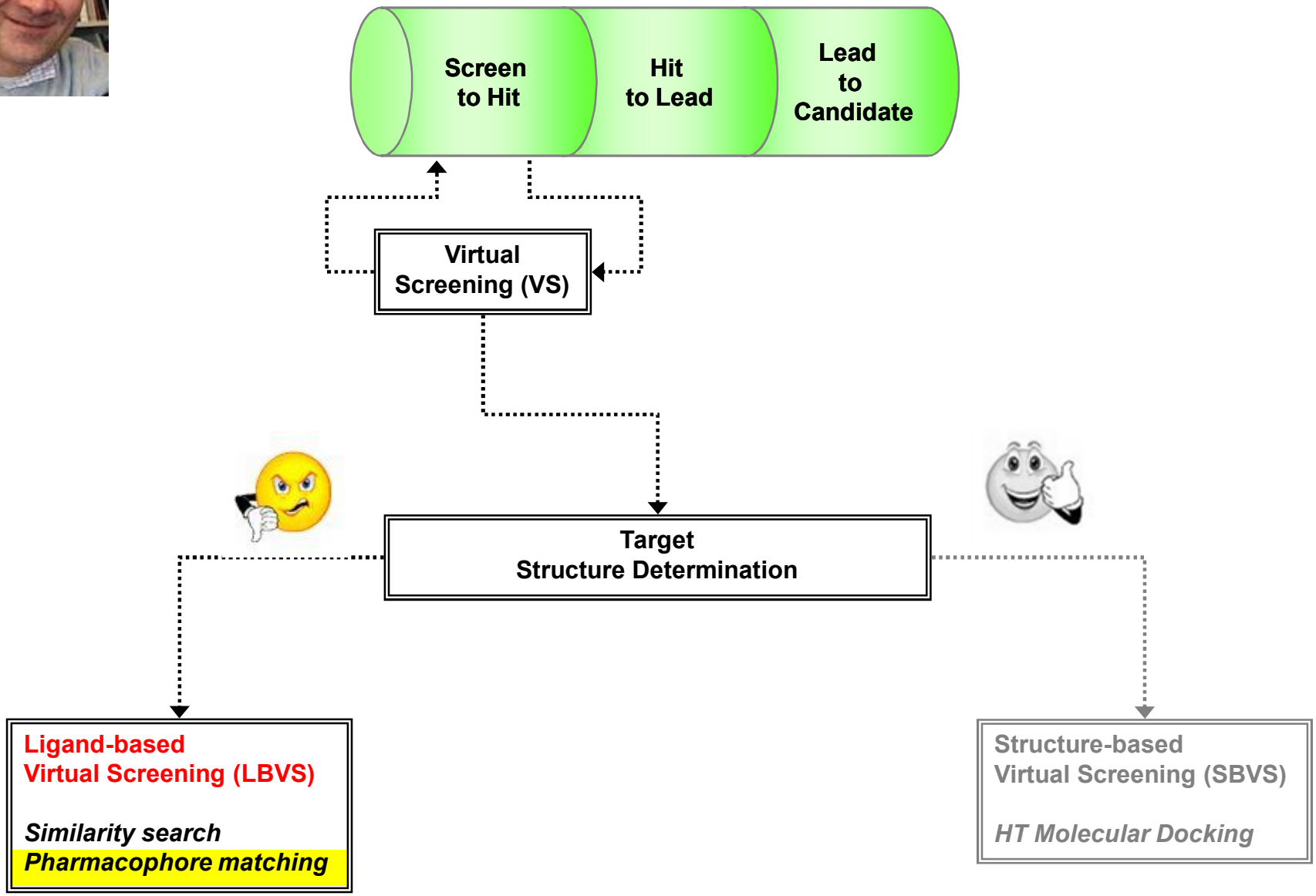
here we are again:



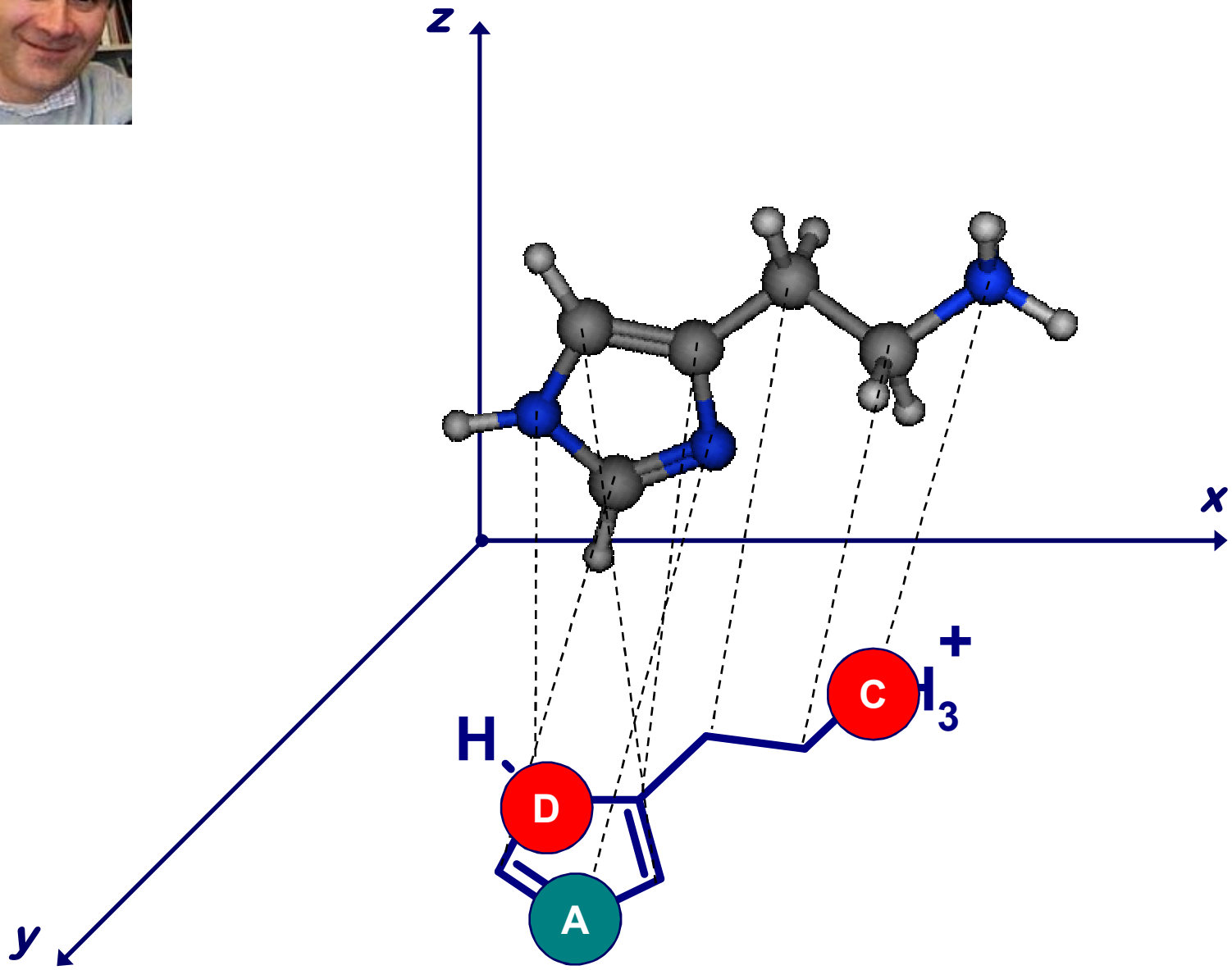
Pharmacophore definition:

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:



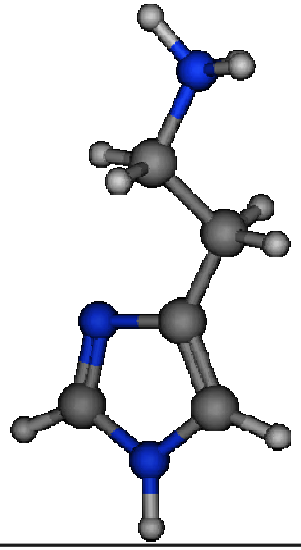
Pharmacophore definition:
1. *conformational selection*

Ligand-Target 3D info

- X-ray info
- Docking

Ligand 3D info

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



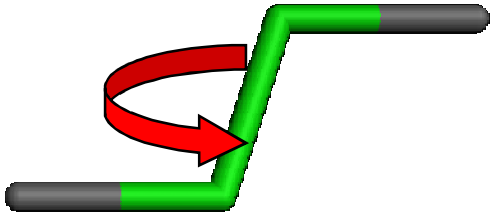
Two very interesting concepts:

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.**

An easy way to determine *molecular rigidity*:

A ***rotatable bond*** is defined as any single non-ring bond, attached to a non-terminal, non-hydrogen atom. ***Amide C-N bonds are not counted because of their high barrier to rotation.***

