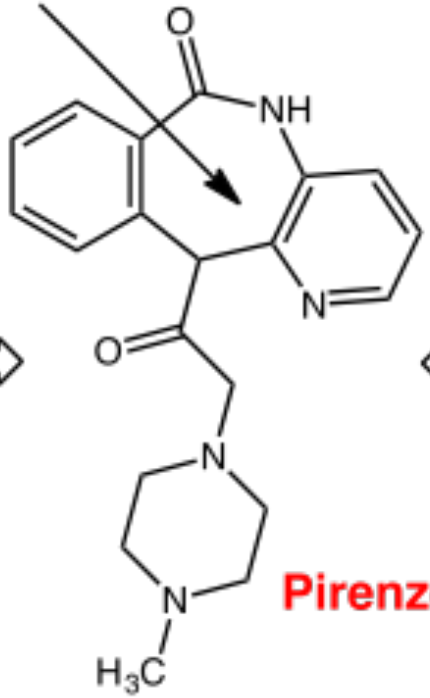
Potency by Topological Exploration of the Lead Compound

Are the C=O and N-H functional groups both needed or would one of them suffice?
What would be the result of changing the hydrogen atom the N-H group?

North

Enlargement or contraction of the ring.
Number and nature of the heteroatom.

Center



Is the pyridine nitrogen atom necessary?
Can the pyridine nitrogen be repositioned?
What about substitution on the pyridine ring?
Can the pyridine be changed to other cycles?

Given the similarity of the west side to east side, considerations for the east side can be applied to west side?

West

East

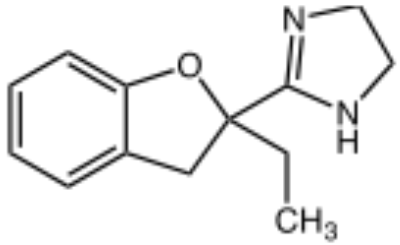
Pirenzepine (a muscarinic antagonist)

South

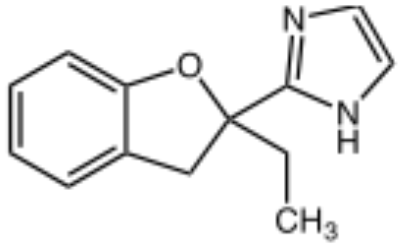
Can the methyl (CH3) group be replaced?
Would it be beneficial to change the piperazine ring?

Rules for Selecting Which Compounds To Synthesize

1) The minor modification rule



Efaroxan (an I_3 receptor agonist)



KU-14R (an I_3 receptor antagonist)

2) The biological logic rule

3) The structural logic rule

4) The right substituent

5) The easy organic synthesis (EOS) rule

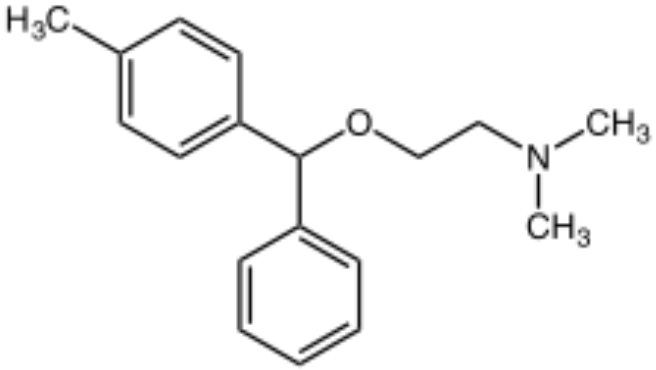
6) Eliminate the chiral centers

7) The pharmacological logic rule

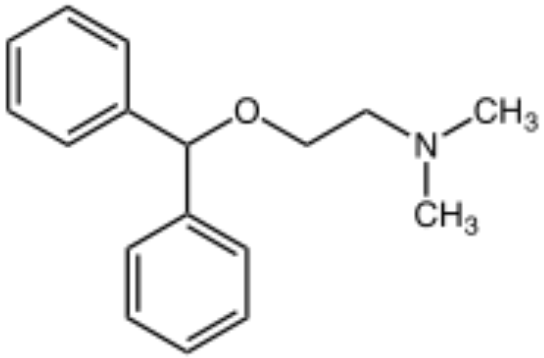
Substituent Groups: Methyl Group

Although lipophilic in nature, a methyl group can make a molecule more hydrophilic due to an entropic effect. If the attachment of a methyl group makes a molecule more compact, the molecule requires less water molecules to form a cluster around it. Furthermore, a methyl group can reduce the crystal lattice energy by hindering intermolecular interactions.

