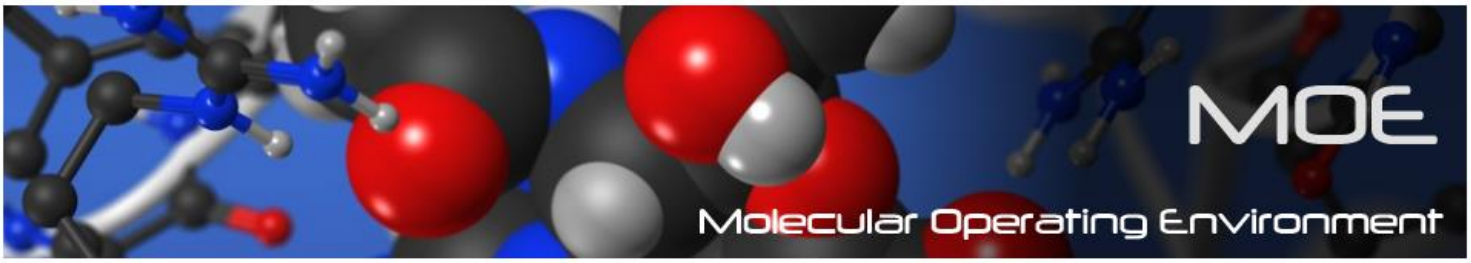
How to find the right drug?

DRUG DESIGN BASED ON PHARMACOPHORE MODELING



http://chemcomp.com/

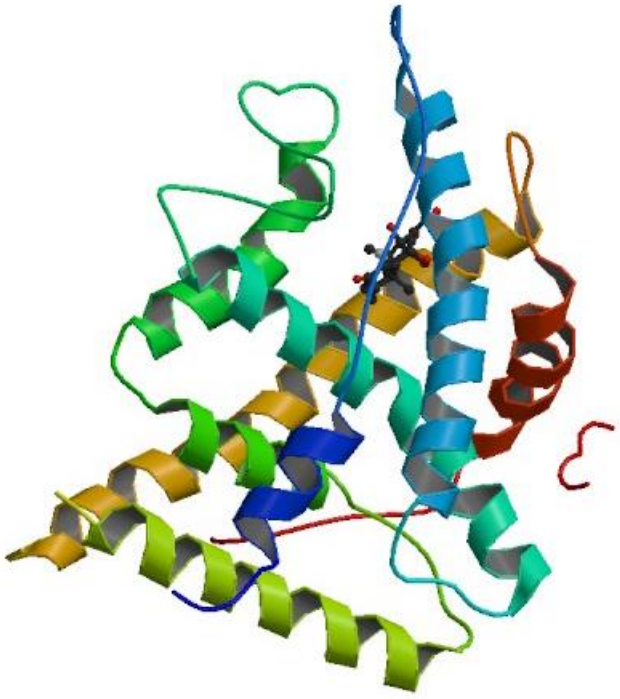
OBJECTIVES

- **Search for ligands of glucocorticoid receptor**

  1. **Creating phramacophore queries from database of inhibitors**
  2. **Identifying potential hits in a chemical database**
  3. **Repeating the database query**
  4. **Modifying the pharmacophore and comparing results**

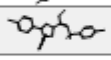
GLUCOCORTICOID RECEPTOR (GR)

- The receptor to which cortisol and other glucocorticoids bind
- Expressed in almost every cell in the human body
- Regulates genes controlling the development, metabolism and immune response
- Pleiotropic effects in different parts of the body



1. CREATING PHRAMACOPHORE QUERIES FROM DATABASE OF INHIBITORS

- Open Inhibitor Database
  - Raise the Open panel
    MOE | RHS | Open
  - Select the database file - **inhibitors.mdb**
  - Open the database
    OK

	mol	CB1 Ki (nM)	name	CB2 Ki (nM)
1		0.0003	NESS 0327	21.0000
2		1.9800	rimonabant	1000.0000
3		5.8000	Compd4	2321.0000
4		7.8000	SLV 319	7943.0000
5		70.3000	Compd3	
6		100.0000	Compd1	
7		141.0000	LY 320135	10000.0000
8		100.0000	Compd2	

- Generating Pharmacophores with the Elucidator
    - Open the Pharmacophore Elucidation panel

      DBV | Compute: Pharmacophore: Elucidate...

