

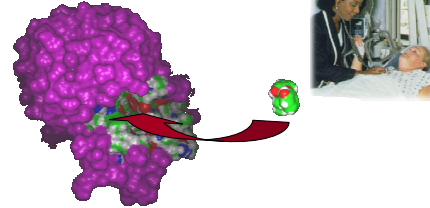
Structure-Based Drug Design

Thomas Funkhouser
Princeton University
CS597A, Fall 2005

Introduction

Drugs

- Molecules that can be introduced to change biological activity



Slide courtesy of Bill Welsh

Introduction

Drug targets

- Enzyme - inhibitors
- Receptor - agonists or antagonists
- Ion channels - blockers
- Transporter - uptake inhibitors
- DNA - blockers

Slide courtesy of Bill Welsh

Structure-Based Drug Design

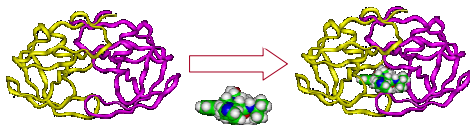
Goal:

- Given a protein structure, and/or its binding site, and/or its active ligand (possibly bound to protein), find a new molecule that changes the protein's activity

Structure-Based Drug Design

Receptor-based drug design:

- Given a protein structure, and/or its binding site, and/or its active ligand (possibly bound to protein), find a new molecule that changes the protein's activity



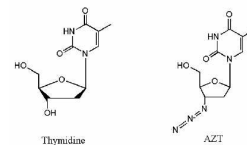
HIV Protease Inhibitor

Example courtesy of Bill Welsh

Structure-Based Drug Design

Ligand-based drug design:

- Given an protein structure, and/or its binding site, and/or its active ligand (possibly bound to protein), find a new molecule that changes the protein's activity



Example courtesy of Joe Corkery

Challenges



Scoring of chemical models

- Activity
- Toxicity
- "Druggability"
- etc.

Search of chemical space

- Add/remove/replace chemical groups
- Conformations
- etc.

Outline



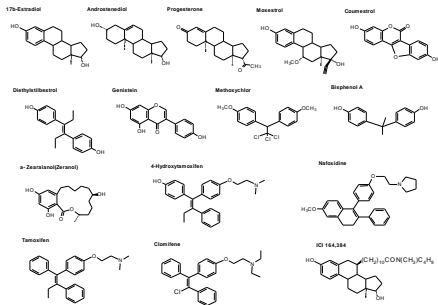
Virtual drug screening

- Ligand-based
 - § 2D structure matching
 - § 3D structure matching
 - § QSAR

De novo drug design

- Models
 - § Simulation
 - § Knowledge-based
- Construction algorithms
 - § Incremental construction
 - § Fragment-based
 - § Stochastic optimization

Ligand-Based Drug Screening



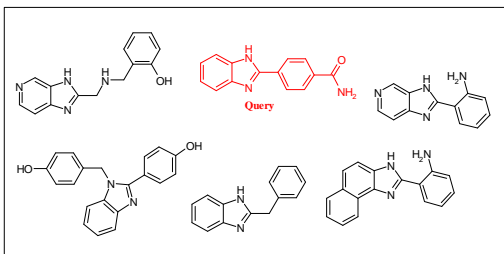
Ligand-Based Drug Screening



Strategies:

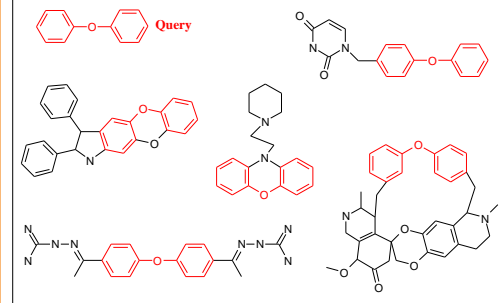
- 2D matching
- 3D matching
- Pharmacore matching
- Quantitative Structure Activity Relationships (QSAR)

2D Structure Matching



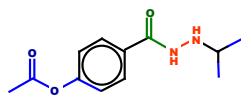
Slide courtesy of Bill Welsh

2D Substructure Matching



Slide courtesy of Bill Welsh

2D Substructure Matching

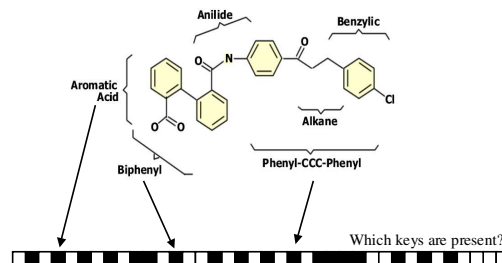


Dictionary of Keys

N-N
O-C(-N)-C
CH₃-Ar-CH₃
C-N-N
N-Ar-Ar-O
N-C-O
N-C-O
OH > 1
CH₃ > 1
N > 1
NH
...

