Facultade de Química
Universidade de Vigo

"Computational approaches in drug discovery: expectations and reality."

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Here we are:

Virtual
Screening (VS)

Target
Structure Determination

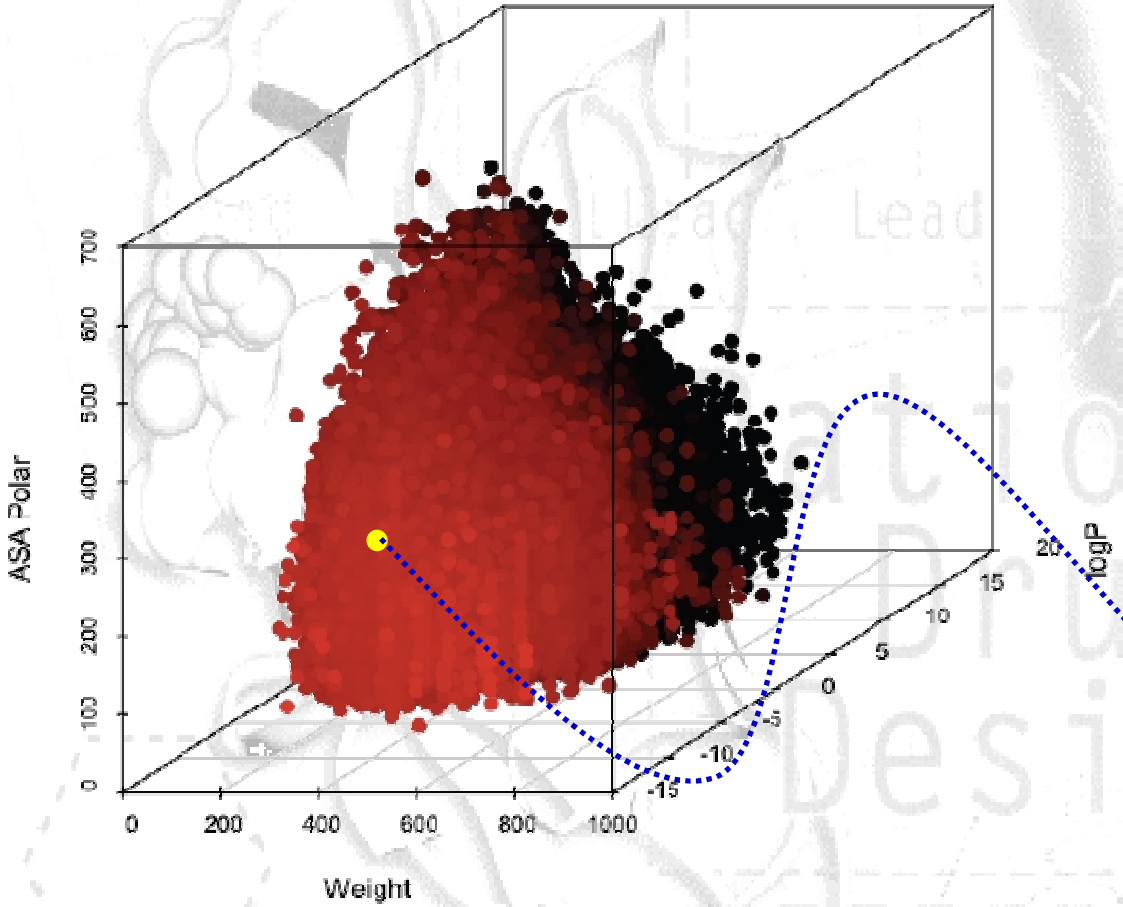
Ligand-based
Virtual Screening (LBVS)

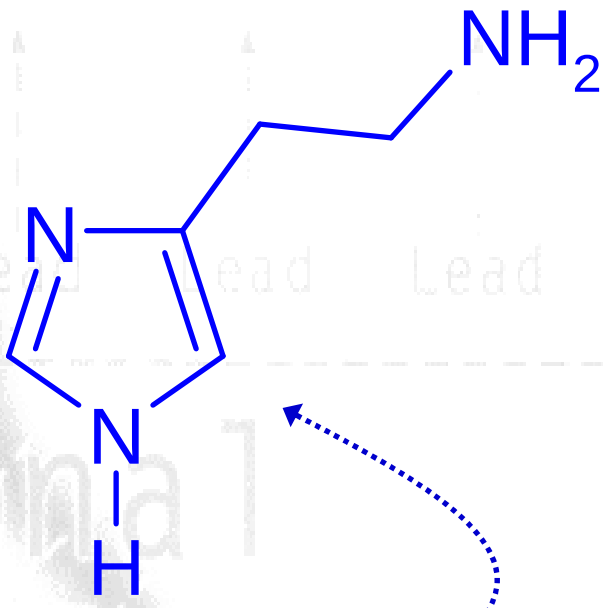
Similarity search
Pharmacophore matching

Structure-based
Virtual Screening (SBVS)

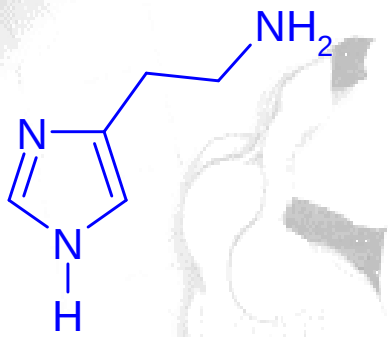
HT Molecular Docking

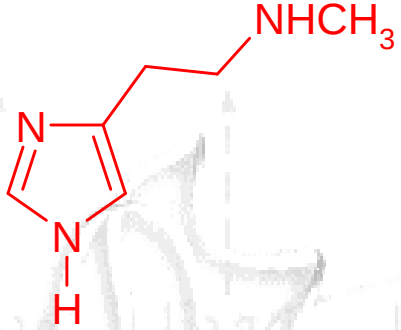
If you have only ONE active compound, could you suggest a possible strategy to fish out novel active analogs?