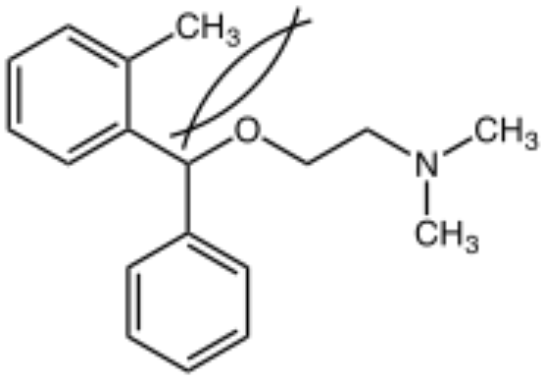
1) Conformational Effects



***p*-Me-Diphenhydramine**



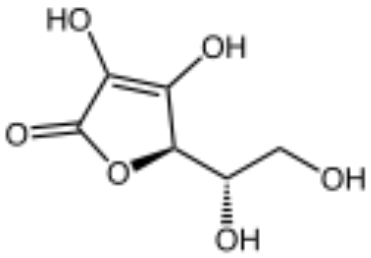
Diphenhydramine (a spasmolytic agent)



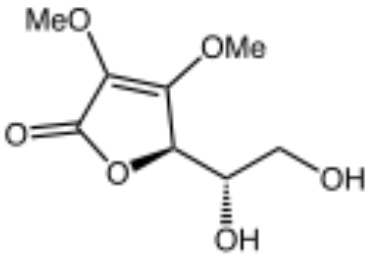
***o*-Me-Diphenhydramine**

Activity ratio	3.7	1.0	0.2

2) Metabolically, the methyl group can be used as a blocking agent.



active



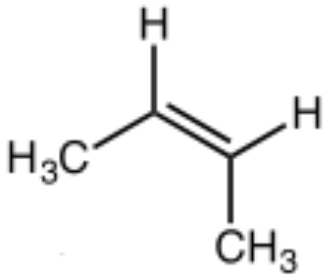
inactive

3) The methyl is an electron donor by inductive effect.

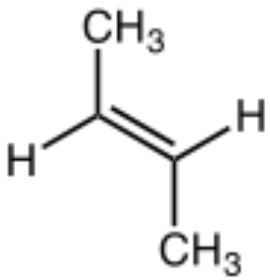
Substitutent Groups: Unsaturated Groups

1) Unsaturated groups such as C=C and C=N are electron acceptors.

2) Possibility of geometric isomerism.

