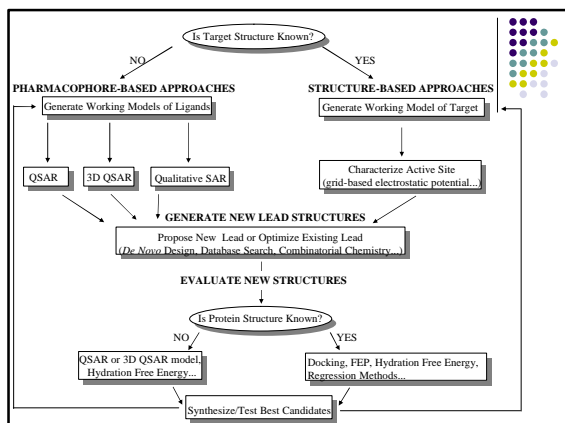


Overview of Computer-Aided Drug Design

Computer Use in Medicinal Chemistry

1. Finding/storing information
 1. Literature searching (Medline, SciFinder...)
 2. Structure searching (Protein Databank, SciFinder)
 3. Cataloging structure-activity data
2. Modeling existing lead compounds
3. Developing new lead compounds



Modeling Existing Lead Compounds

- QSAR
 - Development of a mathematical model that describes in a predictive manner the relationship between structure (represented by numerical descriptors) and activity
- Pharmacophore Model Development
 - Finding a set of functional groups with the same geometric arrangement in a series of compounds with a common biological activity
- 3D QSAR
 - Development of a quantitative model relating structure to biological activity in which the structural descriptors are values for various properties computed at grid points in three-dimensional space
- Docking
 - Development of a model complex of a biological target and a ligand
- Free Energy Perturbation
 - A computational method to determine the differences in free energy involved in transferring different ligands from the aqueous solution to a binding site in a biological target

Group Discussion

- Identify some important questions or limitations of technique based on concepts from organic chemistry

Typical chapter titles in organic chemistry textbooks:

Structure and bonding; Bonding and molecular properties; Alkanes and cycloalkanes; Stereochemistry; Overview of organic reactions; Alkenes; Alkynes; Alkyl halides; Nucleophilic substitutions and eliminations; Structure determination (spectroscopy); Conjugated dienes; Benzene and aromaticity; Electrophilic aromatic substitution; Alcohols and thiols; Ethers, epoxides and sulfides; Nucleophilic addition to carbonyls; Carboxylic acids; Carboxylic acid derivatives; Carbonyl alpha-substitution reactions; Carbonyl condensation reactions; Aliphatic amines; Arylamines and phenols; Carbonyl hydrates; Amino acids, peptides and proteins; Lipids; Heterocycles and nucleic acids

Group Discussion Points

- Questions
 - QSAR – Can QSAR be used with other identification processes? (spectroscopic)
 - Pharmacophore Modeling – Need to determine pharmacophore groups in each molecule with similar characteristics
 - Docking – need structures (stereochemistry often not known for initial lead compounds)
- Limitations
 - QSAR – No visual aspect (how to improve activity not intuitive)
 - Pharmacophore Modeling – Limited to functional groups of similar charge and size
 - Docking – Does not anticipate potential chemical reactions (covalent inhibition)

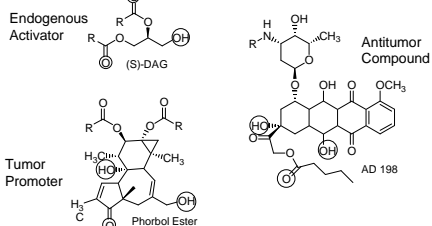
QSAR Example

- Biological activity of indoleacetic acid-like synthetic hormones
- $\text{Log}(1/C) = -k_1(\text{logP})^2 + k_2(\text{logP}) + K_3\sigma + k_4$
 - C: Concentration having a standard response in a standard time
 - P: Octanol/water partition coefficient
 - Log P reflects pharmacokinetic influence on activity – does the compound get where it needs to go?
 - σ reflects pharmacodynamic influence on activity – does the electronic nature of the compound induce activity?

Pharmacophore Modeling Example

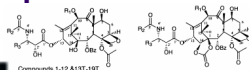
The three molecules below all target protein kinase C

Each molecule can adopt a conformation with common distances separating the circled groups

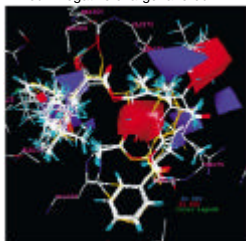
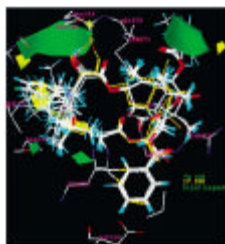


3D QSAR Example

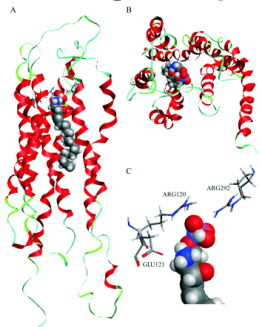
J.Mol. Graph. Model. 21 (2003) 263-272



Blue: Negative charge disfavored
Red: Negative charge favored



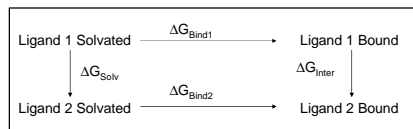
Docking Example



Analysis Exercise

- Visually examine the 1HNI structure of HIV reverse transcriptase
- Focus on the inhibitor and the surrounding residues
- What type of intermolecular interactions can you identify visually?
- Which ones do you think are most important?

Free Energy Perturbation



Most useful quantity to compare drug candidates:

$$\Delta G_{\text{Bind1}} - \Delta G_{\text{Bind2}}$$

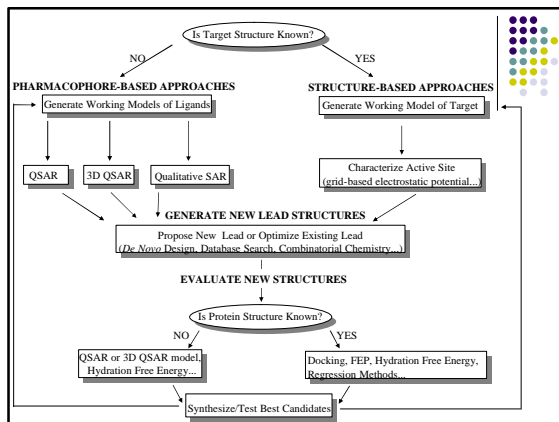
Most computationally feasible quantity:

$$\Delta G_{\text{Solv}} - \Delta G_{\text{Inter}}$$

Since free energy is a state function, any path with the same beginning and end points has the same value, therefore $\Delta G_{\text{Bind1}} + \Delta G_{\text{Inter}} = \Delta G_{\text{Solv}} + \Delta G_{\text{Bind2}}$. Rearrangement demonstrates the previous differences are equivalent.

Developing New Leads

- *De novo* Design
 - Techniques that build a potential ligand into the environment of a biological target of known structure
- Database searching
 - Use of pharmacophore models to query a database for new structures that also contain the requisite 3D arrangement of functional groups
- Combinatorial library design
 - Use of computers to determine a library of compounds enriched in potentially active compounds that can be synthesized combinatorially and rapidly screened



Reading Assignment

- The Organic Chemistry of Drug Design and Drug Action
 - Chapter 2:
 - Section 2.2 A, C, D, G1, H, I
- Textbook of Drug Design and Discovery
 - Sections 4.1-4.3
 - Sections 5.1-5.2