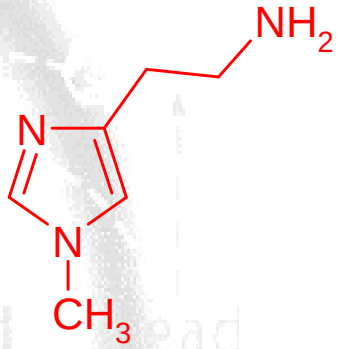


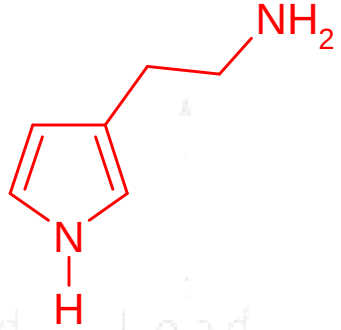


Probably using your chemical nose…

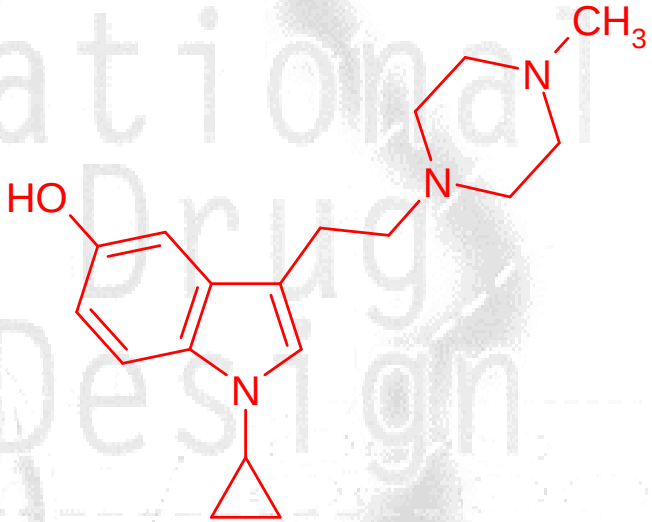




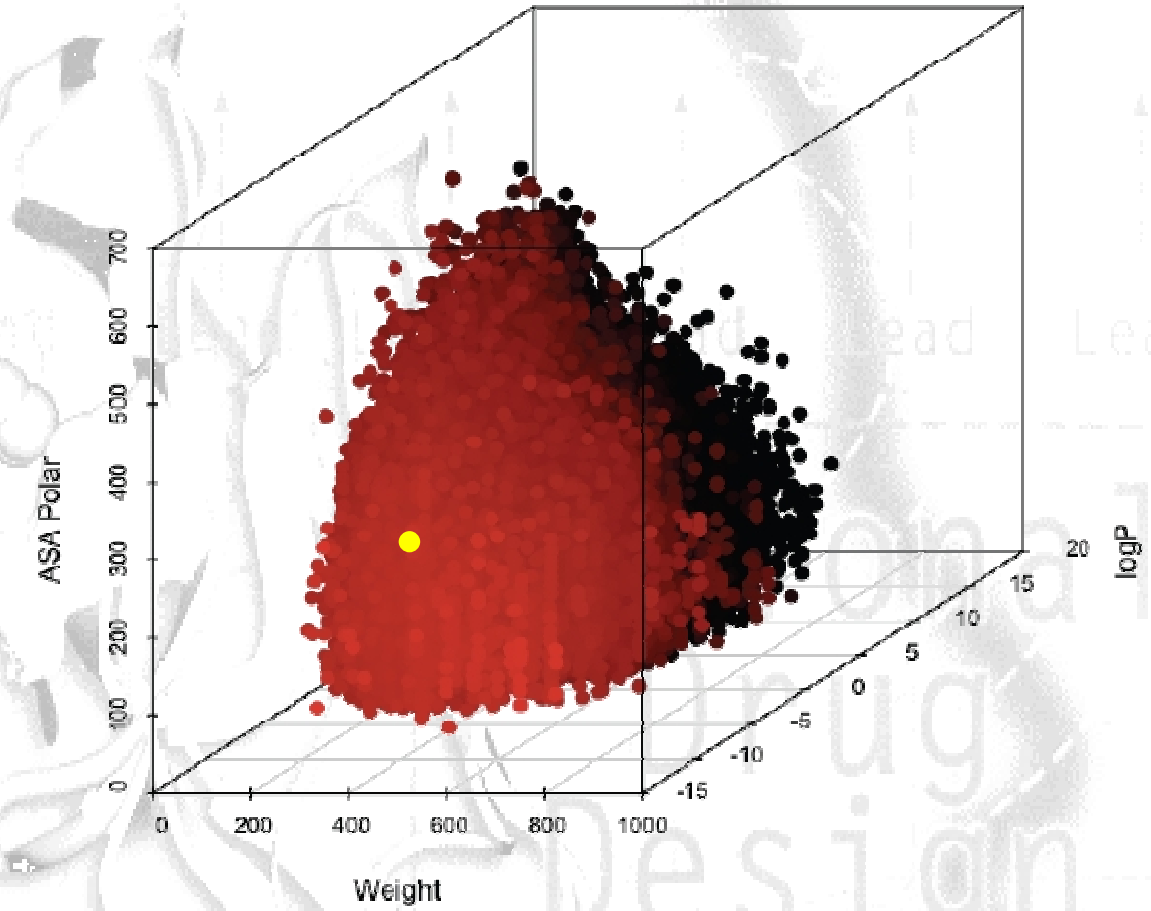




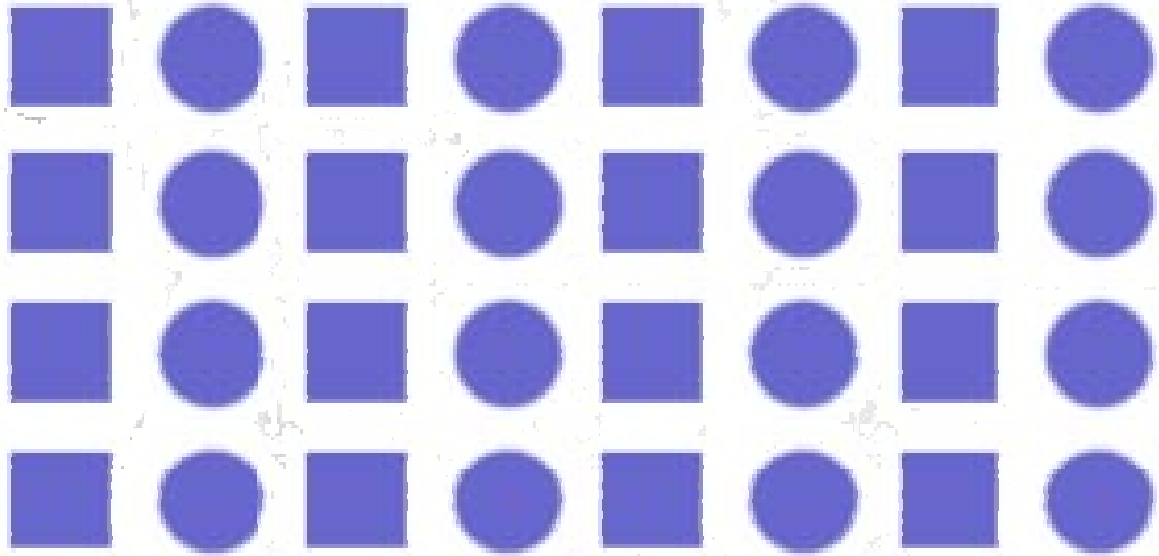
… reaching also more complex hypothesis:



or more smartly?

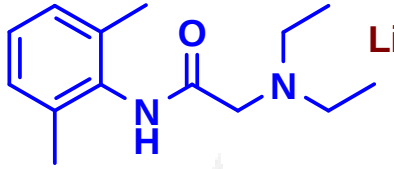


A simple exercise: could you tell me what you are looking?

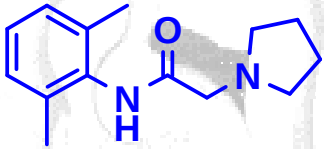


Similarity law: similar objects are typically group together.

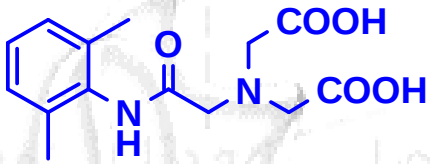
an, sometimes, this is true also in medchem:



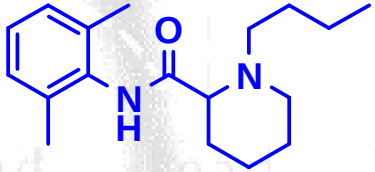
Lidocaine



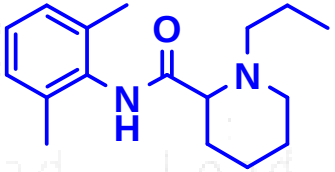
Pyrrocaine



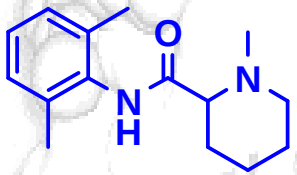
Lidofenin



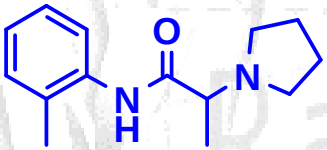
Bupivacaine



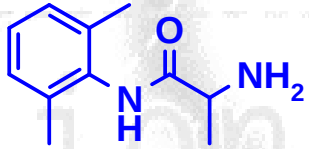
Ropivacaine



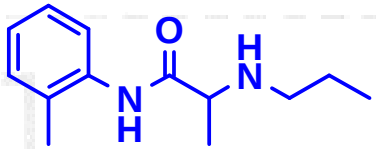
Mepivacaine



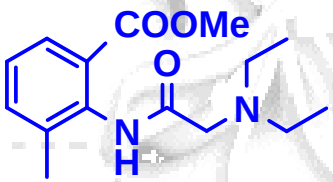
Aptocaine



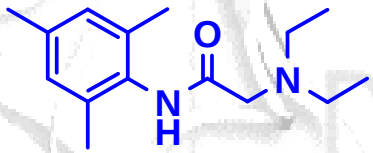
Tocainide



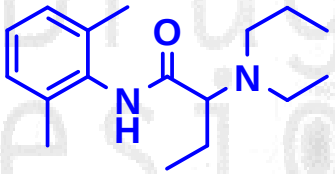
Prilocaine



Tolycaine

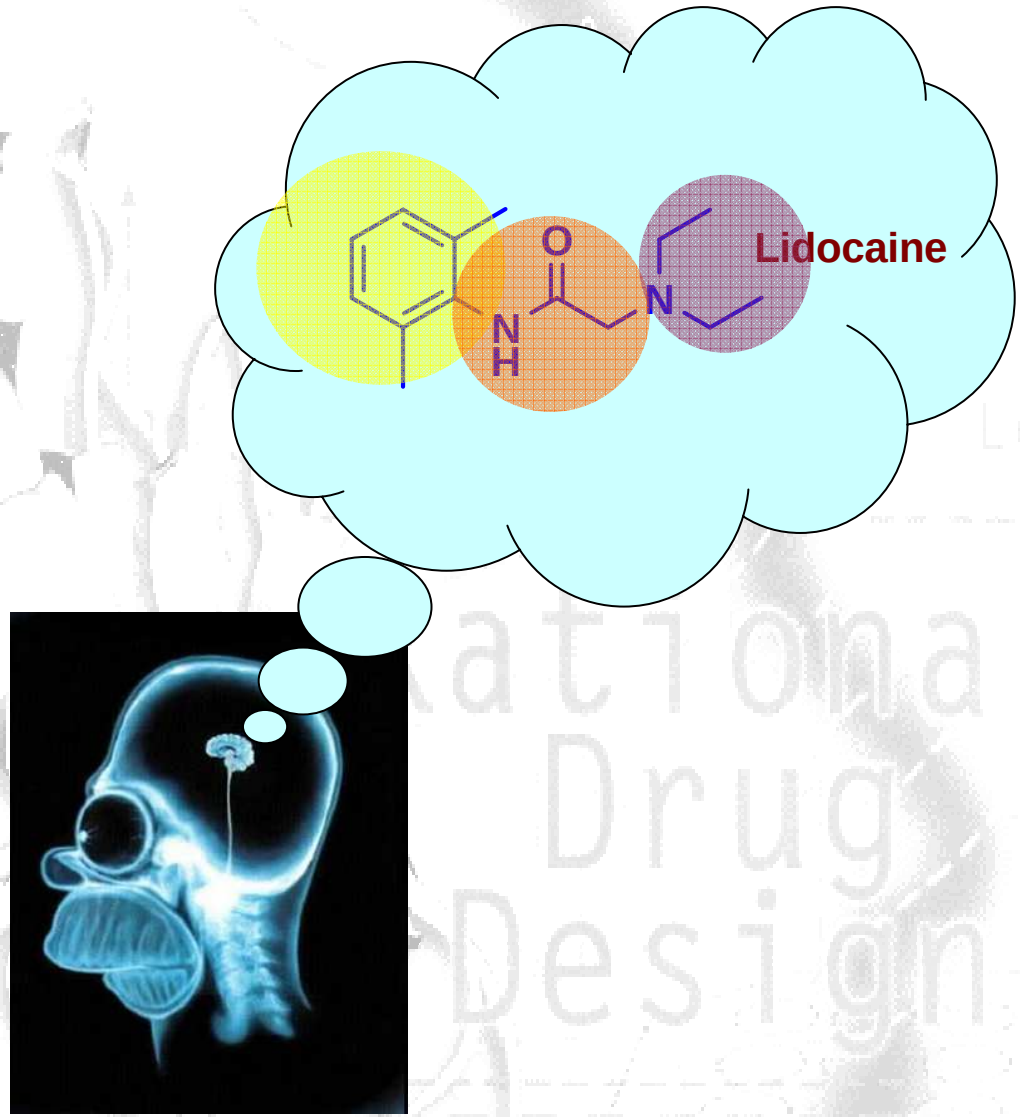


Trimecaine

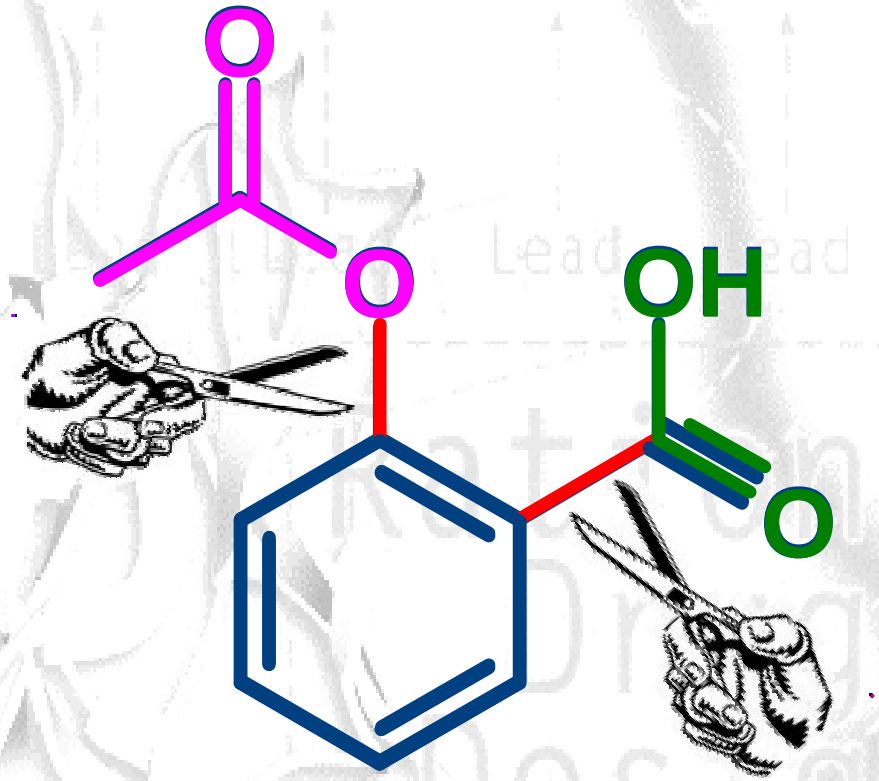


Etidocaine

Tell me what you are thinking:



Exactly "*molecular fragmentation*" could be a possible solution!