      - Database of inhibitors appears as the input
      - Change the output database name and directory
      - Set saving of the generated conformations for future elucidation runs by toggling

      Save Conformations

      - Set the conformation method

      Conformations – Conformation Import

      - Reduce the total number of conformations and the size of the search

      Conformations – Clustered

      - Set the Activity Field

      Activity Field – CB1 Ki
    - Leave the other options at the defaults and start the elucidation

      OK
    - Explore the output database opened in a database viewer

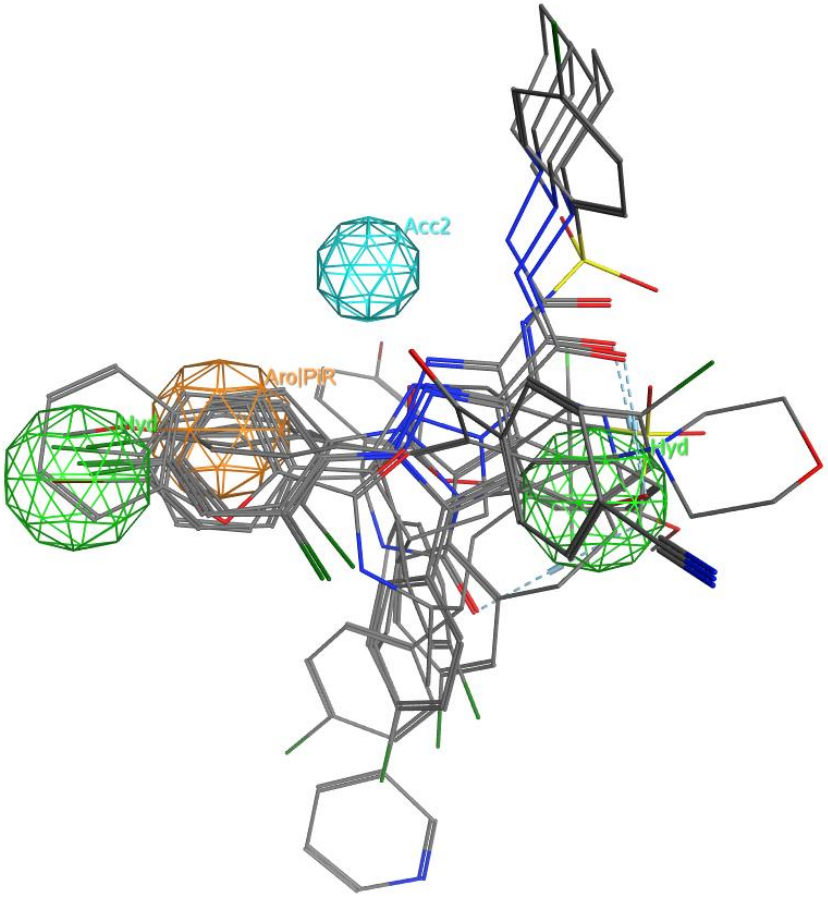
- Browsing Elucidation Results
  - Open the Database Browser

    DBV | File | Browse...

    - View the elucidated queries in the MOE window

    Database Browser: < >

    - Note the similarity of the top queries



- Saving the top query
  - Load the top query into MOE, load the query into the Pharmacophore Query Editor

    Database Browser: Edit

    - Save the query to the MOE pharmacophore file format (*.ph4 file)

    Pharmacophore Query Editor: Save...