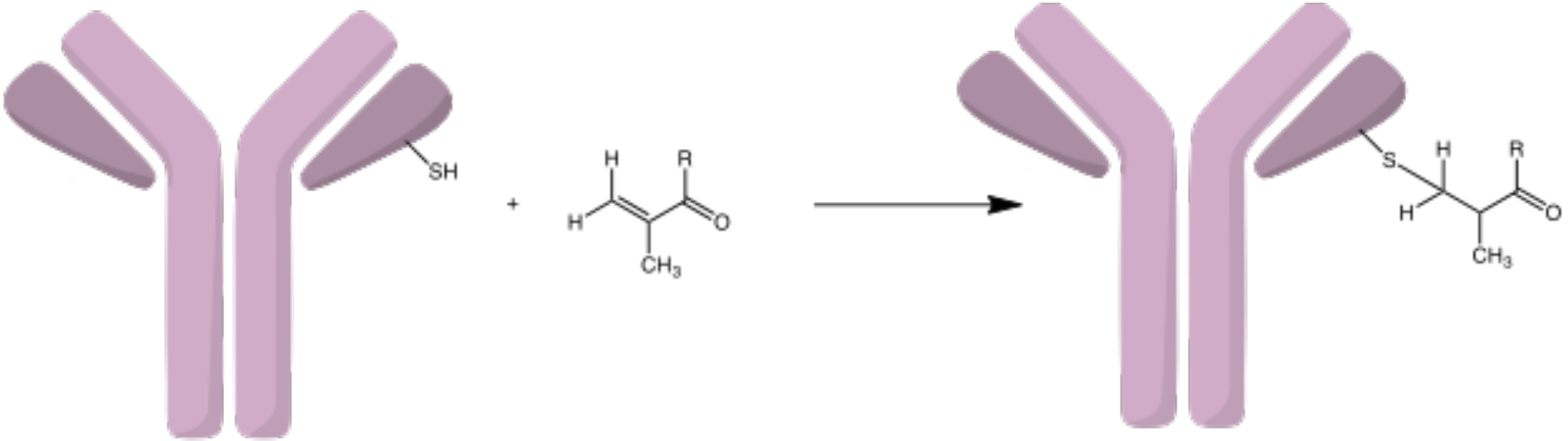


cis isomer



trans isomer

3) Activation through conjugation.



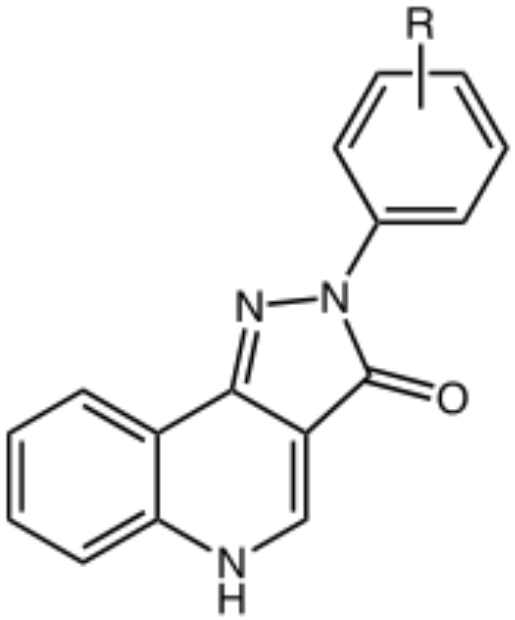
4) Facilitate metabolism.

5) Increase of the narcotic power and the power of toxicity.

Substitutent Groups: Halogen (F, Cl, Br, and I)

1) One in three drugs are halogenated, and halogenated drugs are found in almost all therapeutic classes.

2) Steric effects.



Affinity for the benzodiazepine receptor

R	IC_{50} (μM)
o-Cl	70.00
m-Cl	3.90
p-Cl	0.56

3) Halogens are hydrophobic electron acceptors.

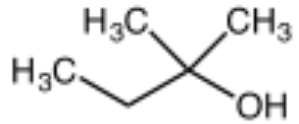
4) F and Cl both confer metabolic stability on drugs.

Substitutent Groups: Acidic and Basic Groups

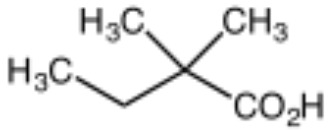
Acidic groups

Carboxylic (-CO2H) and sulfonic acids (-SO3H) confer solubility which is enhanced by salt formation.

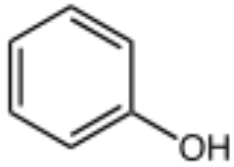
Sulfonic acids are generally not biologically active while the activity of carboxylic is dictated by size of parent molecule. In small molecules, the carboxylic acid group can cause desired and undesired effects.



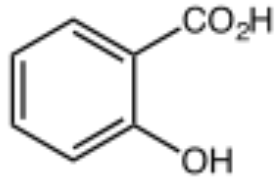
2-Methyl-butan-2-ol
(hypnotic activity)



2,2-Dimethyl-butyric acid
(inactive)



Phenol
antiseptic and toxic



Salicyclic acid
antiinflammatory
and non-toxic

In large molecules the pharmacological activity is maintained in spite of the presence of the carboxylic acid group because of its small size.

Basic groups

Like the acidic groups, the basic groups (that is nitrogen containing groups) confer solubility which is enhanced by salt formation.

The nitrogen is found practically in all drugs such that “no biological activity without nitrogen.”