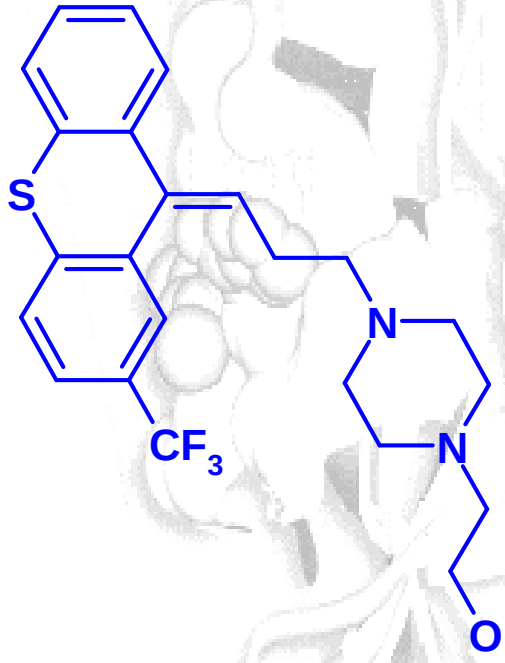


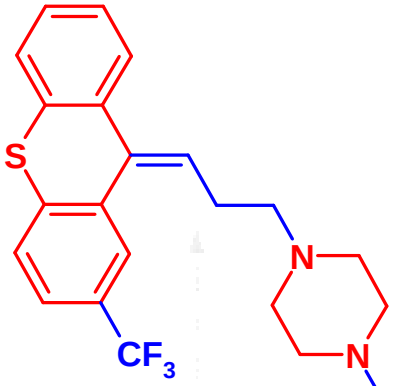
We need some rules:

1:

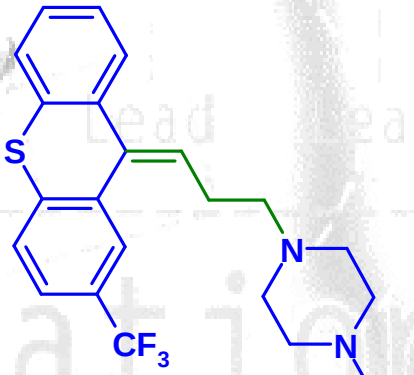
2:

3:

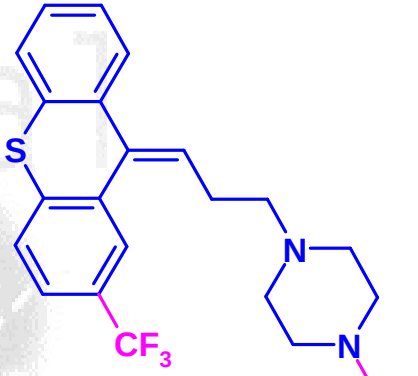




Rings



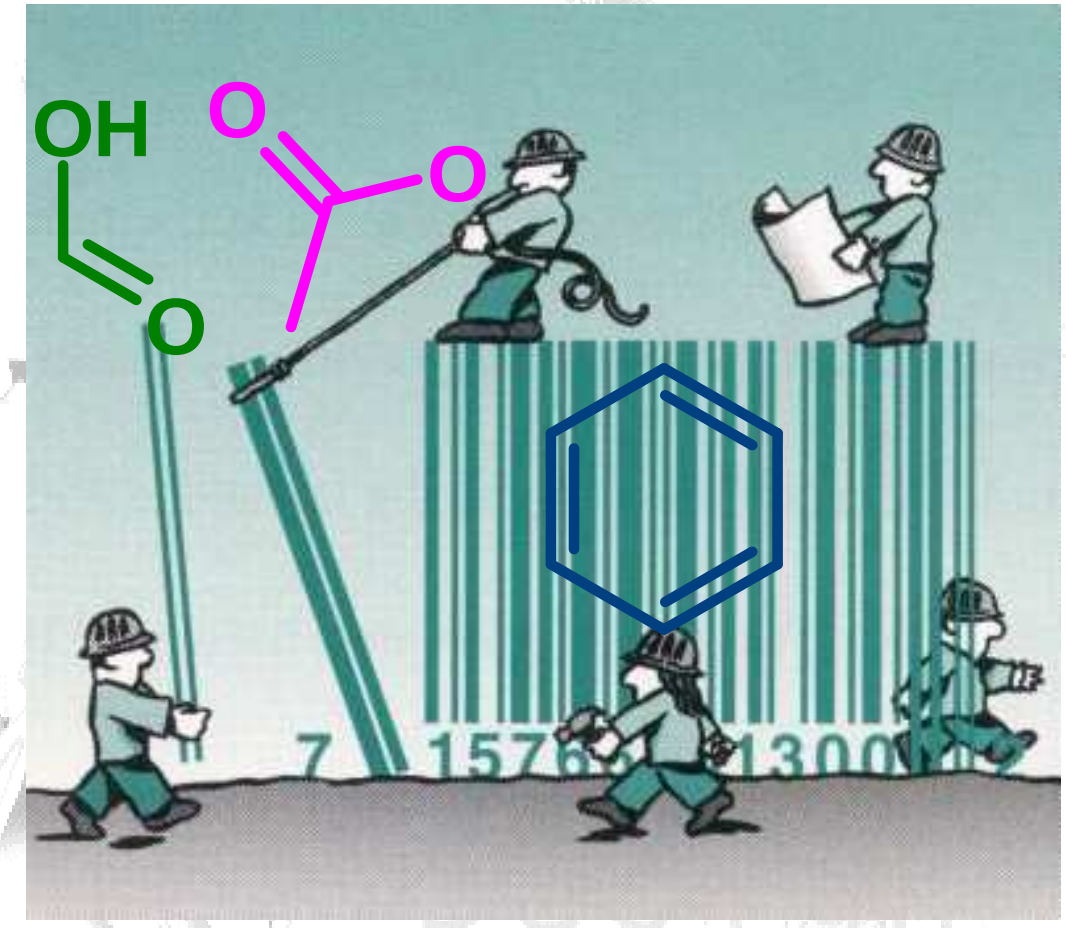
Linkers



Side chains

G.W. Bemis, M. A. Murcko, J. Med. Chem. 1996, 39, 2887 –2893.

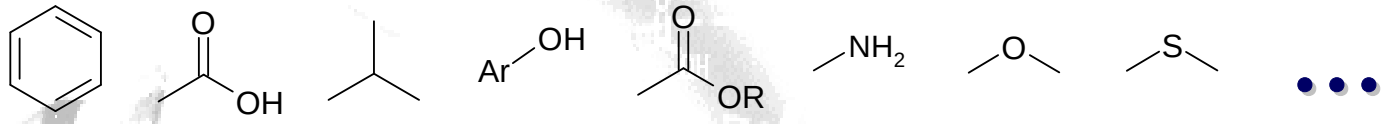
The sequence of fragments is like a molecular bar code…



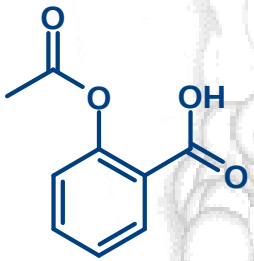
How we can build it up…

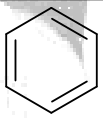
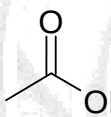
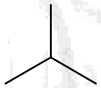
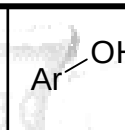
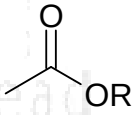
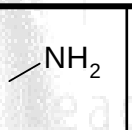
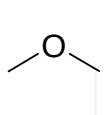
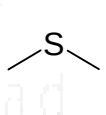
A useful concept: *structural keys*

1. Define all possible chemical fragments (*structural keys*):



2. Assigne un *bit* for the each corrispondence in our molecule:

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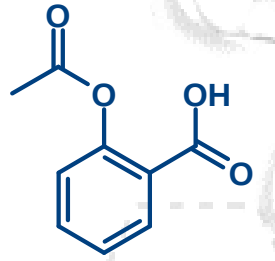
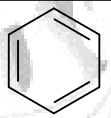
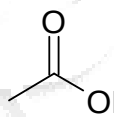
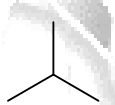
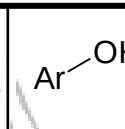
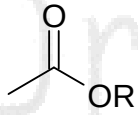
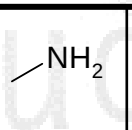
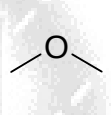
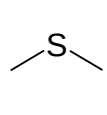
3. Reiterate this procedure for each molecule of the database :

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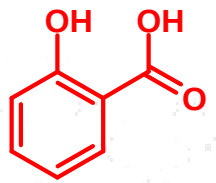
1	1	0	1	0	0	0	0

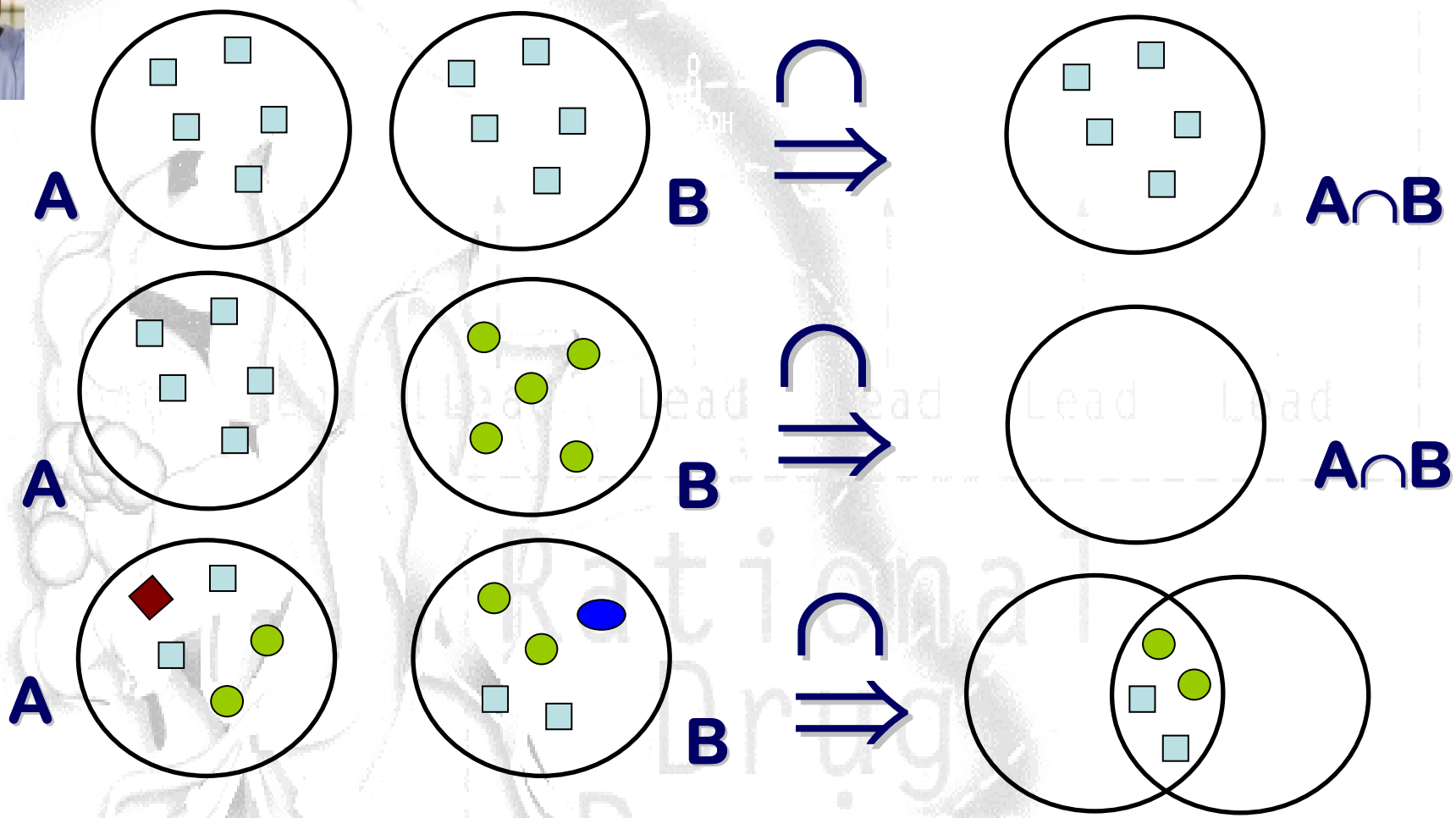


Any standard?

