Medicinal Chemistry/ CHEM 458/658

Chapter 4- Computer-Aided Drug Design

Bela Torok

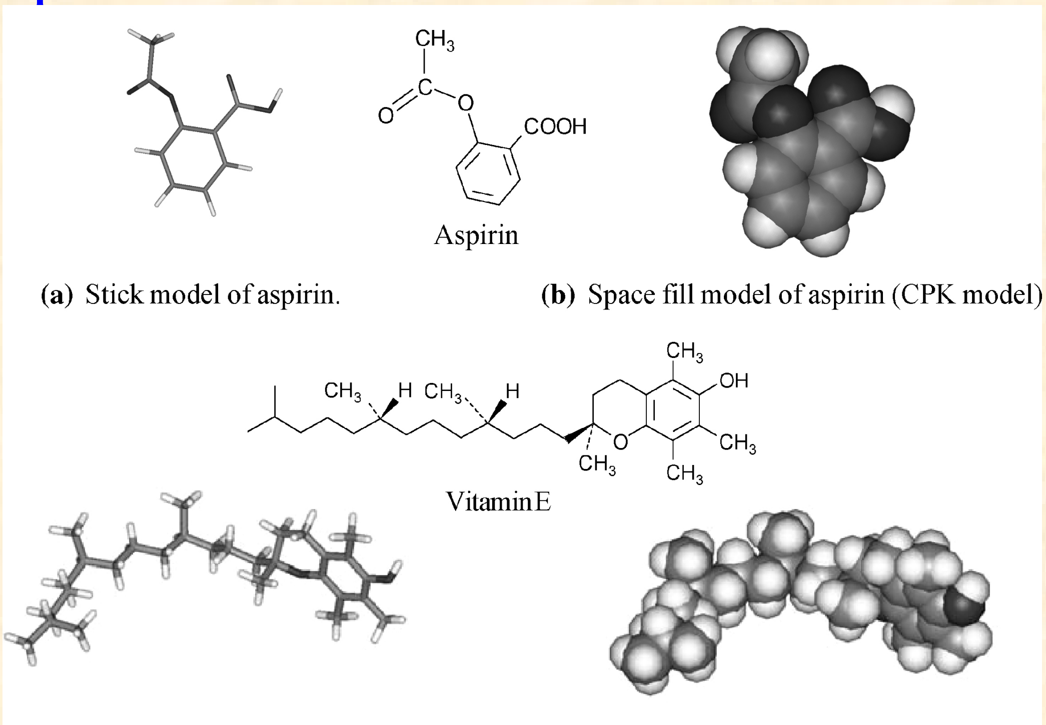
Department of Chemistry

University of Massachusetts Boston

Boston, MA

Computer Aided Drug Design - Introduction

- Development of computers
  - hardware
  - algorithms – softwares
  - computation chemists
  - representation



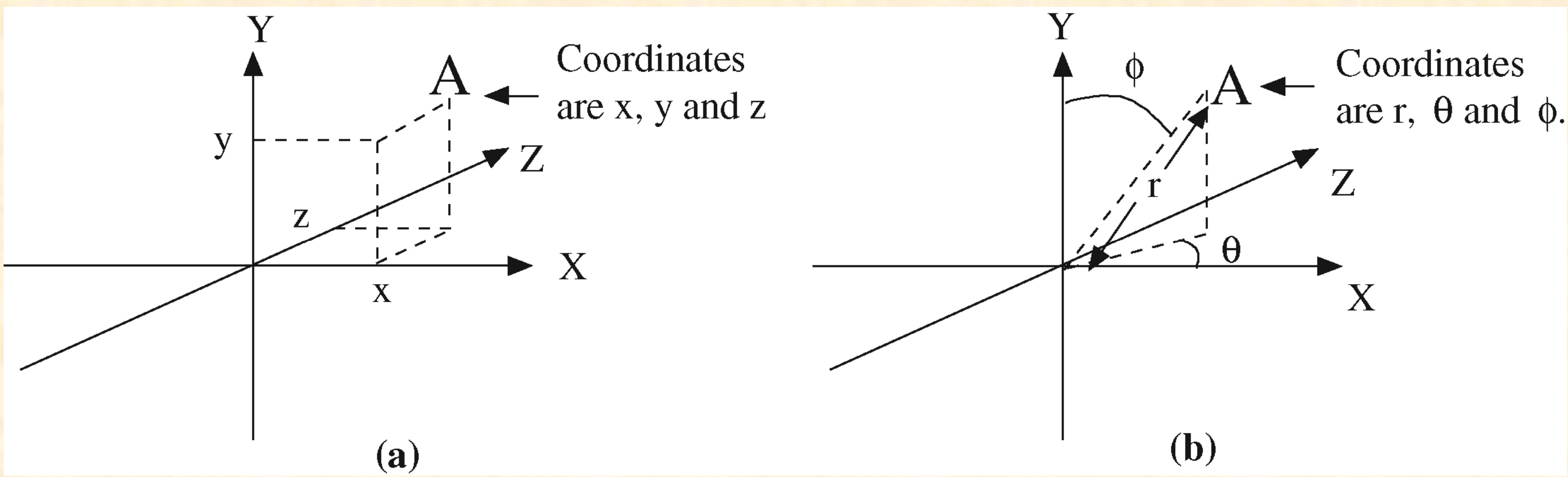
(a) Stick model of aspirin. (b) Space fill model of aspirin (CPK model)

(c) Stick model of Vitamin E. (d) Space fill model of vitamin E.

Computer Aided Drug Design - Introduction

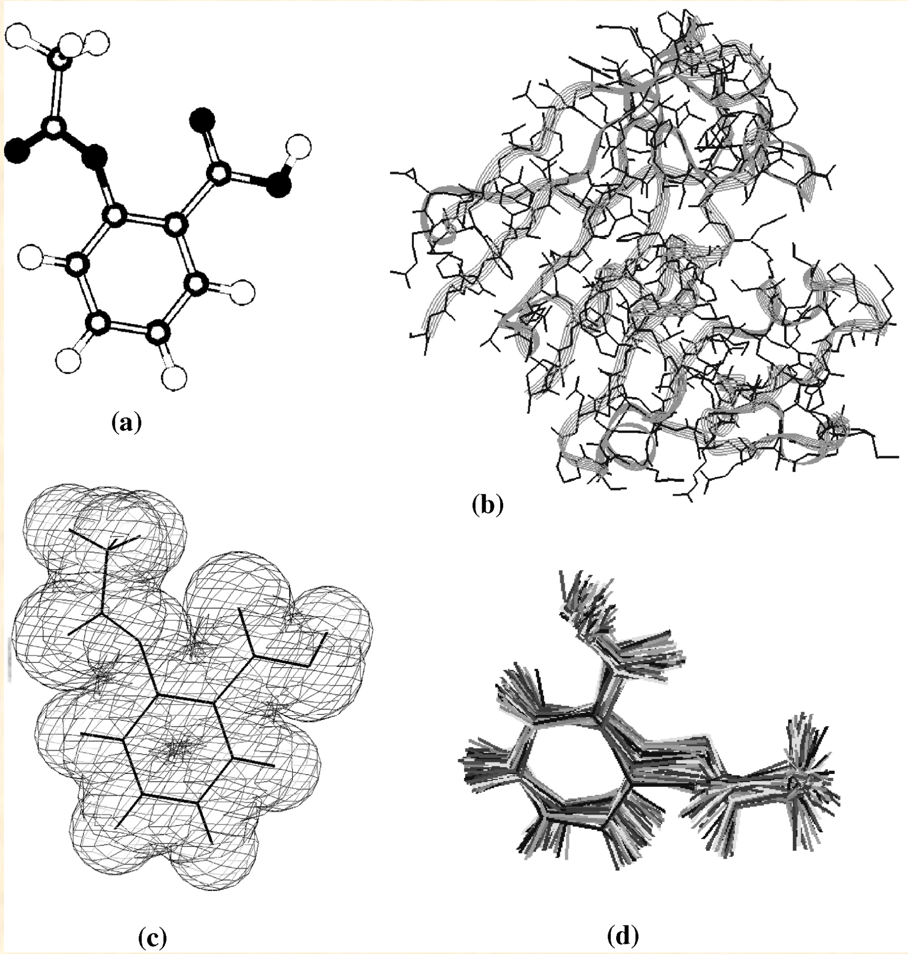
- Models

- Molecular modelling methods
  - Molecular or quantum mechanics
  - Semiempirical vs ab initio methods
  - Cartesian and polar coordinates



Computer Aided Drug Design - Introduction

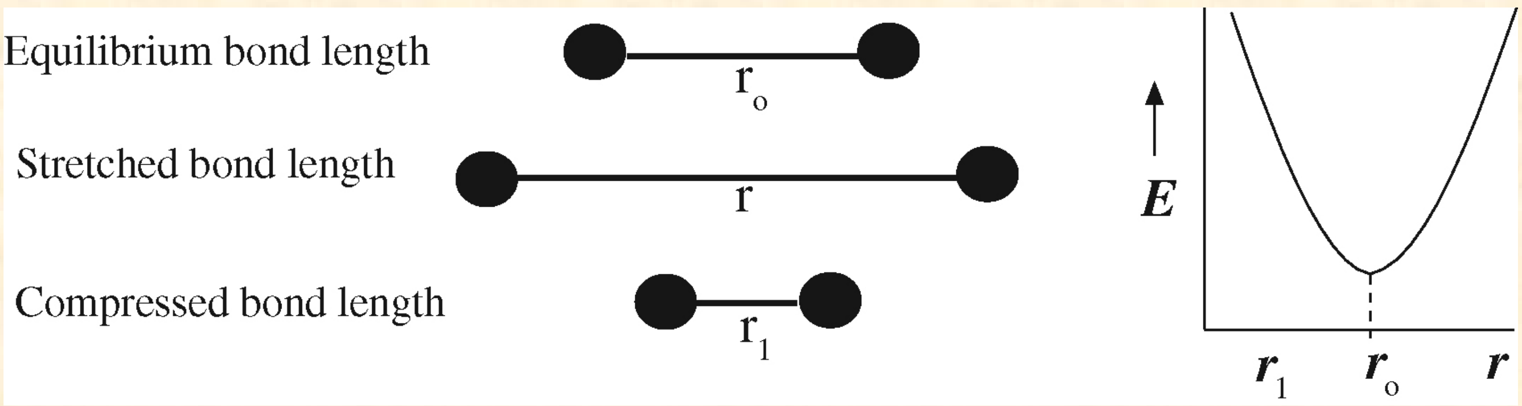
- Computer graphics
  - space fill, CPK (Corey-Pauling-Koulton), stick, stick and ball, mesh, ribbon, surface, molecular dinamics etc.



