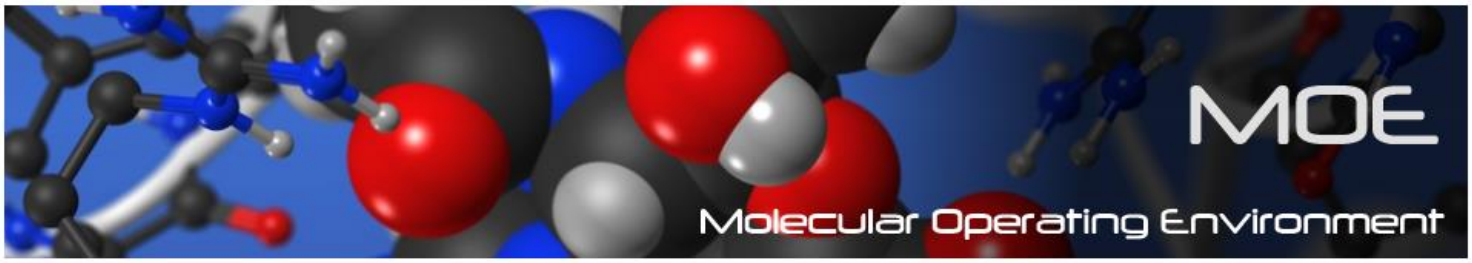
How to find the right drug?

DRUG DESIGN BASED ON MOLECULAR DOCKING



http://chemcomp.com/

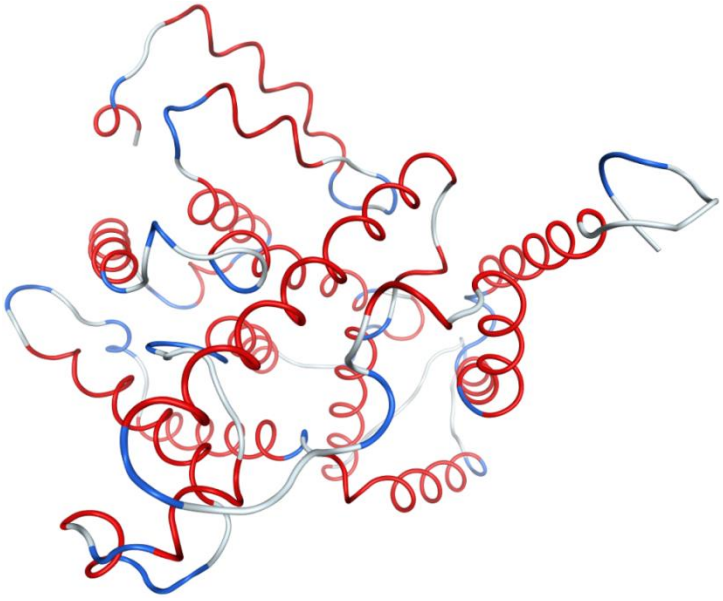
OBJECTIVES

- **Search for ligands of Phosphodiesterase 4**

1. **Structural data loading**
2. **Preprocess the raw crystallographic structure data**
3. **Search for the active sites**
4. **Ligand docking with use of several different protocols**
5. **Analysis of ligand Interactions**

