A Journey from Natural Product Chemistry to Computational Medicinal Chemistry In the Discovery of Novel Drugs

Greetings from Zaheer

Panjwani Center for Molecular Medicine and Drug Research

International Center for Chemical Sciences
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14th May 2012, KMUP

H.E.J. RESEARCH INSTITUTE OF CHEMISTRY

(International Center for Chemical & Biological Sciences)

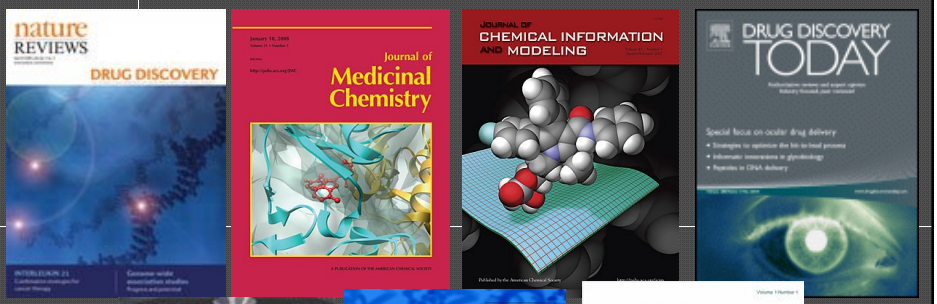
Panjawani Centre for Molecular Medicine and Drug Research

Discovery of Novel Drugs

Drug Discovery is a goal of Research, Methods and Approaches from different science areas

- Multidisciplinary area of research
  - Combinatorial chemistry
  - Bioinformatics
  - Computational-Medicinal Chemistry
  - Molecular Biology
  - Biochemistry
  - Medicine
  - Macromolecular Modeling
  - Pharmacology

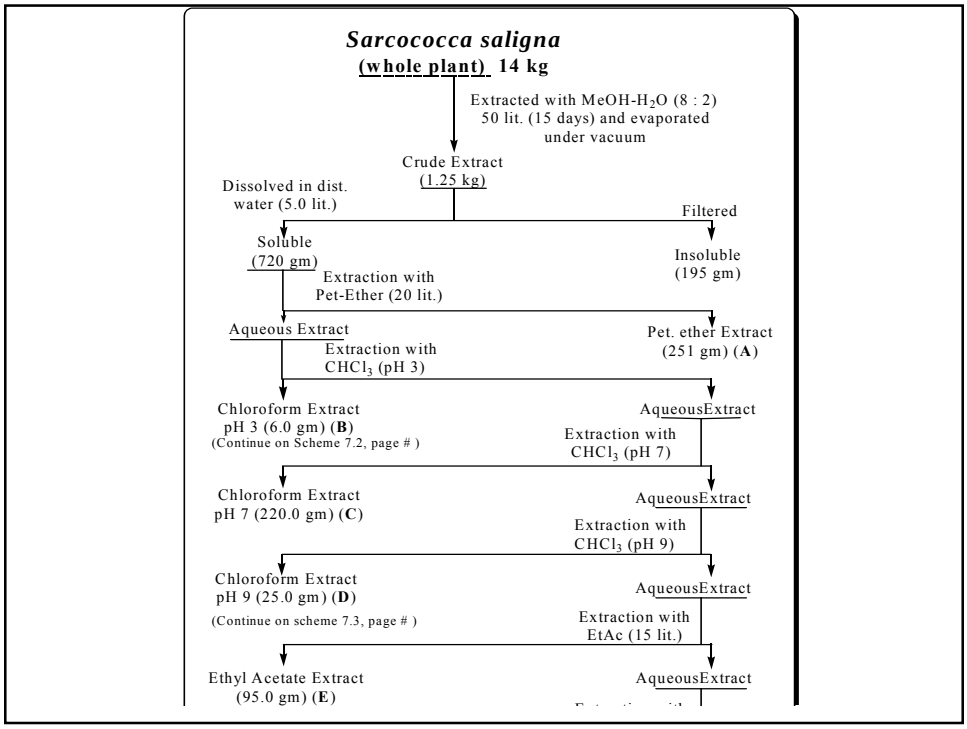
Intense scientific activity: very interdisciplinary approach

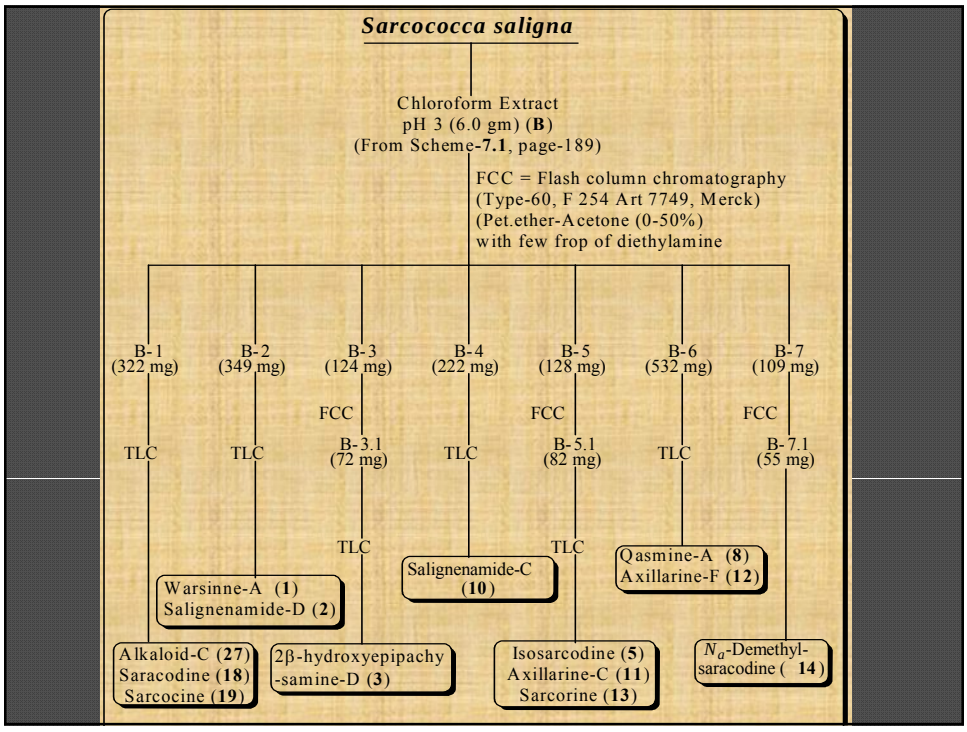


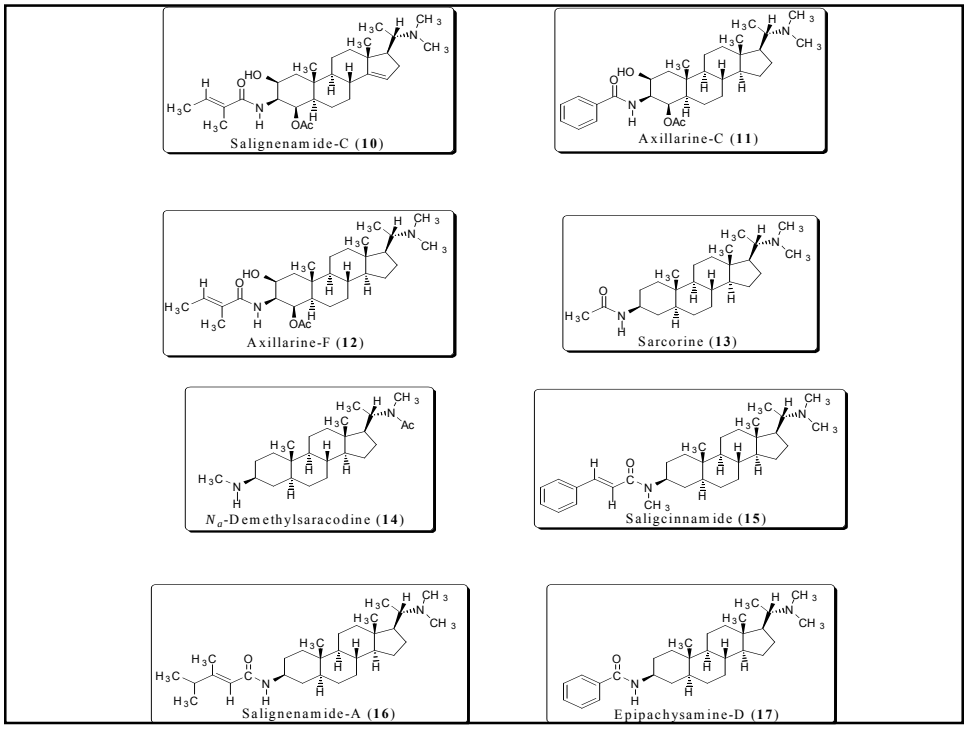
Plant Extract Bank at the ICCBS

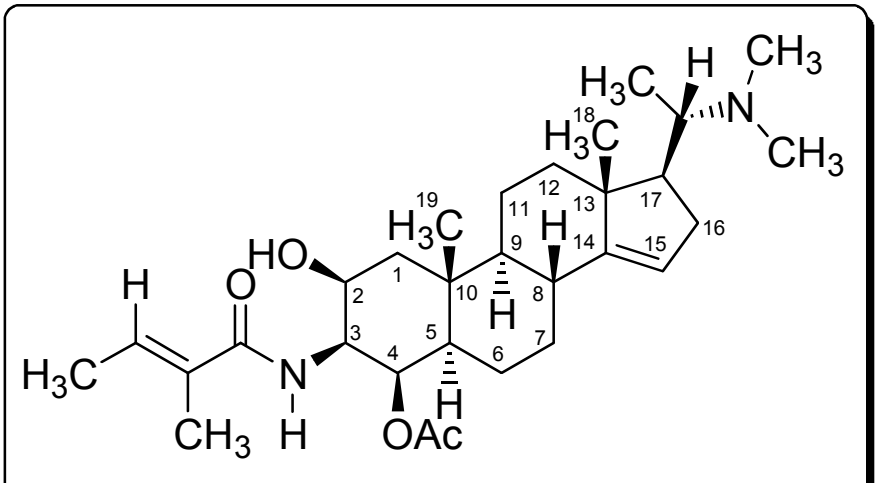
TARGETTED ENZYMES

Enzyme	Target
α-Glucosidase	Diabetes
Acetylcholinesterase	Alzheimer's
β-Lactamase	Antibiotic resistance
Adenosine deaminase	HIV and anticancer
Topoisomerase I	Cancer
Topoisomerase II	Cancer
Phosphodiesterase	Cancer
Urease	Ulcer
β-Glucurinidase	Colon cancer, gall stone
Chymotrypsin	Anti-tumor
Lipoxygenase	Anti-inflammatory, asthma
Thrombin	Anti-clotting


Sarcococca saligna
(whole plant) 14 kg
Extracted with MeOH-H2O (8 : 2)
50 lit. (15 days) and evaporated
under vacuum
Crude Extract
(1.25 kg)
Dissolved in dist.
water (5.0 lit.)
Filtered
Soluble
(720 gm)
Insoluble
(195 gm)
Extraction with
Pet-Ether (20 lit.)
Aqueous Extract
Pet. ether Extract
(251 gm) (A)
Extraction with
CHCl3 (pH 3)
Chloroform Extract
pH 3 (6.0 gm) (B)
(Continue on Scheme 7.2, page #)
AqueousExtract
Extraction with
CHCl3 (pH 7)
Chloroform Extract
pH 7 (220.0 gm) (C)
AqueousExtract
Extraction with
CHCl3 (pH 9)
Chloroform Extract
pH 9 (25.0 gm) (D)
(Continue on scheme 7.3, page #)
AqueousExtract
Extraction with
EtAc (15 lit.)
Ethyl Acetate Extract
(95.0 gm) (E)
AqueousExtract


Sarcococca saligna
Chloroform Extract
pH 3 (6.0 gm) (B)
(From Scheme-7.1, page-189)
FCC = Flash column chromatography
(Type-60, F 254 Art 7749, Merck)
(Pet.ether-Acetone (0-50%)
with few frop of diethylamine
B-1
(322 mg)
B-2
(349 mg)
B-3
(124 mg)
B-4
(222 mg)
B-5
(128 mg)
B-6
(532 mg)
B-7
(109 mg)
FCC
FCC
FCC
TLC
TLC
B-3.1
(72 mg)
TLC
B-5.1
(82 mg)
TLC
B-7.1
(55 mg)
TLC
TLC
Warsinne-A (1)
Salignenamide-D (2)
Salignenamide-C
(10)
Qasmine-A (8)
Axillarine-F (12)
Alkaloid-C (27)
Saracodine (18)
Sarcocine (19)
2β-hydroxyepipachy
-samine-D (3)
Isosarcodine (5)
Axillarine-C (11)
Sarcorine (13)
Na-Demethyl-
saracodine (14)


Salignenamide-C (10)
Axillarine-C (11)
Axillarine-F (12)
Sarcorine (13)
N_a-Demethylsaracodine (14)
Saligcinnamide (15)
Salignenamide-A (16)
Epipachysamine-D (17)


Salignenamide-C (10)

Percentage Yield = 19.7 mg, 1.41 x 10^{-4} %

$[\alpha]^{20}_{D}$ = 38.9° (*c* = 0.3, $CHCl_3$).

UV (MeOH) λ_{max} nm (log ε): 211 and 229.

IR ($CHCl_3$) ν_{max} cm^{-1}: 3329 (NH and OH), 2911 (CH stretching), 1663 (C=O amidic carbonyl), 1624 (C=C stretching).

EI MS *m/z* (rel. int.): 442 (34) [M^+], 427 (100) [M^+-15], 328 (2), 296 (5), 100 (9).

HREI MS: *m/z* (formula, calcd. value): 442.3559 ($C_{28}H_{46}N_2O_2$, 442.3559).