Molecular Mechanics

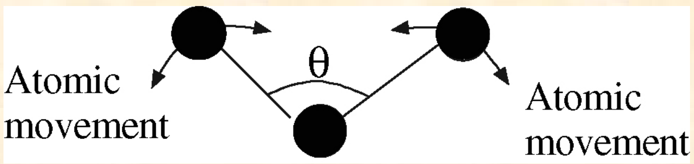
- Basis: $E_{total} = \Sigma$ attractive + repulsive forces

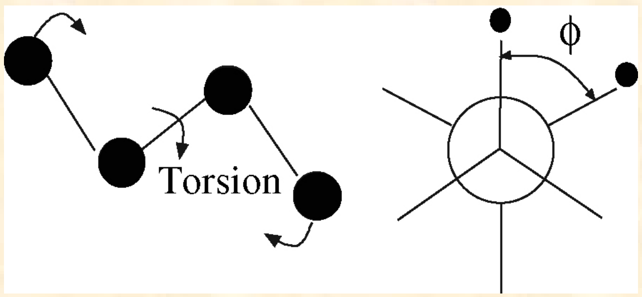
  - mechanical method – atoms are “balls” with respective atomic masses

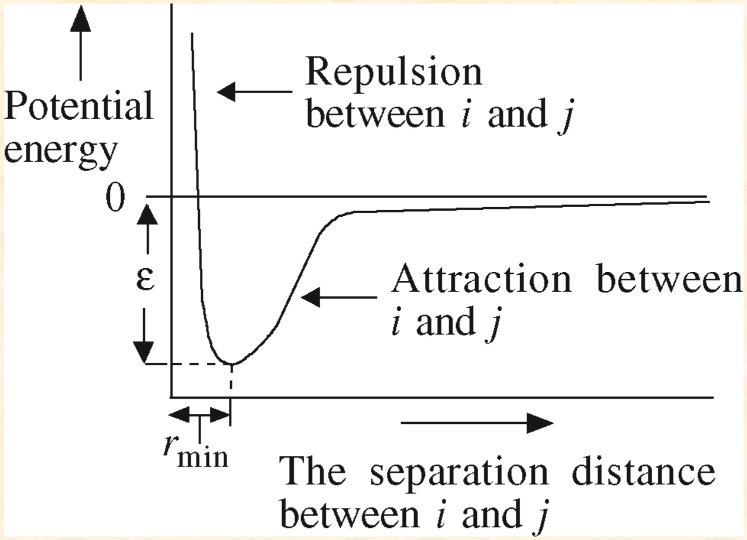


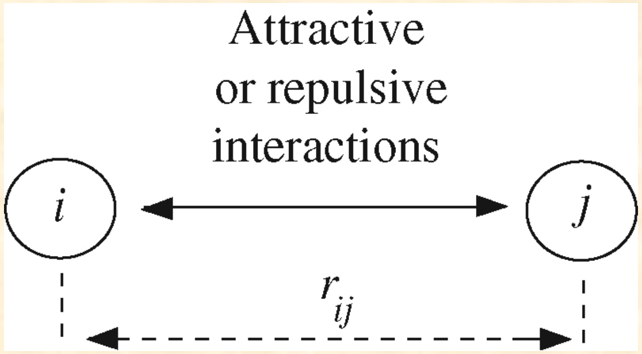
Molecular Mechanics

- $E_{total} = \Sigma\, E_{stretching} + \Sigma\, E_{bend} + \Sigma E_{torsion} + \Sigma E_{vdW} + \Sigma E_{coulombic}$





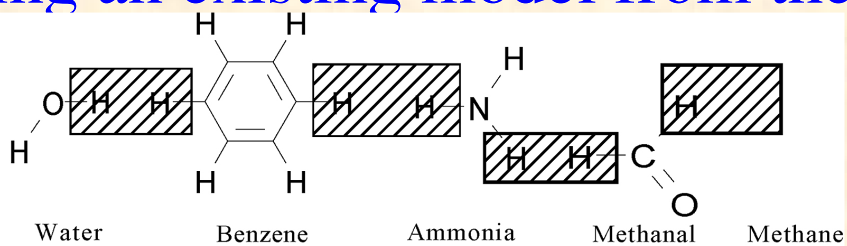




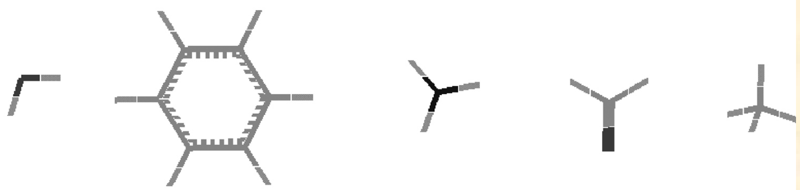
Molecular Mechanics

- Creating a molecular model using molecular mechanics
  - Joining fragments from program database
  - Prepare 2D structure and convert it to 3D structure
  - Converting an existing model from the database

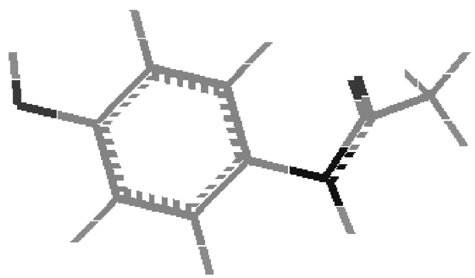
Step 1: the selection of the structure fragments from the data base of the INSIGHT II program. The molecule with the relevant functional group and/or structure is selected



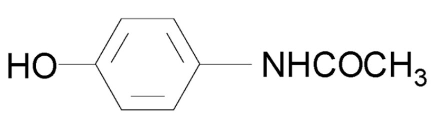
The INSIGHT II models of these structures

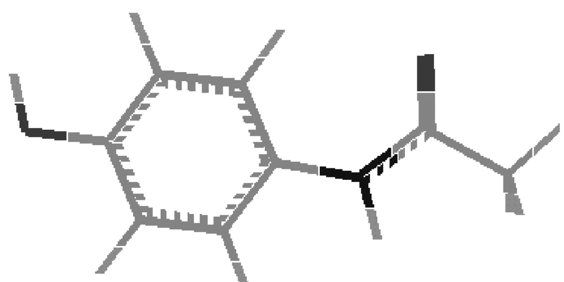


Step 2: the fragments are linked together. Fragments are joined to each other by removing hydrogen atoms (see shaded boxes in step 1) at the points at which the fragments are linked



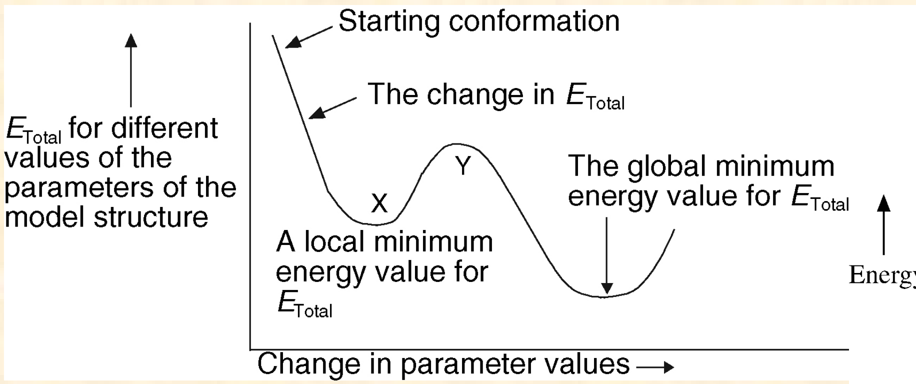
Step 3: the force field of the model is minimised to give the final structure

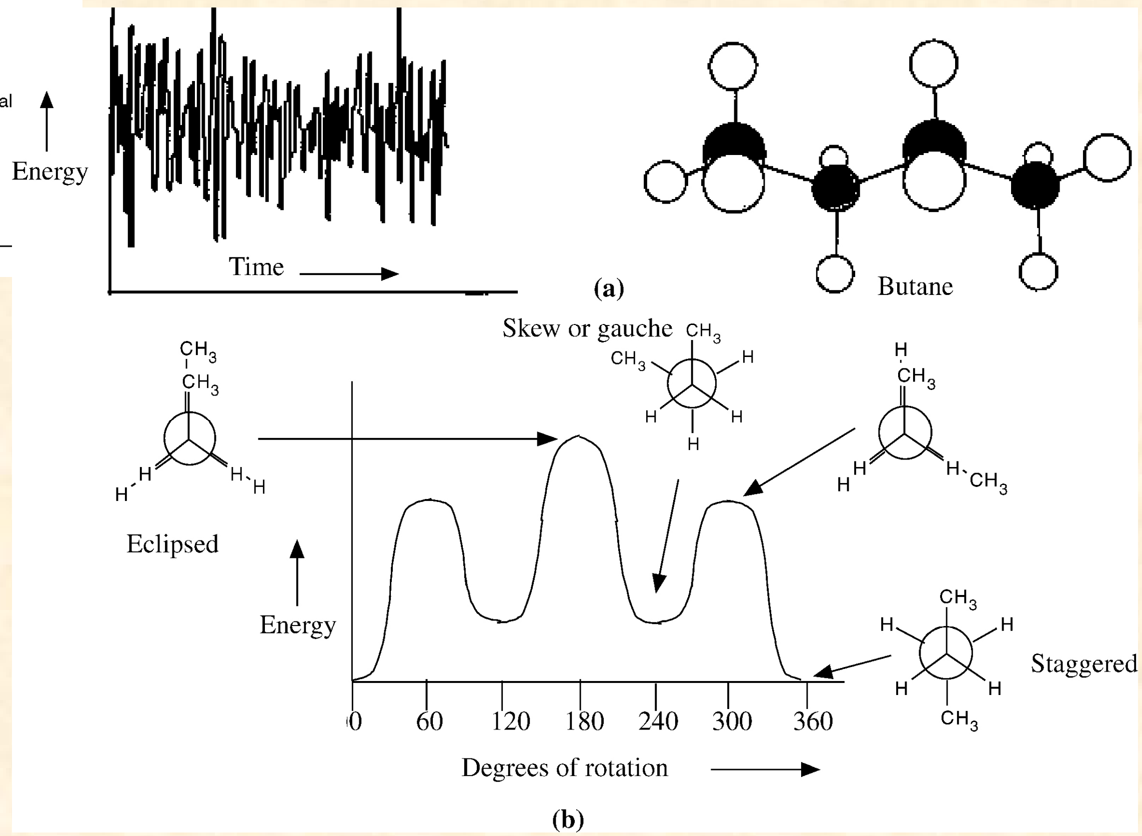




Molecular Dynamics

- Creating a dynamic molecular model
  - atomic coordinates (twist, bend, stretch etc.)
  - conformational analysis





Quantum Mechanics

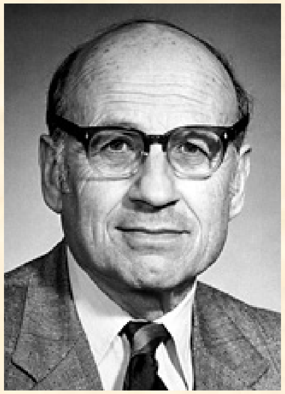
- Schrodinger equation, Born-Oppenheimer approximation

  - simplification – Hartree-Fock approximation

    – Density Funtional Theory

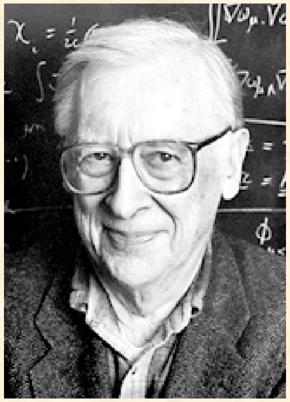
Practice – Gaussian 03 (or 98) *ab initio* methods