MACCS (Molecular ACCess System) a collection of 166 functional groups representing the most accessible medchem chemical space.

MACCS keys, MDL Information Systems Inc., San Leandro, CA.

Do you remember the Eulero-Venn diagrams?

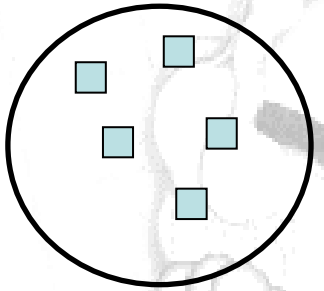


… and the intersection set A∩B?

Now, I can introduce you the Jaccard e Tanimoto index!

$$\text{Jaccard o Tanimoto Index} = \frac{A \cap B}{A_{solo} + B_{solo} + A \cap B}$$

Tanimoto, T.T. (1957) IBM Internal Report 17th Nov see also ***Jaccard, P. (1901) Bulletin del la Société Vaudoisedes Sciences Naturelles 37, 241-272*** .

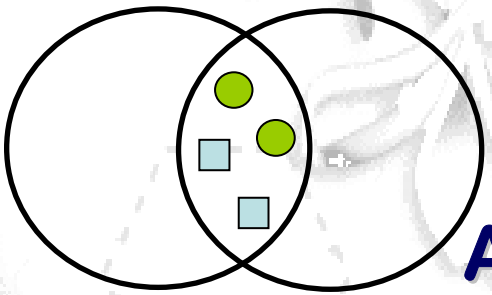


A∩B

= 1

A∩B

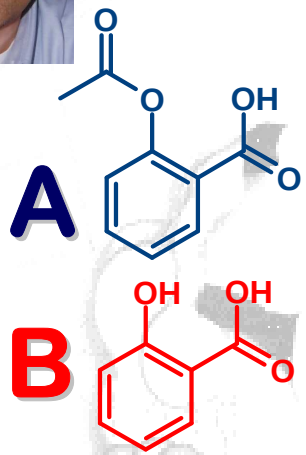
= 0

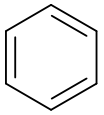
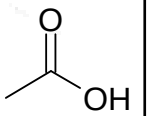
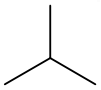
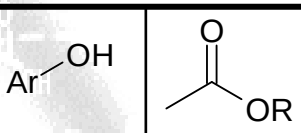
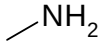
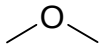
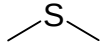


A∩B

$$= \frac{4}{1+1+4} = 0.66$$

Eureka… now it's really easy!



							
1	1	0	0	1	0	0	0
1	1	0	1	0	0	0	0

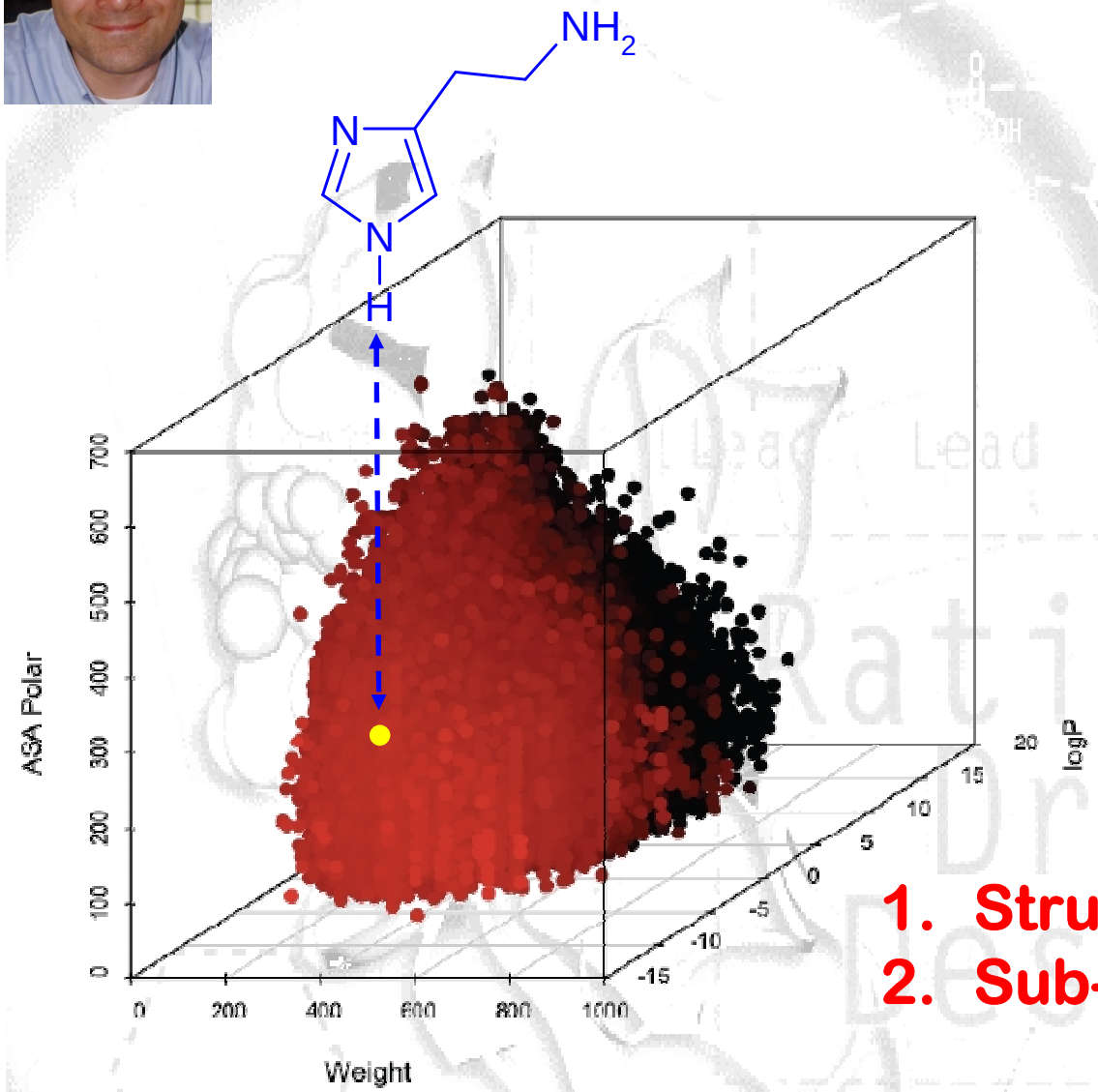
Fragments only in A = 1

Fragments only in B = 1

Fragments in A∩B = 2

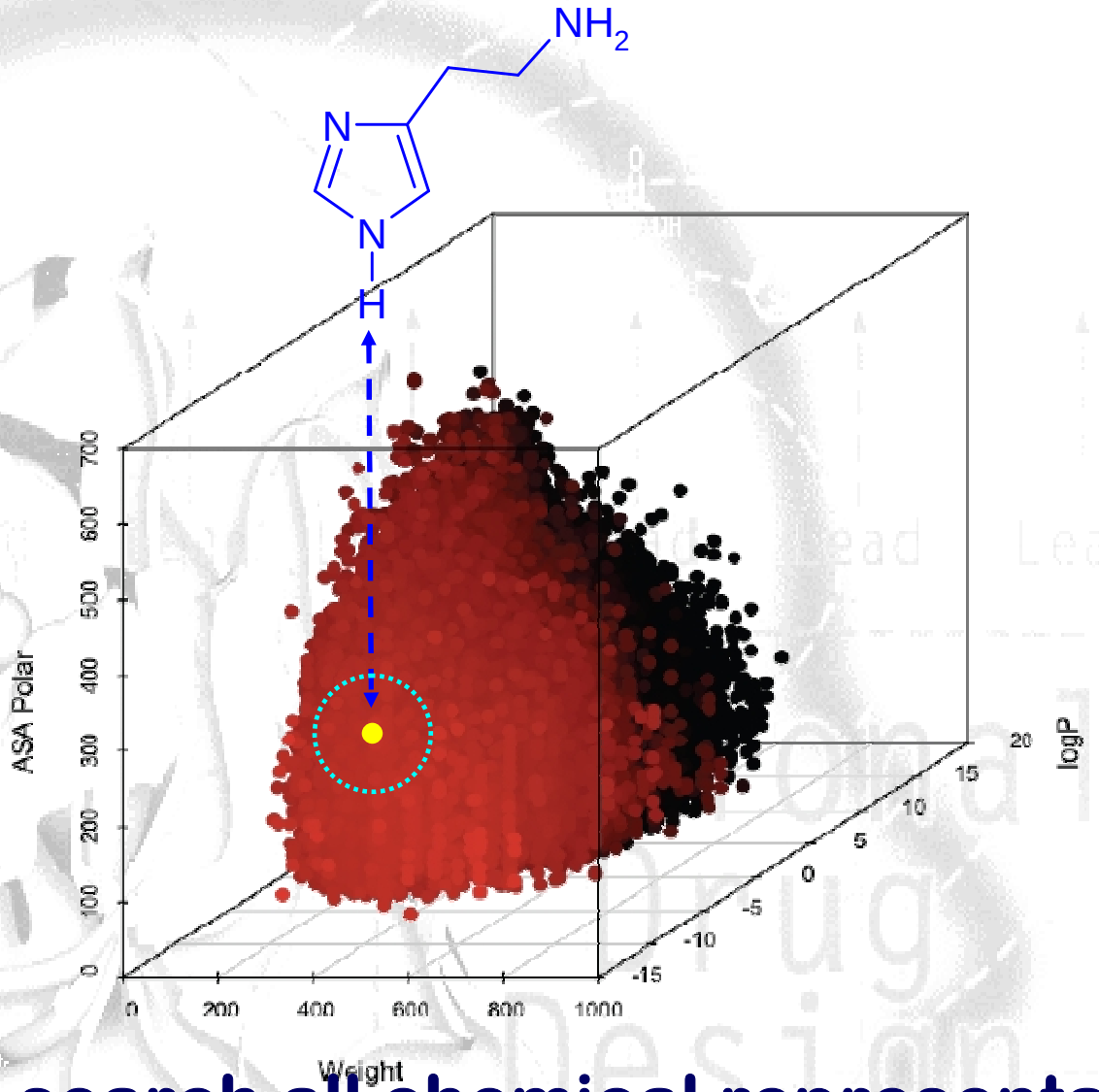
Tanimoto similarity index $= \frac{2}{1+1+2} = 0.5$

Now we can smartly explore our molecular haystack!



