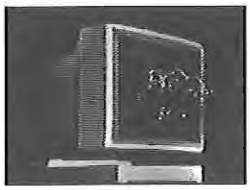
SY10 MOLECULAR MODELING IN DRUG DESIGN

ผศ.ดร.จิราภรณ์ อังวิทยาธร

คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล

Molecular Modeling in Drug Design

Jiraporn Ungwitayatorn



Traditional Approaches

random screening and chance discovery

↓

quantitative structure-activity relationships (QSARs)

↓

rational drug design

(molecular biology, crystallography, NMR, computer graphics and modeling)

↓

genomic projects, bioinformatics, combinatorial chemistry

2-Dimensional QSAR

-classical QSAR studies have related the biological activity of the drug to physicochemical properties, e.g., lipophilicity, electronic property, molar refractivity, etc

-results are usually summarized in equation

3-Dimensional QSAR

-stereochemistry has major influence in the biological activity of the drugs

-drug binding site is a chiral environment and performs discrimination between the different enantiomers of an optically active drugs

3-Dimensional QSAR

-drugs must have a 3-D structural feature which is complementary to the binding site to exert higher affinity with the target and may be result in higher activities

-molecular modeling techniques are used to understand the 3-D requirements

- 3-D structural features, e.g., molecular fields, spatial arrangement of pharmacophoric atoms

Molecular Modeling in Drug Design

" interlinked activities "

1. Molecular Graphics
   display 3D-structures of molecules
   display molecular properties, etc.
2. Computational Chemistry
   calculate atomic and molecular properties through equations

Molecular Modeling in Drug Design

3. *Statistical Modeling*
   perform QSAR (MLR, PLS)
4. *Chemical Data/ Information Management*
   molecular structures database
   organic synthetic methods database
   molecular properties database

Bioinformatics and Computer-Aided Drug Design

-*bioinformatics offers a means to get to a structure through sequence*
-*computer-aided drug design offers a means to get to a drug through structure*

Bioinformatics and Computer-Aided Drug Design

-*once a disease target molecule is identified typically a protein, the protein can be used to screen libraries of molecules produced by combinatorial chemistry techniques*
-*computers and computer-operated robots are essential to the process of screening the molecules and tracking the large volume of data generated by high throughput screening*

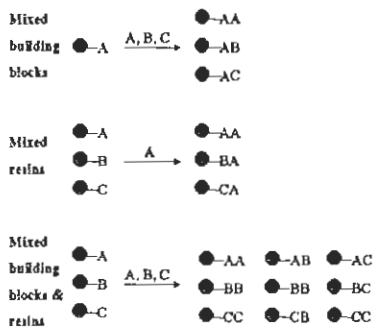
Combinatorial Chemistry

-*elaborate extension of the solid phase peptide synthesis(SPPS)*
-*simultaneously produce many compounds with desired structure (products should be as diverse as possible)*

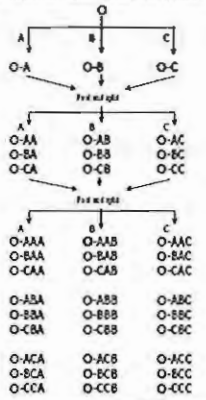
Combinatorial Chemistry

-*the technology used in combinatorial synthesis is dominated by robots designed to greatly accelerate the rate at which compounds can be produced.*
-*the chance of finding active compounds in a library increases with diversity and dissimilarity of the compound set*

Combinatorial Chemistry



Combinatorial Chemistry



Direct Drug Design

new molecules are conceived either:

- *on the basis of similarities with known references structures*
- *on the basis of their complementarity with the 3D structure of known active sites ("docking")*