– Gamess



Walter Kohn

"for his development of
the density-functional theory"



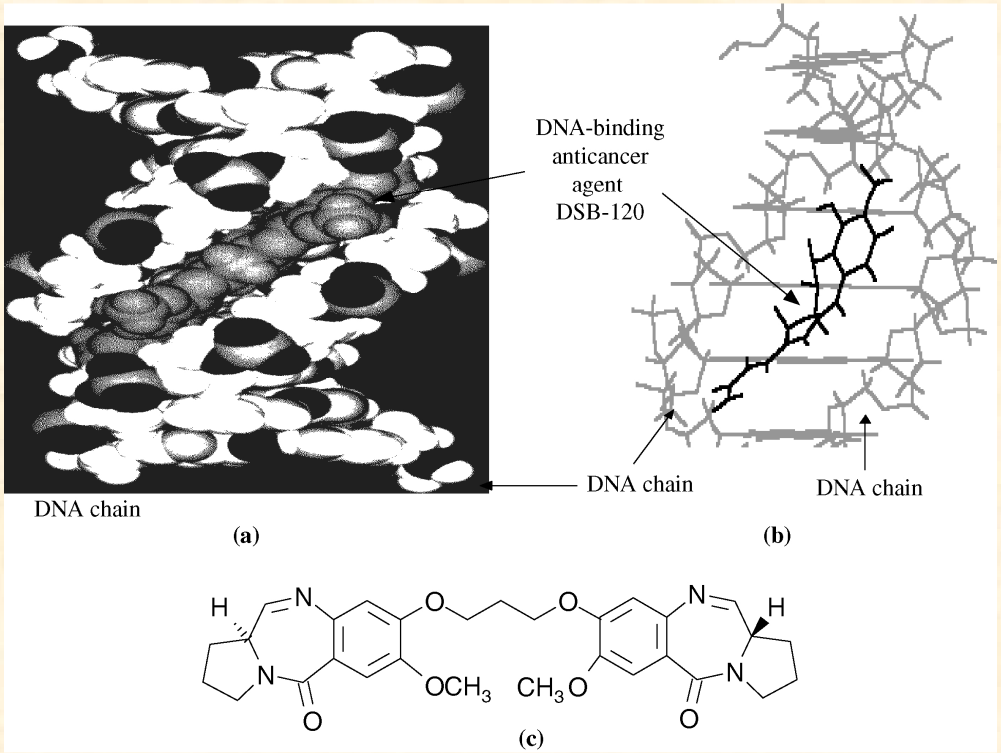
John A. Pople

"for his development of
computational methods in quantum chemistry"

The Nobel Prize in Chemistry 1998

Docking

- Produce and investigate the complex of large biomolecule (host) and the drug (or candidate) (ligand)



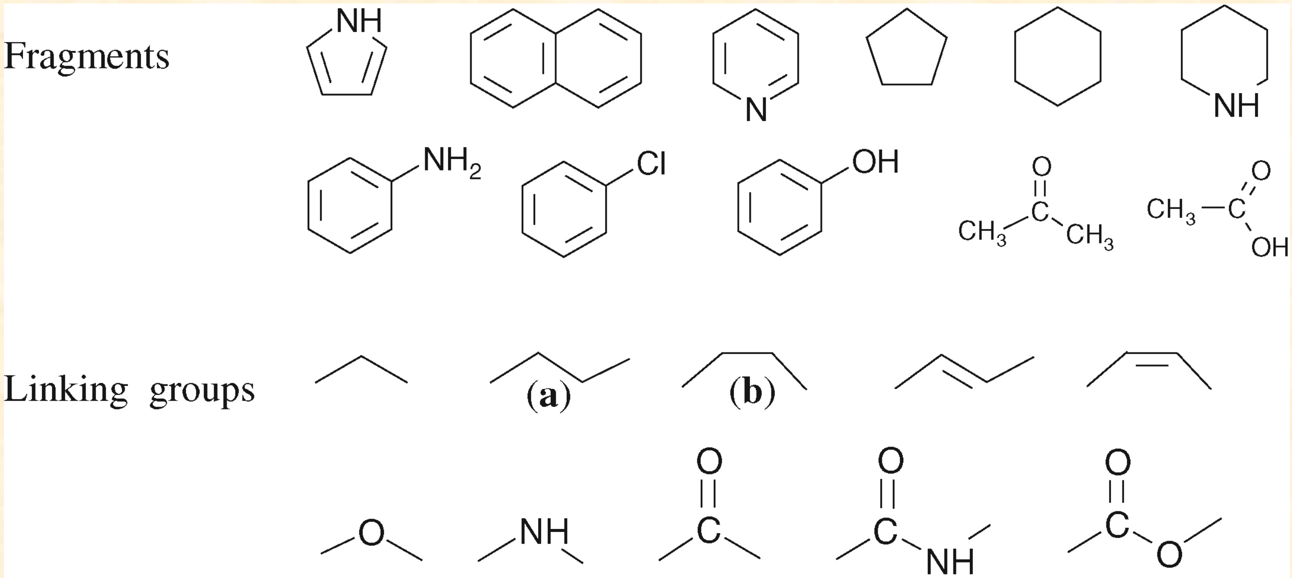
- $E_{\text{binding}} = E_{\text{target}} + E_{\text{ligand}} - E_{\text{target-ligand}}$

Global $E_{\min} \rightleftarrows$ Bioactive conformer

Docking

- De novo design

Using docking programs to design <u>new</u> lead structures



The template method

The component fragment method

Docking

- A case study

  Inhibition of FBPase (Kimberly Stieglitz)

  Start: - build and optimize the drug candidate

  ChemDraw and import to Gaussian

  or get crystal structure (CCD)

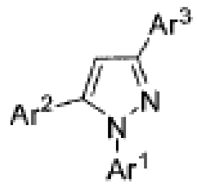
  - get protein (enzyme or receptor) structure

  PDB

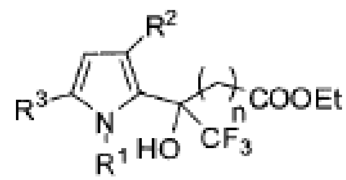
Docking

- A case study

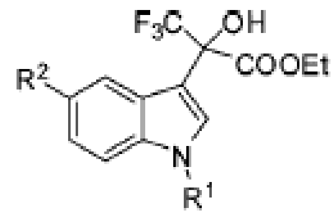
  Inhibition of FBPase - list of compounds



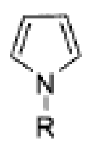
	Ar1	Ar2	Ar3
1	3-CF_3Ph	Ph	Ph
2	3-CF_3Ph	4-FPh	4-FPh
3	Ph	4-FPh	4-FPh
4	4-O_2NPh	Ph	Ph



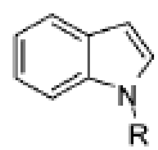
	R1	R2	R3	n
5	H	H	H	1
6	CH_3	H	H	1
7	H	CH_3	CH_3	1
8	H	H	H	0



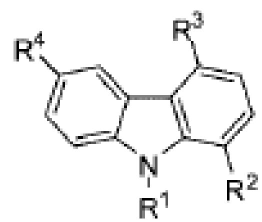
	R1	R2
9	CH_3	H
10	H	5-I
11	H	CH_3



	R
12	Ph-SO_2-
13	4-MePh-SO_2-
14	2-MePh-SO_2-
15	4-MeOPh-SO_2-
16	4-O_2NPh-SO_2-



	R
17	Ph-SO_2-
18	4-MeOPh-SO_2-
19	4-O_2NPh-SO_2-
20	β-naphthyl-SO_2-
21	4-CF_3Ph-CO-
22	4-FPh-CO-
23	4-O_2NPh-CO-



	R1	R2	R3	R4
24	H	H	H	H_3COOC-
25	H	CH_3	CH_3	H_3CO-
26	4-MeOPh-SO_2-	H	H	H
27	4-O_2NPh-SO_2-	H	H	H
28	β-naphthyl-SO_2-	H	H	H

Schematic representation of the inhibitor candidates used in this study.

Docking

- A case study

  Inhibition of FBPase - protein structure

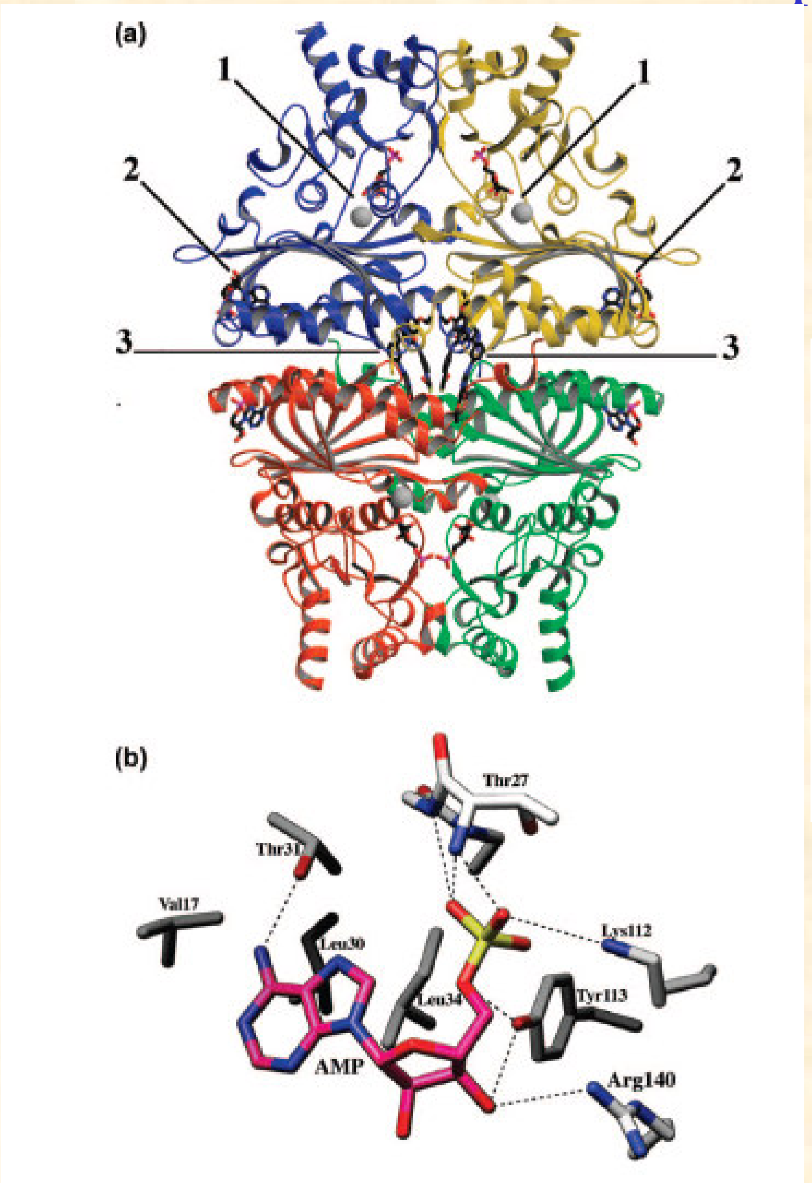


Figure 1. (a) The FBPase is a homotetramer. The three potential targets are shown: (1) the active site of FBPase, (2) the allosteric binding site of AMP, (3) the tetrameric allosteric inhibitor site. PDB coordinates 1KZ8[13,14] were used. The figure was drawn using POVScript+.[37] (b) A closeup of the AMP binding pocket is shown. The three programs used are Dock6, Autodock4, and Surflex and were tested using the crystallographic ligand AMP moved out of the binding pocket (as explained in results section). This figure was drawn using POV-Script+.[37] The three conformers of AMP were superimposed with a rmsd of <2.0 Å[5] from actual AMP atoms in the crystallographic structure.

