Outline (Handout #4)
Drug design (I)
I. The process of drug design and development
   A. Definition of Lead compound
   B. Discovery of lead compounds
   C. Lead modification/SAR
II. US drug regulation

I. The process of drug design and development

Diseases targeted

From hit to lead

Lead modification

Drug candidate selection

Drug delivery studies

ADME studies  Efficacy model studies  Toxicity studies
A. Definition of Lead compound
   ◼ The starting compound to design a drug

B. Discovery of lead compounds
1. From natural products

   Lead compounds
   ▶ Flora
   ▶ Microorganisms
   ▶ Animals
   ▶ Marine chemistry
   
   e.g., From poppies to morphine
   e.g., penicillin
   e.g., from teprotide to captopril
   No drug approved yet

2. From existing drugs
   a. Alternative medicine/Medical folklore
      e.g., From coca leaves to cocaine to procaine
   b. “Me too” drugs
      When patents are expired, other companies develop the similar products
   c. Enhance a side effect
      Sildenafil (Viagra)-From anti-hypertension drug to erectile disfunction (An observation of the “side effect” during its clinic trial)
3. From endogenous substances
   a. Ligands of receptors
      Agonists and antagonists
      i.e. sympathetic and parasympathetic drugs
   b. Substrates/products of enzymes
      structural analogues
      i.e. Folic acid and aminopterin and dihydrofolate reductase
   c. Modulators/second massagers
      e.g. Antibodies
4. Other ways
   Computer-aided design

C. Lead modification/SAR

Pharmacophore/auxophore

(A) Definition
   When a drug molecule binds to a receptor, frequently, only a small part (pharmacophore) of the drug molecule interacts with the receptor. The other part of the drug molecule is called auxophore.

(B) Example—morphine derivatives and µ opioid receptor

\[
\begin{align*}
\text{CH}_3 & \\
\text{OR} & \\
\text{OR}' & \\
\text{OR} & \\
\end{align*}
\]
i. Classes of opioid agonists

(1) Endogenous opioid agonists

(2) Exogenous opioid agonists

a. Natural products: Opium products (extract from the poppy)

b. Synthetic and semisynthetic opioid agonists

Morphine analogues
Benzomorphans
Phenylpiperidines
Open chain opioid analogues

The extract of the seed capsule of the poppy plant contains Morphine
Codeine
Thebaine
Papaverine

(1). Endogenous opioid agonists:

Enkephalin (5 amino acids)

Tyr-Gly-Gly-Phe-Leu(Met)

Dynorphin (13-17 amino acids)

Tyr-Gly-Gly-Phe-Leu-......13-17 aa.

Endorphin (31 amino acids)

Tyr-Gly-Gly-Phe-Leu(Met)-......31 aa

(2) Exogenous opioid agonists

a. Natural products: Extract from the poppy plant.

The extract of the seed capsule of

the poppy plant contains

Morphine
Codeine
Thebaine
Papaverine
b. Synthetic and semi-synthetic opioid agonists
   
a). Morphine analogues
   
   b). Benzomorphan

   General structure of benzomorphans
c). Phenylpiperidines

Morphine

Meperidine

Meperidine (Demerol): only about 20% of the potency of morphine.

Ketobermidone: About 620% of the potency of meperidine.

Anileridine: About 350% of the potency of meperidine.

Fentanyl (Sublimaze): 100 times higher than morphine; 1000 times higher than meperidine.
d). Open chain opioid analogues

- Morphine
- Methadone

General structure of open chain opioid analogues

Propoxyphene (Darvon; Darvocet)

ii. Structural model for opioid receptor/ligand interaction
(Beckett and Casy J Pharm Pharmacol 6:986, 1954)

- Anionic site
- Cavity
- Flat lipophilic surface
- H-bond acceptor site
(1). With morphine

(2). With phenylpiperidine
(3). With Benzomorphans

Anionic site
Flat lipophilic surface
Cavity
H-bond acceptor site

(4). With endogenous peptides

Anionic site
Flat lipophilic surface
Cavity
H-bond acceptor site
(iii) Pharmacophore of opioid agonists