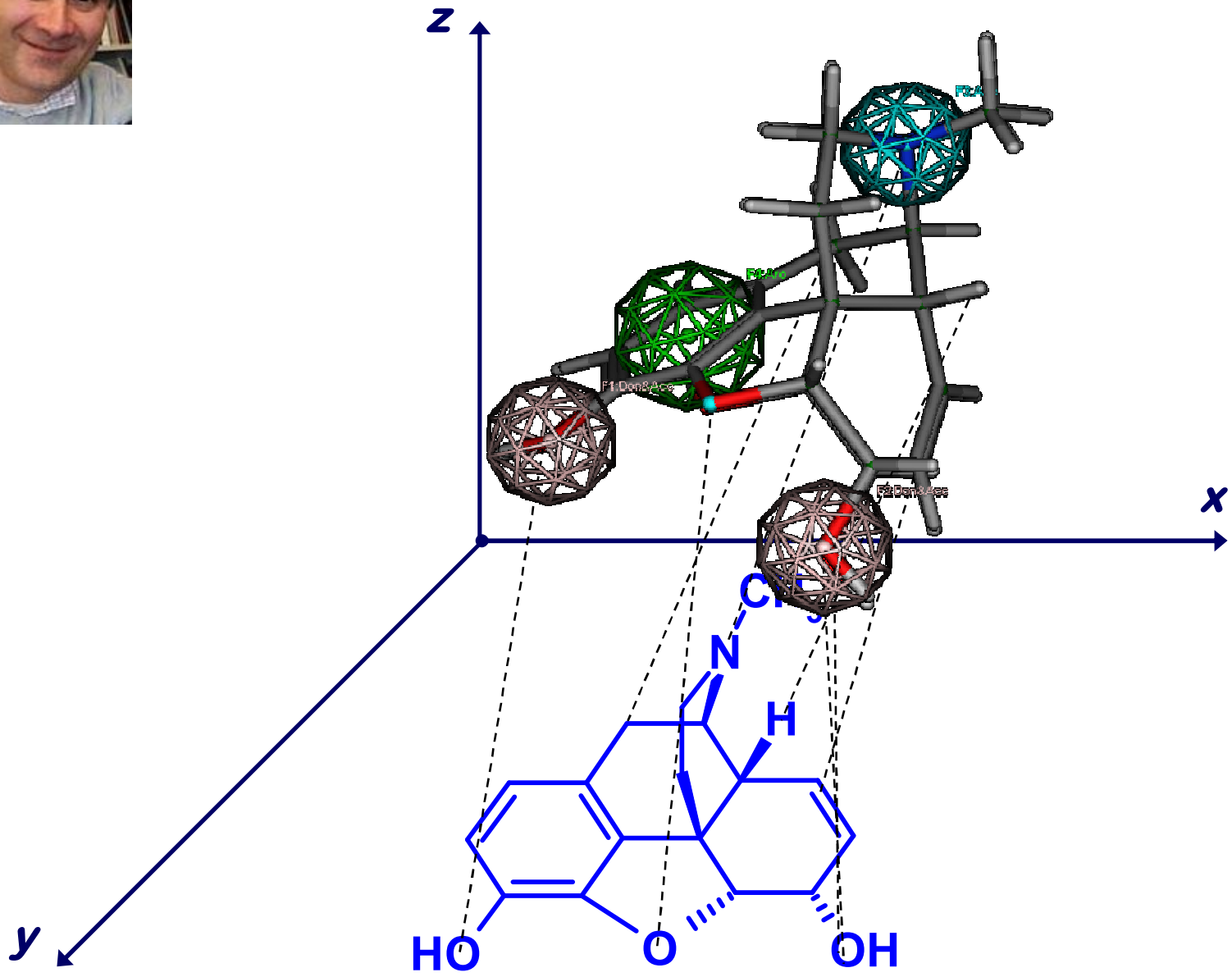


… and it is easily countable!!!