Drug-Receptor Interaction

The biological activity of a drug is related to its affinity for the receptor, that is, the stability of the drug-receptor complex. The dissociation constant, *K*d, for the complex is used to measure the strength of the interaction between the drug and the receptor.

$$K_d = \frac{[\text{drug}][\text{receptor}]}{[\text{complex}]}$$

[drug] = drug concentration
[receptor] = receptor concentration
[complex] = complex concentration

The smaller the *K*d the greater the affinity of the drug for the receptor. Furthermore, the experimental measurement of the equilibrium constant allows for a direct calculation of the △G.

$$\Delta G = -RT \ln K_d$$

The interaction between a drug and a receptor is governed by:

electrostatic interaction: this is the net result of the attraction between the positively charged nuclei and the negatively charged electrons of two molecules attracting each other.

steric interaction: shape complementarity
enthalpy–entropy compensation:
the strength of functional group contributions

Pharmacological Space

Pharmacological space comprises chemical space, target space, and disease space. As such, the medicinal chemist is constantly faced with choices on which disease to attempt to treat, which proteins to target, which assays to employ, and which compounds to synthesize and in what order.

Sir James Black (Nobel Laureate in Physiology and Medicine, 1988)

Black's rules for a drug discovery project

1) Is the project purged of wishful thinking?
2) Is a chemical starting point identified?
3) Are relevant bioassays available?
4) Will it be possible to confirm laboratory-specificity in humans?
5) Is a clinical condition relevant to the specificity mentioned in rule 4?
6) Does the project have a champion, that is, someone with the necessary passion, conviction, and energy?

Chemical Space & Target Space

Current data indicate that drugs tend to form clusters in chemical space since approximately 80% of yearly approved drugs are only incremental improvements on existing drugs. This is reflected in the equally low number new protein targets discovered annually.

Drug-Like Space

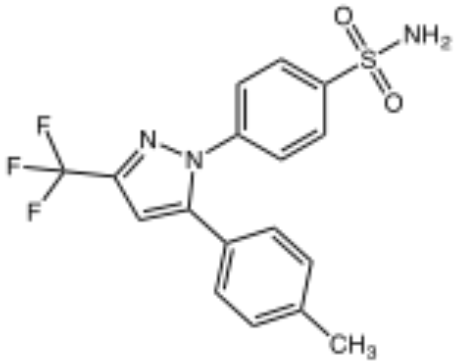
- New chemical entity that must be patentable and registrable.
- Synthesized in 4 steps having high chemical yields (>99%); no use of heavy metal or generation of environmentally problematic waste; no chromatographic purification step.
- Stable up to 70 °C even in humid air and light.
- Crystalline, not polymorphous, not hygroscopic, so that it is suitable for tablet formation.
- Soluble in water for the formation of stable blood-isotonic solutions.
- Oral bioavailability >90% with no interindividual variation.
- Very high-activity and pharmacokinetic profile enable once-a-day-dosage at 5−10 mg.

Target space, unlike chemical space, is limited and distinct. Drug targets include proteins, DNA, RNA, carbohydrates, and phospholipid membranes.

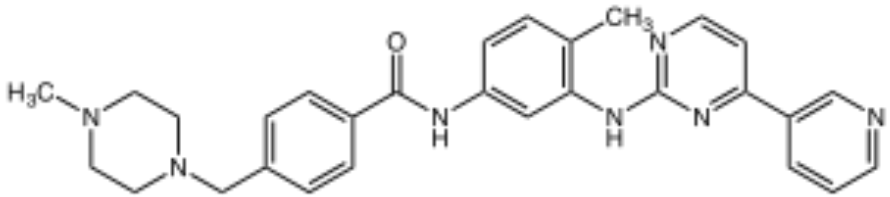
Systems Biology: A New Paradigm for Drug Discovery

The “one target, one drug” model has sustained drug development for the last five decades. However, the significant decrease in the submission and approval of new drugs call for a new paradigm for bringing drugs to the market.

As indicated by advances systems biology and chemical biology, most drugs interact with multiple targets given rise to both beneficial and adverse side effects.



Celecoxib
main effect: anti-inflammatory
second effect: reduces the number of adenomatous polyps
primary target: COX-2 inhibitors
off-target: inhibitor of carbonic anhydrase II and 5-lipoxygenase



Imatinib
main effect: treatment of chronic myelogenous leukemia and gastro intestinal cancer
second effect: left ventricular contractile dysfunction (cardiotoxic)
primary target: BCR-ABL tyrosine kinase inhibitor
off-target: no specific tyrosine kinase inhibitor

Hence, therapeutic strategies centered on biological pathways rather than single proteins must be examined.

Summary

It is impossible to synthesize all conceivable chemical structures, hence the medicinal chemist must carry out any given project with a balance of intuition and available information.

Next Lecture, 2016/04/25

Spatial Organization, Receptor Mapping
and Molecular Modeling