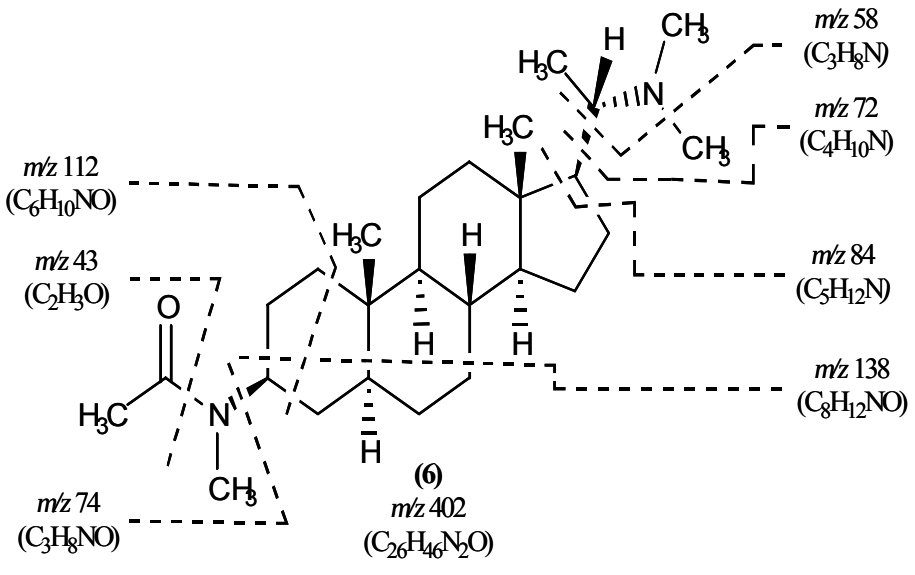
^{1}H-NMR ($CDCl_3$, 500 MHz)**:**

^{13}C-NMR ($CDCl_3$, 125 MHz)**:**

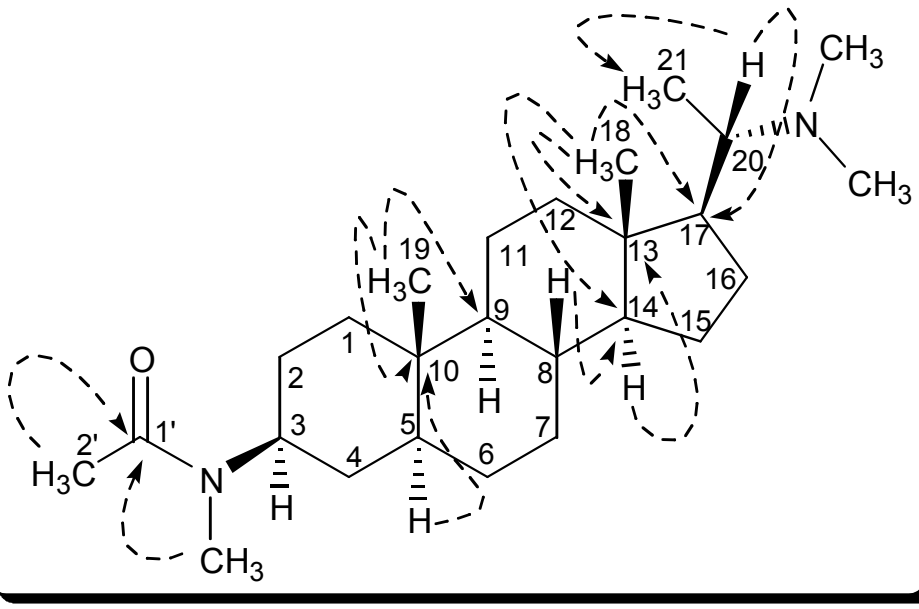
HMBC ($CDCl_3$, 500 MHz)**:**

HOHAHA ($CDCl_3$, 500 MHz)**:**

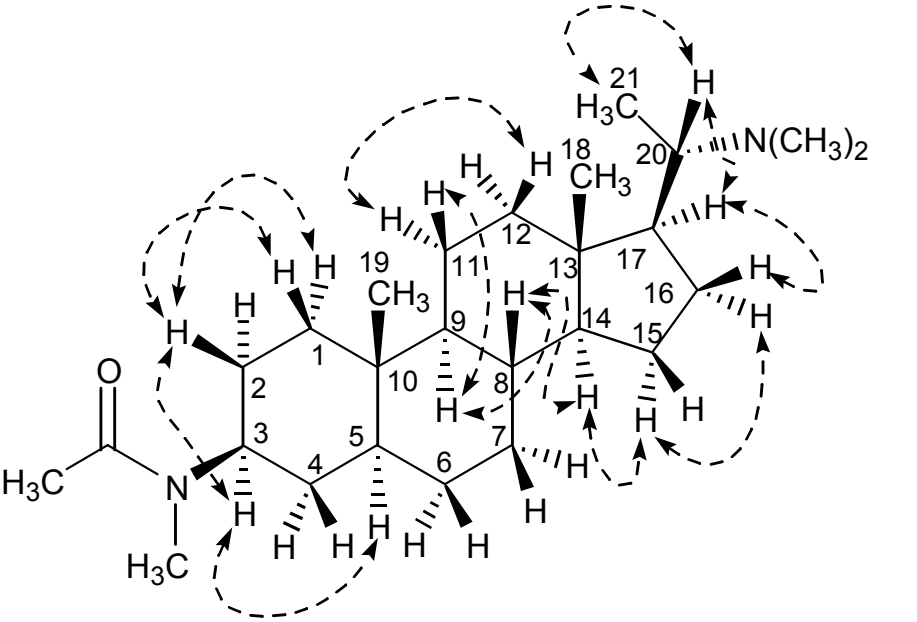
ROESY ($CDCl_3$, 500 MHz)**:**



Mass Fragmentation Pattern

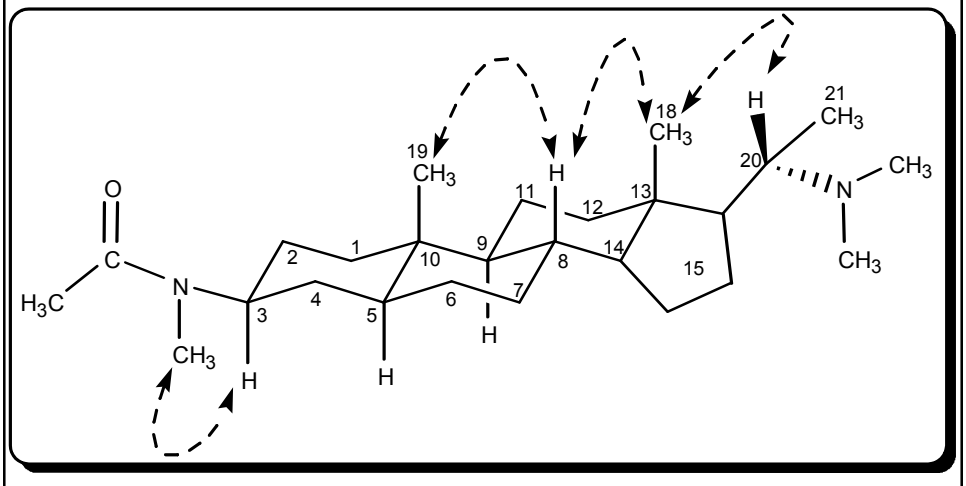


Important HMBC Correlations

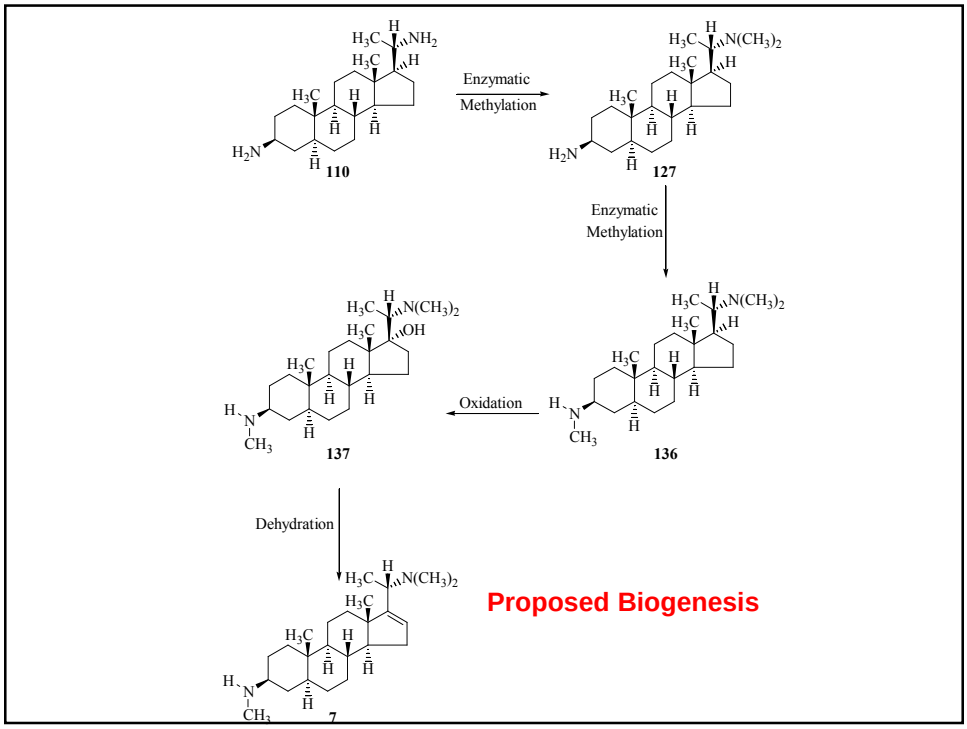


Selected HOHAHA Correlations

C. No.	^{1}H-NMR δ (*J* in Hz)	Multiplicity	^{13}C-NMR (δ)
1	1.61, 1.52	CH_2	32.6
2	1.25, 1.35	CH_2	28.7
3	3.54 m	CH	52.2
4	1.98, 1.10	C	39.8
5	1.22	C	46.0
6	1.21, 1.25	CH	28.8
7	1.53, 1.62	CH_2	31.9
8	1.35	CH	35.5
9	1.24	CH	54.9
10	--	C	35.5
11	1.31, 1.52	CH_2	21.1
12	1.42, 1.91	CH_2	31.5
13	--	C	41.8
14	1.05	CH	56.5
15	1.61, 1.03	CH_2	24.8
16	2.85, 1.82	CH_2	27.6

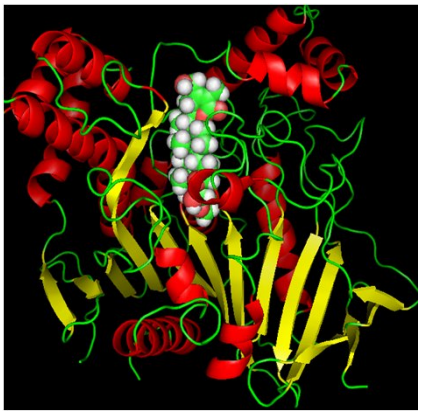


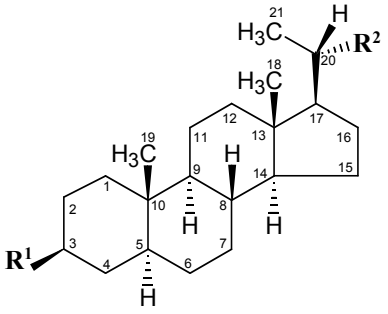
Important ROESY Correlations

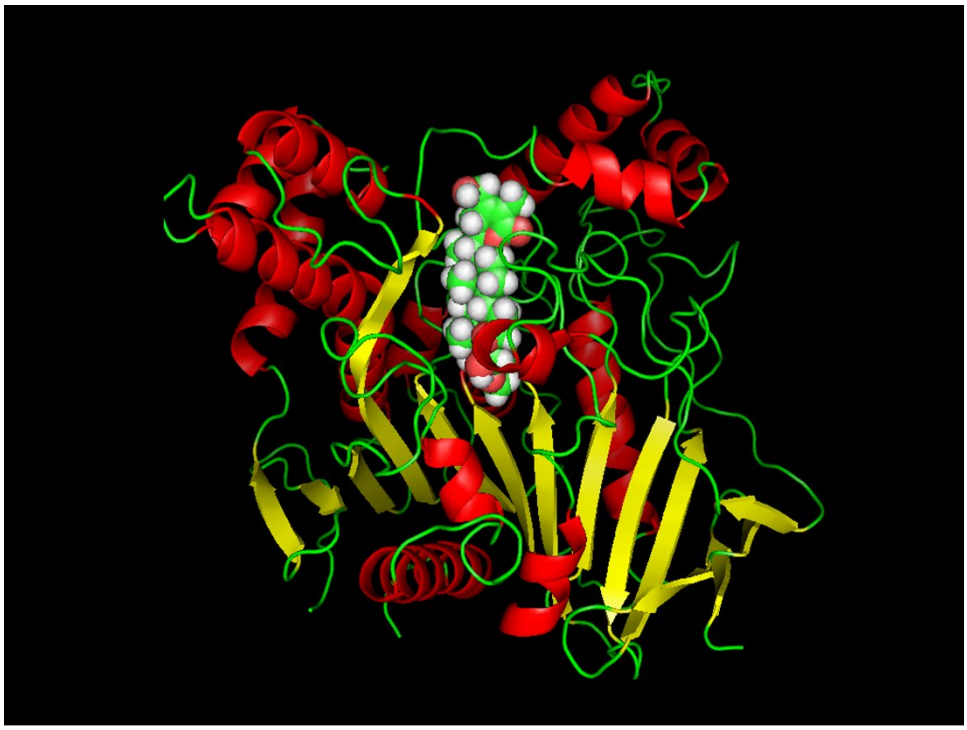


Summary of the *In vitro* Anticholinesterase Activities

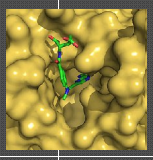
No.	Acetylcholinesterase			Butyrylcholinesterase		
	IC_{50} (µM) Mean±SEM)♣	K_i * (µM) mean±SEM	Inhibition	IC_{50} (µM) mean±SEM♣	K_i * (µM) mean±SEM	Inhibition
1	61.3 ± 2.02	134 ± 6.58	NC	38.36 ± 2.75	26.3 ± 1.44	NC
2	185.2 ± 7.66	-	-	23.78 ± 0.16	-	-
3	78.2 ± 2.33	-	-	28.96 ± 0.01	16.2 ± 0.14	NC
4	6.21 ± 0.23	10.7 ± 0.19	NC	3.65 ± 0.023	9.1 ± 0.26	NC
5	6.35 ± 0.22	4.1 ± 0.06	NC	4.07 ± 0.108	3.4 ± 0.09	NC
6	10.31 ± 0.13	21.8 ± 0.73	NC	1.893 ± 0.06	8.25 ± 3.15	UC
7	20.29 ± 1.82	14.2 ± 0.15	NC	1.89 ± 0.06	1.75 ± 0.03	NC
8	249 ± 10.3	250 ± 9.19	UC	25.7 ± 0.63	30 ± 1.26	NC
9	82.5 ± 2.22	70 ± 3.06	NC	20.95 ± 3.2	29± 0.9	NC
10	15.99 ± 0.13	16 ± 0.73	NC	6.91 ± 0.06	7 ± 3.15	NC
11	182.4 ± 5.54	-	-	18.24 ± 0.25	-	-
12	227.9 ± 8.67	126 ± 9.71	NC	17.99 ± 0.22	20.3 ± 0.67	NC
13	69.99 ±2.6	90.3 ± 2.03	NC	10.33 ± 0.21	7.5 ± 1	UC
14	204± 4.95	216 ± 4	NC	16.55 ± 0.20	15 ± 0.4	NC
15	19.99 ± 0.12	12.2 ± 0.15	NC	4.84 ± 0.12	6.6 ± 0.15	NC