Methadone

Morphine
\( (R = R' = H) \)

Codeine
\( (R = CH_3, R' = H) \)

Heroin
\( (R = R' = COCH_3) \)

Levorphanol

Meperidine
\( (\text{Demerol}) \)

Dextropropoxyphene
\( (\text{Darvon}) \)

Methadone

Figure 2.15 (From Wilson and Gisvold’s)
Stabilization of conformations by secondary bonding forces
Summary

a. Additional conformational flexibility allows the drug to bind the opioid receptor more effectively.
b. Remove half of the cyclohexene ring (not a part of the pharmacophore, the molecule becomes less potent but lower addictive.
c. Removing the methylene of the cyclohexane ring resulting in less potency but easier analog synthesis.
d. The piperidine ring can be open.
e. Sometimes adding groups to the pharmacophore can result in better potency.

Morphine  Benzomorphan  Meperidine (Demerol)  Methadone

Morphine  Etorphine
(3200 times more potent than morphine)
B. Structural modifications of the lead compound (to increase potency and the therapeutic index)

1. Drug molecule evaluation
2. Branching and elongation
3. Ring transformation
4. Isosteric replacement

1. Lead molecule evaluation
   - Analysis of individual functional groups:
     - Name of functional group
     - Shape of functional group
     - Hydrophobic vs. hydrophilic character
     - Polar vs. nonpolar character
     - Acidic vs. basic ($pK_a$) character
     - Binding interactions
     - Chemical/enzymatic stability
   - Analysis of the whole drug molecule:
     - Looking for functional group balance: water solubility and absorption
     - Ionization issues: effect on solubility and absorption
     - Drug combinations: acid-base interactions
     - Drug interactions with biological target: good fit or not?
     - Stability and bioavailability: route of administration
2. Branching and elongation

(a) Chain branching

1. 10-Aminoalkylphenothiazine
   i. Promethazine predominately with antispasmodic/antihistamine [Histamine (H1) receptor antagonism] activities
   ii. Promazine
       Antispasmodic/antihistamine activities are significantly reduced but sedative/tranquilizing (Dopamine receptor antagonism) activities are significantly higher when compared to promethazine
   iii. Trimeprazine (Withdrawn from the market)
       Reduced tranquilizing activity but enhanced antipruritic (anti-itch) activity

(b) Homologous series-Alkyl and aromatic

\[
\begin{align*}
\text{Neuraminidase inhibition (IC50, nM)}
\end{align*}
\]

<table>
<thead>
<tr>
<th></th>
<th>H-</th>
<th>(\text{CH}_3)-</th>
<th>(\text{CH}_3\text{CH}_2)-</th>
<th>(\text{CH}_3\text{CH}_2\text{CH}_2)-</th>
<th>(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2)-</th>
<th>(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2)-</th>
<th>(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2)-</th>
</tr>
</thead>
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<tr>
<td></td>
<td>6300</td>
<td>3700</td>
<td>2000</td>
<td>180</td>
<td>300</td>
<td>200</td>
<td>150</td>
</tr>
<tr>
<td>e.g., Carbocyclic influenza neuraminidase inhibitors</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Fig. 2.31, Foye's Effect of alkyl chain length on activity of morphine
3. Ring transformation
Ring structures often increase the rigidification of the compound

2. Ring transformation
a. Opening and closure
   (1). Opening of the ring of statins (HMG-CoA reductase inhibitors)
In vivo hydrolysis

Mevastatin (Inactive prodrug)

Active form

HMG-CoA (C6)

Intermediate

Mevalonic acid (C6)

More solubility
Better selectivity for hepatic cells
(Minimal penetration into peripheral cells)

Lovastatin

Simvastatin

Pravastatin

Rosuvastatin

Atorvastatin

Fluvastatin

HMG-CoA reductase

HMG-CoA reductase

H3C CH3

H3C CH3

H3C CH3

H3C CH3

H3C CH3
(2) Opening of the estrogen ring structure

Fig. 2.37. (Foye's) Noncyclic analogs of estradiol.