    - Set the directory, Enter the filename and save the file

    OK

- Saving a modified query
    - Deselect everything by clicking empty space in the MOE main window
    - Add new feature of pharmacohore – Ligand Shape volume

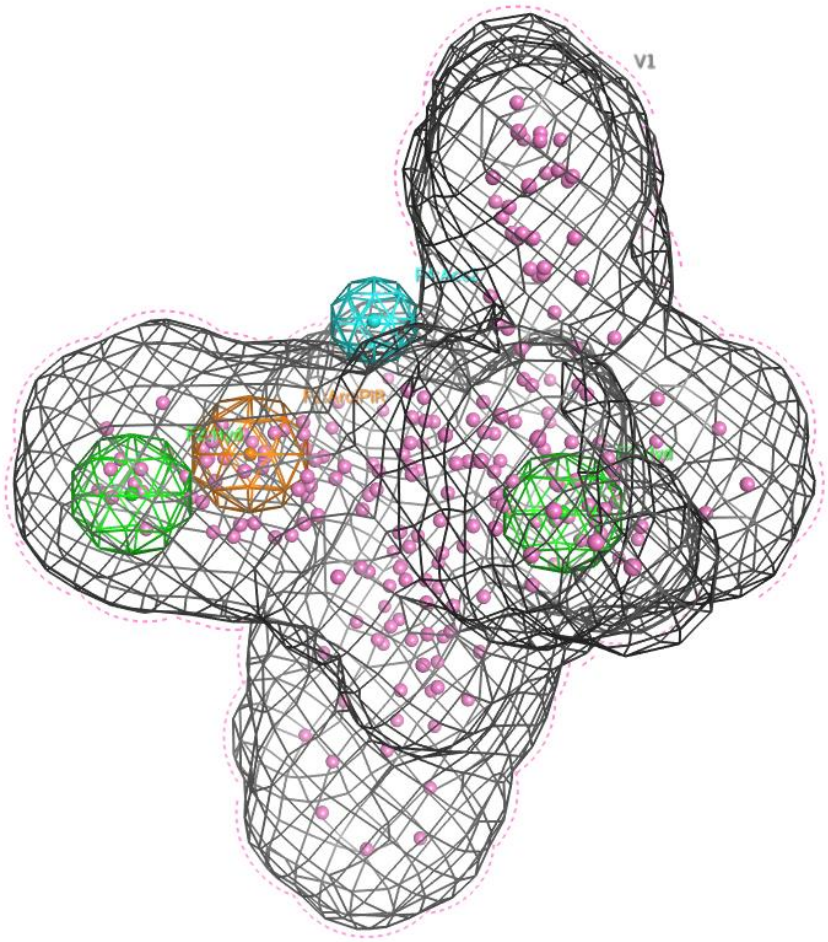
      Pharmacophore Editor: Volume – Ligand Shape

      - Save the modified query to the MOE pharmacophore file format (*.ph4 file)

      Pharmacophore Query Editor: Save...

      Set the directory, Enter the different filename and save the file

      OK
    - Close the Database Browser and Query Editor



2. IDENTIFYING POTENTIAL HITS IN A CHEMICAL DATABASE

- Launch the Pharmacophore Search panel

a) from the Pharmacophore Editor

- Open query

  MOE | RHS | Open

  - Select the pharmacophore query and open query

  OK

- Open Search panel

  Pharmacophore Editor: Search...

  - Supply a list of search databases

  - Select database to search **searchdatabase.mdb**

b) from the database of conformations to be searched

- Open searched database

  MOE | RHS | Open

  - Select database to search **searchdatabase.mdb**

  OK

- Open Search Panel

  DBV | Compute | Pharmacophore | Search

  - Set the query

- Searching the database with the query

Pharmacophore Search

- Select the database to search

Input: searchdatabase.mdb

- Subrange searched molecules by toggling **Subrange**

- Set the subrange to **Start: 1 End: 10000**

- Set the output the hits to a database by pressing

Results – Conformations

- Set the output database

Browse...

- Go with the defaults and search with the current query

Search

- Wait till the search is complete

- Check in the status line the number of hits and total molecules searched when the search is finished

query	number of hits	total molecules searched
query1		
query2		

4. REPEATING THE DATABASE QUERY

- Repeat the searching process with the second query

- Open a new query into the editor panel

Pharmacophore Editor: Open...