21
H3C
H
R2
20
18
H3C
12
17
19
H3C
11
13
16
H
9
14
15
1
10
8
2
H
H
3
5
7
R1
4
6
H

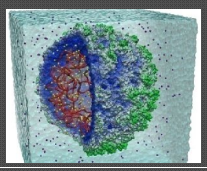


Topics in CADD

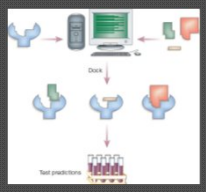


Docking

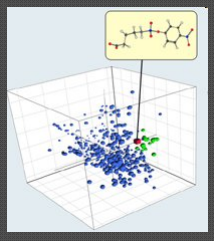
Pharmacophore modeling



MD simulation



Virtual screening



QSAR

Bioinformatics tools in DD

- Comparison of Sequences: Identify targets
- Homology modelling: active site prediction
- Systems Biology: Identify targets
- Databases: Manage information
- In silico screening (Ligand based, receptor based): Iterative steps of Molecular docking.
- Pharmacogenomic databases: assist safety related issues

Insilico methods in Drug Discovery

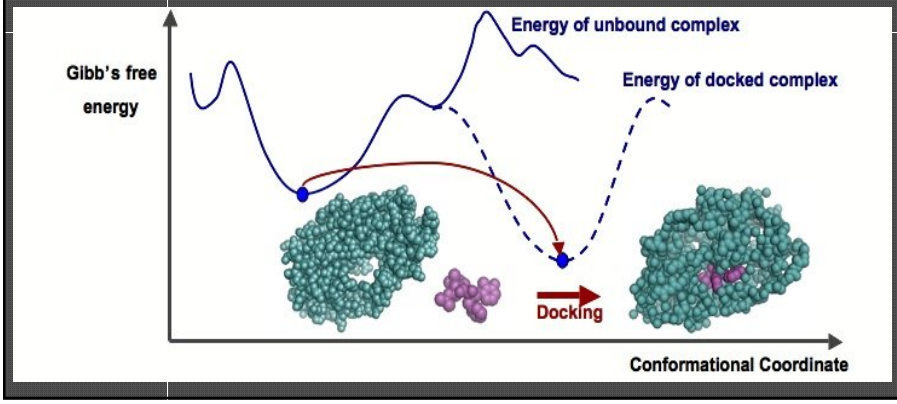
- Molecular docking
- Virtual High through put screening.
- QSAR (*Quantitative* structure-activity relationship)
- Pharmacophore mapping
- Fragment based screening

Molecular Docking

- Docking is the computational determination of binding affinity between molecules (protein structure and ligand).
- Given a protein and a ligand find out the binding free energy of the complex formed by docking them.

DOCKING

..\Downloads\Video\videoplayback.wmv



Molecular Docking: classification

- Docking or Computer aided drug designing can be broadly classified
  - » Receptor based methods- make use of the structure of the target protein.
  - » Ligand based methods- based on the known inhibitors

Receptor based methods

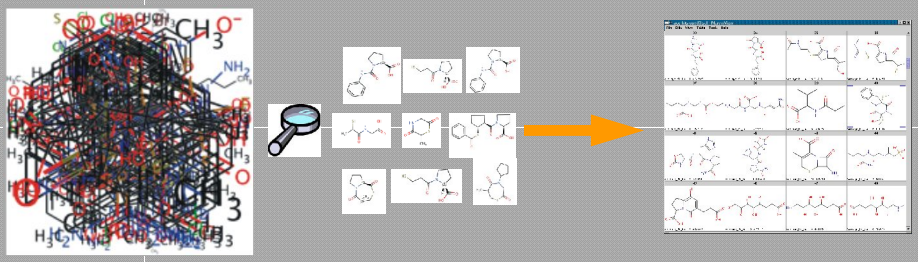
- Uses the 3D structure of the target receptor to search for the potential candidate compounds that can modulate the target function.
- These involve molecular docking of each compound in the chemical database into the binding site of the target and predicting the electrostatic fit between them.
- The compounds are ranked using an appropriate scoring function such that the scores correlate with the binding affinity.
- Receptor based method has been successfully applied in many targets

Ligand based strategy

- In the absence of the structural information of the target, ligand based method make use of the information provided by known inhibitors for the target receptor.
- Structures similar to the known inhibitors are identified from chemical databases by variety of methods,
- Some of the methods widely used are similarity and substructure searching, pharmacophore matching or 3D shape matching.
- Numerous successful applications of ligand based methods have been reported

Ligand based strategy

Search for *similar* compounds



database known actives structures found

Binding free energy

- *Binding free energy* is calculated as the sum of the following energies
  - Electrostatic Energy
  - Vander waals Energy
  - Internal Energy change due to flexible deformations
  - Translational and rotational energy
- Lesser the binding free energy of a complex the more stable it is

Components of molecular docking

A) Search algorithm

- To find the best conformation of the ligand and the protein system.
- Rigid and flexible docking

B) Scoring function

- Rank the ligands according to the interaction energy.
- Based on the energy force-field function.

Virtual High Throughput Screening

- Less expensive than High Throughput Screening
- Faster than conventional screening
- Scanning a large number of potential drug like molecules in very less time.
- HTS itself is a trial and error approach but can be better complemented by virtual screening.

Pharmacophore mapping

- It is a 3D description of a pharmacophore, developed by specifying the nature of the key pharmacophoric features and the 3D distance map among all the key features.
- A Pharmacophore map can be generated by superposition of active compounds to identify their common features.
- Based on the pharmacophore map either *de novo* design or 3D database searching can be carried out.

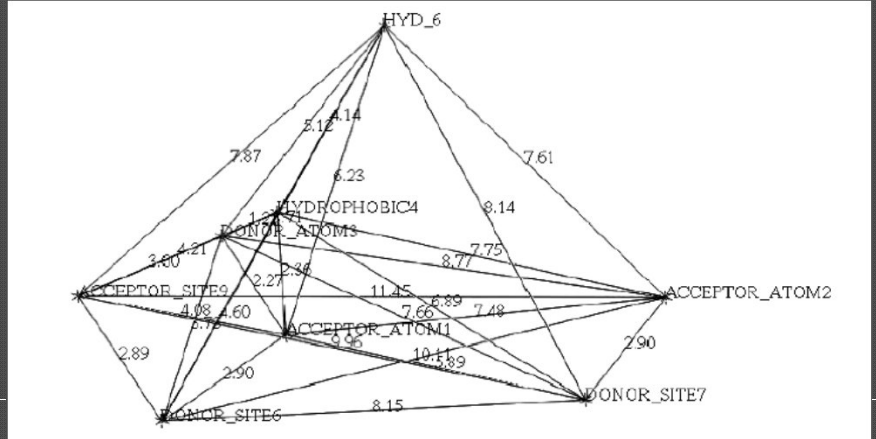


FIGURE 1.5 A pharmacophore map developed from a set of GSK3 inhibitors. The pharmacophore features include hydrogen bond acceptor atoms, hydrogen bond donor atoms, hydrogen bond donor site, hydrogen bond acceptor site, and hydrophobic centers. This 3D picture also shows the distance relationship between various pharmacophoric features present in the map.

Increased application of structure based drug designing is facilitated by:

- ✓ Growth of **targets** number
- ✓ Growth of **3D structures determination** (PDB database)
- ✓ Growth of **computing power**
- ✓ Growth of **prediction quality** of **protein-compound** interactions

Summary: role of Bioinformatics?

- Identification of homologs of functional proteins (motif, protein families, domains)
- Identification of targets by cross species examination
- Visualization of molecular models
- Docking, vHTS
- QSAR, Pharmacophore mapping

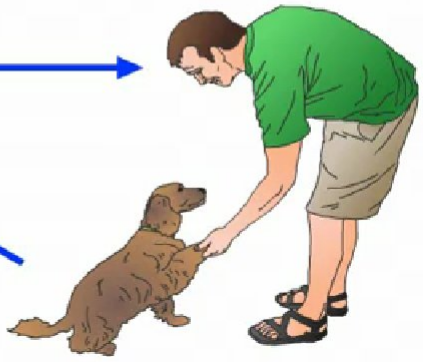
Example: use of Bioinformatics in Drug discovery

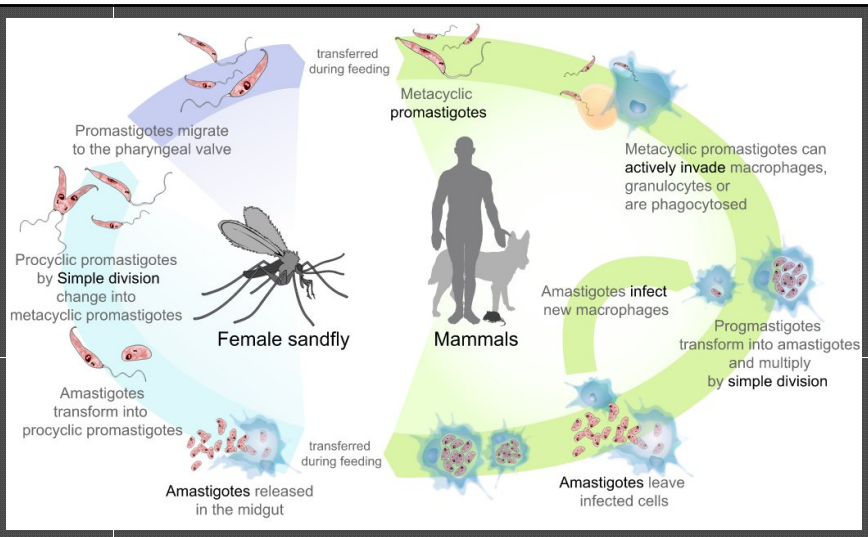
Identification of novel **anti-*Leishmanial* agents**

- **Leishmaniasis** is a disease caused by parasites that belong to the genus Leishmania
- It is transmitted by the bite of certain species of sand fly.
- Cutaneous leishmaniasis is the most common form of leishmaniasis. Visceral leishmaniasis is a severe form in which the parasites have migrated to the vital organs.

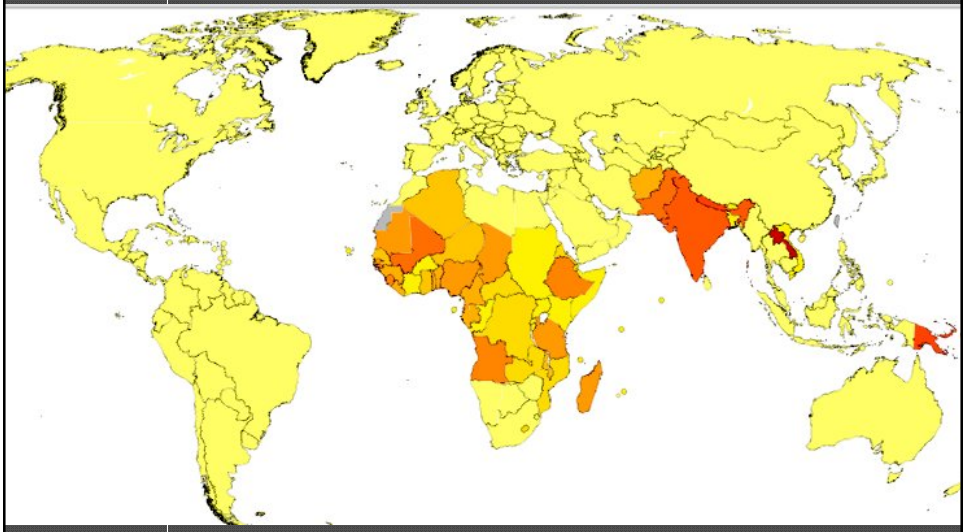
Sand flies are very small and may be hard to see. They are only about one-third the size of typical mosquitoes. They fly without making any noise.

Sand flies become infected with the parasite by biting an infected animal such as a rodent, a dog, or biting an infected person. The infected sand flies can then spread the parasite by biting other animals and people.



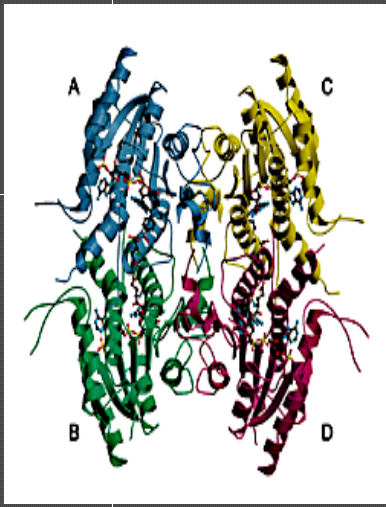


Replication of parasite happening inside the sand fly, they are transmitted after blood meal, these flies delivers these parasite which replicated abundantly in the digestive tract this is how they penetrate to mammalian host including human and dog. Intercellular replication occur

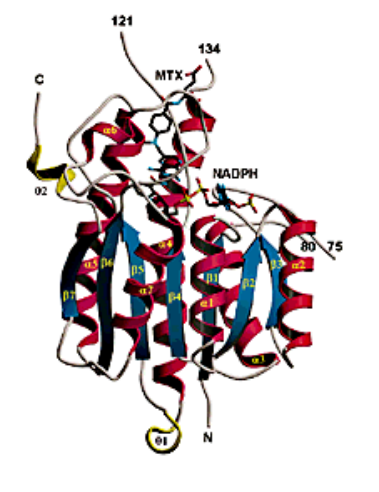


- Distribution in the world not restricted in some part of word but a large region of undeveloped world recently move to several other part and vary serious indicator 12 million people are infected and 350 millions are at risk world wide.
- 16-18 million people carry this parasite only in Latin America