Docking

- A case study

  Inhibition of FBPase - docking

Table 1. Results of Docking Studies and the Experimental IC_{50} Data of the Molecules Utilized in the Inhibition of FBPase

entry	inhibitor	Dock6,energy score	Autodock, estimated inhibition constant, K_i	Surflex, energy score	X-score		IC_{50} (μM)
					K_d	final binding energy (kcal/mol)	
1	**21**	−16.96	3.99×10^{-7}	2.84	5.70	−7.78	3.09
2	**7**	−16.05	1.14×10^{-4}	3.33	4.85	−6.62	4.81
3	**1**	−18.38	1.69×10^{-7}	3.61	6.26	−8.54	6.04
4	**9**	−17.33	4.11×10^{-7}	3.39	5.16	−7.03	11.86
5	**10**	−16.71	4.72×10^{-11}	2.97	5.05	−6.88	13.33
6	**5**	−14.01	7.05×10^{-5}	3.39	4.27	−5.83	25.74
7	**8**	−14.53	1.69×10^{-5}	3.30	4.91	−6.69	25.74
8	**11**	−15.37	5.85×10^{-7}	3.65	4.73	−6.45	35.97
9	**6**	−15.91	7.56×10^{-5}	2.96	4.60	−6.27	41.79
10	**2**	−18.62	2.23×10^{-7}	3.11	6.17	−8.42	75.45
11	**12**	−20.59	9.72×10^{-15}	2.08	4.47	4.47	76.15
12	**16**	−20.63	1.01×10^{-3}	1.67	4.55	−6.20	109.03
13	**17**	−21.73	8.15×10^{-14}	2.61	5.22	−7.12	119.26
14	**22**	−19.83	1.98×10^{-7}	2.81	5.94	−8.10	129.43
15	**3**	−19.00	9.43×10^{-8}	2.10	6.21	−8.47	150.60
16	**27**	−23.73	3.12×10^{-5}	2.81	5.19	−7.08	176.98
17	**19**	−25.66	5.68×10^{-4}	2.27	4.95	−6.75	184.95
18	**15**	−21.35	6.65×10^{-6}	2.73	4.39	−5.98	245.60
19	**26**	−18.53	7.93×10^{-7}	2.85	5.52	−7.53	>250
20	**14**	−20.36	4.93×10^{-6}	2.71	4.90	−6.68	>250
21	**18**	−22.22	1.36×10^{-7}	2.74	4.56	−6.22	>300
22	**23**	−17.79	9.60×10^{-5}	2.95	4.78	−6.52	>300
23	**4**	−12.94	2.20×10^{-7}	2.73	5.08	−6.92	>300
24	**20**	−25.66	5.68×10^{-4}	2.27	4.94	−6.75	>300
25	**28**	−22.92	6.29×10^{-8}	2.37	5.76	−7.82	>300
26	**24**	−19.02	3.01×10^{-8}	3.26	5.67	−7.73	>300
27	**25**	−16.40	2.76×10^{-7}	3.39	5.79	−7.90	>300
28	**13**	−22.76	3.31×10^{-6}	2.93	4.51	−6.16	>300

Docking

- A case study

  Inhibition of FBPase - enzyme inhibition assays

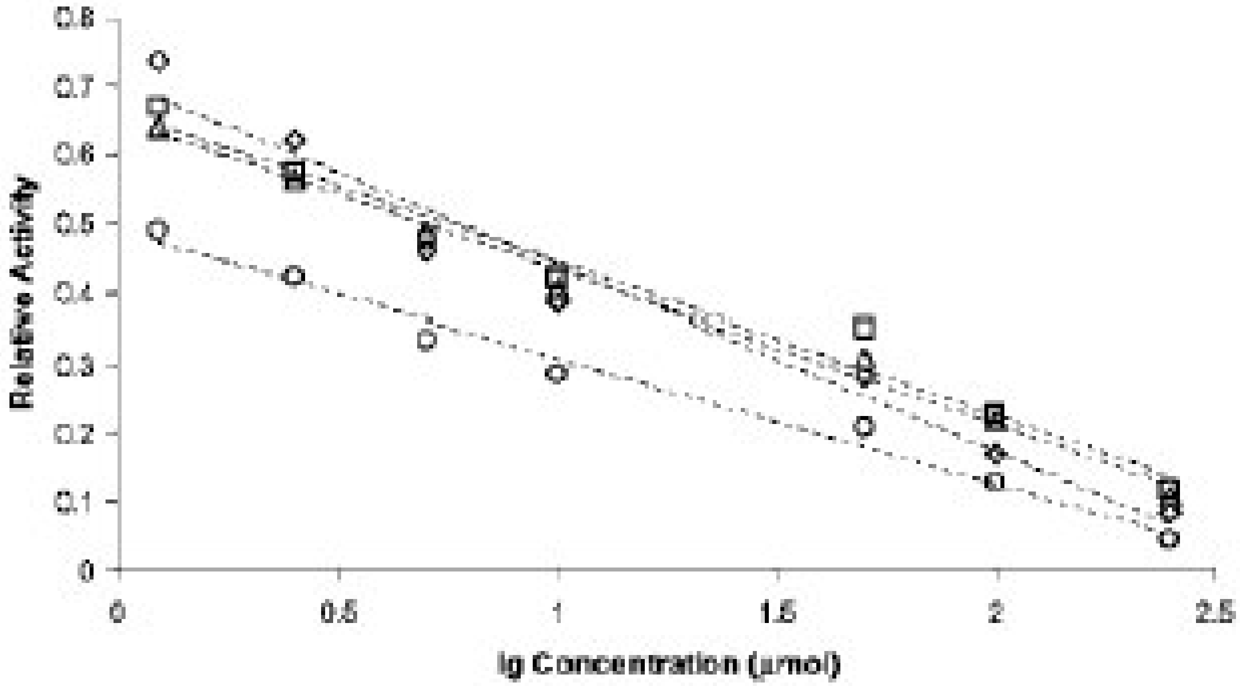


Figure 3. Effect of inhibitor concentration on the activity of FBPase for IC_{50} determination of the three inhibitor lead compounds and the natural inhibitor AMP: (◇) AMP; (△) 1; (□) 7; (○) 21.

Docking

- A case study
  Inhibition of FBPase - visualization

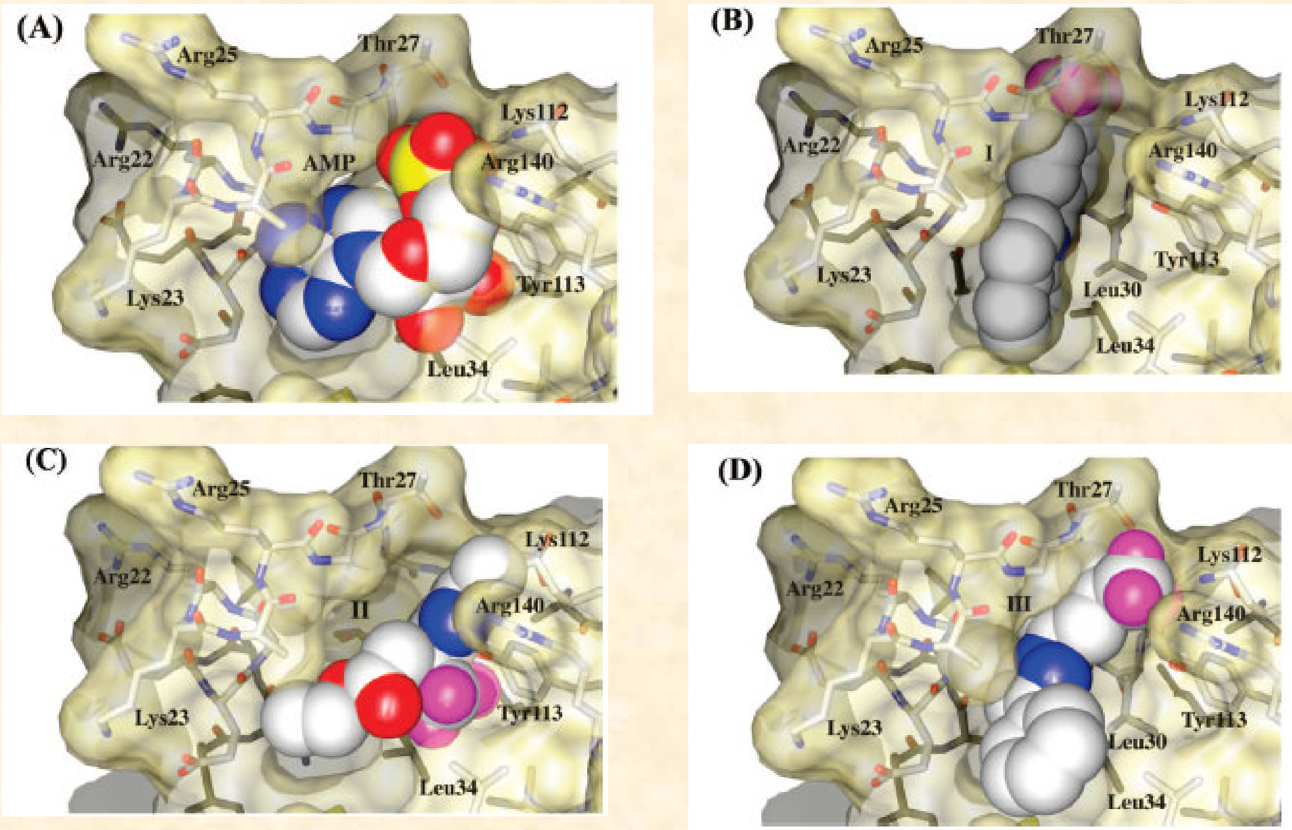


Figure 4. Comparison of AMP (A) in the AMP binding pocket of FBPase, PDB code 1FTA, with the docking results of the three best actual inhibitors (B) **21**; (C) **7**, and (D) **1** from Table 1: carbon, gray; fluorine, magenta; nitrogen, blue; oxygen, red; phosphorus, yellow.