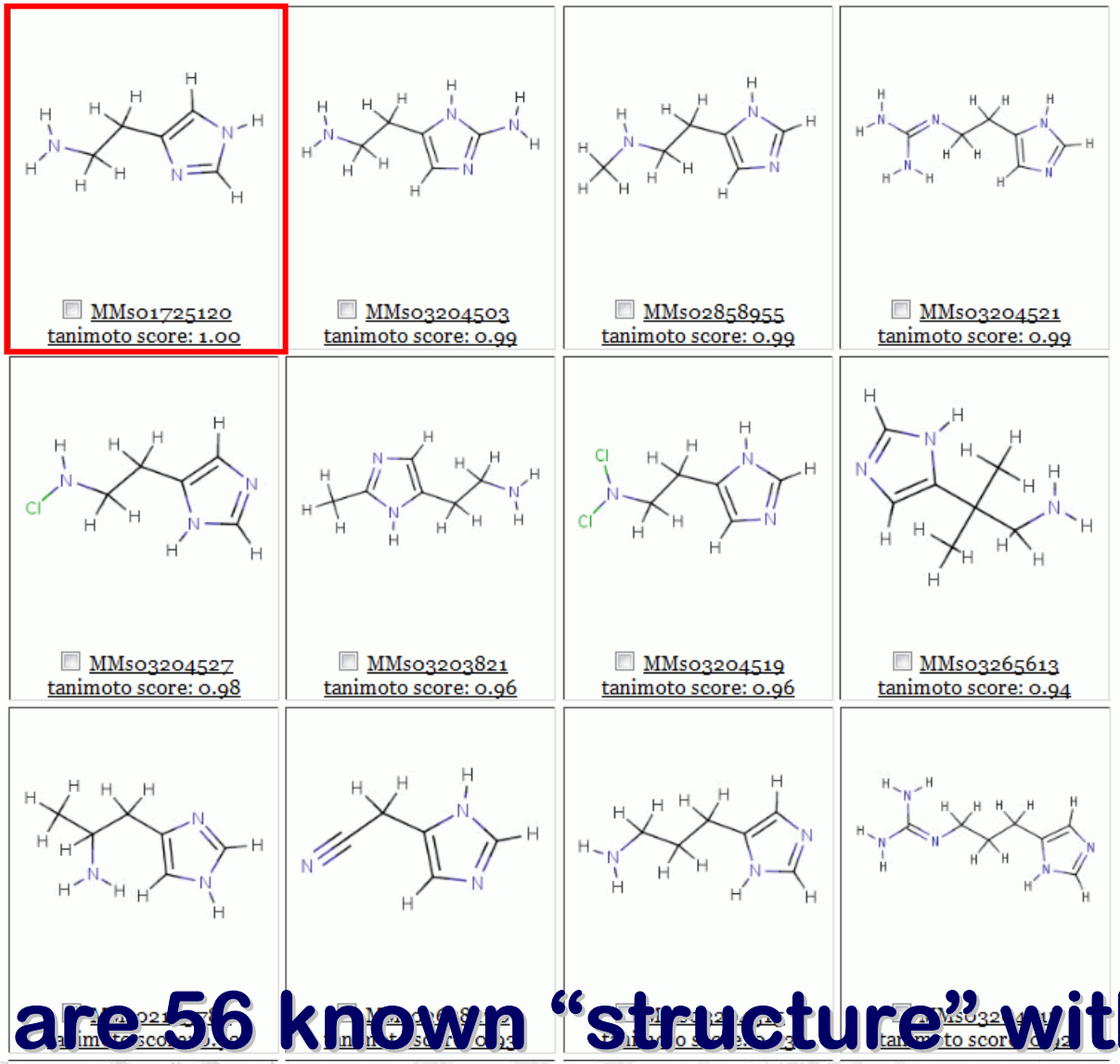
1. Structure similarity search;
2. Sub-structure search.

Here the first example:



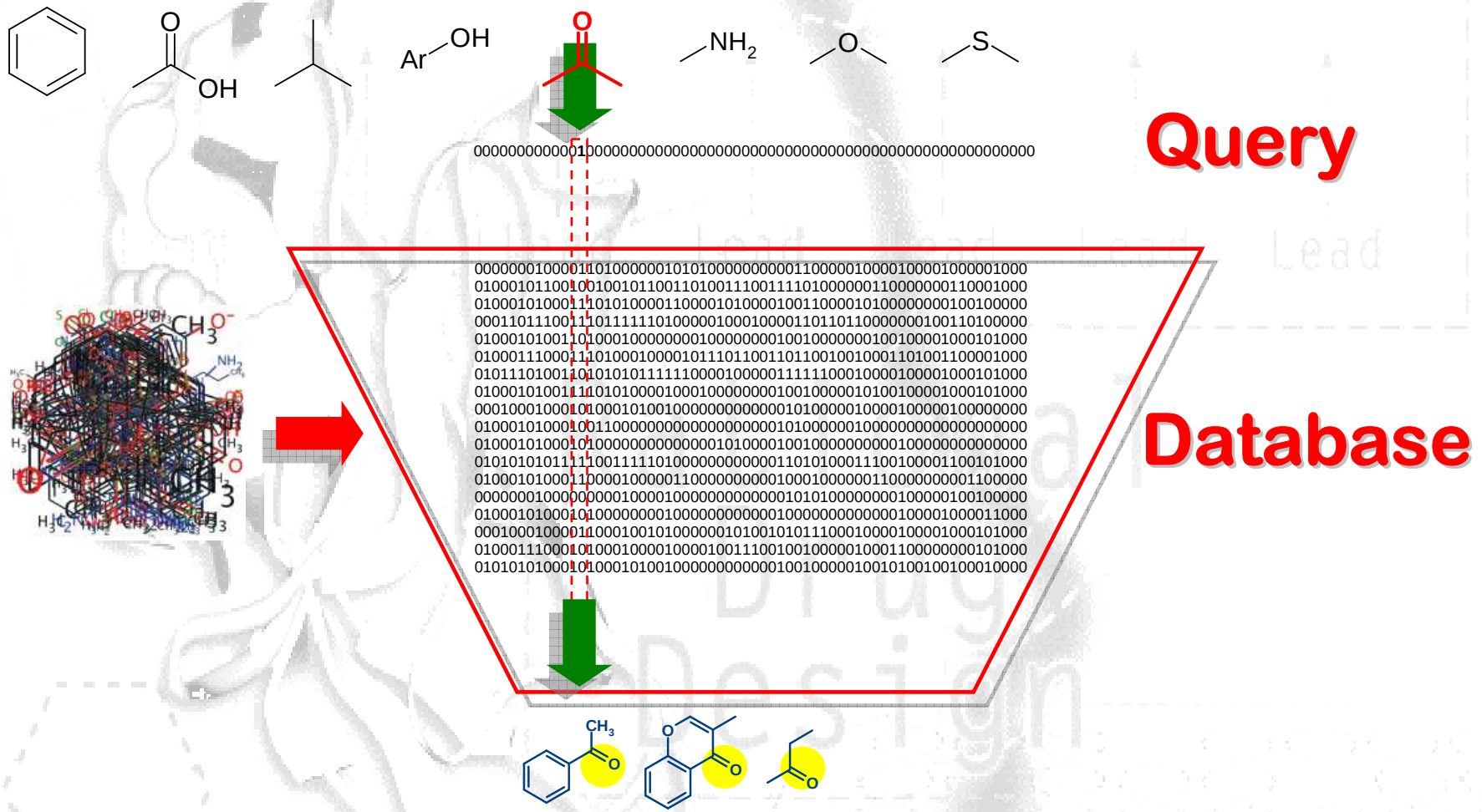
Please, search all chemical representations with Tanimoto index > 0.85?

and look a possible result:

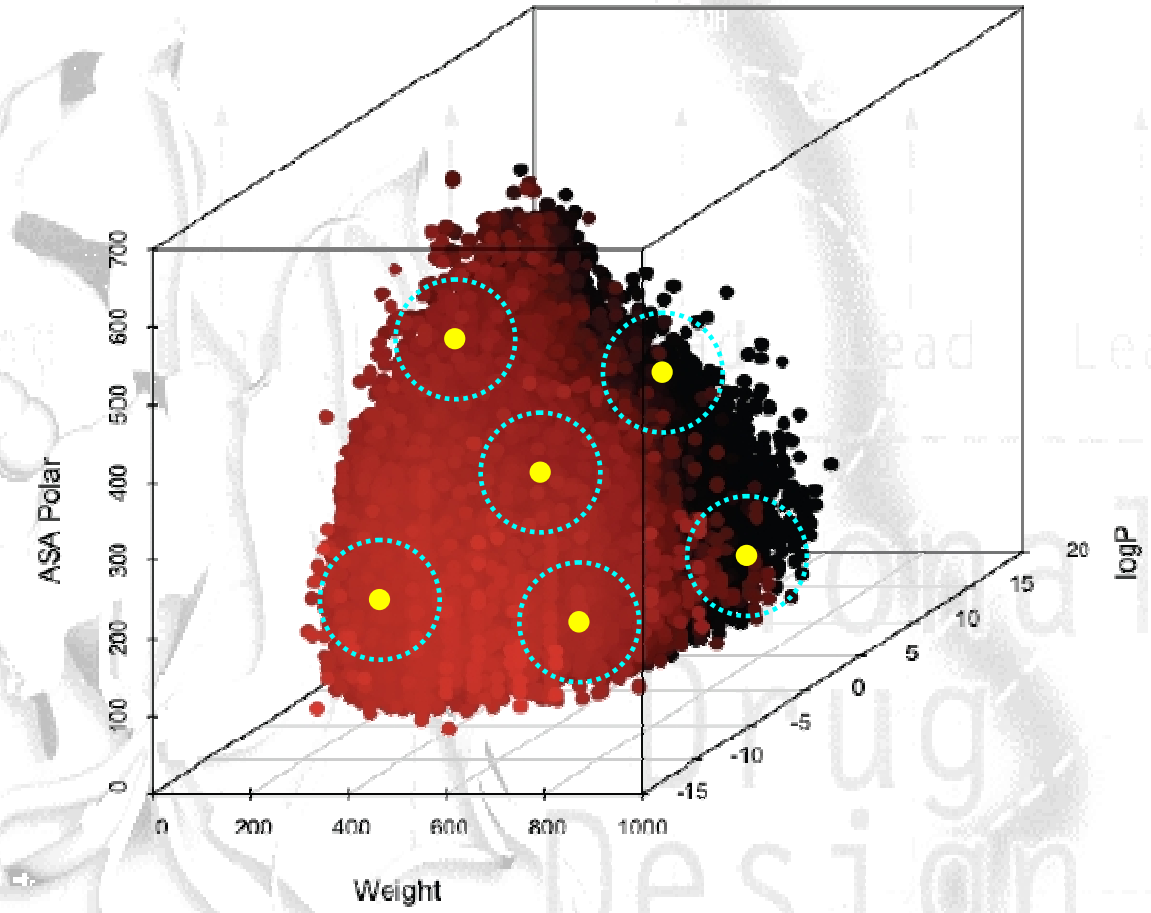


There are 56 known "structure" with a Tanimoto similarity index> 0.85!