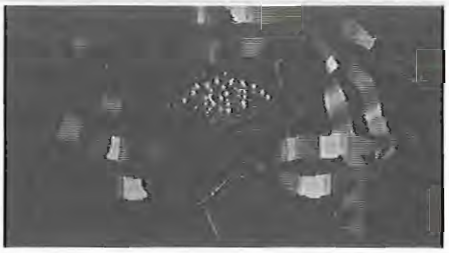
Direct Drug Design

require

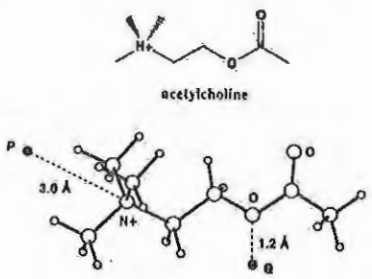
X-ray crystal structure of receptor

X-ray crystal structure of receptor-ligand complex

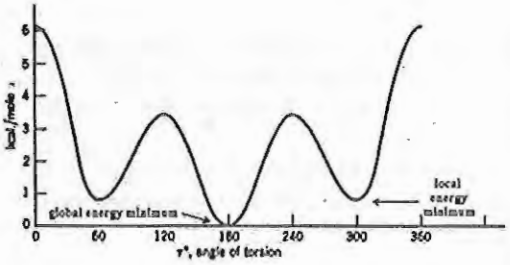
➡ *receptor binding site*



Conformational Analysis



Conformational energy



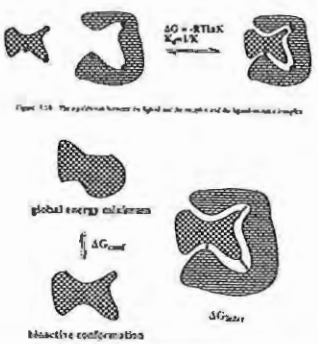
Bioactive Conformations

-not necessarily the lowest energy conformation of the molecule in solution, in crystal or in the gas phase

-can be identified by:

- -observed conformations of ligands in crystal structures of ligand-receptor complexes
- - making conformational restriction analogues

Bioactive Conformations

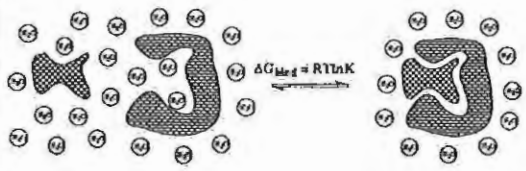


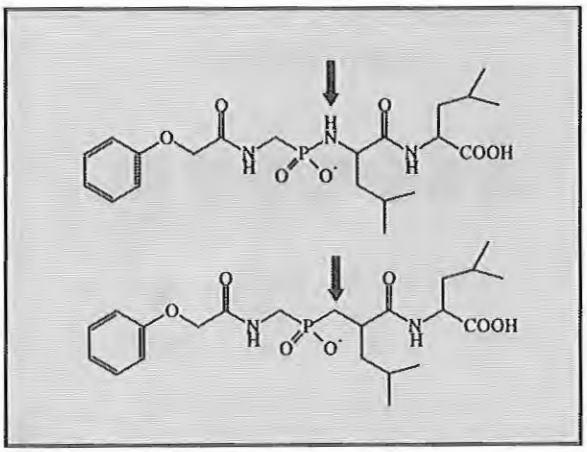
Solvation Effects

molecular modeling

- in vacuo
- no solvent effects
- solvation energy should be added

Solvation Effects





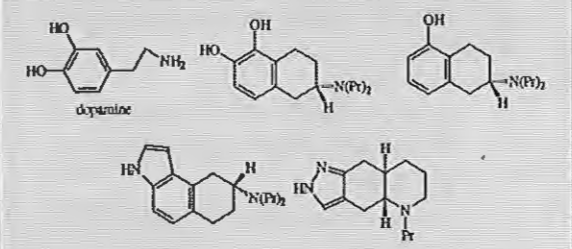
Indirect Drug Design

- shape and electronic complementarity between the receptor and the ligand
  - > 3-D pharmacophore study
  - > volume operations

3D-Pharmacophore Study

- select common pharmacophore for all active compounds
- conformational analysis to identify low-energy conformations of each active molecule
- molecular superimposition to find a common 3D-pharmacophore for all active compounds