Docking

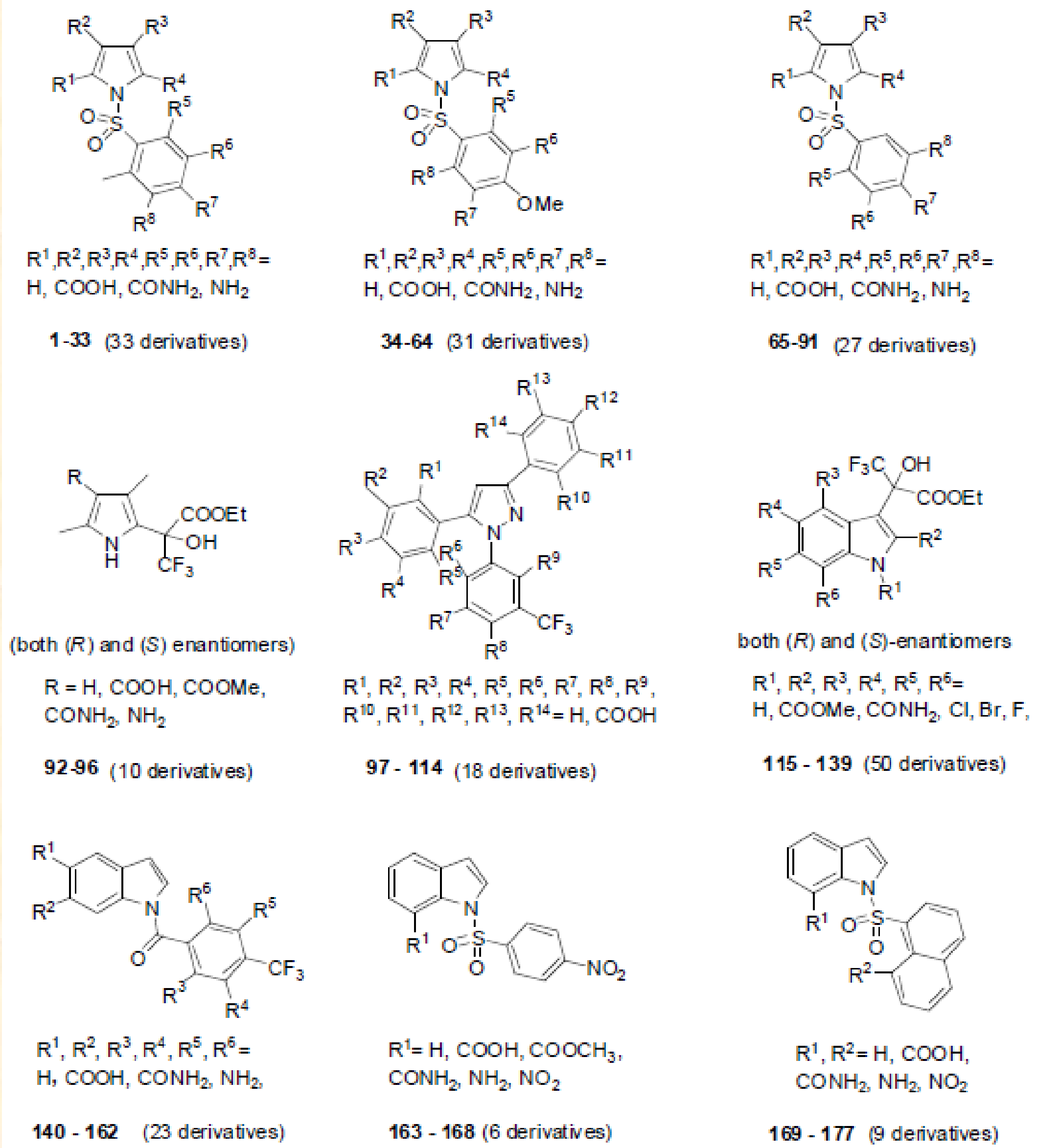


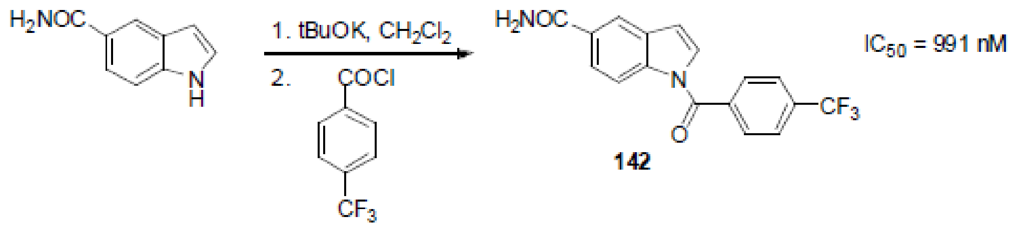
Figure 2 Schematic representation of the library of pyrrole, pyrazole and indole-based potential FBPase inhibitor candidates used in this study (for individual structures, see Supporting Information)

Docking

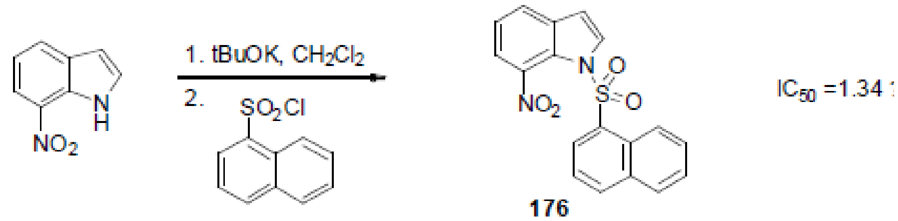
Table 1. Docking data of AMP and the 13 best inhibitor candidates

compound	Surflex 2 Energy score	Dock 6 Energy score	Autodock 4 Final Docked Energy	X-Score Energy Score
AMP	4.00	-25.66	-15.23	-23.38
142	5.33	-25.19	16.03	-23.47
(*R*)-95	5.09	-19.32	-14.26	-16.81
100	4.82	-21.85	-9.17	-22.68
106	4.70	-26.85	-15.70	-22.90
(*S*)-120	4.60	-21.54	-12.02	-16.57
147	4.27	-21.41	-11.77	-23.52
21	4.13	-35.68	-15.59	-15.43
176	4.12	-25.76	-15.36	-22.52
84E	4.02	-34.22	-18.50	-25.20
164	2.91	-33.53	-15.97	-20.26
84	4.43	-31.18	-15.25	-23.84
160	4.15	-29.48	-9.42	-16.04
152	3.47	-29.46	-9.22	-24.32

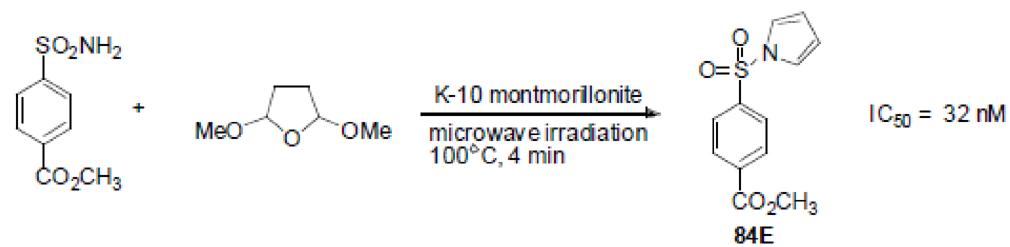
Docking



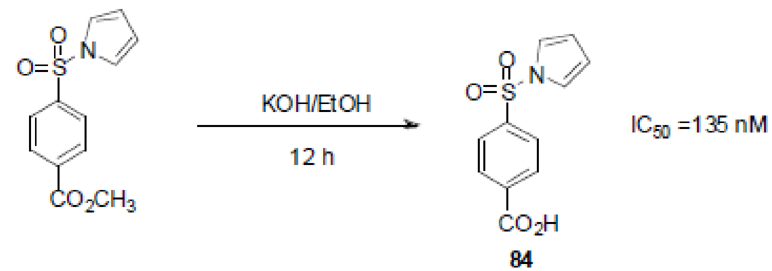
H2NOC
1. tBuOK, CH2Cl2
2. COCl
CF3
142
IC50 = 991 nM



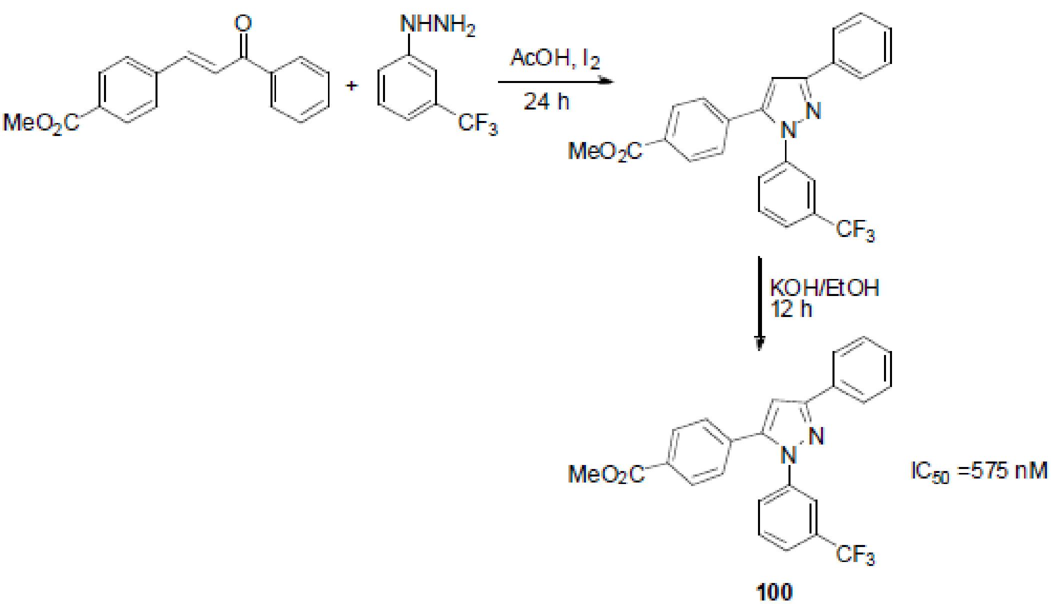
NO2
1. tBuOK, CH2Cl2
2. SO2Cl
176
IC50 =1.34



SO2NH2
CO2CH3
MeO
OMe
K-10 montmorillonite
microwave irradiation
100°C, 4 min
84E
IC50 = 32 nM