... but we can also run a sub-structure search!



And don't forget:



1- similarity = diversity

Here we are again:

Virtual
Screening (VS)

Target
Structure Determination

Ligand-based
Virtual Screening (LBVS)

Similarity search
Pharmacophore matching

Structure-based
Virtual Screening (SBVS)

HT Molecular Docking

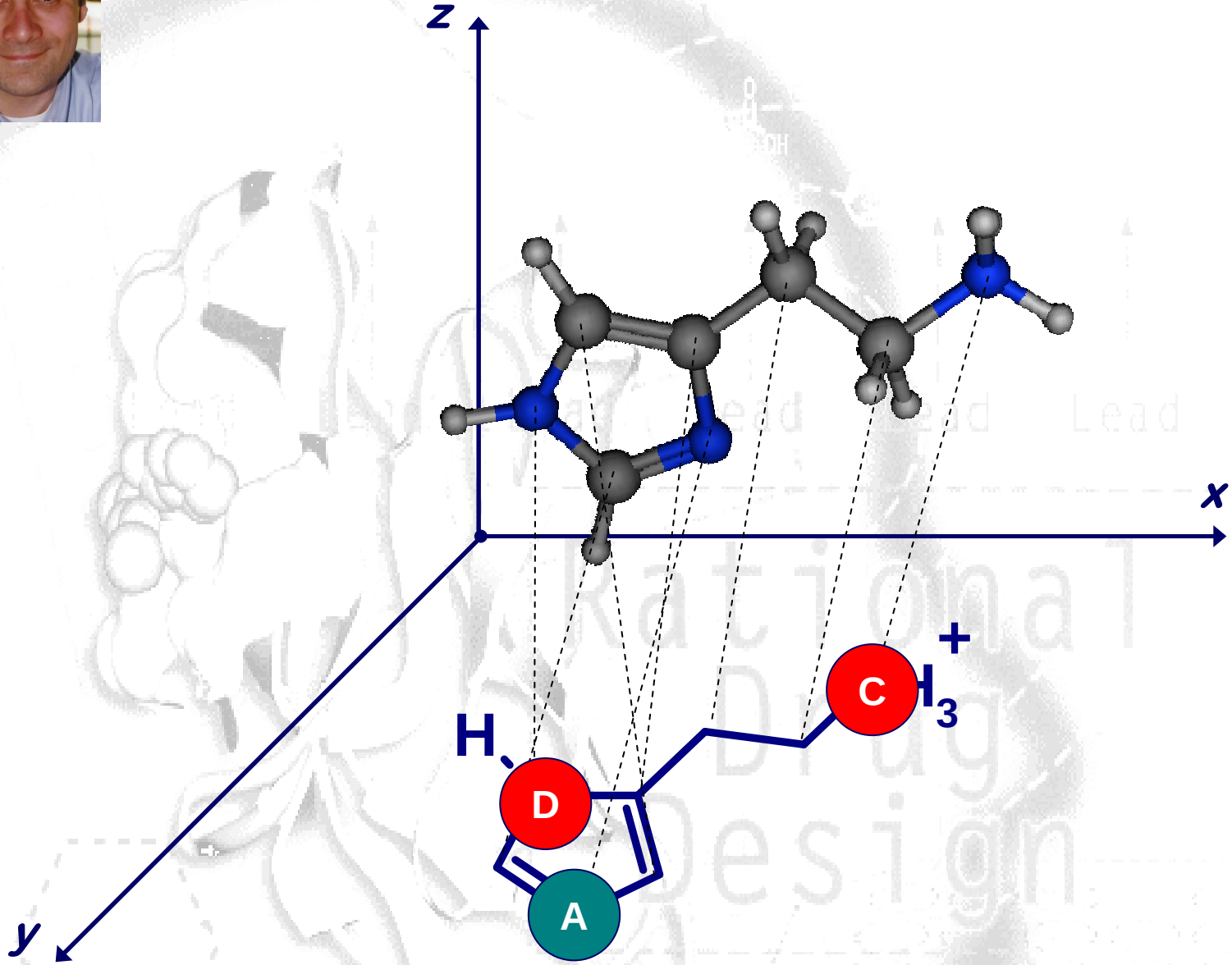
Pharmacophore definition:

A "*pharmacophore*" is a three-dimensional substructure of a molecule that carries ("phoros") the essential features responsible for a drug's ("pharmacon") biological activity. Alternatively described as an ensemble of interactive functional groups with a defined geometry. Basically, one tries to talk the protein language by finding the "structural and chemical complementaries" (pharmacophore hypothesis) to target receptors.

.... a quick refresh: what is the goal of every SAR study?

The generation of pharmacophoric hypothesis (models)!!!!!

the shadow of the reality:



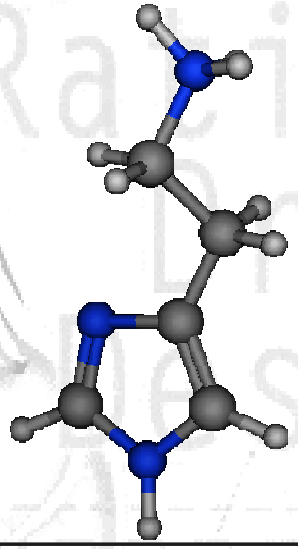
Pharmacophore definition:
1. *conformational selection*

Ligand-Target 3D info

- X-ray info
- Docking

Ligand 3D info

- X-ray info
- Conformational Analysis
- Rigid active analogs

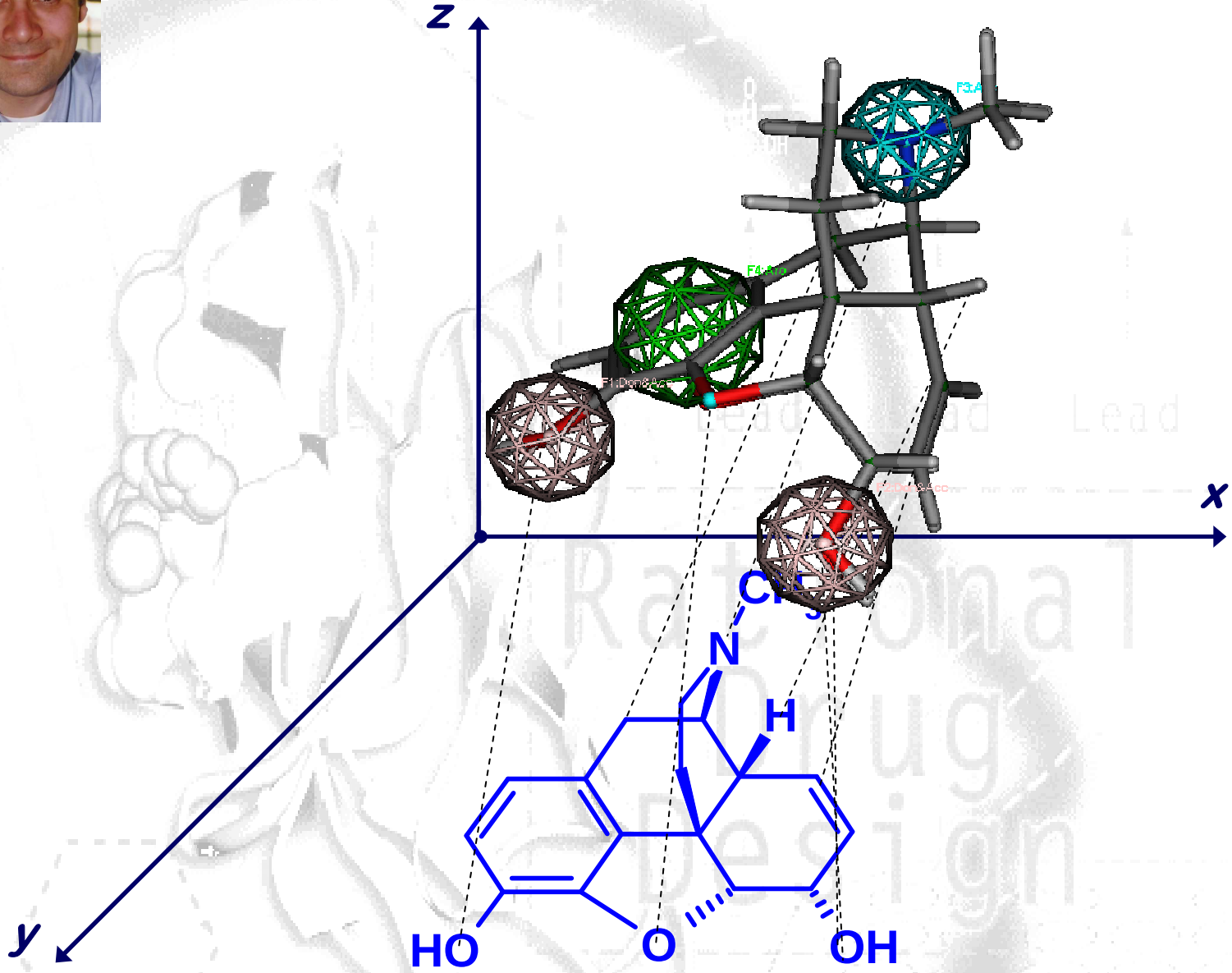


Two very interesting concepts:

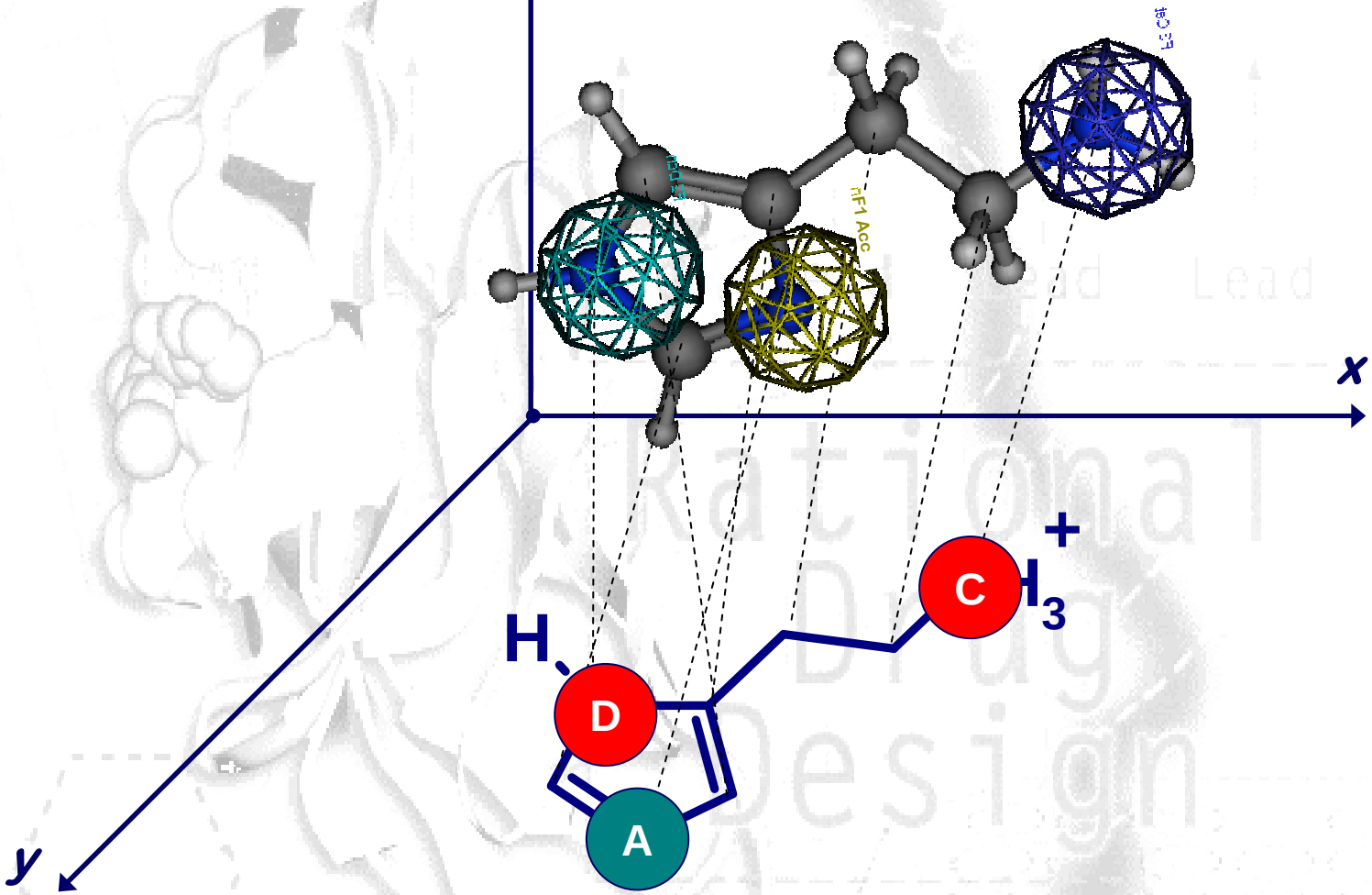
Stability as a measure of the geometrical deformability of an object;

Rigidity as a measure of the reduction degree of the geometrical deformability of an object.

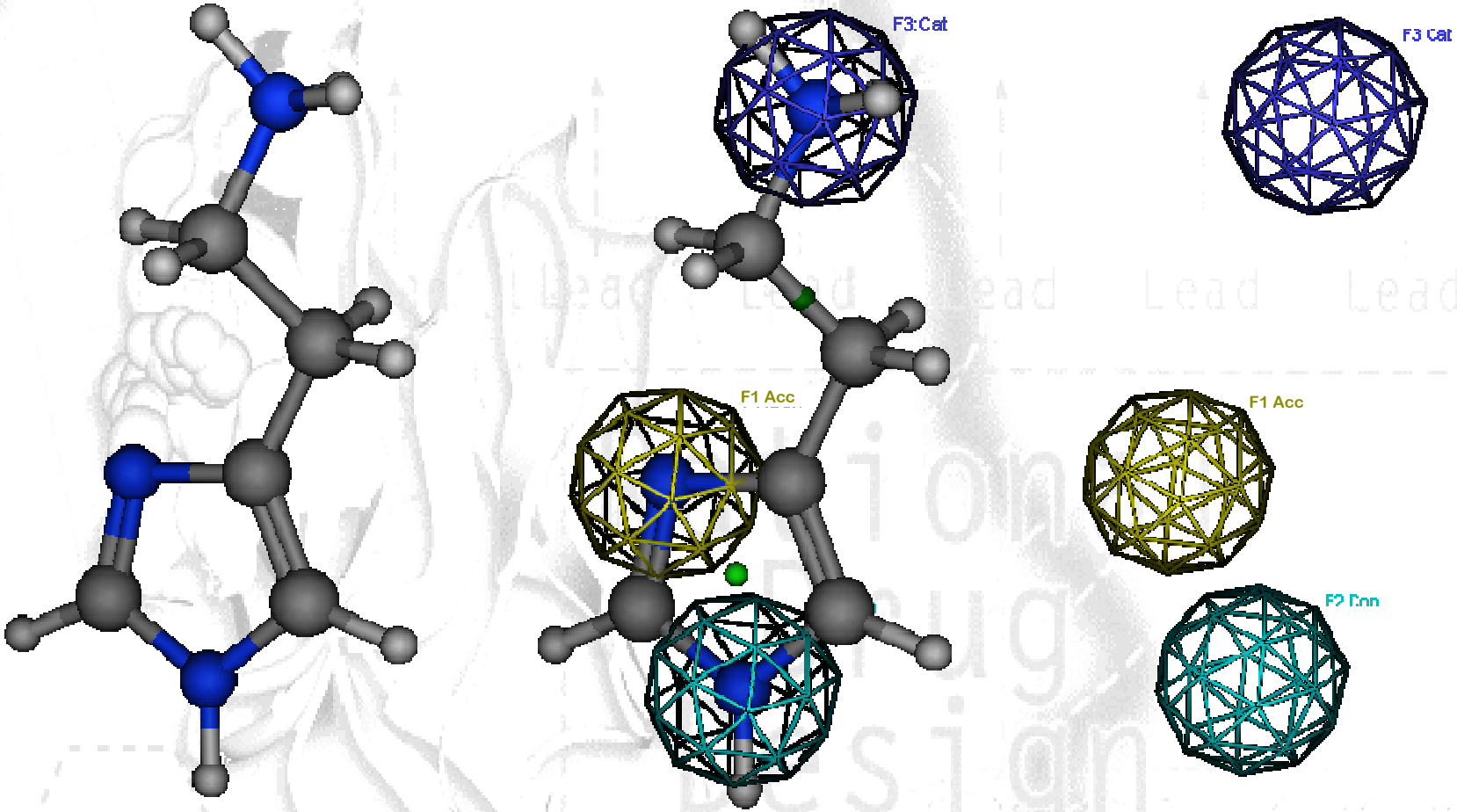
The magic behavior of cyclization:



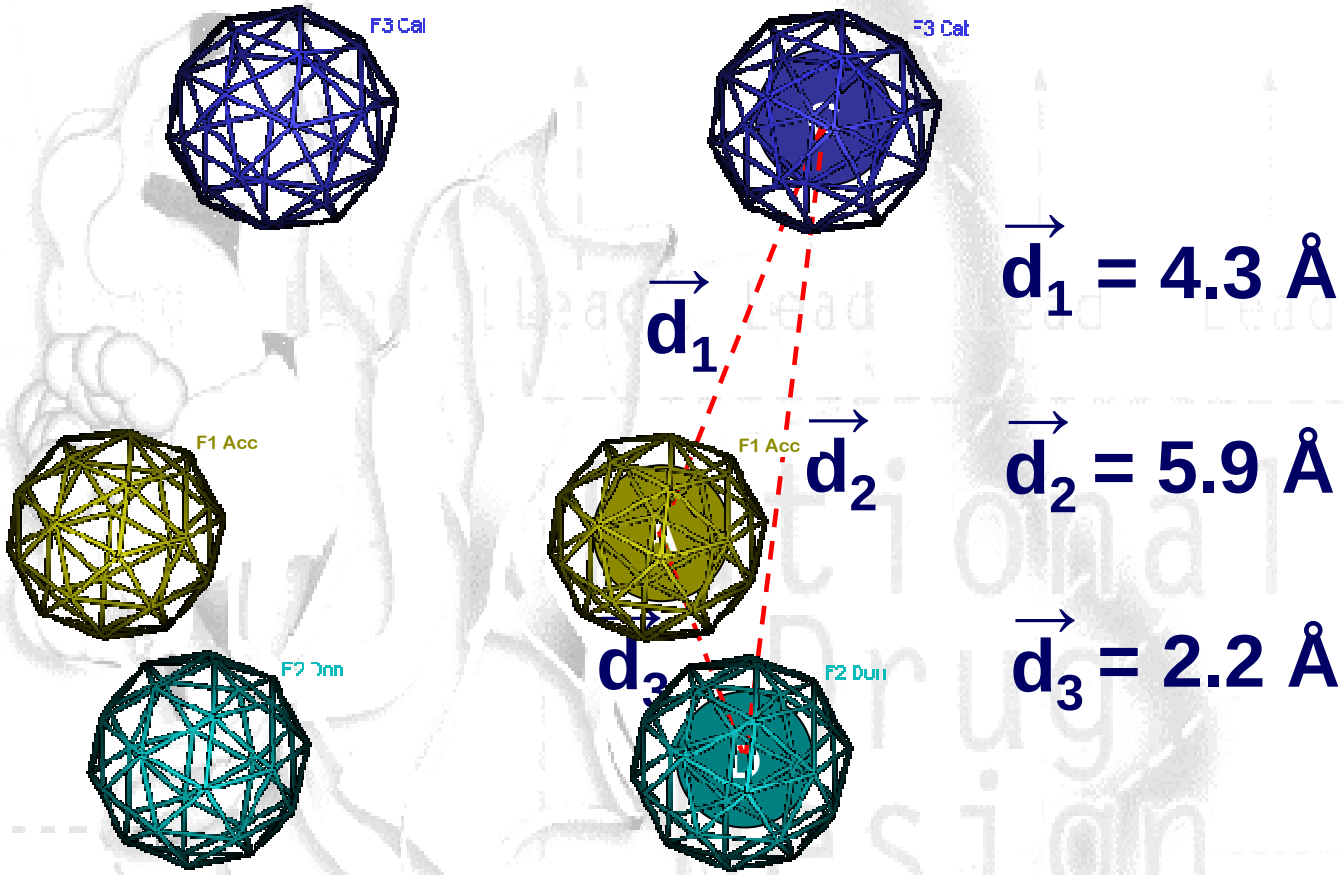
Pharmacophore definition:
2. *Pharmacophoric keys selections*



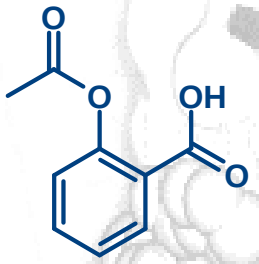
Pharmacophore definition:
2. *Pharmacophoric keys selections*