Dopamine-2 receptor agonists



Molecular Superimposition

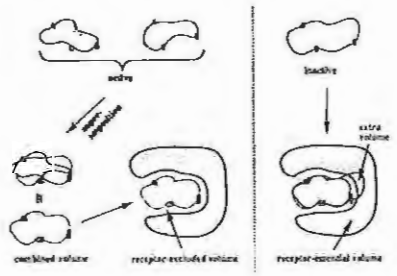
superimposed based on

- atoms or site points
  - ➡ shape complementarity to the binding sites
- electronic properties
  - electronic complementarity
  - ➡ e.g., electrostaic fields

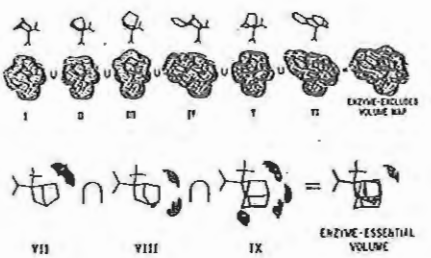
Volume Operations

- to find receptor (enzyme) **excluded volumes** and receptor (enzyme)**essential volume**
  - ➡ information about the dimensions of the receptor cavity
- an inactive compound may fit the 3D-pharmacophore model but may have extra volume which interferes with binding to the receptor

Volume Operations



Volume Operations

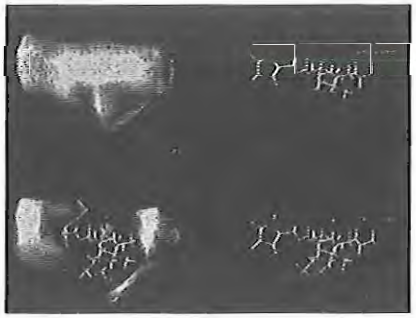


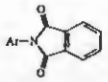
CoMFA Methods

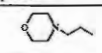
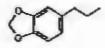
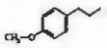
-most widely used 3-D QSAR, developed by Cramer, et al.
-biological properties of molecules are related to their electrostatic and steric fields
-can be applied to a broad variety of biological systems and also to noncongeneric series of molecules

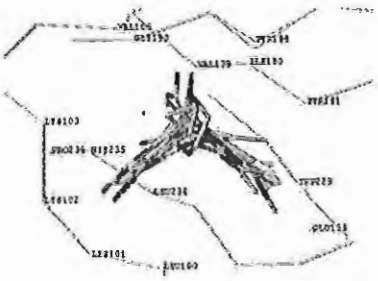
CoMFA

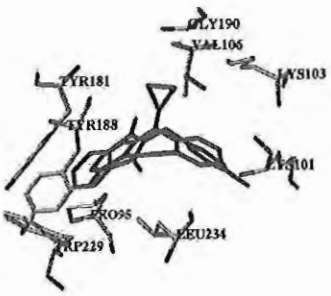
power of CoMFA technique
-needs no direct knowledge of the geometries of the target molecules
-is a good tool for predicting activity of synthetic candidates and proposing new synthetic candidates