KOH/EtOH
12 h
CO2CH3
CO2H
84
IC50 =135 nM



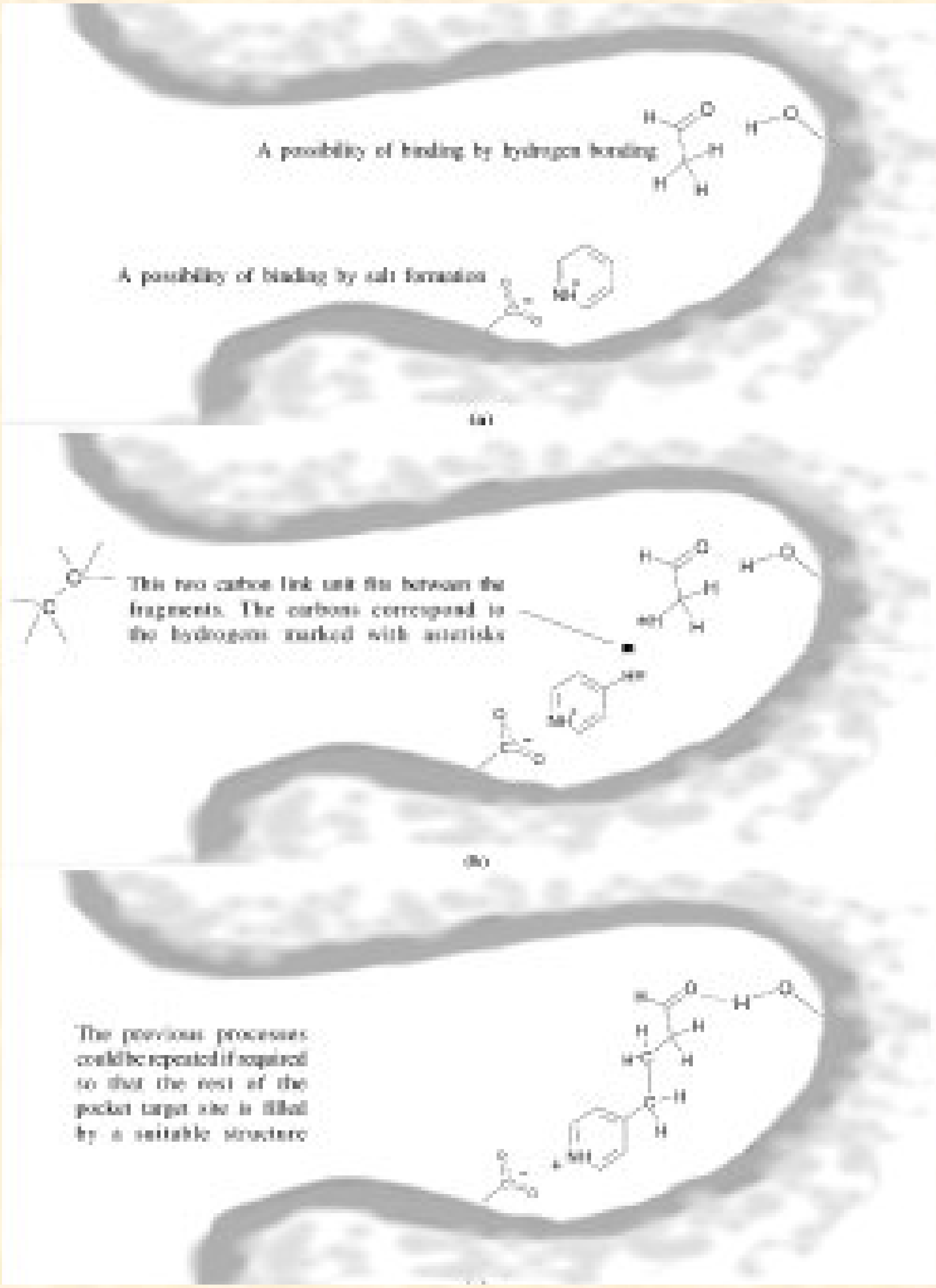
MeO2C
NHNH2
CF3
AcOH, I2
24 h
KOH/EtOH
12 h
100
IC50 =575 nM

Comparing 3D Structure by Overlays

- Binding small molecules to the active sites

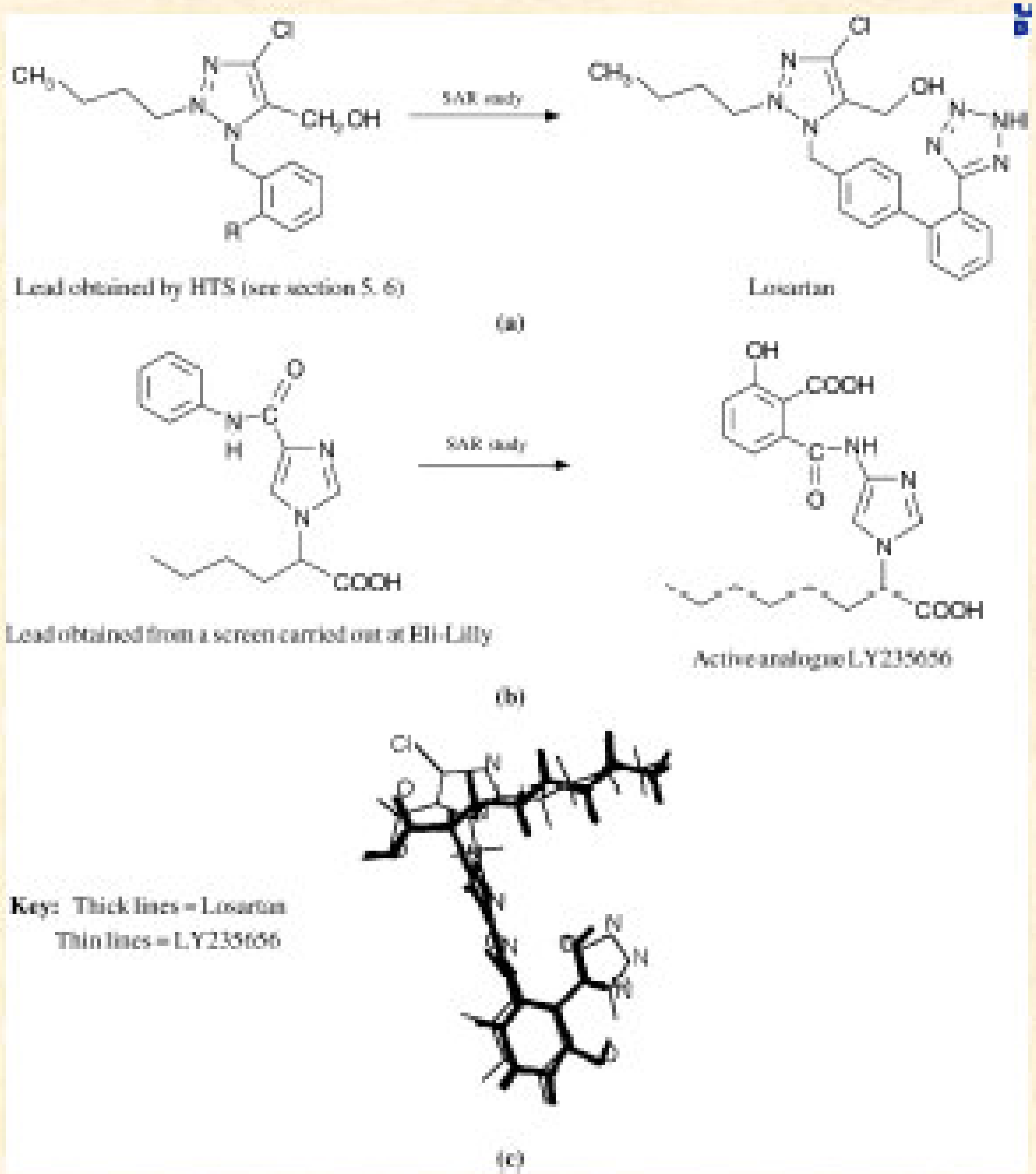
- design a linker between them

- use an active compound to design a new one



Comparing 3D Structure by Overlays

- Case study



Pharmacophores

- Pharmacophore – biologically active ligand

- a tool to search new active compounds
  structurally diverse compounds – same pharmacophores
  3D map

- HR X-ray crystallography and NMR

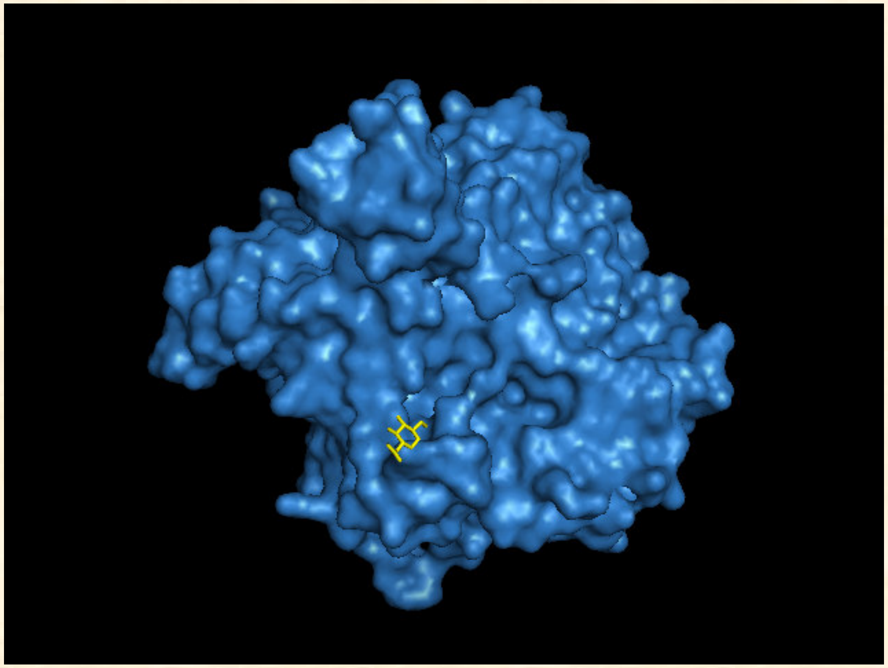
  PDB!

- Analysis of the structures of ligands
  frequently used when there is no information about the target
  analysis – 3D overlays (DISCO, HipHop)
  potential binding group – 3D map - perceived pharmacophore

Pharmacophores

A case study

Inhibition of AChE - Marianna Torok, Seema Bag



Pharmacophores

Typical pharmacophore features are:
- Hydrophobic
- Aromatic
- Hydrogen bond donor/acceptor
- Cation/anion

The features need to match different chemical groups with similar properties, in order to identify novel ligands.

Ligands receptor interactions are typically "polar positive", "polar negative" or "hydrophobic".

A well-defined pharmacophore model includes both hydrophobic volumes and hydrogen bond vectors.