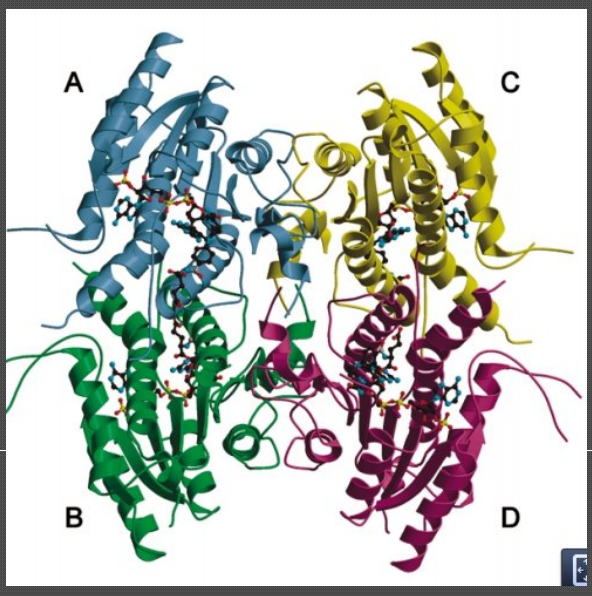
PTR1 structure



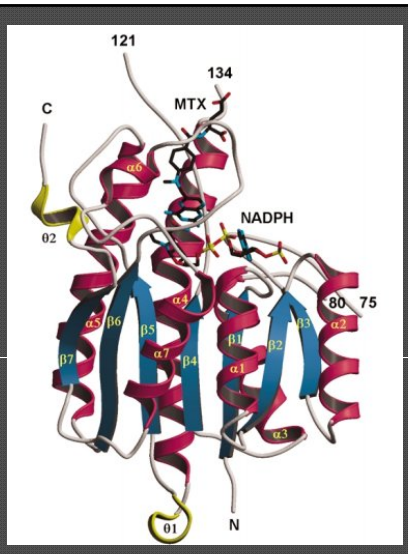
tetramer



monomer

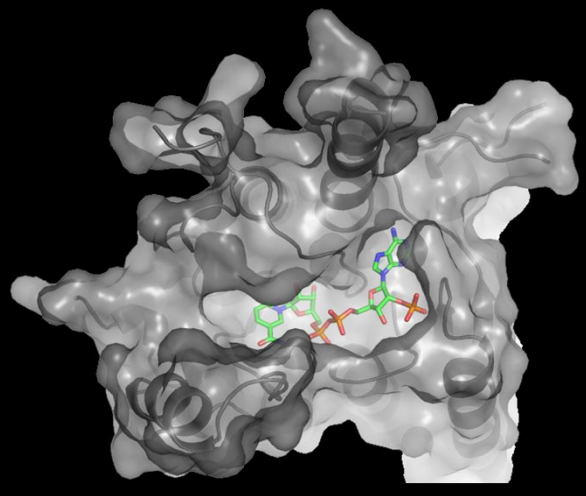


Functional Tetramer with individual subunits color

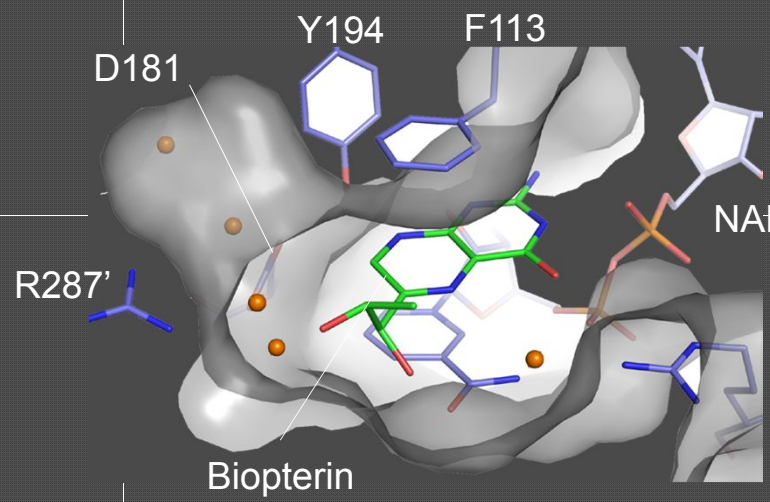


subunit forms a single α/β-domain constructed around a seven-stranded parallel β-sheet sandwiched between two sets of α-helices

PTR1 structure

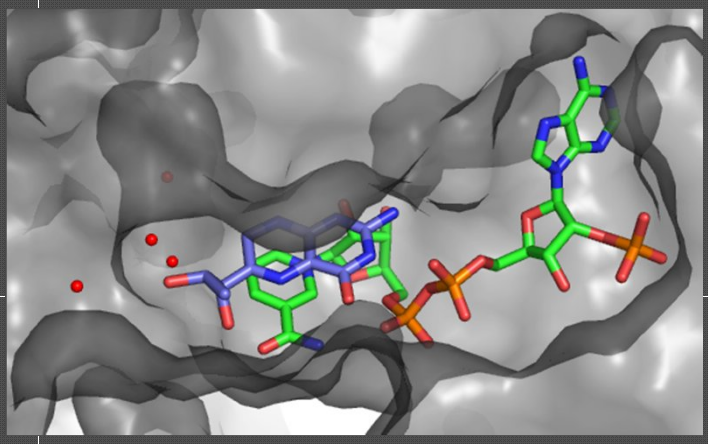


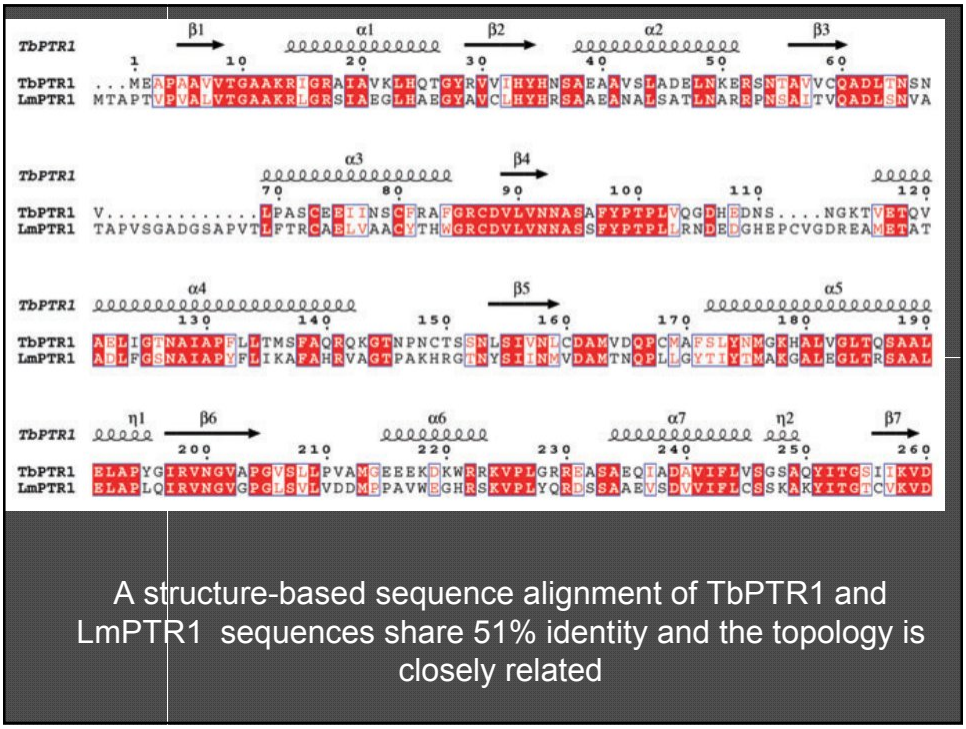
Ptr1 active site



Docking

Water at the active site

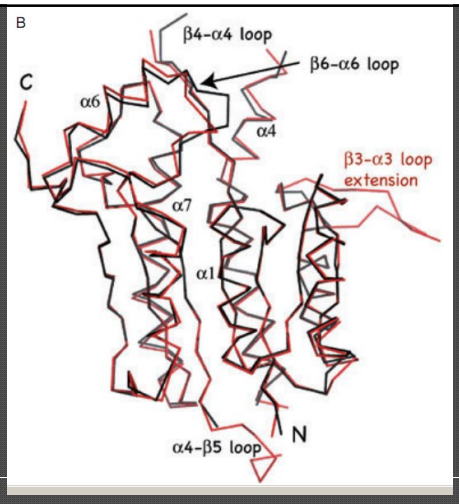




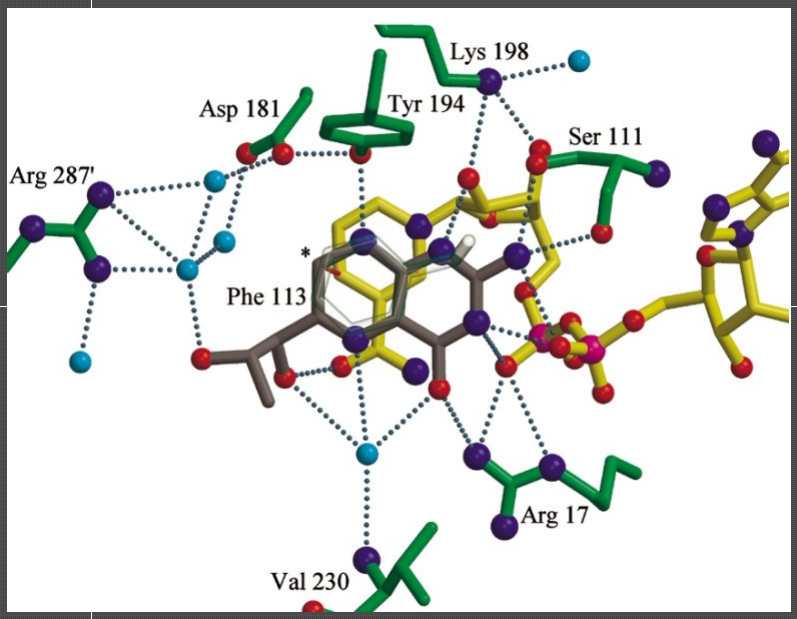
A structure-based sequence alignment of TbPTR1 and LmPTR1 sequences share 51% identity and the topology is closely related

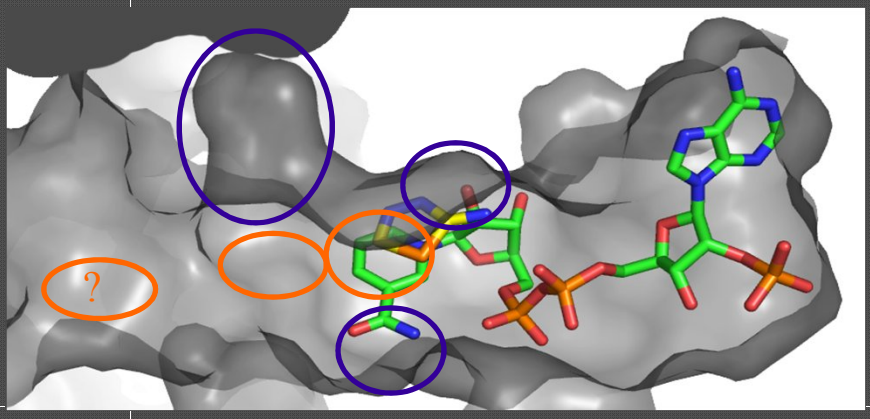
Red : LmPTR1

Black: TbPTR1



- The TbPTR1 sequence is shorter than LmPTR1 due to two deletions and a truncation at the N-terminus.
- In TbPTR1 a short β3-a3 loop is well ordered whereas in LmPTR1, the loop is extended by 13 residues and generally disordered
- A second, smaller deletion of four residues occurs at the C-terminal segment of the loop linking β4 and α4 in TbPTR1

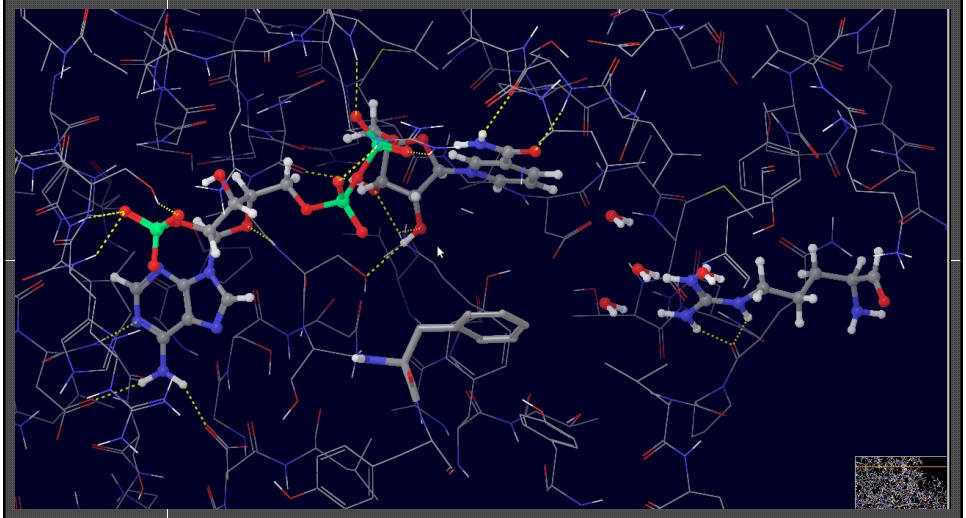




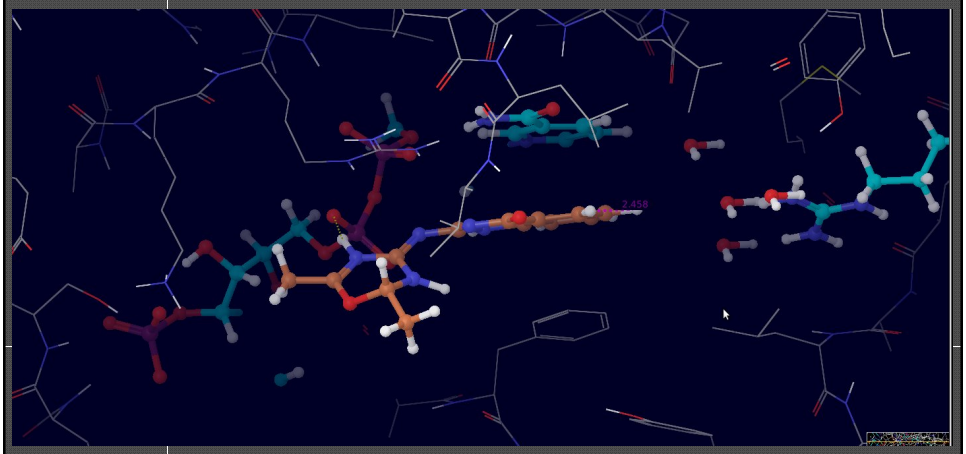
Hydrophobic bed

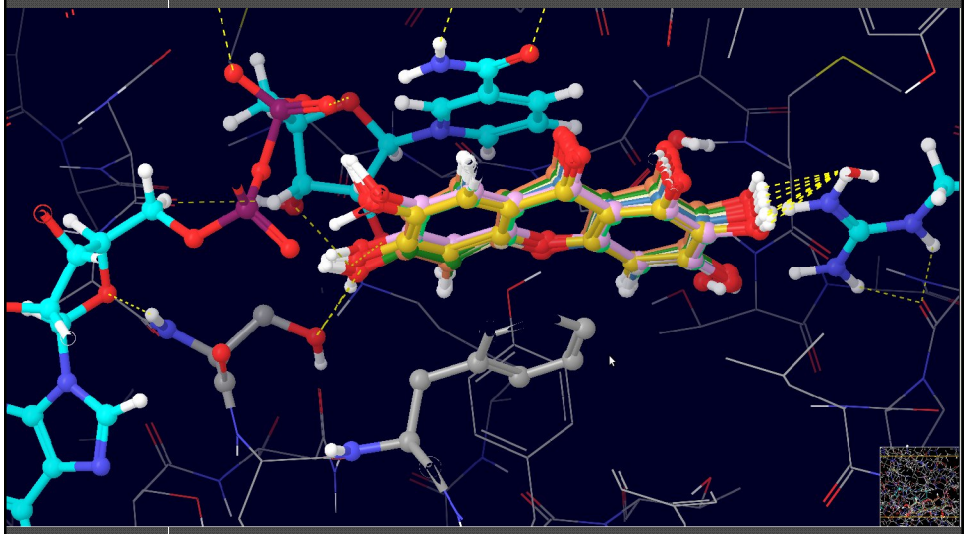
Hydrophilic bed

Active site is an L-shaped depression nearly 30 Å in length, 22 Å wide and 15 Å deep, formed by the C-terminal ends of the β-sheet, where the cofactor binds in an extended conformation.