PHOSPHODIESTERASE 4

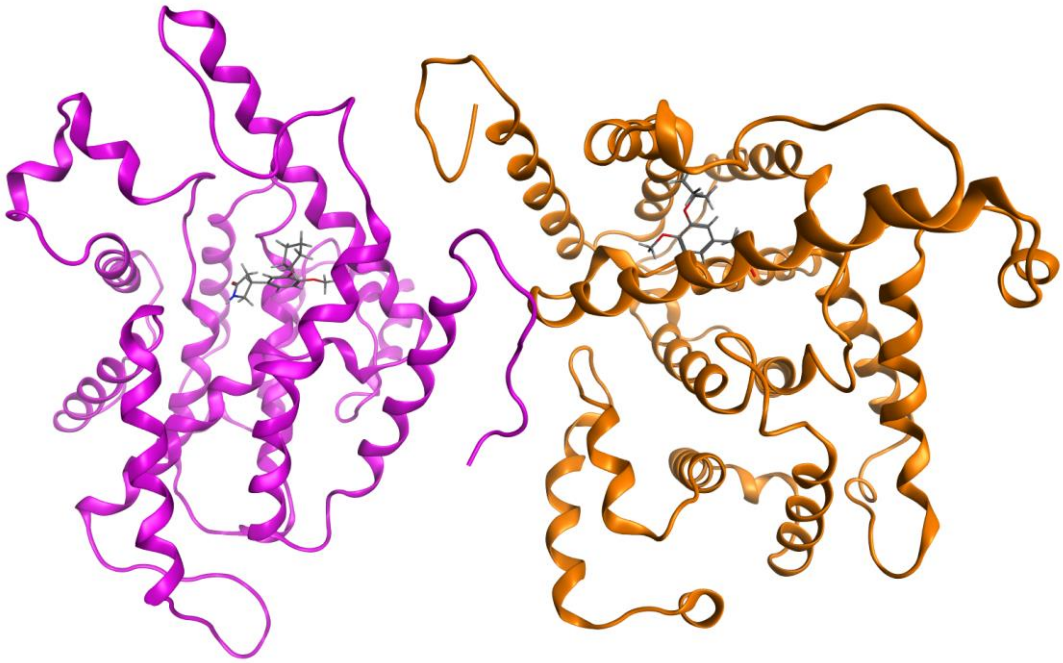
- Phosphodiesterase catalyzes the hydrolysis of the intracellular second messenger cyclic AMP
- Important in many biological processes
- Attractive target for the treatment of asthma



1. STRUCTURAL DATA LOADING

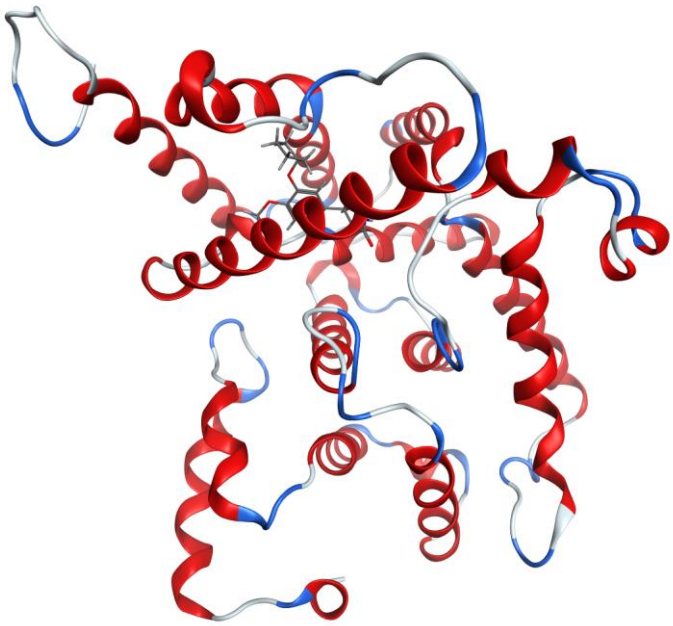
- Download the crystal structure of **PDE4B2B**
  - http://www.rcsb.org/
  - Search by PDB ID – 1RO6
  - Download Files as PDB File (Text)
  - Open MOE
  - **MOE | File | Open | $/Downloads/1ro6.pdb**
    - In the Load PDB File panel press OK.

- Try different display options
  - **MOE | Footer | Ribbon**
  - **MOE | RHS | Hide | All Atoms**
  - **MOE | RHS | Show | Ligand**
  - **MOE | RHS | Center**



2. STRUCTURE PREPARATION

- Deleting identical structures and waters
  - Open the Sequence Editor by pressing SEQ in the upper right corner of the MOE Window
  - Select strings 2 4 5 6 using ctrl and press delete
  - Close the Sequence Editor



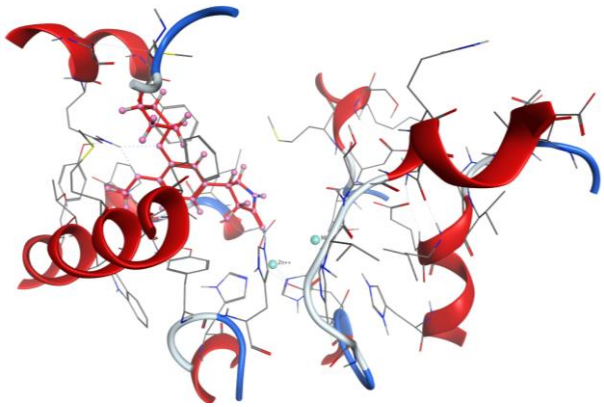
- Correct Structural Issues
  - **MOE | Compute | Prepare | Structure Preparation**
  - Press Correct in the panel