Slide courtesy of Bill Welsh

2D Substructure Matching



Slide courtesy of Bill Welsh

2D Substructure Matching



Tanimoto coefficient:

$$T = \frac{|A \cap B|}{|A \cup B|}$$

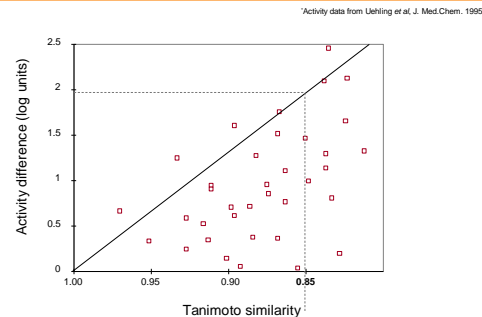
struct A: 00010100010101000101010011110100 13 bits
struct B: 00000000100101001001000011100000 8 bits

A & B: 00000000000101000001000011100000 6 bits A ∩ B
A or B: 000101001101010001101010011110100 15 bits A ∪ B

$$T = 6 / 15 = 0.4$$

Slide courtesy of Bill Welsh

2D Substructure Matching



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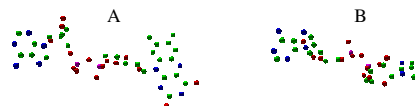
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3D Structure Matching



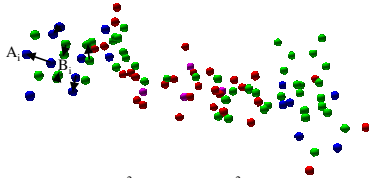
Search database of molecules for ones with similar 3D shape and chemistry



3D Structure Matching

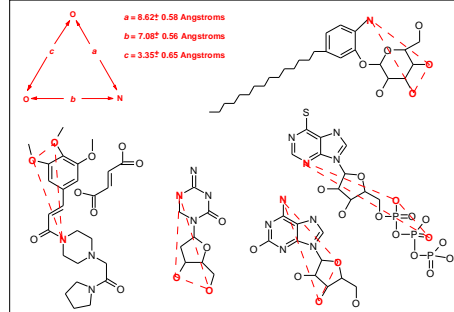


Search database of molecules for ones with similar 3D shape and chemistry



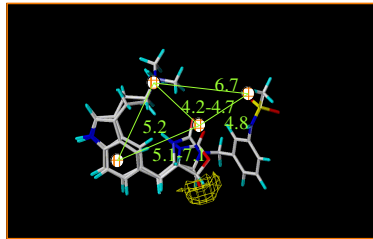
$$d(A, B) = \sum_{A_i \in A} \|A_i - B\|^2 + \sum_{B_j \in B} \|A - B_j\|^2$$

3D Substructure Matching



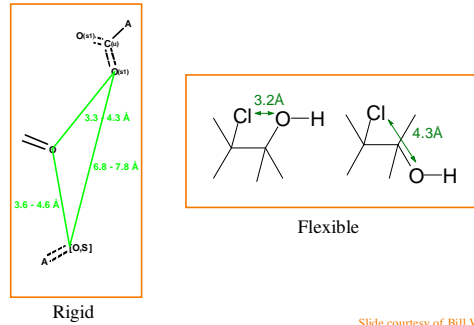
Slide courtesy of Bill Welsh

3D Substructure Matching



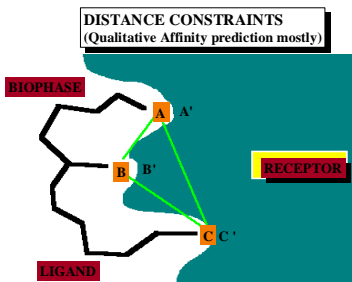
Slide courtesy of Bill Welsh

3D Substructure Matching



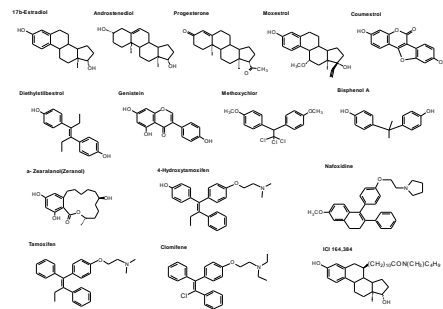
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3D Substructure Matching



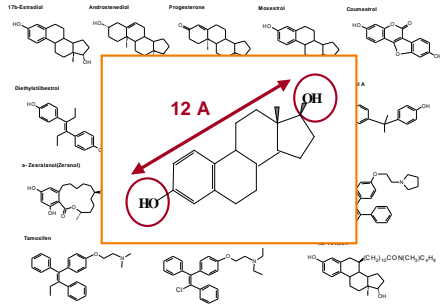
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Pharmacore Matching