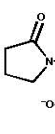


Phe113, Tyr194, Arg117 and
four water molecule

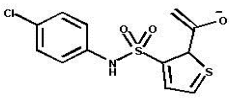




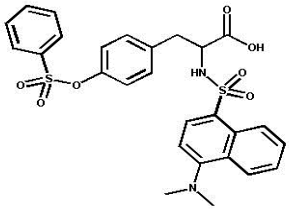
Examples of bioactive molecule design using docking-based virtual screening



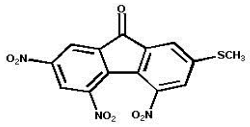
Human carbonic anhydrase
Unity, FlexS, FlexX
IC_{50} = 0.6 (nM)
J Med Chem 2002 & Angew Chem Intl Ed Engl 2001



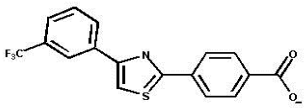
AMPC β-lactamase
DOCK (Northwest Univ. version)
Ki = 26 (μM)
Structure 2002



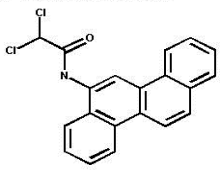
Thymidylate synthase
DOCK
Ki = 1.4 (μM)
BBA-Mol Basis Dis 2002



Adenovirus proteinase
EUDOC
Ki = 3.09 (μM)
FEBS Lett 2001

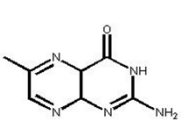


Retinoic acid receptor
ICM
ED_{50} = 2 (μM)
Proc Natl Acad Sci USA 2000

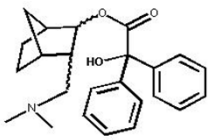


Hypoxanthine Phosphoribosyl transferase (HPRT)
DOCK
Ki = 0.5 (μM)
Chem Biol 2000

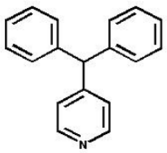
Examples of bioactive molecules design using pharmacophore-based virtual screening



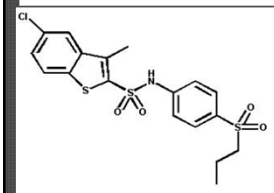
tRNA-guanine transglycosylase (TGT)
SuperStar, DrugScore, Unity, FlexX
Ki = 0.25 (μM)
J Med Chem 2003



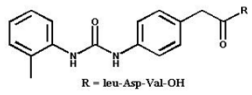
Dopamine transporter (DAT)
Quanta, Chem-X
Ki = 7.3 (μM)
J Med Chem 2003



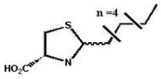
Dopamine transporter (DAT)
Quanta, Chem-X
Ki = 0.255 (μM)
Bioorg Med Chem Lett 2003



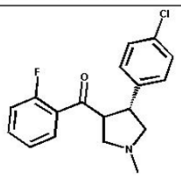
Serine protease chymase
CATALYST
Ki = 0.909 (μM)
Bioorg Med Chem Lett 2003



Antigen α4β1
CATALYST
IC_{50} = 0.0006 (μM)
J Med Chem 2002

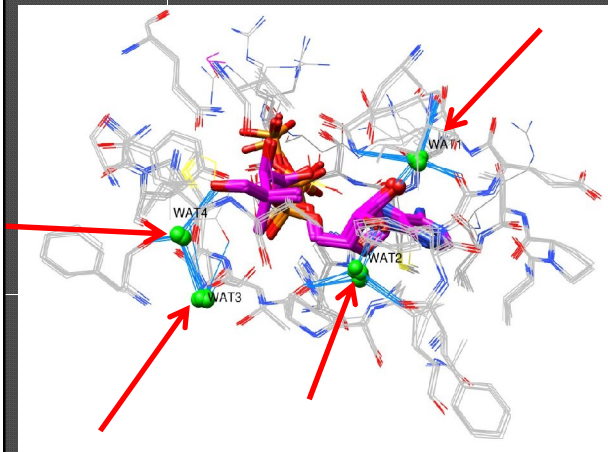


EDG3
CATALYST
IC_{50} = 10 (μM)
J Med Chem 2002



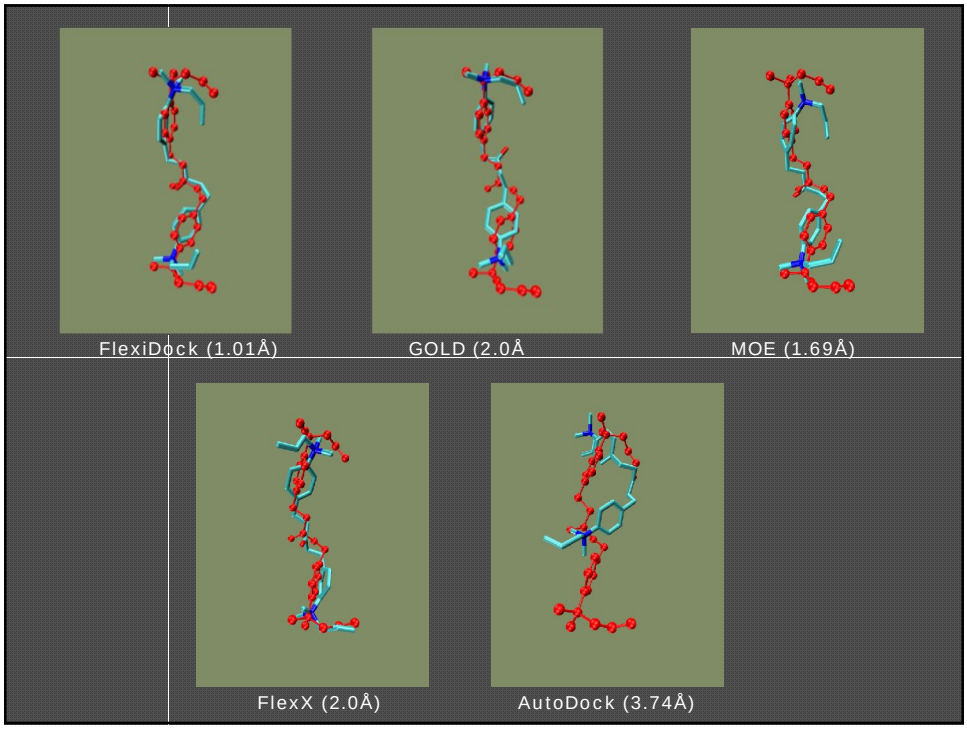
Dopamine transporter (DAT)
Quanta, Chem-X
IC50 = 0.084 (μM)
Bioorg Med Chem Lett 2001

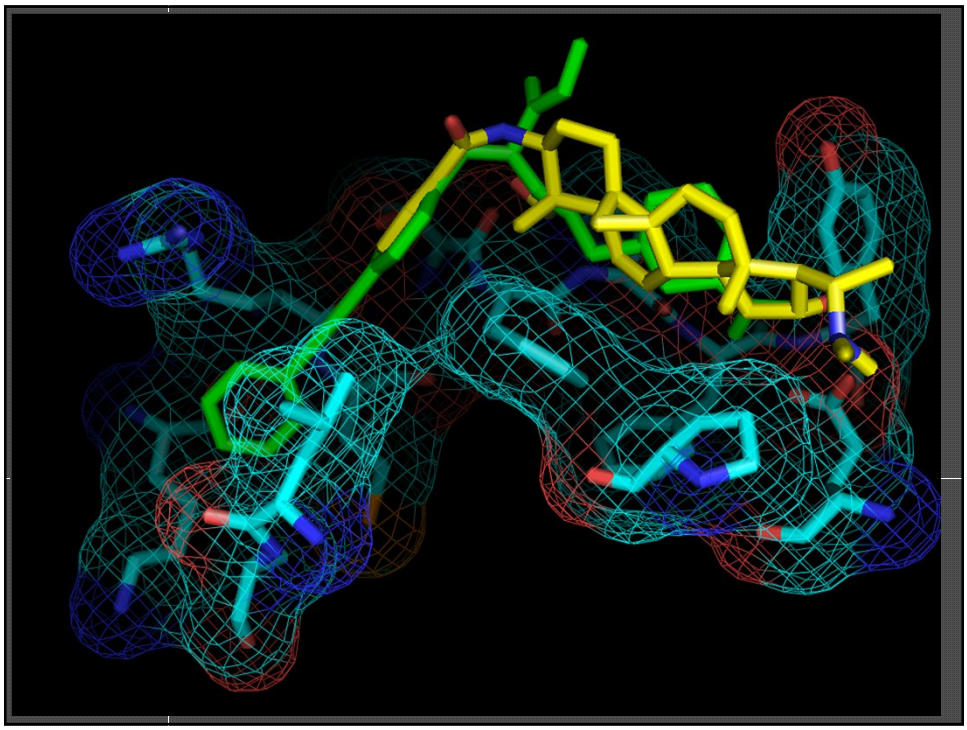
Crystal Structures Comparison

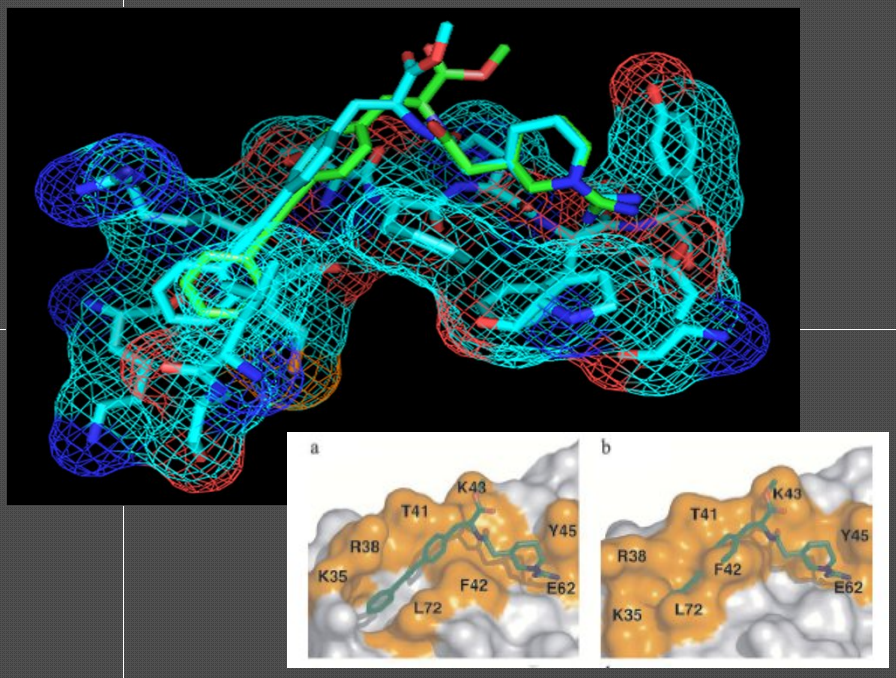


Label	H-bond partners	Temp factor
W1	ASP161-O, GLN164-NE2, GLY158-O	22.2
W2	PHE156-O, PRO38-O	25.1
W3	THR39-O, W4	18.9
W4	PHE67-O, W3	20.9

60


FlexiDock (1.01Å)
GOLD (2.0Å
MOE (1.69Å)
FlexX (2.0Å)
AutoDock (3.74Å)





Preparing a Compound Database

- Retrieving a Compound Database - ZINC/Drug-like subset (version 10, 2010) was downloaded from ZINC website
- Over 13 million compounds classified over three pH ranges along with their stereomers, tautomers, protonated, and ionized forms
- First selection criteria of druggable compounds was performed by analyzing the molecular structures of eight ligands (six inhibitors and two substrate forms of bioptreins) co-crystallized with LmPTR-1
- Customization of pre-defined FILTER application (OpenEyes's Scientific Software programme) was done as per our ranges of molecular descriptors
- From over 13 million to over 4.4 million (29.54% compounds have passed the filter criteria).

Lipinski's Rule (Pfizer)

HTS Drug Like (Rule of 5)

- Molecular weight ≤ 500
- Number of Hydrogen bond acceptors (sum of O and N) ≤ 10
- Number of Hydrogen bond donors (sum of NH and OH) ≤ 5
- Lipophilicity cLogP ≤ 5

Lead Like

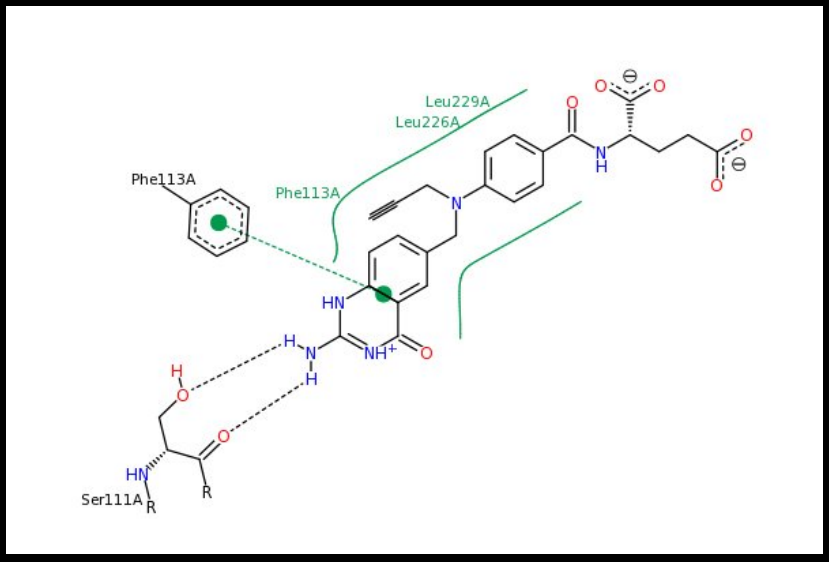
- Molecular weight ~ 300
- Fewer Hydrogen bond acceptors
- Lipophilicity cLogP ≤ 3
- Low to high affinity for target receptor

Extracting Pharmacophoric Features

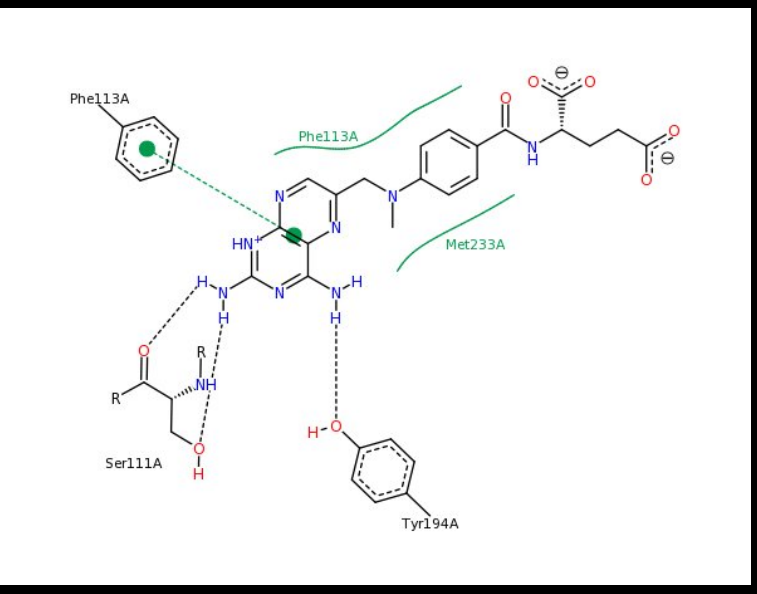
- **Hydrogen bond interactions** (hydrogen bond donors and acceptors as directed vectors with distance constraints of **2.2 – 3.8 Å**)
- **Electrostatic interactions** (positive and negative ionizable regions which are divided into positively ionizable areas represented by atom or groups of atoms that are likely to be protonated at physiological pH, and negatively ionizable areas that are likely to be deprotonated at physiological pH with distance constraints of **1.5 – 5.5 Å**
- **Aromatic interactions** (pi-pi and cation-pi interactions with distance constraints of **3.5 – 5.5 Å**
- **Hydrophobic features** with distance constraint of **1.0 – 5.9 Å**.
- **Excluded volume spheres** those areas that are inaccessible to any potential ligand, thus reflecting possible steric restraints as claimed by the macromolecular environment.