- Optimize hydrogen bond network
  - **MOE | Compute | Prepare | Protonate3D**
  - Press OK in the panel

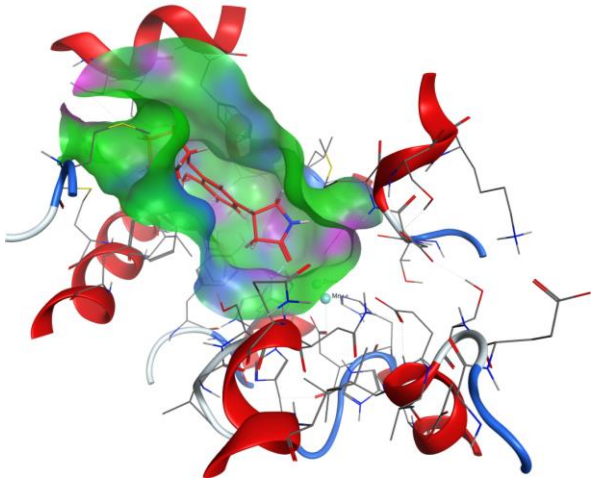
- Setup the Force field
  - **MOE | Footer | Potential Setup | Load menu | MMFF94x**

3. IDENTIFICATION OF THE BINDING SITE

- Identify the active site
  - **MOE | Compute | Site Finder**
  - Press Apply in the Site Finder panel
  - Select the first site in the list
  - Press **Isolate: Atoms and Backbone** in the Site Finder panel
  - Close the Site Finder panel
  - **MOE | RHS | Show | Ligand**
  - **MOE | Select | Ligand**
  - **MOE | Footer | Atoms | Color | Red**

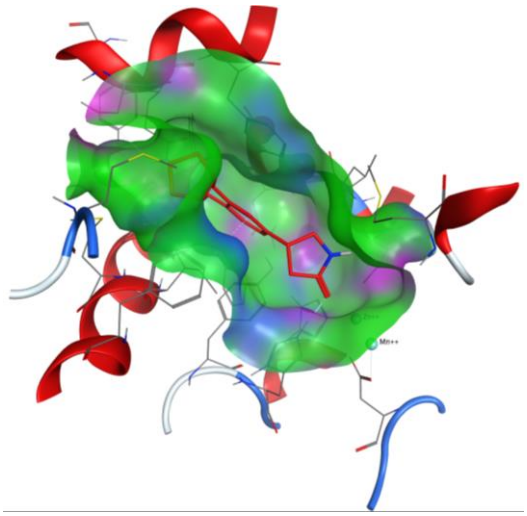


- Draw a surface around the binding site
  - **MOE | RHS | Surfaces and Maps**
  - Press Create in the panel
  - Press **Color | ActiveLP** in the panel
  - Set the transparency of the binding pocket
  - Close the panel



4. DOCKING SIMULATIONS

- Show only the ligand and pocket residue atoms
  - **MOE | RHS | SiteView**



- Open the Dock panel
  - **MOE | Compute | Dock**
  - In the Dock panel set Protocol: Rigid Receptor and press Run

