

Structural Modification to Lead Compounds

Structural Modifications

- Goals
 - Increase Potency
 - Increase Bioavailability
 - Increase therapeutic index (ratio of drug concentrations giving undesirable and desirable effects)
- e.g., LD_{50} (lethal dose for 50% of the test animals)
- ED_{50} (effective dose to give maximum effect in 50% of test animals)
- Should therapeutic index be large or small?
- Should the threshold value be the same for every disease?

Types of Structural Modifications

- Homologation
- Chain Branching
- Ring-chain Transformations
- Bioisosterism
- Peptidomimetics

Homologation

Homologation - increasing size by a constant unit (e.g., CH_2)
Effect of carbon chain length on drug potency

Figure 2.3

Pharmacokinetic explanation: Increasing chain length increases lipophilicity and ability to cross membranes; if lipophilicity too high, it remains in the membrane

Pharmacodynamic explanation: Hydrophobic pocket increases binding with increasing length; too large and does not fit into hydrophobic pocket

Table 2.1

Branched chain groups are less lipophilic than straight chain groups.

Chain Branching

Often lowers potency and/or changes activity; interferes with receptor binding

structure 2.40

10-Aminoalkylphenothiazines (X = H)

$R = CH_2CHNMe_2$ promethazine

antispasmodic/antihistamine activities predominate

$R = CH_2CH_2CH_2NMe_2$ promazine
greatly reduced antispasmodic/antihistamine activities
greatly enhanced sedative/tranquilizing activities

$R = CH_2CH(CH_3)CH_2NMe_2$ trimetopazine

reduced tranquilizing activity
enhanced antipruritic (anti-itch) activity

All bind to different receptors


Ring-Chain Transformations

Transformation of alkyl substituents into cyclic analogs, which generally does not affect potency.



structure 2.40

Chlorpromazine (antipsychotic)

(**2.40**, X = Cl, R = CH₂CH₂CH₂NMe₂) and

(**2.40**, X = Cl, R = CH₂CH₂CH₂N)

have equivalent tranquilizing effects

Trimepazine (**2.40**, X = H, R = ) and
Methdilazine (**2.40**, X = H, R = ) have
similar antipruritic (anti-itch) activities.

Ring-chain transformation can have pharmacokinetic effects, such as increased lipophilicity or decreased metabolism.

Bioisosterism

Bioisosteres - substituents or groups with chemical or physical similarities that produce similar biological properties. Can attenuate toxicity, modify activity of lead, and/or alter pharmacokinetics of lead.

Classical Isosteres

Two classical isostere definitions:
Grimm: groups having same # valence electrons
Erlenmeyer: groups with identical peripheral electron layers

Table 2.2

Non-Classical Isosteres

Table 2.3

Do not have the same number of atoms and do not fit steric and electronic rules of classical isosteres, but have similar biological activity.

Examples of Bioisosteric Analogues

Table 2.4

Changes in Activity by Bioisosterism

If the S in phenothiazine neuroleptic drugs (2.40) is

replaced by -CH=CH- or -CH₂-CH₂- bioisosteres, then dibenzazepine antidepressant drugs (2.43) result.

Changes resulting from bioisosteric replacements:

Size, shape, electronic distribution, lipid solubility, water solubility, pK_a, chemical reactivity, hydrogen bonding

Effects of bioisosteric replacement:

1. **Structural** (size, shape, H-bonding are important)
2. **Receptor interactions** (all but lipid/H₂O solubility are important)
3. **Pharmacokinetics** (lipophilicity, hydrophilicity, pK_a, H-bonding are important)
4. **Metabolism** (chemical reactivity is important)

Bioisosteric replacements allow you to tinker with whichever parameters are necessary to increase potency or reduce toxicity.

Bioisosterism allows modification of physicochemical parameters

- Multiple alterations may be necessary:
- If a bioisosteric modification for receptor binding decreases lipophilicity, you may have to modify a different part of the molecule with a lipophilic group.
- Where on the molecule do you go to make the modification?

Peptidomimetics

Peptides are important endogenous molecules - neurotransmitters, hormones, neuromodulators

Peptide drugs - analgesics, antihypertensives, antitumor agents

Peptides generally do not make good drug candidates

- rapidly proteolyzed in GI tract and serum
- poorly bioavailable
- rapidly excreted
- bind to multiple receptors

Peptidomimetic - a compound that mimics or blocks the biological effect of a peptide, but without undesirable characteristics

- Use the peptide as a lead - modify to minimize undesirable pharmacokinetic properties
- Try to mimic structure of the peptide when it is bound to the target receptor
- Replace as much of the peptide backbone as possible with nonpeptide fragments - leave the pharmacophoric groups
- Initially, retain conformational flexibility, but then refine to more conformationally-rigid analogs to hold groups in bioactive conformation.

Phenylalanine Peptidomimetics

Figure 2.9

Increased lipophilicity and conformational rigidity - better absorption and poor recognition by proteases

Conformationally-Restricted Peptides

Figure 2.10

Secondary Structure Mimetics

Figure 2.11

Scaffold Peptidomimetics

Arg-Gly-Asp (RGD)
common β -turn motif
that binds to receptors

structures 2.66-2.69

RGD peptidomimetics

Peptide Backbone Isosteres

Peptide amide bond replaced with alternative groups

Table 2.5

(statine)

Assigned Reading

- 2.2 through the end of 2.2E.4 and 2.2E.7
- Problems 2.4 - 2, 5, 6, 7, 12
- Part II – copy for in-class peer review 3/22
– copy for grading 3/24