b. Enlargement and contraction

Fig. 2.33. Isosteric substitution of thiophene for benzene and benzene for pyridine. (Tripelennamine and methaphenilene, antihistaminic drugs)
c. Reorganization
Naphtyl-fused diazepines (Patani and LaVoie Chem Rev 96:3147)

\[
\begin{align*}
\text{IC50} &\quad 1000 \text{ nM} \\
\text{IC50} &\quad 260 \text{ nM}
\end{align*}
\]

\[
\begin{align*}
\text{IC50} &\quad 1000 \text{ nM} \\
\text{IC50} &\quad 55 \text{ nM}
\end{align*}
\]

d. Ring-chain transformation
(1). Trimeprazine and methdilazine

Transformation of alkyl substituents into cyclic analogs does not affect the tranquilizing potency but might increase the lipophilicity.

(2) Sultopride and DU122290
4. Isosteric replacement

(a) Definition

Replacement or modification of functional groups with other groups having similar properties (electronic and steric arrangement of atoms, groups, radicals and molecules) is known as “isosteric replacement,” or “bioisosteric replacement.”

![Fig. 2.34. (Foye’s) Isosteric replacement of chlorine in thiazide diuretics. Comparison of physicochemical properties of the substituents.](image)
Figure 2.28 (From Wilson and Gisvold's) Examples of how isosterism produces drugs that inhibit the activity of the native metabolite.

Figure 2.27 (From Wilson and Gisvold's) Examples of isosteric ring systems.
Table 2.7. (Foye's) Comparison of physical properties of N\textsubscript{2}O and CO\textsubscript{2}

<table>
<thead>
<tr>
<th>Property</th>
<th>N\textsubscript{2}O</th>
<th>CO\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscosity at 20°C</td>
<td>148 × 10\textsuperscript{-6}</td>
<td>148 × 10\textsuperscript{-6}</td>
</tr>
<tr>
<td>Density of liquid at 10°C</td>
<td>0.856</td>
<td>0.858</td>
</tr>
<tr>
<td>Refractive index of liquid, D line 16°C</td>
<td>1.193</td>
<td>1.190</td>
</tr>
<tr>
<td>Dielectric constant of liquid at 0°C</td>
<td>1.593</td>
<td>1.582</td>
</tr>
<tr>
<td>Solubility in alcohol at 15°C</td>
<td>3.250</td>
<td>3.130</td>
</tr>
</tbody>
</table>

(c) Classification

Bioisosteric groups can be subdivided into two categories: classical and nonclassical bioisosteres.

(From Foye’s)

Classical bioisosteres

A. Monovalent atoms and groups
B. Divalent atoms and groups
C. Trivalent atoms and groups
D. Tetrasubstituted atoms
E. Ring equivalents

Nonclassical bioisoteres

A. Exchangeable groups
B. Rings versus noncyclic structure
i. Functional groups that satisfy the original conditions of Langmuir and Grimm are referred to as classical bioisosteres.

Table 2.8. Grimm (1925)'s Hydride Displacement "Law" (Foye's)

<table>
<thead>
<tr>
<th>C</th>
<th>N</th>
<th>O</th>
<th>F</th>
<th>Ne</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH</td>
<td>NH</td>
<td>OH</td>
<td>FH</td>
<td></td>
</tr>
<tr>
<td>CH₂</td>
<td>NH₂</td>
<td>OH₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₃</td>
<td>NH₃</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.9. (Foye's) Classical bioisosteres (Groups within the row can replace each other)

Monovalent bioisosteres:
- F, H
- CH, NH, OH
- F, OH, NH or CH₂ for H
- SH, OCH
- CI, Br, CF₃