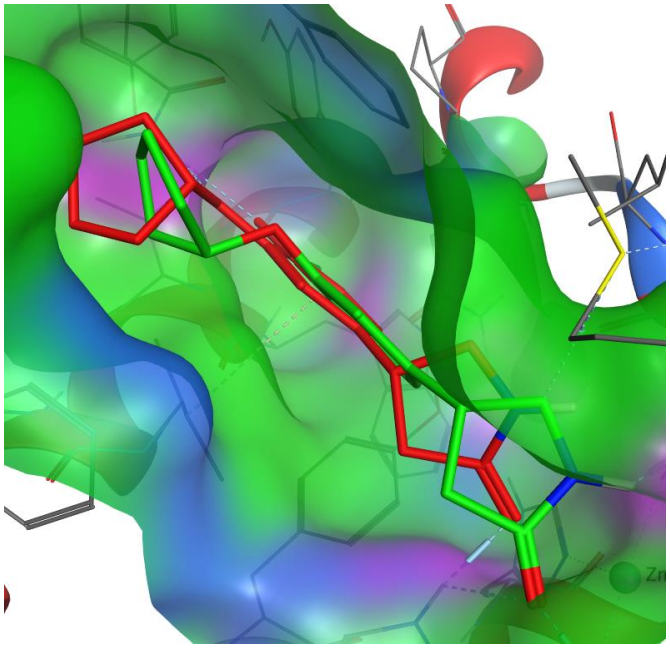
	mol	rseq	mseq	S	rmsd	rmsd_refine	E_conf	E_place	E_score1	E_refine	E_score2
1		1	1	-8.9385	1.8954	1.1300	30.2364	-83.5292	-9.5943	-50.0045	-8.9385
2		1	1	-8.6937	1.6794	1.5013	30.8530	-129.8541	-9.4578	-46.7046	-8.6937
3		1	1	-8.1812	6.4746	5.8313	28.2536	-76.7929	-10.3435	-58.4576	-8.1812
4		1	1	-7.4943	4.0462	0.9234	34.4957	-79.7363	-9.5807	-33.5665	-7.4943
5		1	1	-7.2197	0.6348	2.3095	28.4378	-75.0434	-10.2634	-24.1777	-7.2197
6		1	1	-7.0860	3.8828	1.0214	29.7339	-92.0652	-10.0537	-21.1683	-7.0860
7		1	1	-6.8872	3.9661	1.8803	31.3296	-74.1856	-9.4735	-22.9958	-6.8872
8		1	1	-6.6955	0.8871	1.5925	29.6665	-76.7087	-10.5738	-15.6781	-6.6955
9		1	1	-6.6928	0.8421	1.3267	30.1384	-80.0752	-9.3735	-19.2304	-6.6928
10		1	1	-6.6346	3.7831	1.7399	28.6132	-67.0618	-9.3482	-17.7971	-6.6346
11		1	1	-6.4189	3.9407	1.5452	39.5849	-69.8085	-9.4199	-17.8201	-6.4189
12		1	1	-5.3169	6.4044	0.9294	30.3371	-71.8969	-9.2872	-5.8503	-5.3169
13		1	1	-5.3007	6.6084	1.0369	29.2755	-72.0718	-9.7812	-5.2744	-5.3007
14		1	1	-5.0893	6.4839	1.7352	29.9078	-68.8564	-10.6579	-5.3237	-5.0893
15		1	1	-4.9790	6.6891	0.9509	29.0592	-68.8232	-10.0315	-4.0998	-4.9790
16		1	1	-4.9481	6.6717	1.3940	31.2565	-70.4891	-10.1917	-3.4556	-4.9481
17		1	1	-3.7253	5.7267	1.1168	39.5527	-94.6181	-9.4435	10.0425	-3.7253

S	The final score
rmsd	The root mean square deviation of the pose, in Å, from the original ligand
rmsd_refine	The root mean square deviation between the pose before refinement and the pose after refinement
E_conf	The energy of the conformer
E_place	Score from the placement stage
E_score1 and 2	Score from rescoring stages 1 and 2
E_refine	Score from the refinement stage

- Repeat previous steps with following protocols:
  - **Virtual Screening**
    - Ligand: MDB file | Browse | $/sample/mol/1RO6_ligands.mdb
    - Retain 30
  - **Rigid receptor + library of ligands**
    - Ligand: MDB file | Browse | $/sample/mol/1RO6_ligands.mdb
    - Retain 10
  - **Induced Fit+ library of ligands**
    - Ligand: MDB file | Browse | $/sample/mol/1RO6_ligands.mdb
    - Retain 10

5. ANALYSIS OF LIGAND INTERACTIONS

- Browse poses from the output database
  - **Database Viewer | File | Browse**
    - **Atoms | Color | Green**
    - Press arrows for browsing



- Show original ligand interactions
  - **MOE | Compute | Ligand Interactions**
    - Receptor: Complex #1 1RO6.A
    - Ligand: Complex #1 1RO6.A
    - Press Apply
    - See the figure 1
- Show selected ligand interactions
  - **MOE | Compute | Ligand Interactions**
    - Receptor: Complex #2 1RO6.A
    - Ligand: Complex #2 1RO6.A
    - Press Apply
    - See the figure 2

- Overlie two ligands
  - **MOE | Compute | Ligand Interactions**
    - Receptor and Ligand: Overly
    - Press Apply
    - See the figure 3