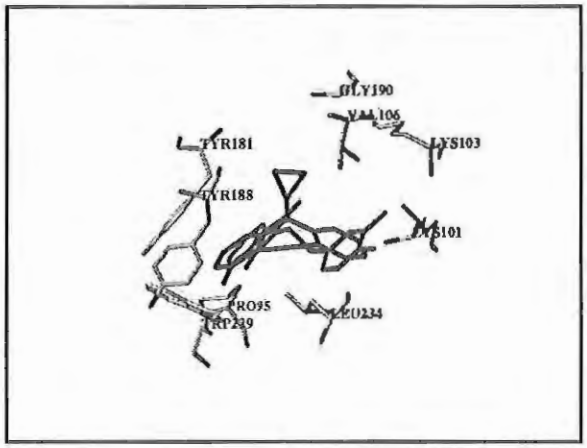


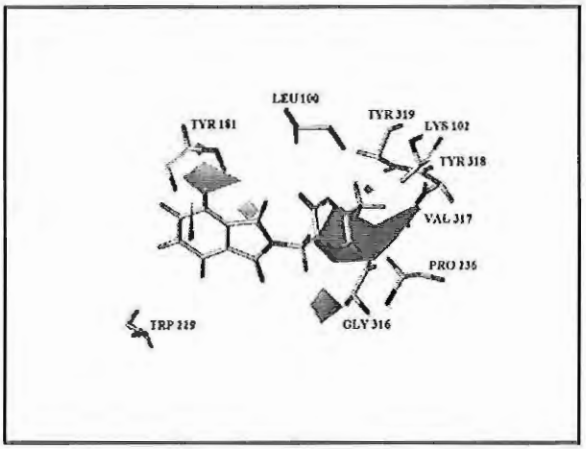


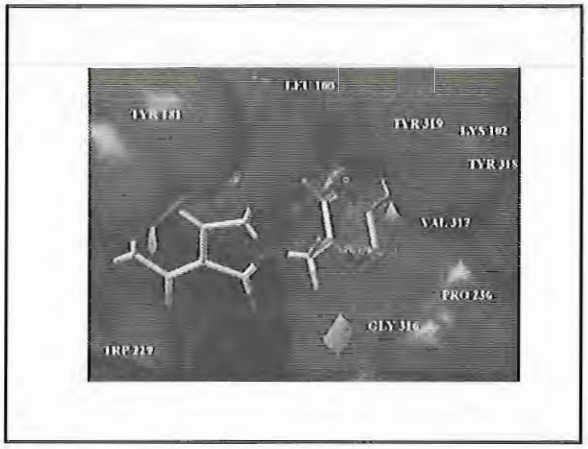
Compound	% Inhibition	Compound	% Inhibition
	62		11
	84		8
	21		41
	32		20
	76		78
	3		

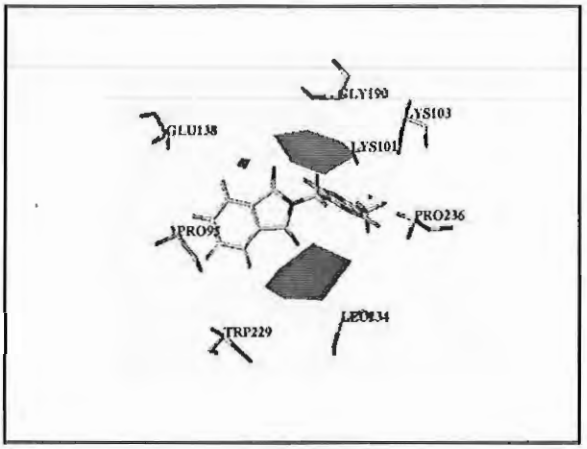












References

- Hoeltje, H.-D., and Flokers G. Molecular Modeling: Basic Principles and Applications, vol 5, VCH, New York, 1996.
- Hopfinger, A.J., 'Computer-Assisted Drug Design', J Med Chem 1985, 28, 1133-1139.
- Cohen, N.C., Guidebook on Molecular Modeling in Drug Design, Academic Press, New York, 1996.
- Kubinyi, H. 3D QSAR in Drug Design: Theory Methods and Applications, Escom, Leiden, 1993.
- van de Waterbeem, H., Testa, B., Folkers G. Computer-Assisted Lead Finding and Optimization, Wiley-VCH, New York, 1997.

Web resources

- **Introduction to Molecular modeling**
  http://www.netsci.org/Science/Compchem/feature01.html
  http://www.netsci.org/Science/Cheminform/
- **Practise in Molecular Modeling**
  http://www.ch.cam.ac.uk/SGTL
- **The Representation of Molecular Models Rendering Techniques.**
  http://scsg9.unique.ch/fin/eng/toc.html
- **Molecular Modeling Information**
  http://cmm.info.nih.gov/modeling

Web resources

- Molecular Modeling Lecture Notes
  http://www.nd.edu/~chem647/outline.html
- Basic Modeling Concepts
  http://www.amber.ucsf.edu/amber/0Net/Index.html
- Molecular Modeling: History, Links
  http://sugar.chem.utk.edu/~bakergrp/modeling.htm
- Molecular Modeling Information
  http://cmm.info.nih.gov/modeling/