Divalent bioisosteres:
- −C=O, −C=O, −C=NH, −C=C−

Trivalent atoms or groups:
- −C=O, −N=O
- −P=O, −As=O

Tetrasubstituted atoms:
- −N⁺, −C⁺, −P⁺, −As⁺

Ring equivalents:
Example #1:
Clozapine, lozapine, and quetiapine

Example #2:
Naphtyl-fused diazepines (Benzodiazepine receptor binding affinity
(Patani and LaVoie Chem Rev 96:3147)

Example #3:

Example #4:

Figure 2.28 (Wilson and Gisvold’s) Examples of how isosterism produces drugs that inhibit the activity of the native metabolite
Example #5

\[ \text{HO} \quad X \quad \text{X} \]

\( \alpha \)-Tocopherol \( X = C_{14}H_{29} \)

**Fig. 2.36. (Foye's) Tetravalent bioisosteres of \( \alpha \)-tocopherol**

**Table 3. Isosteres Based on the Number of Peripheral Electrons**

<table>
<thead>
<tr>
<th>no. of peripheral electrons</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{N}^+ )</td>
<td>P</td>
<td>S</td>
<td>Cl</td>
<td>ClH</td>
<td></td>
</tr>
<tr>
<td>( \text{P}^- )</td>
<td>As</td>
<td>Se</td>
<td>Br</td>
<td>BrH</td>
<td></td>
</tr>
<tr>
<td>( \text{S}^- )</td>
<td>Sb</td>
<td>Te</td>
<td>I</td>
<td>IH</td>
<td></td>
</tr>
<tr>
<td>( \text{As}^+ )</td>
<td>PH</td>
<td>SH</td>
<td>SH(_2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{Sb}^- )</td>
<td>PH(_2)</td>
<td>PH(_3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ii. Nonclassical bioisosteres

- Do not obey steric and electronic definitions of classical bioisosteres
- Do not necessarily have the same number of atoms as the substituent they replace.

Example #1

![Example #1](image)

Fig. 2.37. (Foye’s) Noncyclic analogs of estradiol

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Table 2.10. (From Foye’s) Nonclassical Bioisosteric Replacements
Fig. 2.38. (Foye’s) Bioisosteric replacement of m-OH of isoproterenol (β-adrenergic agonist) with a sulfonamido group and similar hydrogen-bonding capacity to a possible drug receptor.

Determination of molecular similarities

(1) Allen in 1911—Molecular number

\[ N = aN_1 + bN_2 + cN_3 + \ldots + zN_i \]

For example:

- \( N_1, N_2, N_3, \ldots, N_i \) = Atomic number of each element of the molecule
- \( a, b, \ldots, z \) = Number of atoms of each element present in the molecule

<table>
<thead>
<tr>
<th>Atomic number</th>
<th>Molecular number</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH(_4^+)</td>
<td>(7 + (4 \times 1)) (= 11)</td>
</tr>
<tr>
<td>Na(^+)</td>
<td>11</td>
</tr>
</tbody>
</table>
II. U.S. Drug regulation (Chapter 12, Foye’s)

- FDA Food and Drug administration
  - Preclinical Investigation
    - Good Laboratory Practices
    - Requires no FDA approval
  - Investigational New Drug Application (INDA)
    - Institutional Review Board
    - Requires FDA approval
  - New Drug Application (NDA)
  - Abbreviated New Drug Applications (Me-too drugs)
  - Over-The-Counter Regulations
  - Regulating Marketing (Drug advertising and promotion)
    - Advertising and labeling
  - Violations and enforcement
    - Recall, injunction, seizure of products

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**U.S. Drug regulation (Chapter 12, Foye’s)**

Fig. 11.1. New Drug Application (NDA) review process. (http://www.fda.gov/cder/handbook/nda.htm. Accessed March 2007.)
Fig. 11.2. Generic Abbreviated New Drug Application (ANDA) review process. (http://www.fda.gov/cder/handbook/generic.htm. Accessed March 2007.)

Fig. 11.3. Over-the-counter (OTC) drug monograph review process. (Adapted from http://www.fda.gov/cder/handbook/otc.htm. Accessed March 2007.)