66

Complex	Pharmacophoric features[a]	xclusion volume s	Amino acid residues[b]
Lm PTR-1:HBI	$HYD,HYDAC_6,HYDDON_5$	6	**R17**, L18, N109, A110, **S111**, S112, **F113**, L143, S146 ,N147, V180, **D181**, A182, M183, T184, **L188**, Y191, **Y194**, **K198**, P224, G225, **L226**, S227, V228, **L229**, **V230**, M233,W238, H241, D251, S252, Y283, R287
Lm PTR-1:MTX	$AR,HYD,HYDAC_{10},HYDDON_4$	5	**R17**, L18, N109, A110, **S111**, S112, **F113**, Y114, P117, L143, S146, N147, M179, V180, **D181**, M183, T184, L188, L189, G190, Y191, **Y194**, **K198**, P224, G225, **L226**, S227, V228, **L229**, **V230**, D231, D232, M233, P234, V237, H241, D251, Y283
Lm PTR-1:TAQ	$AR,HYD,HYDAC_2,HYDDON_5$	3	**R17**, L18, N109, A110, **S111**, S112, **F113**, L143, S146, N147, M179, V180, **D181**, M183, T184, **L188**, Y191, **Y194**, **K198**, P224, G225, **L226**, S227, V228, **L229**, **V230**, M233, D251, Y283, R287
Lm PTR-1:H4B	$AR,HYD,HYDAC_5,HYDDON_6$	4	**R17**, L18, N109, A110, **S111**, S112, **F113**, Y114, L143, S146, N147, M179, V180, **D181**, A182, M183, T184, **L188**, Y191, **Y194**, **K198**, P224, G225, **L226**, S227, V228, **L229**, **V230**, M233, H241, D251, Y283, R287
Lm PTR-1:CB3	$AR_2,HYD_3,HYDAC_2,HYDDON_3,NI_2$	6	**R17**, L18, N109, A110, **S111**, S112, **F113**, P115, L143, S146, N147, M179, V180, **D181**, A182, M183,

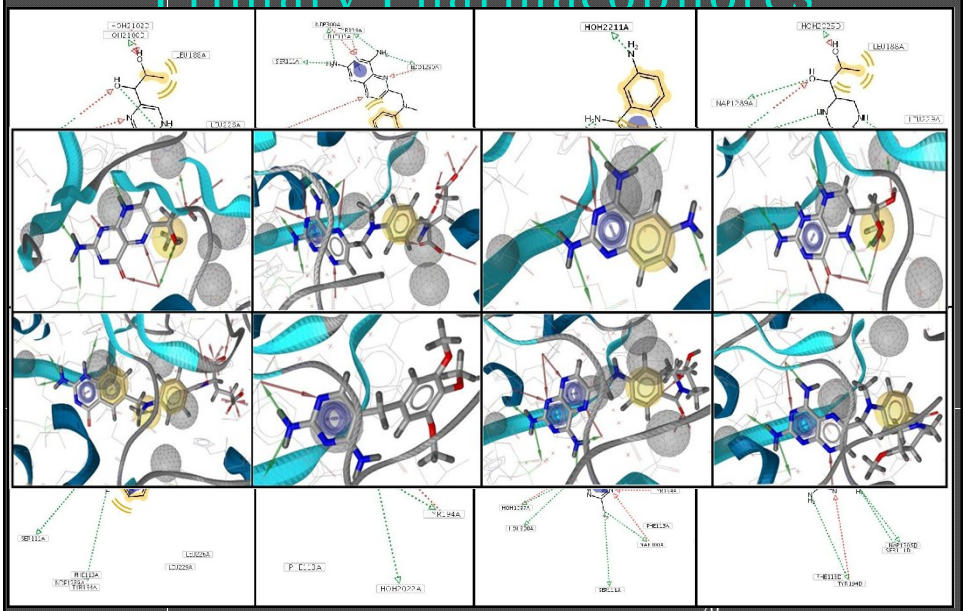


CB3_2BFA



MTX_1E7W

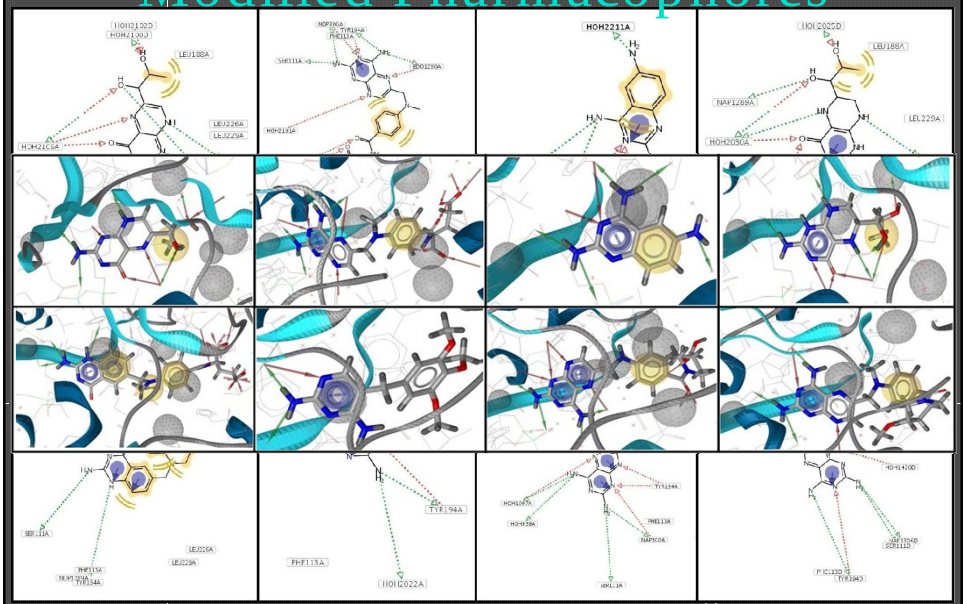
Primary Pharmacophores



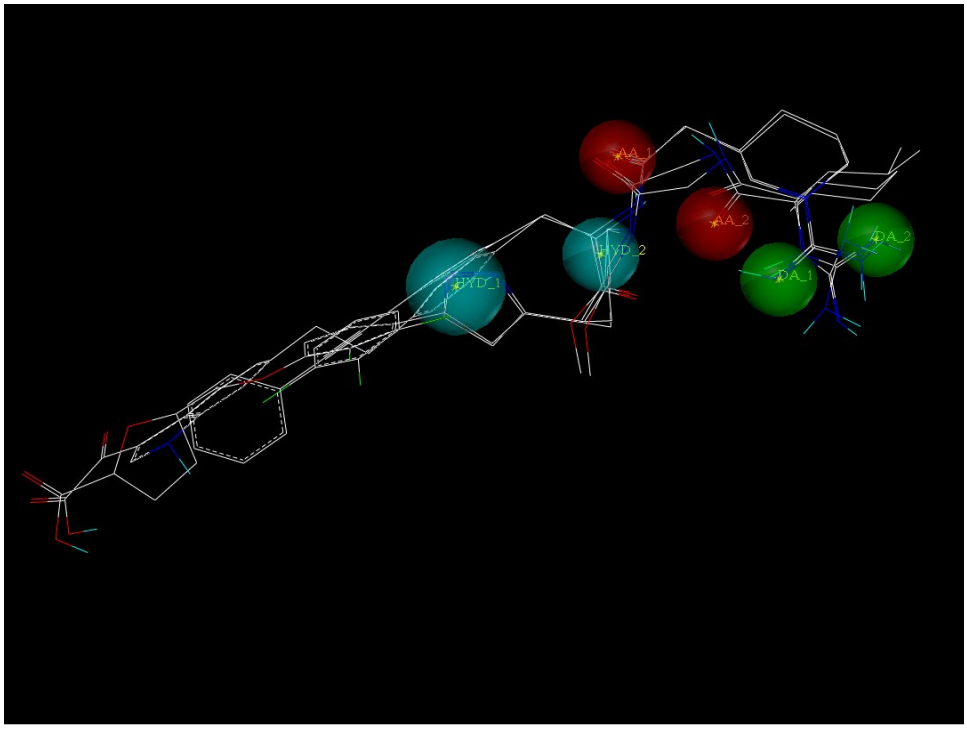
- Examination of structural issues; binding site, ligand (especially the ones that have double bond type), proposed interaction patterns and their features
- Comparing them with the literature to sort out information available from the original PDB literature.
- Multiple features, resembling the situation in the binding pocket. For instance, an amine might function as hydrogen bond donor and as a positive ionizable feature; a hydroxyl group can face the appropriate interactions partners to accept and donate hydrogen bonds. This issue was overcome **by observing manually and compare with the interactions**.
- Primary pharmacopohore queries were also cured manually by deleting pharmacophoric features that have unfavorable distances and angles.

71

Modified Pharmacophores



72



- Deleted features were also omitted from the Ligandscout's modified pharmacophore models, now named them as **secondary pharmacophore models**.

Aligning and shared pharmacophoric features

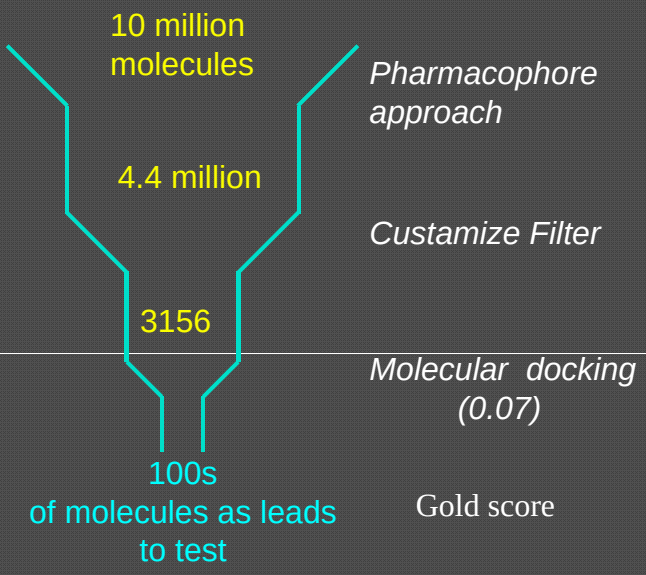
- FEI was chosen as the reference point for aligning all the eight secondary pharamacophoric models.
- After alignment, a shared feature pharmacophore was extracted form that alignment.
- Total **3,156 compounds** out of over 4.4 million (0.07%) are fitted.

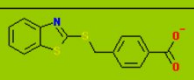
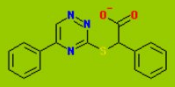
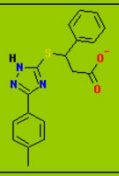
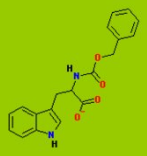
74

- After successful re-docking protocol, all 3,156 were docked,
- Top 100 ranked poses as selected on the basis of GoldScore were retained for visual interactions,
- Interactions between Phe113, Tyr194, Ser111, Leu226, Leu229, ASP181
- Total 56 compounds were short listed and finally 9 compounds were selected for testing

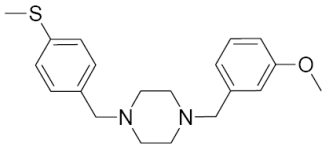
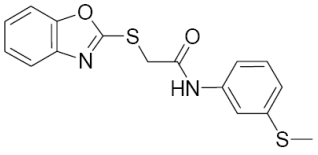
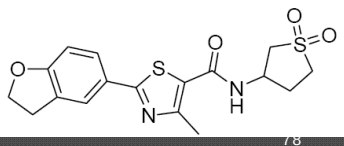
75

Filtering the results



Compound	Gold Score	Flexx score	Chemical Structure
1	52.54	-25.14	
2	54.76	-17.37	
3	54.66	-24.43	
4	52.84	-24.47	

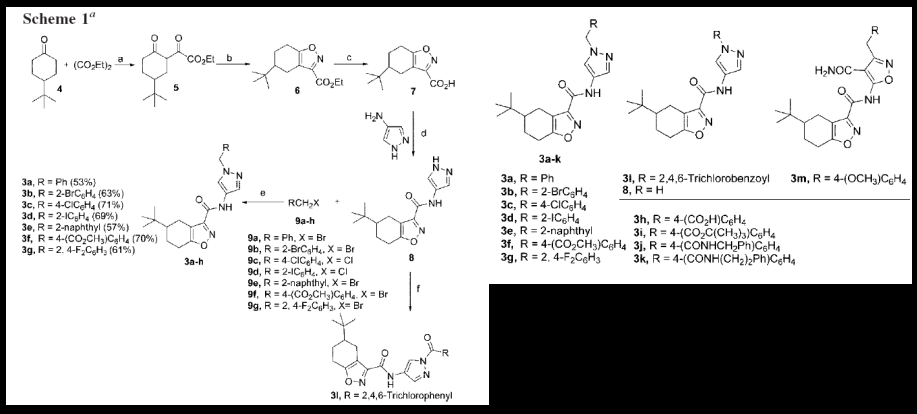
Identified Hits

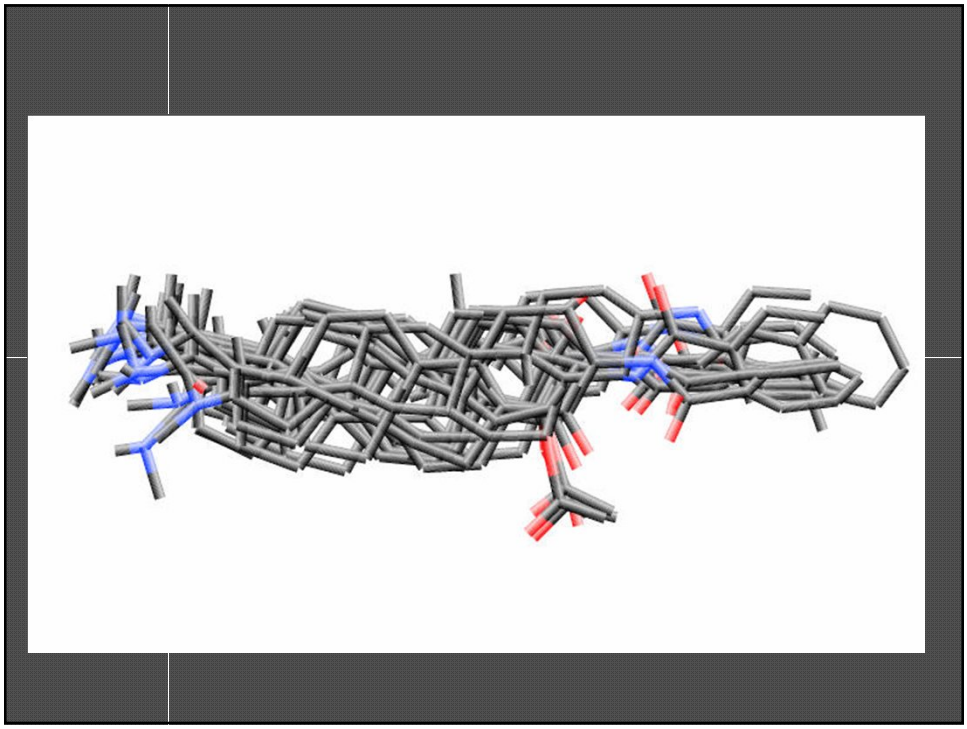
S. No.	ID	Structure	IC_{50} (μM)
4	PS-01-28		258.6
5	PS-01-29		1.5
6	PS-01-154		1140.3

QSAR

- QSAR is statistical approach that attempts to relate physical and chemical properties of molecules to their biological activities.
- Various descriptors like molecular weight, number of rotatable bonds LogP etc. are commonly used.
- Many QSAR approaches are in practice based on the data dimensions.
- It ranges from 1D QSAR to 6D QSAR.