- Select the second query – doubleclick will load it

- Search again in the same database as previously

– Set a different name of the output database

- When the second search is done, fill the results in the table and open the output database

Pharmacophore Search - Results: Open...

3. MODIFYING THE PHARMACOPHORE AND COMPARING RESULTS

- To get more hits reduce the excluded volume radii or increase the feature radii
    - Open the Pharmacophore Editor for editing **Pharamacophore Search: Edit...**
    - Edit the features

- To get fewer hits decrease feature radii or increase excluded volume radii
    - Open the Pharmacophore Editor for editing **Pharamacophore Search: Edit...**
    - Edit the features

- Compare results

- Viewing Pharmacophore Search Results

  - Open a Database Viewer and view the hit molecules aligned to the query

  Pharmacophore Search - Results: Open...

  - Launch the Database Browser from the output database

  DBV | File | Browse...

  - Open the System Manager popup panel

  MOE | RHS | System

    - The browsed molecule will appear as the last item
    - Set the rendering of the browser atoms

    Atoms: Ball-and-Stick

  - To compare results to the query open the query

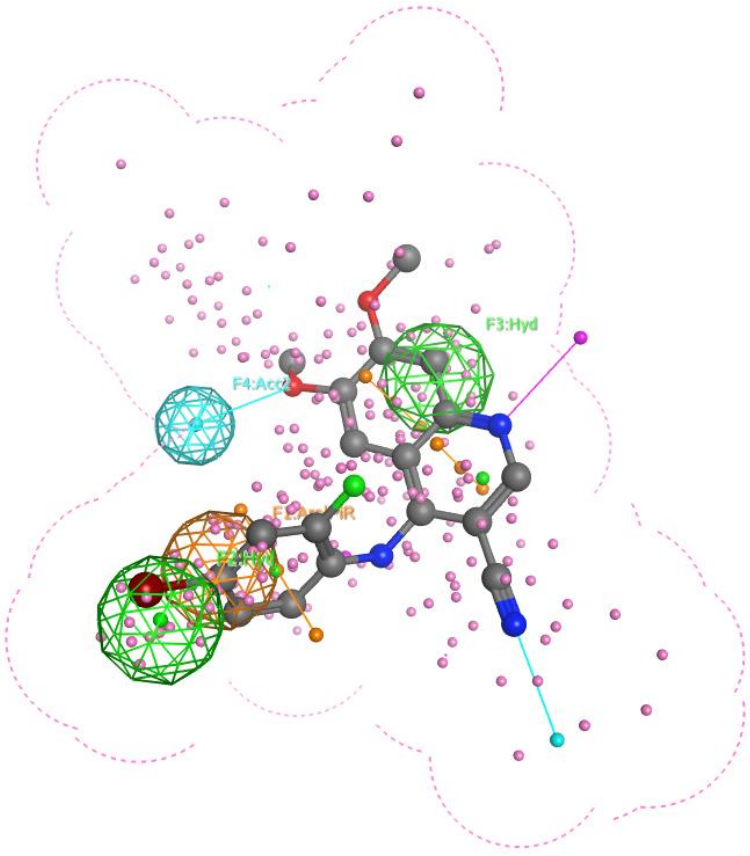
  MOE | RHS | Open

    - Select the exterior volume in the query editor and hide it

    Pharmacophore Editor: V1 – hiding eye button

  - Scroll through the hit structures and visually compare them to the pharmacophore query

    Database Browser: < | >



- Closing the system
  - Close the Database Browser
    Database Browser - Close
  - Close the Pharmacophore Editor
    Pharmacophore Editor - Close
  - Close the Pharmacophore Search panel
    Pharmacophore Search - Close
  - Delete all objects from the MOE system
    MOE | RHS | Close
    OK

Used Abbreviations:

MOE
The MOE Window, which is primary interface window of graphical MOE, containing the 3D rendering area

DBV
A Database Viewer, used for examining the contents of MOE databases. More than one can be open at any given time.

MOE | RHS
The Right Hand Side button bar of the MOE window

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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