Pharmacophores

Select molecules: 50 – 100 highly active molecules

Training set + test set

PHASE
Version 3.0

Prepare Ligands

Create pharmacophoric sites

Find common pharmacophore using binary decision tree

Alignment

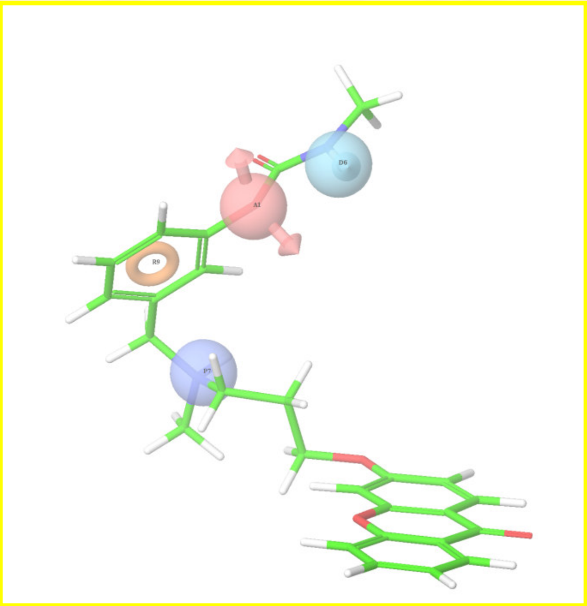
Build QSAR model

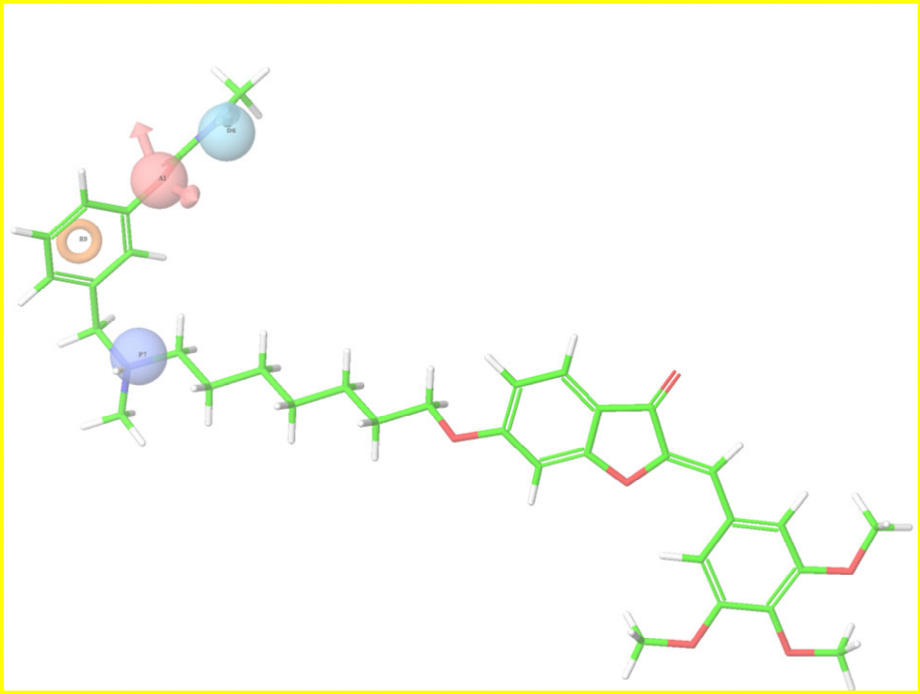
r^2 & q2 value

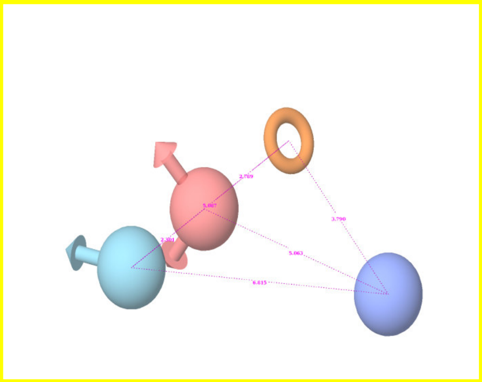
Screen/design for more potent analogs

Pharmacophores

Pharmacophoric points on active molecules

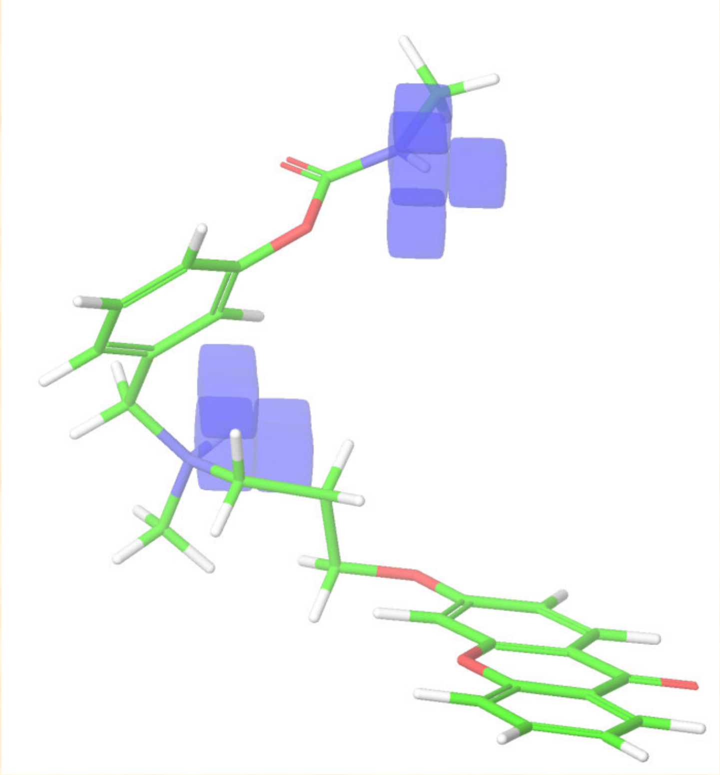




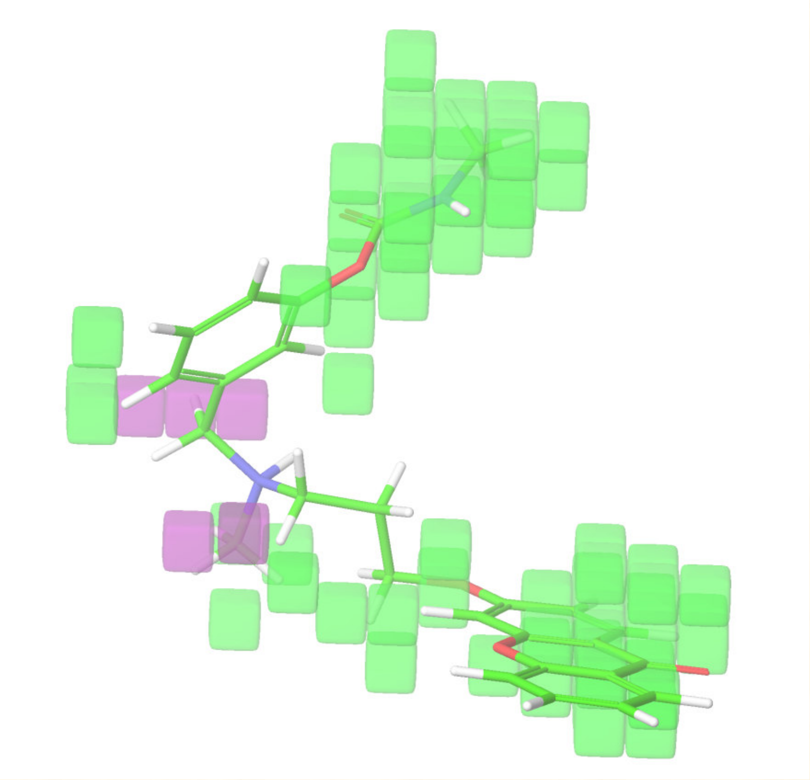


Pharmacophores

Interpretation



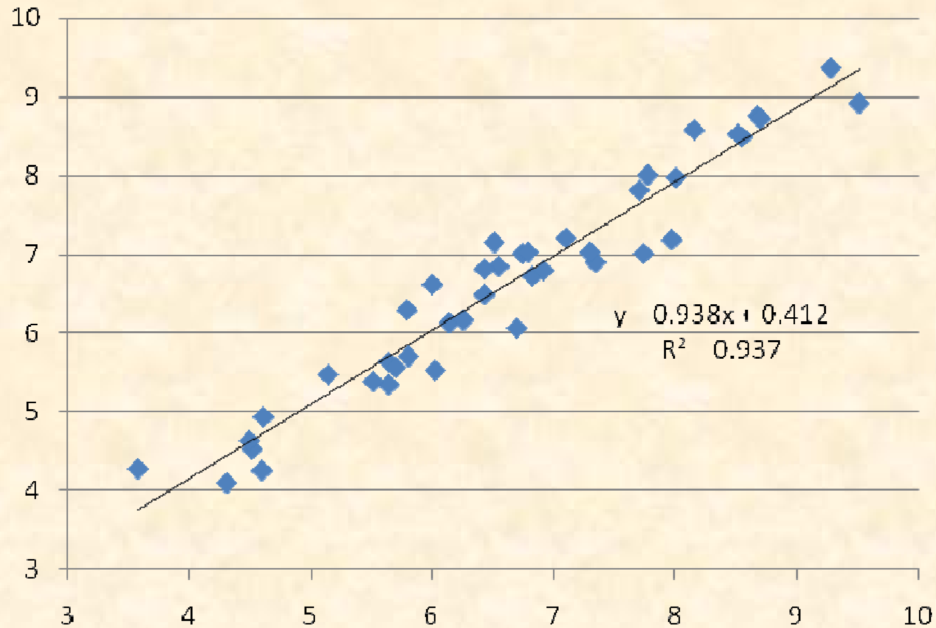
H-donor



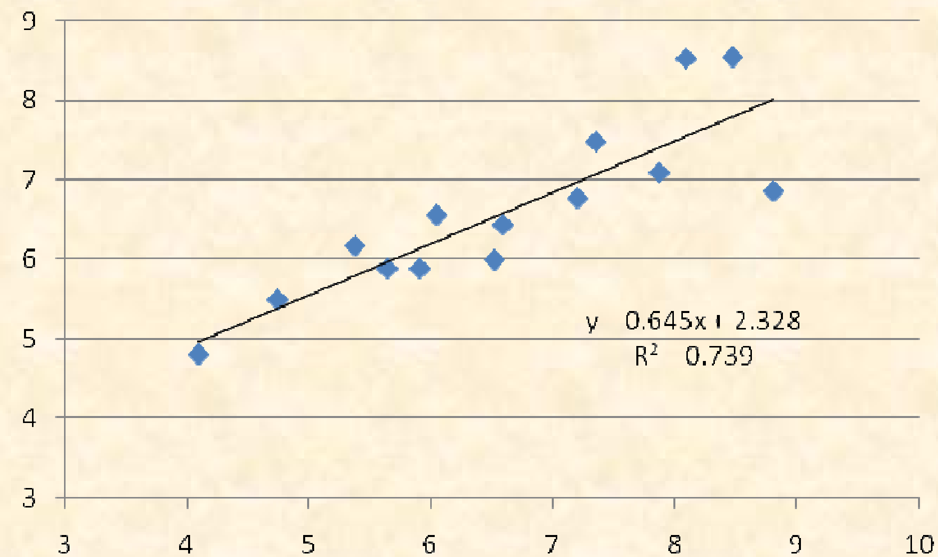
Hydrophobic

Pharmacophores

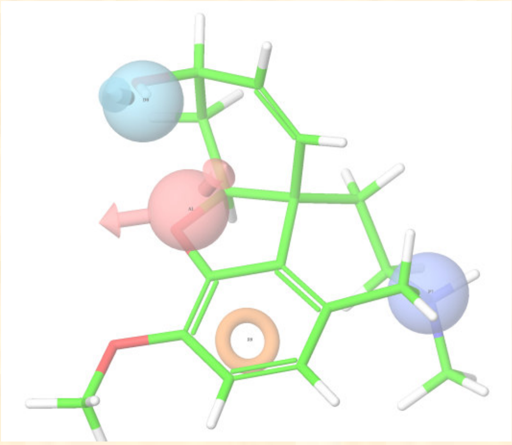
Actual vs Predicted Activity for training set of the molecules