Structural Analogs of two hits (2 and 3)



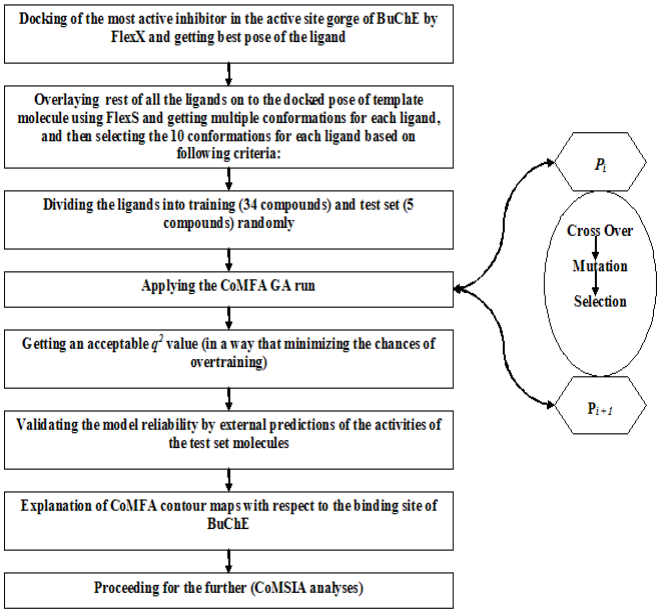


Align Molecules for QSAR/CoMFA

- **Docking**
  - Superimpose all of the molecules on docked pose of the most active compound
  - All of the ligands were docked by FlexX and then, the top most conformation of each ligand suggested by FlexX score, was used to build a CoMFA model, which resulted in negative correlation (q^2 = -0.244)
  - Next all of the ligands were docked by GOLD and again using the single top ranked conformation of each compound, ended up with almost the same negative correlation (q^2 = -0.255)
- **Next Strategy**
  - to use, the multiple conformation of each ligand.
  - Its decided to use the top conformation of most active compound as template and align rest of the ligands on to it.

82

Next Overall Strategy

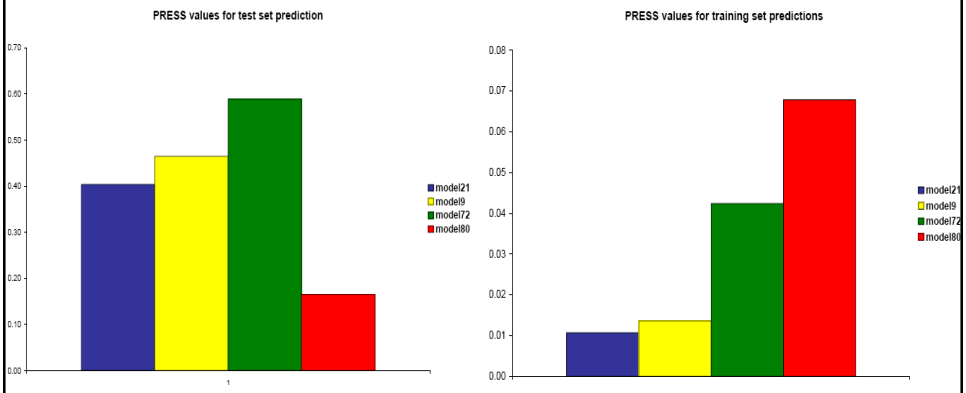


Selection from various Models

- **Based on q^2 values , 4 models have been selected for subsequent studies**
- **Cutoff q^2 value set to >= 0.65**
  - **Model72**
  - **Model80**
- **Cutoff q^2 value set to >= 0.90**
  - **Model9**
  - **Model21**

84

Selection of Final Model



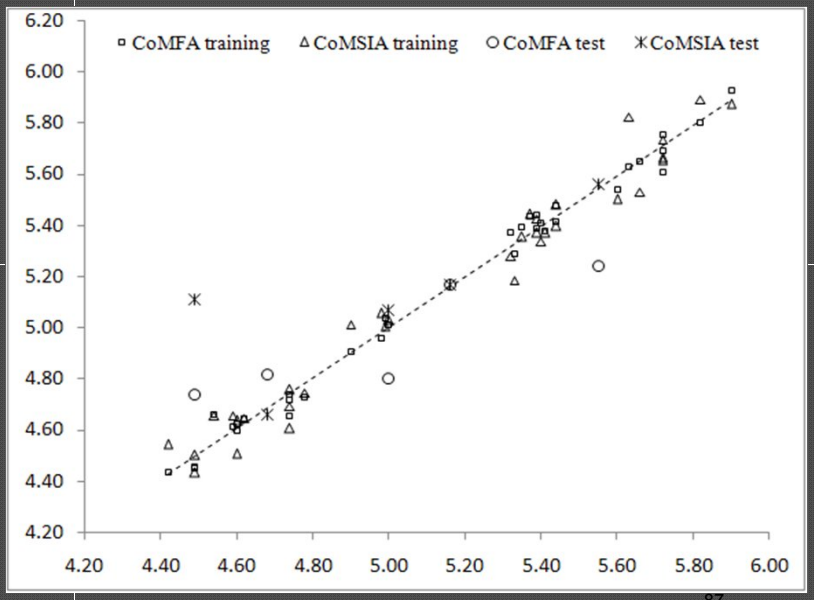
External Prediction	Model9	Model21	Model72	Model80
Predictive r-squared	0.325	0.413	0.145	0.760

$$\text{predictive r-squared} = \frac{\text{SSD - PRESS}}{\text{SSD}}$$

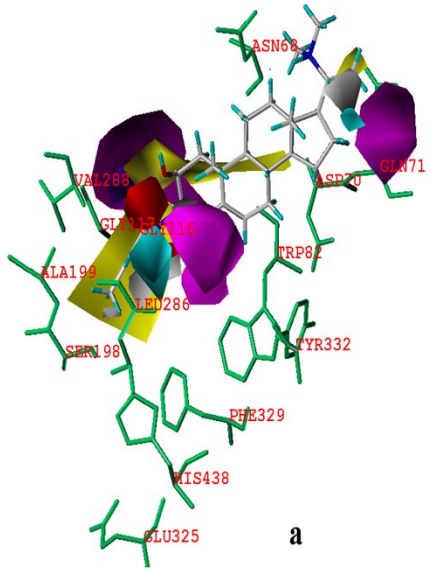
Models Statistics

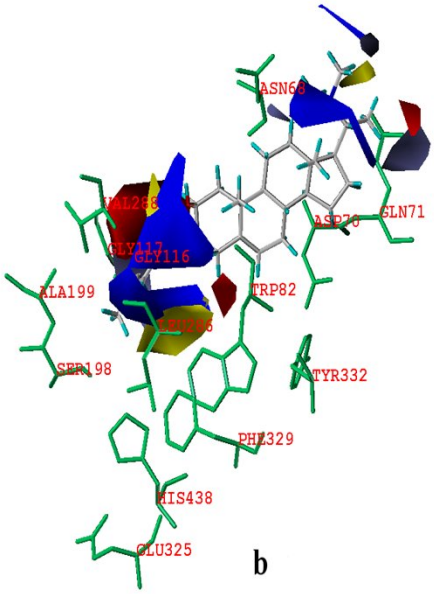
Parameters	Model9	Model21	Model72	Model80
q^2	0.902	0.911	0.730	0.701
r^2	0.998	0.998	0.994	0.990
Standard Error of Estimate	0.022	0.020	0.040	0.050
F	2326.92	2957.134	738.562	460.228
No. of Components	6	6	6	6
Fraction				
Steric	0.499	0.484	0.500	0.537
Electrostatic	0.501	0.516	0.500	0.463

Prediction of Activities



87





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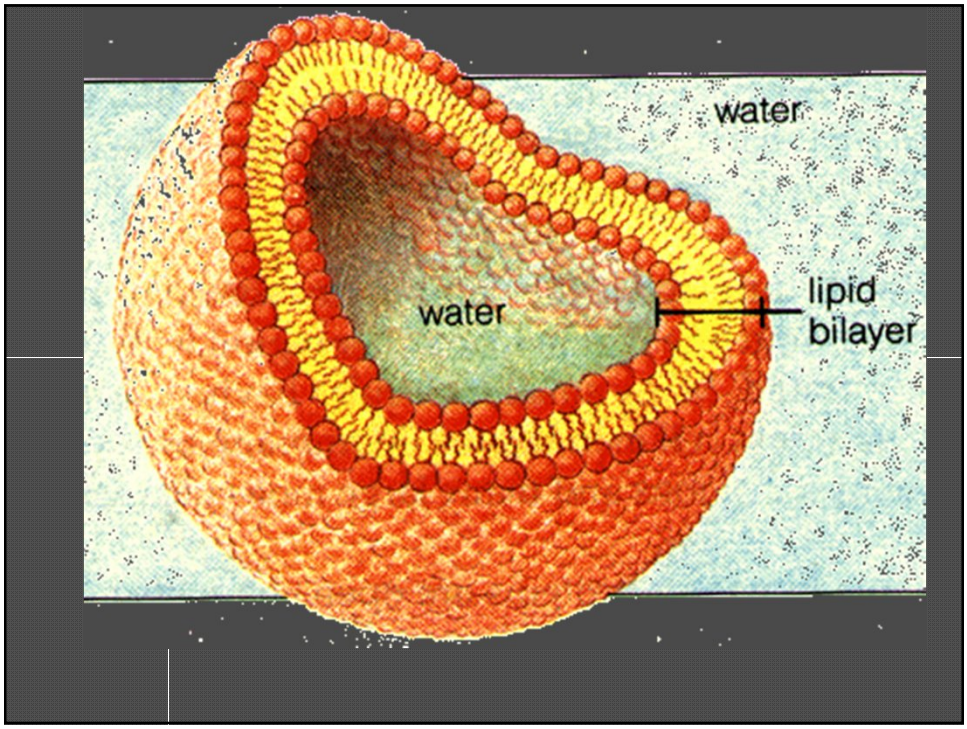
SIMULATION OF LIPID BILAYER WITH NANOPARTICLES AND PLA2 ENZYME USING VMD/NAMD SOFTWARE

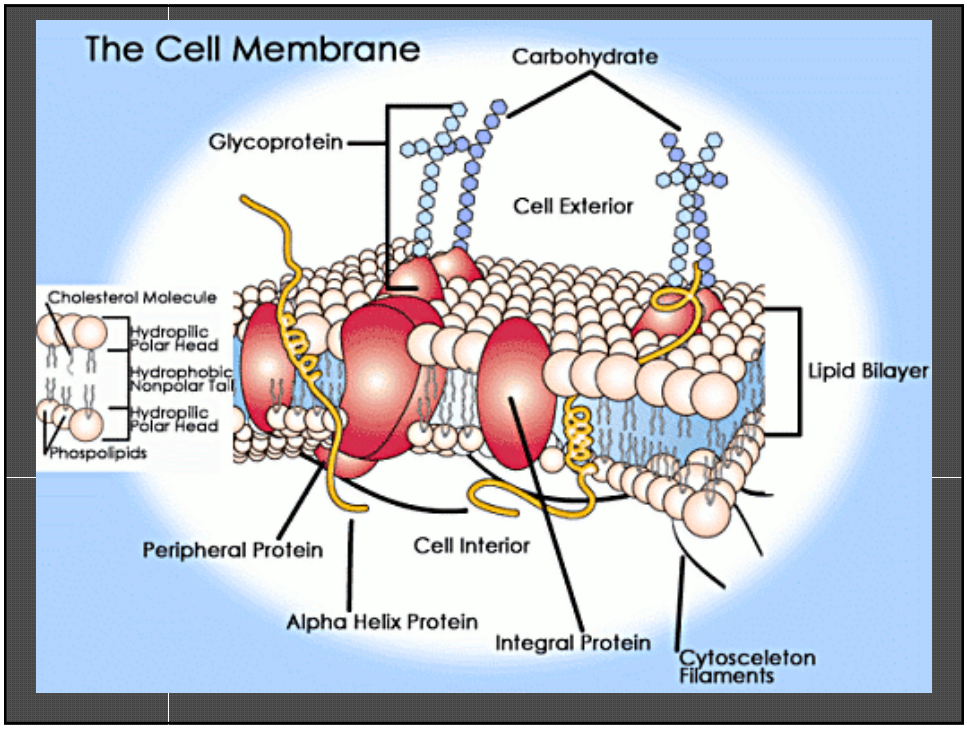
Silica inhalation through mining, tunneling, rock drilling, sand blasting, or working with concrete has been linked to silicosis.