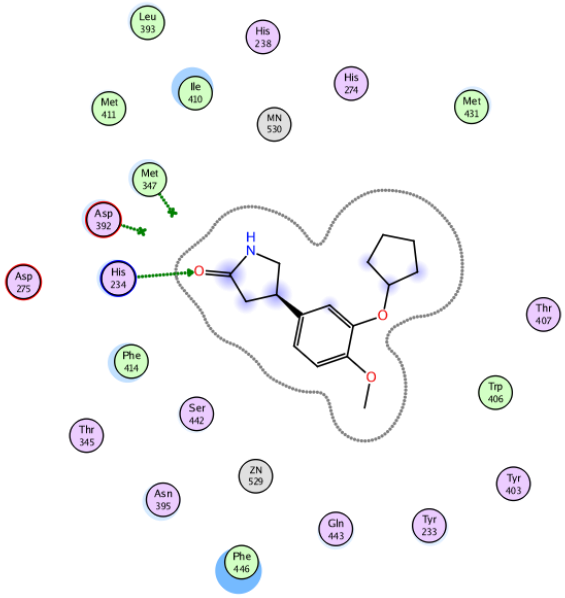


Figure 1: The original ligand.

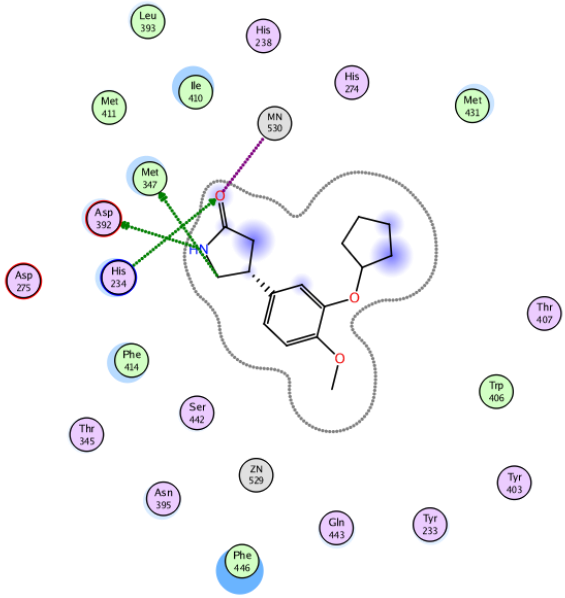


Figure 2: The selected ligand.

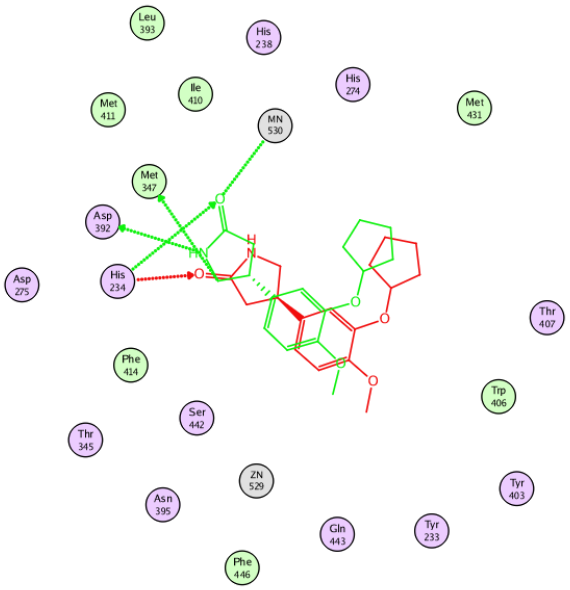
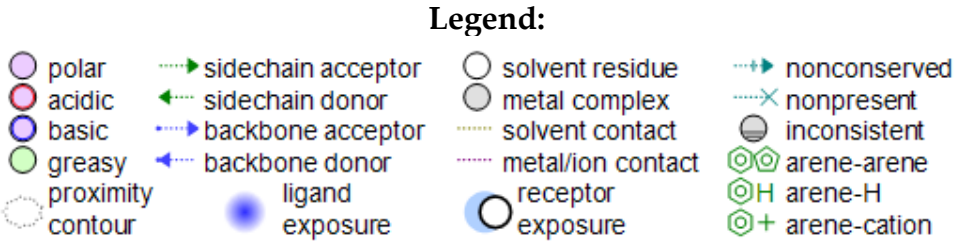


Figure 3: The two ligand overlay.



REFERENCE:

Molecular Operating Environment (MOE), 2013.08; Chemical Computing Group Inc., 1010 Sherbooke St. West, Suite #910, Montreal, QC, Canada, H3A 2R7, 2015.

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