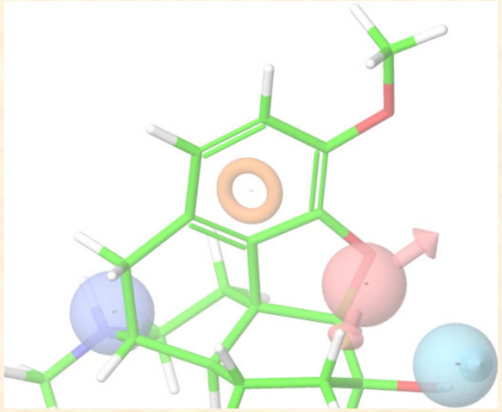
Actual vs Predicted Activity for the test set of molecules



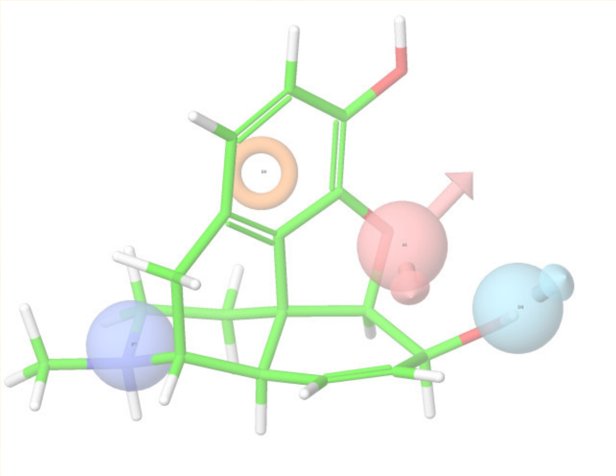
Pharmacophores



galanthamine



dihydrocodein



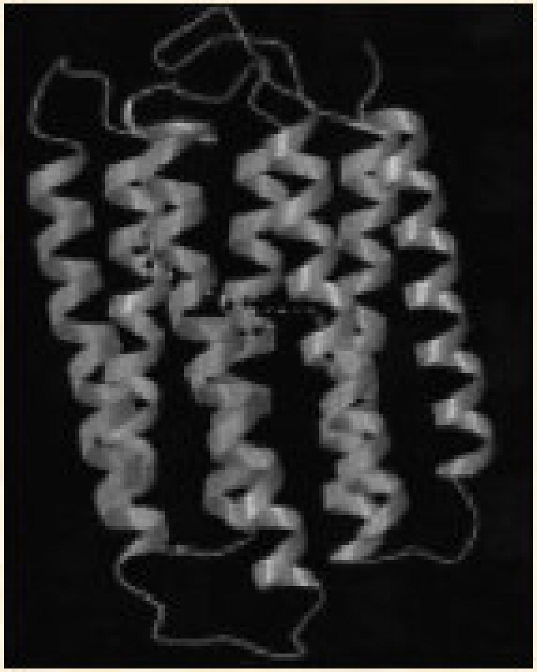
morphine

Modelling Protein Structures

- Protein structure - required

- template based approach
  template should have similar structure
  template must have an X-ray or NMR structure available
  section of template structure should match

bacteriorhodopsin

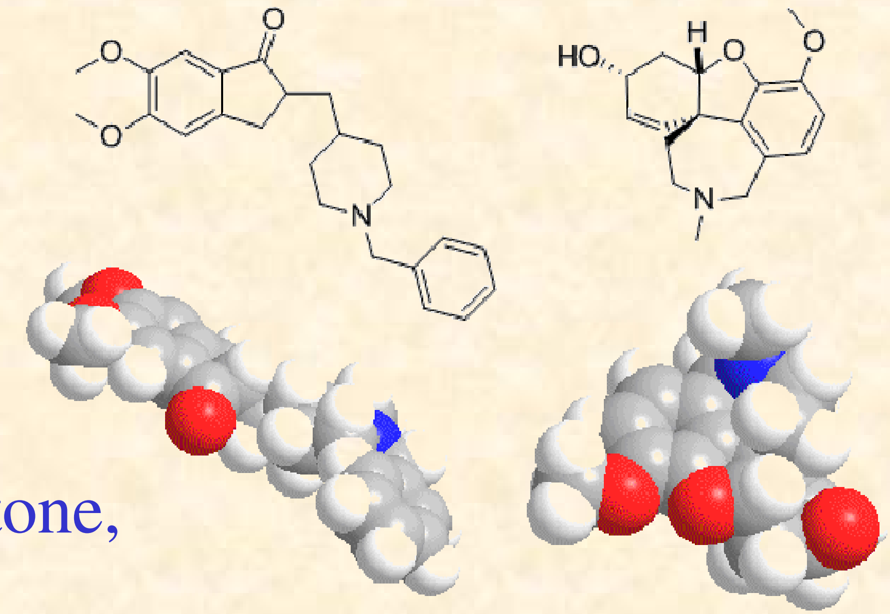


Modeling Protein Structures

Solvent Mapping (Sandor Vajda, BU)

16 solvents:
ethanol, acetaldehyde, acetonitrile, benzaldehyde, isopropanol, methanol, dimethyl ether, urea, benzene, t-butanol, isobutanol, cyclohexane, methanamine, acetamide, phenol, acetone, dimethylformamide and ethane)

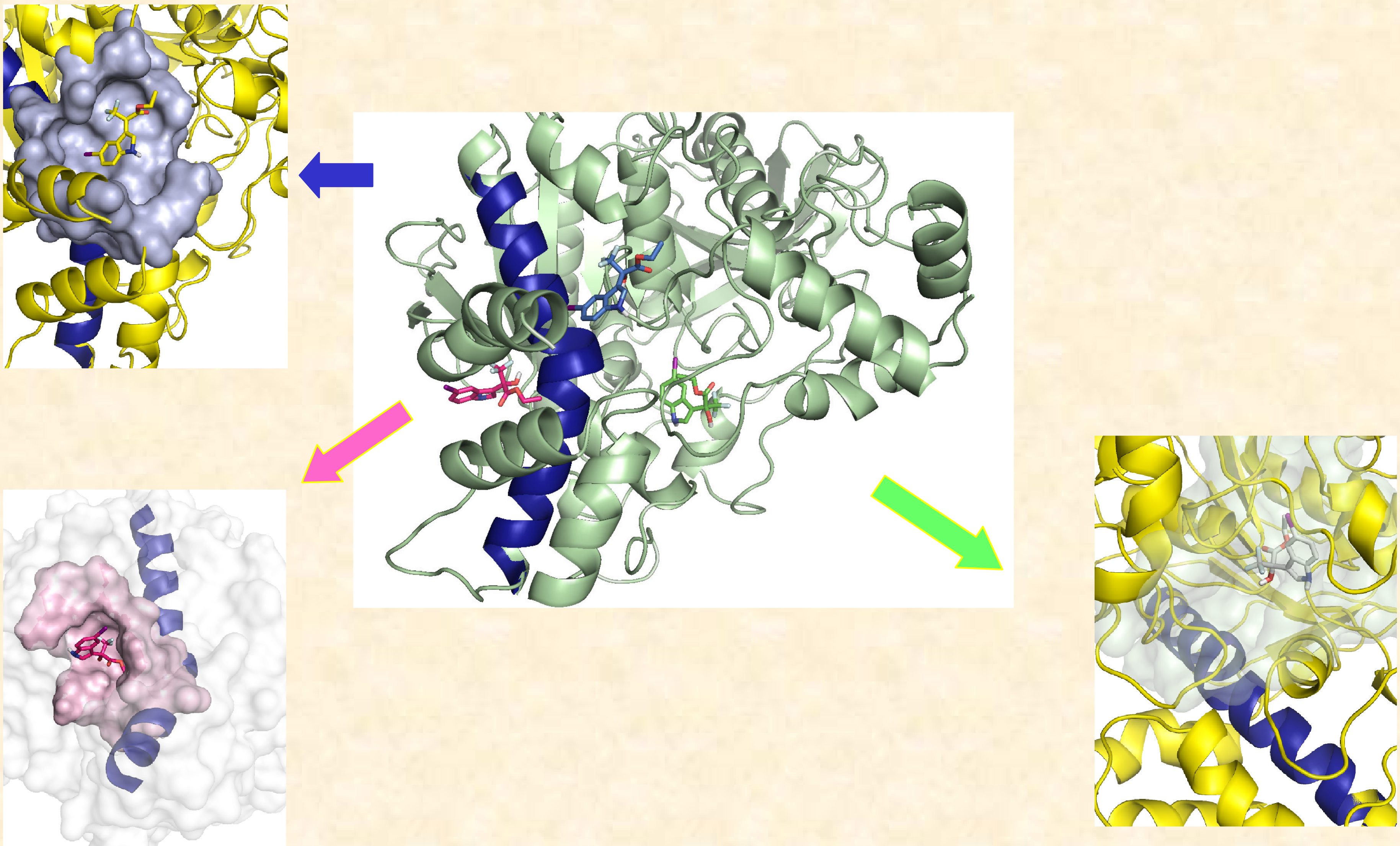
will be used in rigid-body fragment docking



donezepil
(IC_{50} = 23 nM)

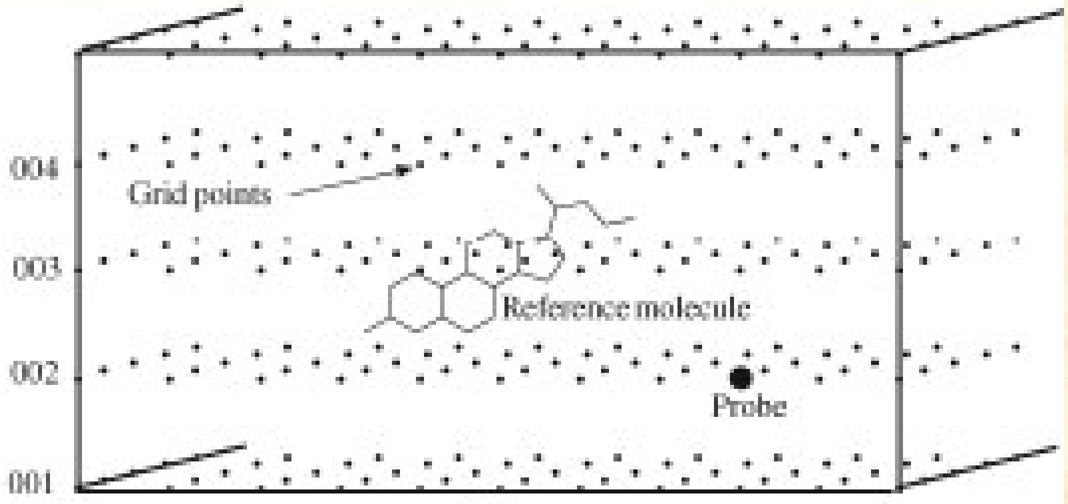
galanthamine (GAL)
(IC50 = 2.0 μM)

Modeling Protein Structures



3D QSAR

- Similar structures, common pharmacophore - same activities, different potency



(a)

Compound	Activity	Calculated grid point energies							
		S001	S002	....	S999	E001	E002	....	E999
Compound 1	a								
Compound 2	b								
Compound 3	c								
etc.	etc.								

(b)