Ligands for Estrogen Receptor Slide courtesy of Bill Welsh

Pharmacore Matching



Slide courtesy of Bill Welsh

Outline

Virtual drug screening

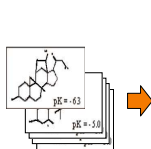
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 - ∅ QSAR ←

De novo drug design

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QSAR

Learn model for activity as function of descriptors (properties) computed from molecules

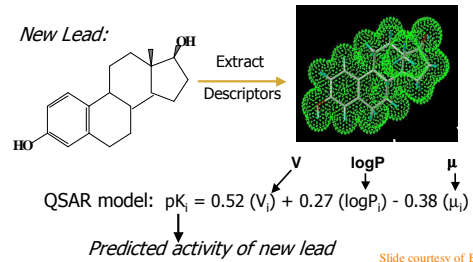


Compound	Activity (pK _i) Y [*]	Descriptors (X)		
		Mol. Vol. (Å ³)	LogP	Dipole Mom (μ)
1	2.34	420	2.8	0.97
2	1.89	332	4.6	2.23
3	0.23	198	-0.3	3.36
4	3.67	467	3.7	0.45
5	2.55	359	-1.5	1.77
etc.	etc.	etc.	etc.	etc.

Slide courtesy of Bill Welsh

QSAR

Use model to predict activities for new leads from their descriptors



Slide courtesy of Bill Welsh

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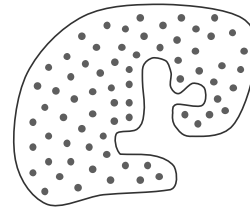
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De Novo Drug Design

General Strategy:

- ∅ Given a protein structure
- Build model of binding site
- Construct molecule that fits model

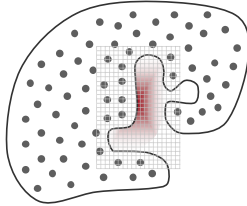


De Novo Drug Design



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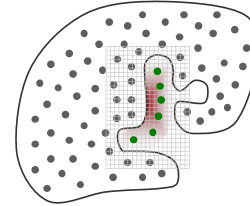


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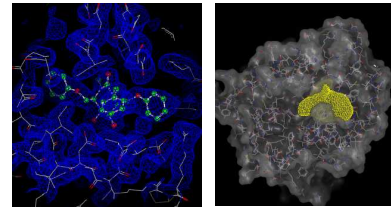
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Binding Site Models



Example courtesy of Joe Corkery

Binding Site Models

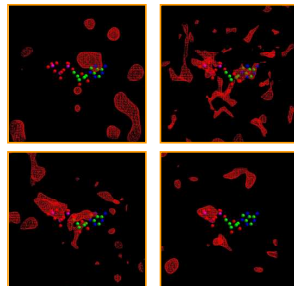


Simulation

- e.g., GRID

Knowledge-based

- e.g., X-SITE



Predicted
Binding Site
Model for
Ikp8-1-H-ATP-1_
using GRID
[Goodford85]

Outline



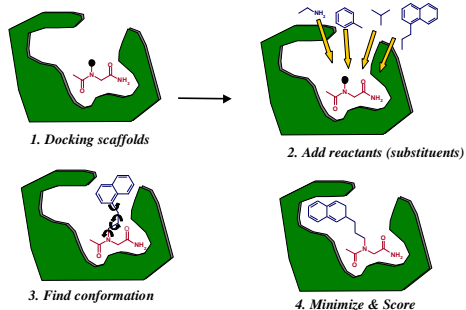
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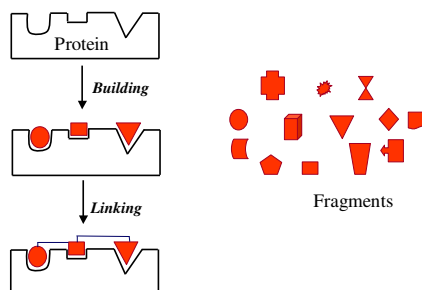
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Incremental Construction



Slide courtesy of Bill Welsh

Fragment-Based Methods



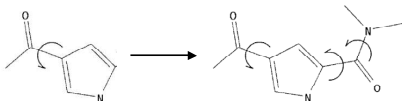
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Stochastic Optimization



Monte Carlo search of chemical space:

- Start from initial drug
- Make random state changes (add/delete/move chemical group)
- Accept up-hill moves with probability dictated by "temperature"
- Reduce temperature after each move
- Stop after temperature gets very small



Summary



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Discussion



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