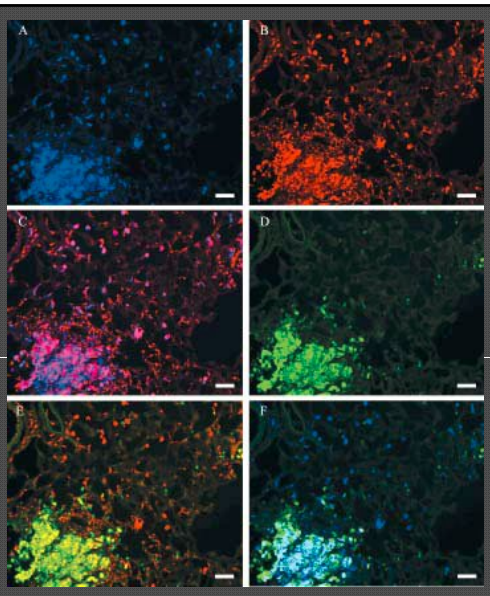
A pulmonary disease characterized by a severe decline in respiratory function and premature death

- Fine respirable-sized crystalline silicon dioxide mineral dusts (quartz or other polymorphs), are well-documented etiological agents for pulmonary fibrosis by epidemiological studies of human occupational exposures and by animal model inhalation or installation studies.
- Causes lung cancer

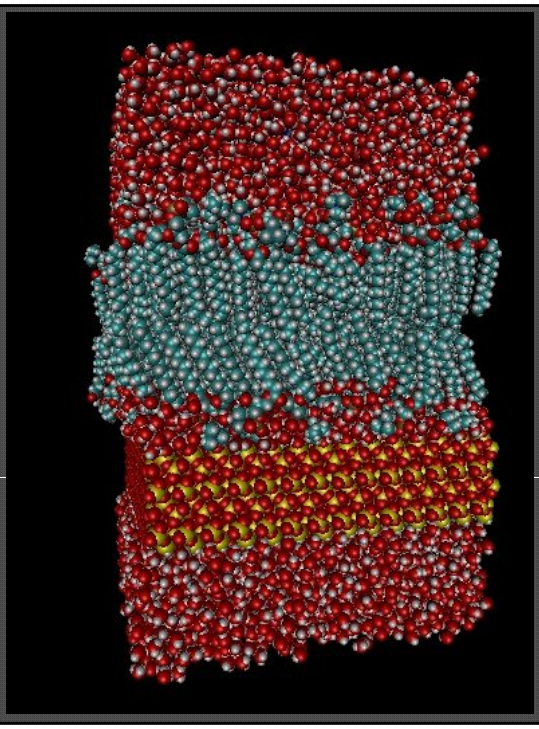
- The goal of this proposed project is to develop and explore computational models that can be used to understand,explore and expand our knowledge on the effects that certain nanoparticles play when interacting with biological tissue.

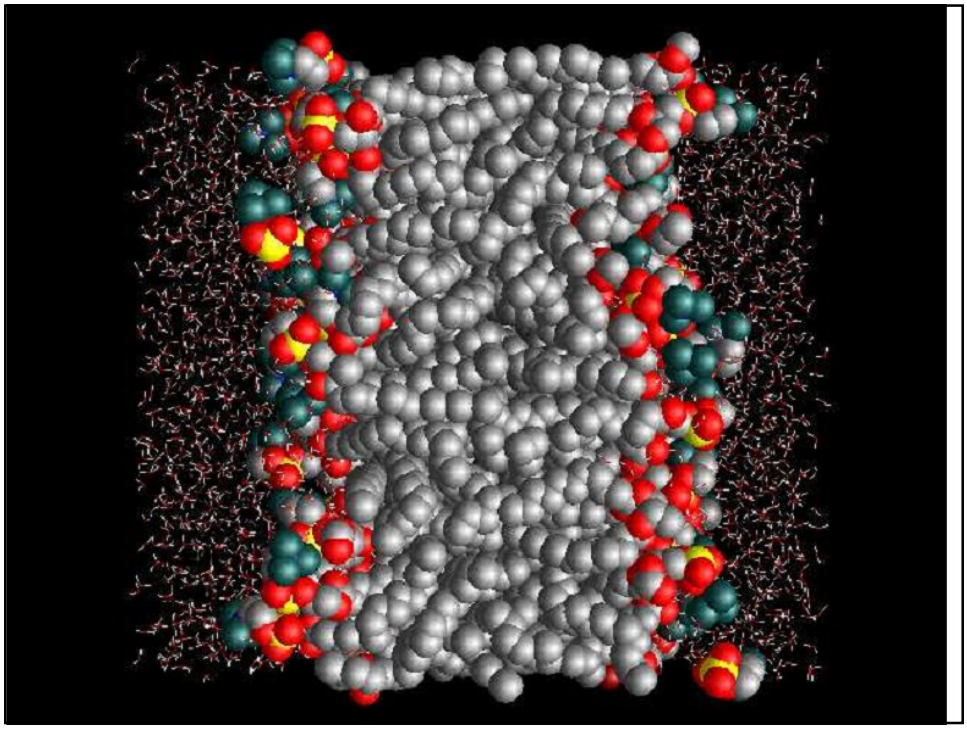

water
water
lipid
bilayer


The Cell Membrane
Carbohydrate
Glycoprotein
Cell Exterior
Cholesterol Molecule
Hydrophilic
Polar Head
Hydrophobic
Nonpolar Tail
Hydrophilic
Polar Head
Phospolipids
Lipid Bilayer
Peripheral Protein
Cell Interior
Alpha Helix Protein
Integral Protein
Cytosceleton
Filaments



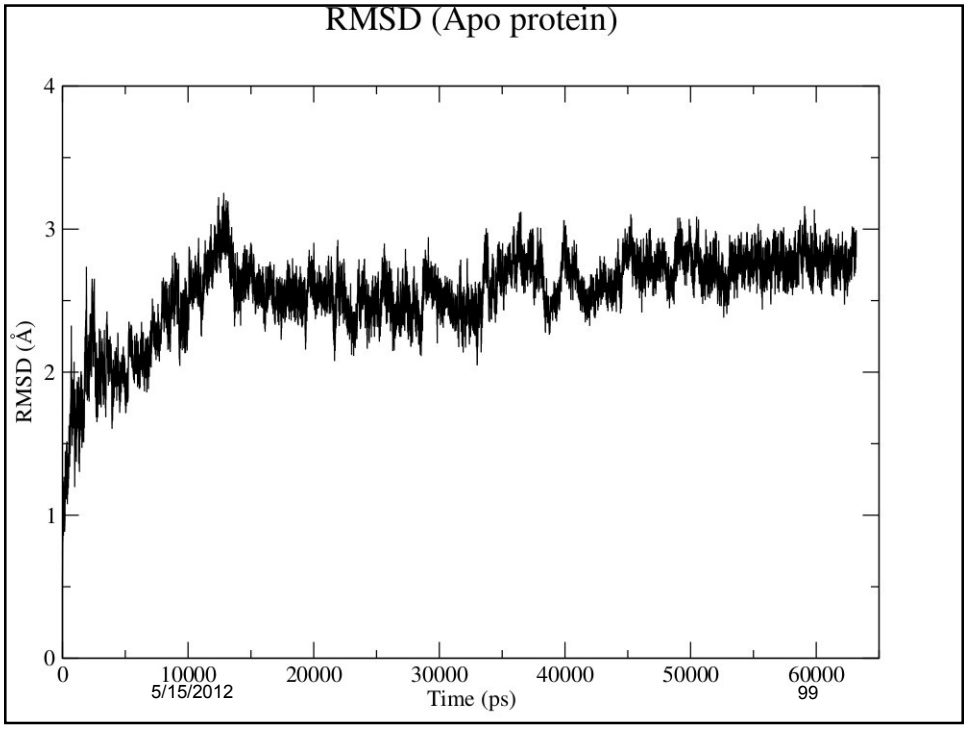
Identification of cells expressing in silica-treated rat lung.

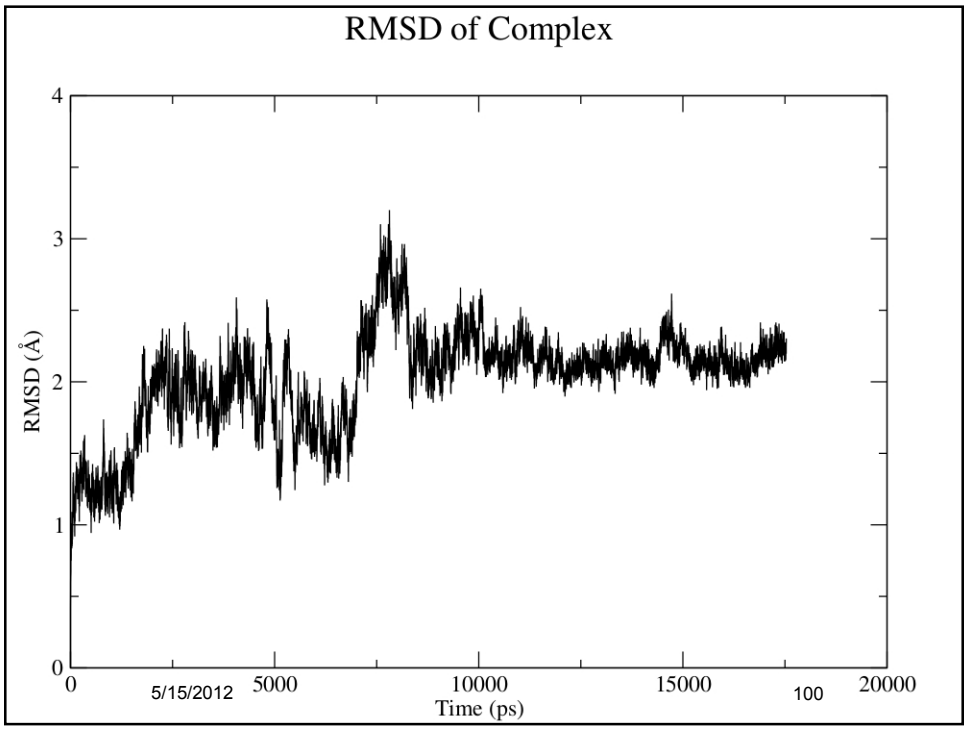


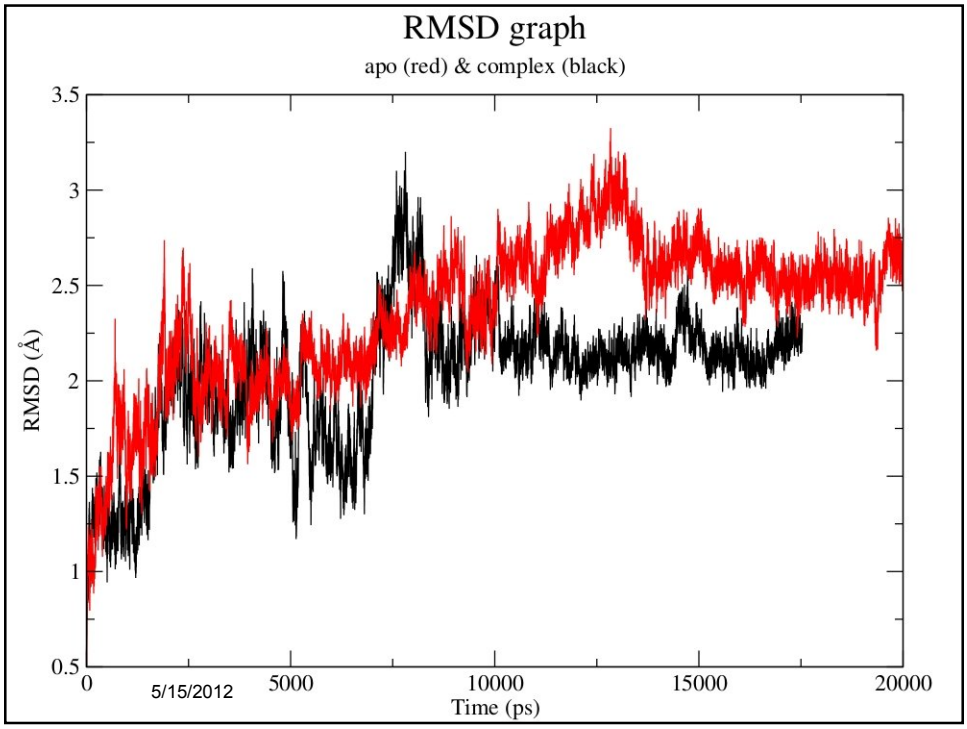


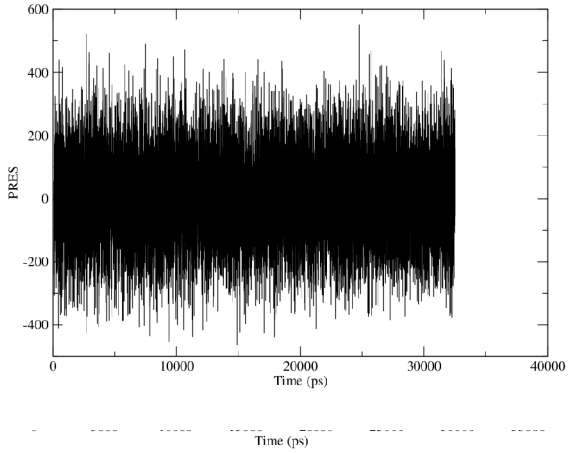
VMD

98


RMSD (Apo protein)
RMSD (Å)
Time (ps)
0
1
2
3
4
0
10000
20000
30000
40000
50000
60000


RMSD of Complex
RMSD (Å)
Time (ps)
0
1
2
3
4
0
5000
10000
15000
20000


RMSD graph
apo (red) & complex (black)
RMSD (Å)
Time (ps)
3.5
3
2.5
2
1.5
1
0.5
0
5000
10000
15000
20000


PRES
Time (ps)
600
400
200
0
-200
-400
0
10000
20000
30000
40000

Not all chemists wear white coats...

Computer Experiments

- provide atomistic picture of (bio)chemical systems
- help to characterize and understand reaction mechanisms

  ⇒ planning of laboratory experiments
  ⇒ computational modelling of catalysts and enzymes
  ⇒ rational design of drugs and biomimetics

Current Limits and Future Perspectives

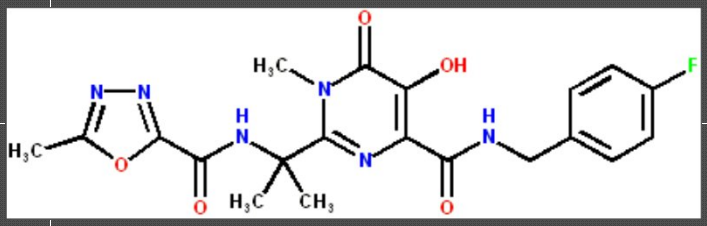
- accuracy of electronic structure method
- system size
- limited time scale

⇒ improved QM/MM methods
⇒ long time scale techniques

Thanks for Your Time

First clinically-approved:

- Prof. J. Andrew McCammon and his colleagues used **AutoDock** and the **Relaxed Complex Method** to discover novel modes of inhibition of HIV integrase. Researchers at Merck Pharmaceutical Company have used McCammon's work to design new drugs that target integrase, which led in October 2007 to the first clinically-approved HIV Integrase inhibitor: Isentress™ (raltegravir).



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