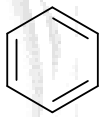
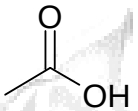
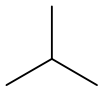
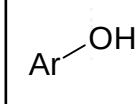
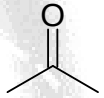
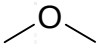
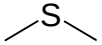


Pharmacophore definition:
3. *Interaction triangle*



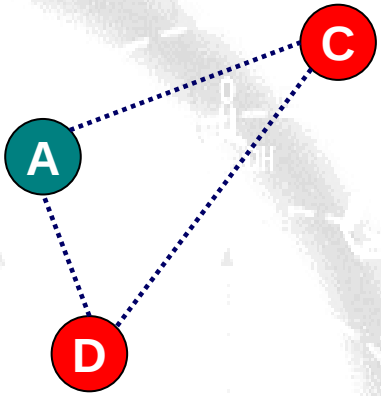
Pharmacophore definition:
4. *From structural key to pharmacophoric key*



							
1	1	0	0	1	0	0	0
Ar	Ac	H	D	A	A	A	H

Ar = aromatic
Ac = acid
H = hydrophobic
D = H-bonding donor
A = H-bonding acceptor
C = cation
An = anion

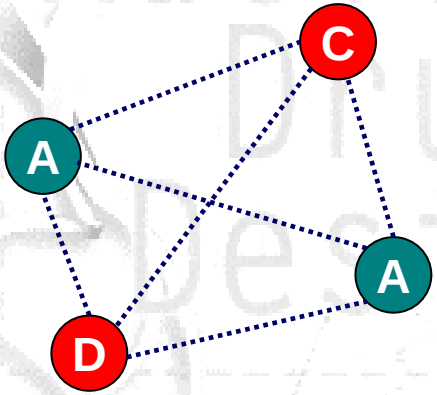
The triangle saga :



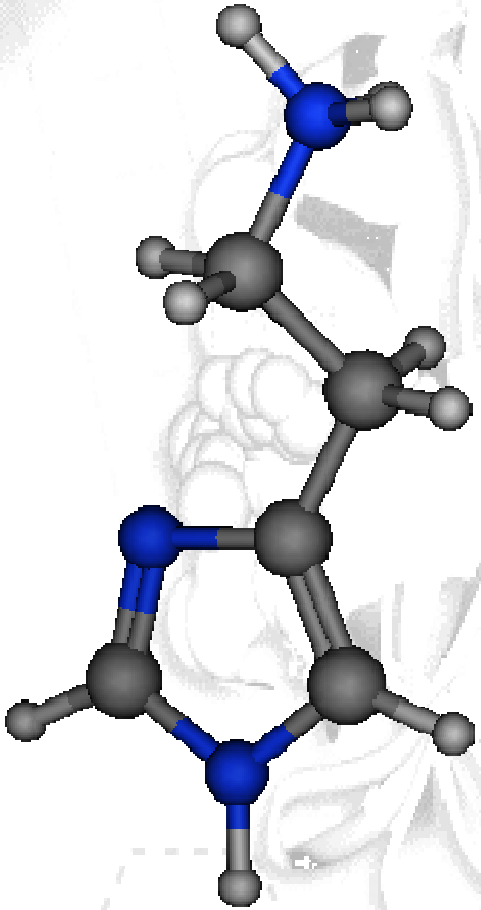
Any pharmacophoric triangle can be described as a three characters string: **ACD**

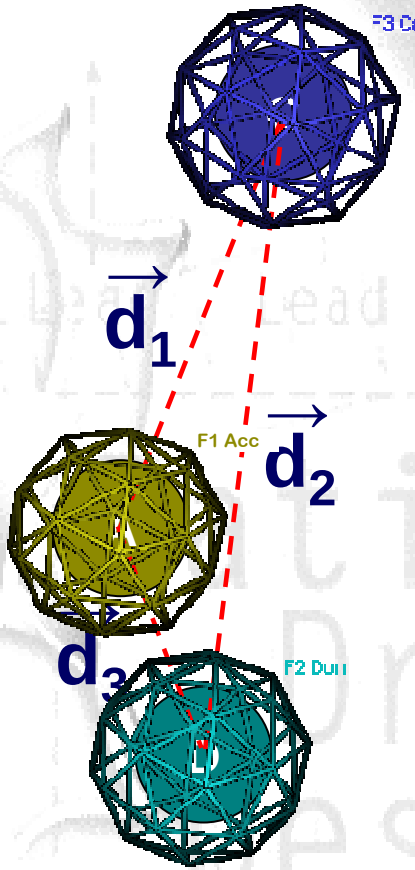
For any triangle we cal calculated numerical descriptors: **perimeter, sides length.**

Any polygons can be subdivided into a sum of triangles:



Here is another interesting 3D→1D chemical representation transformation!

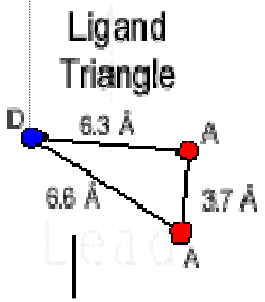


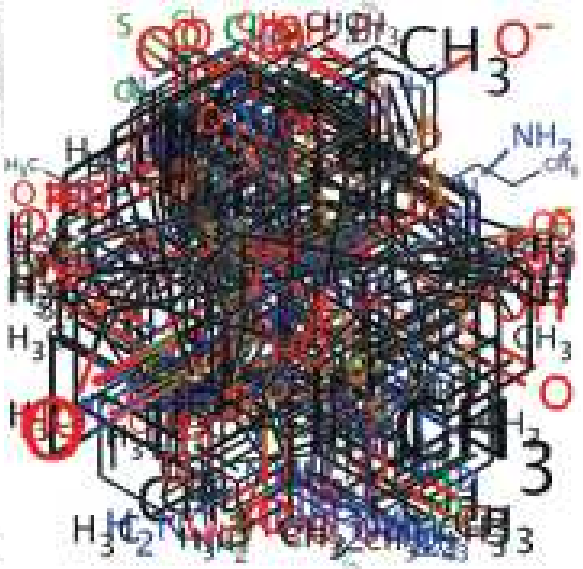


ACD 462 12

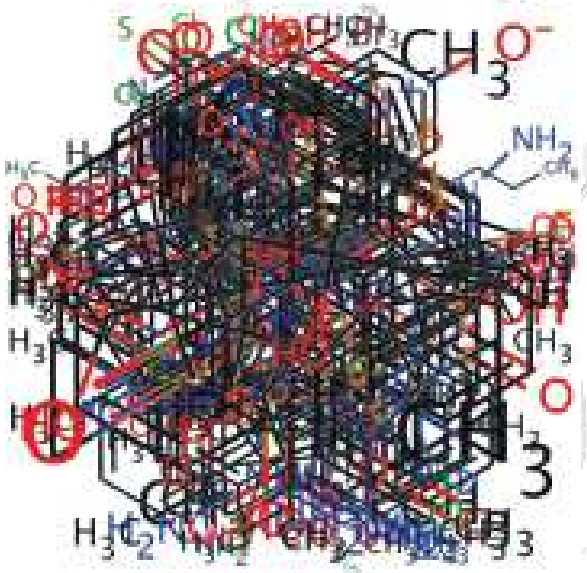
3D 2D 1D

Pharmacophore definition:
5. *Geometric hashing scheme*





What we need for a good fishing?



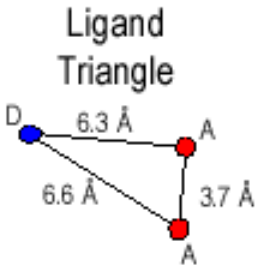
① generation of a collection of good conformers for each chemicals;

② generation of all plausible pharmacophoric hypothesis;

③ generation of all possible pharmacophoric triangles;

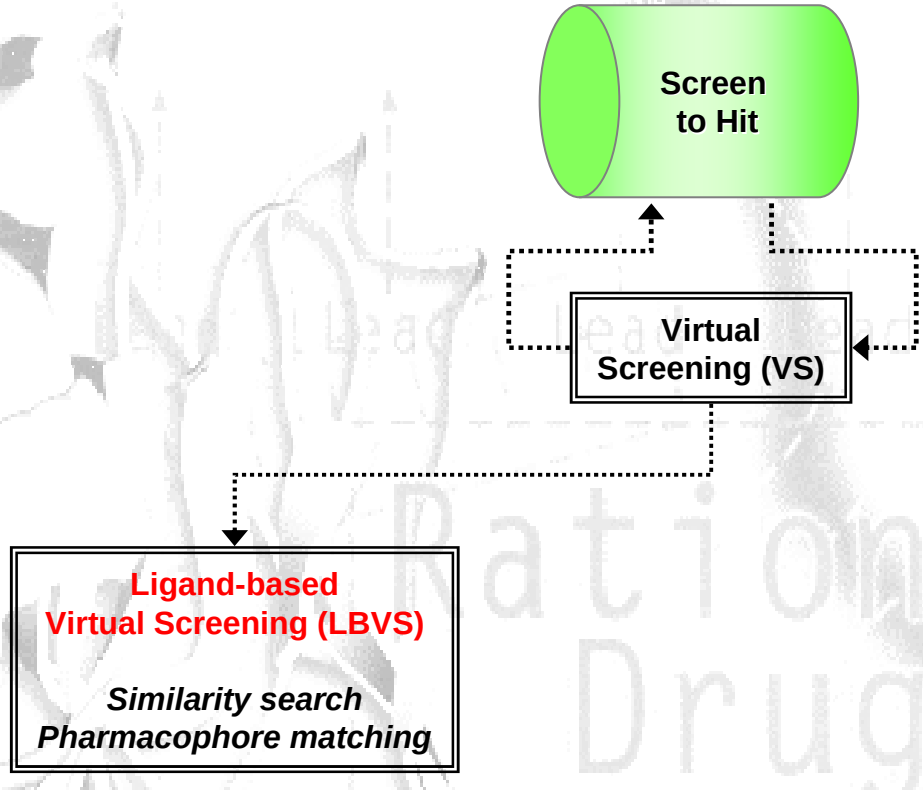
④ generation of all possible pharmacophoric strings.

Pharmacophore definition:
5. *Geometric hashing scheme*

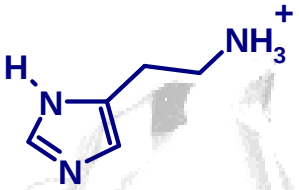


D = HBond Donor
A = HBond Acceptor
H = Hydrophobic Point

Here is a possible work-flow:



Here is a possible work-flow:



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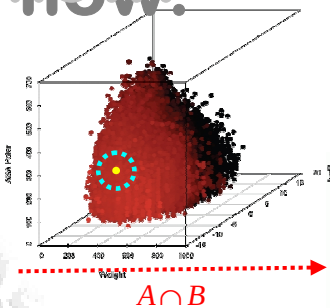

$$\frac{A \cap B}{A_{solo} + B_{solo} + A \cap B}$$