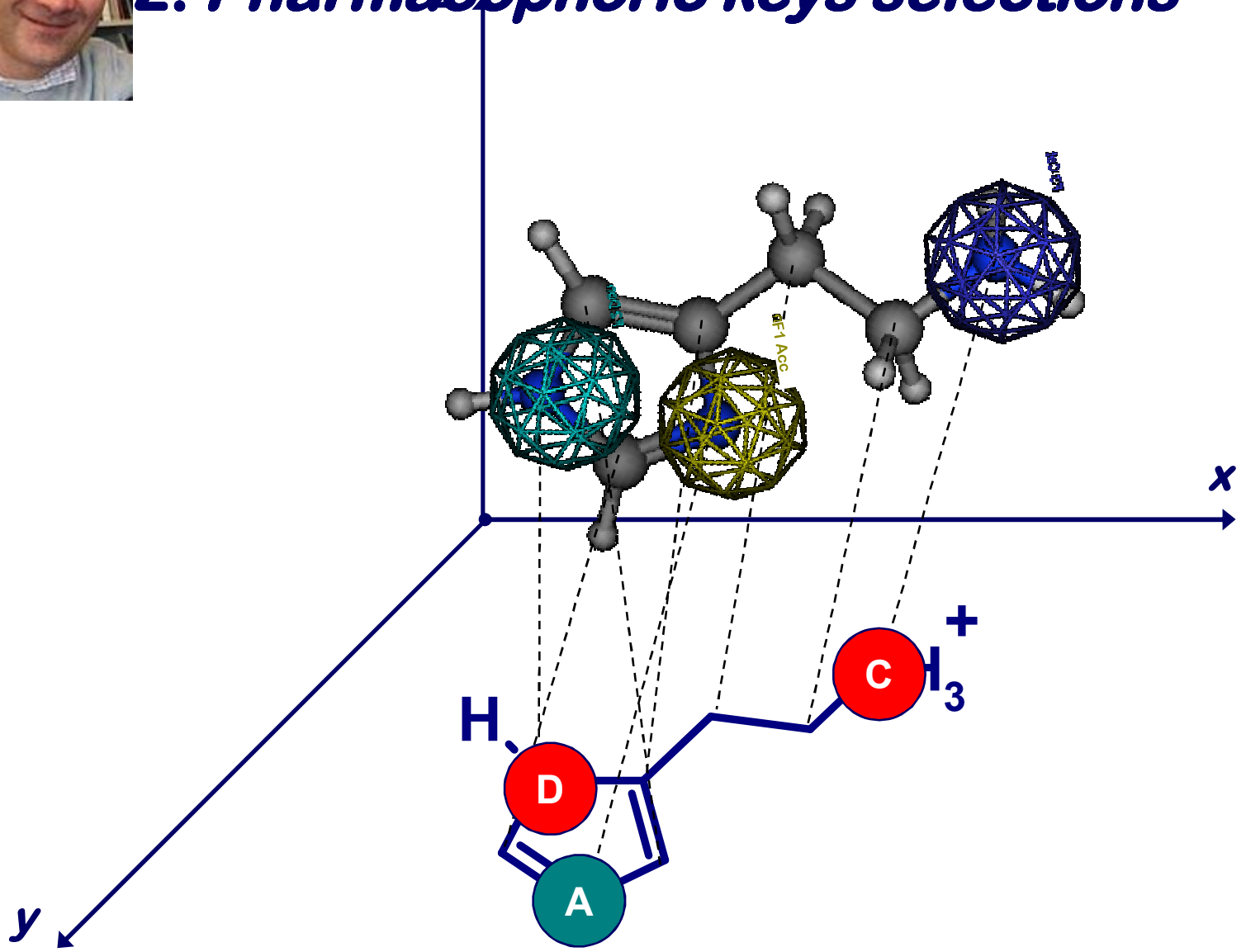
A golden rule in pharmacophore depiction:

Among all the active compounds always choose the more rigid!

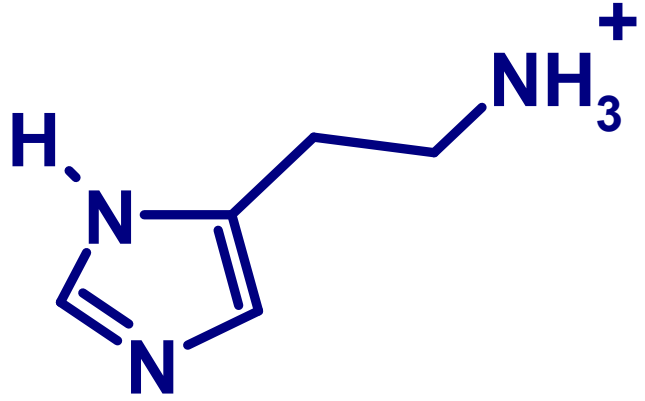
The magic behavior of cyclization:

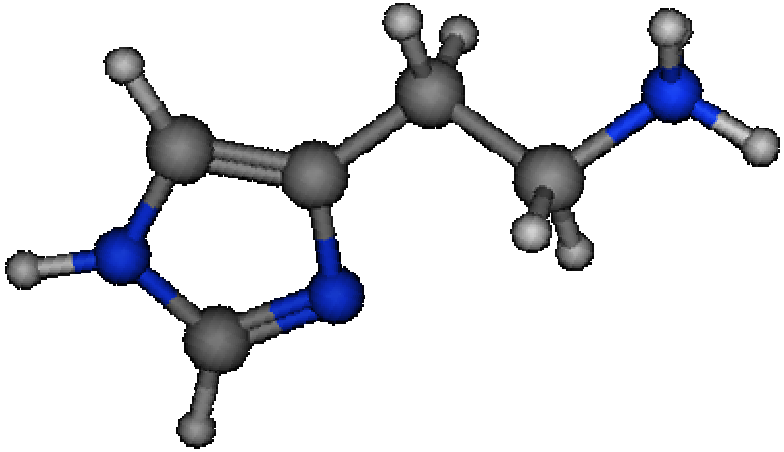


Pharmacophore definition:
2. *Pharmacophoric keys selections*



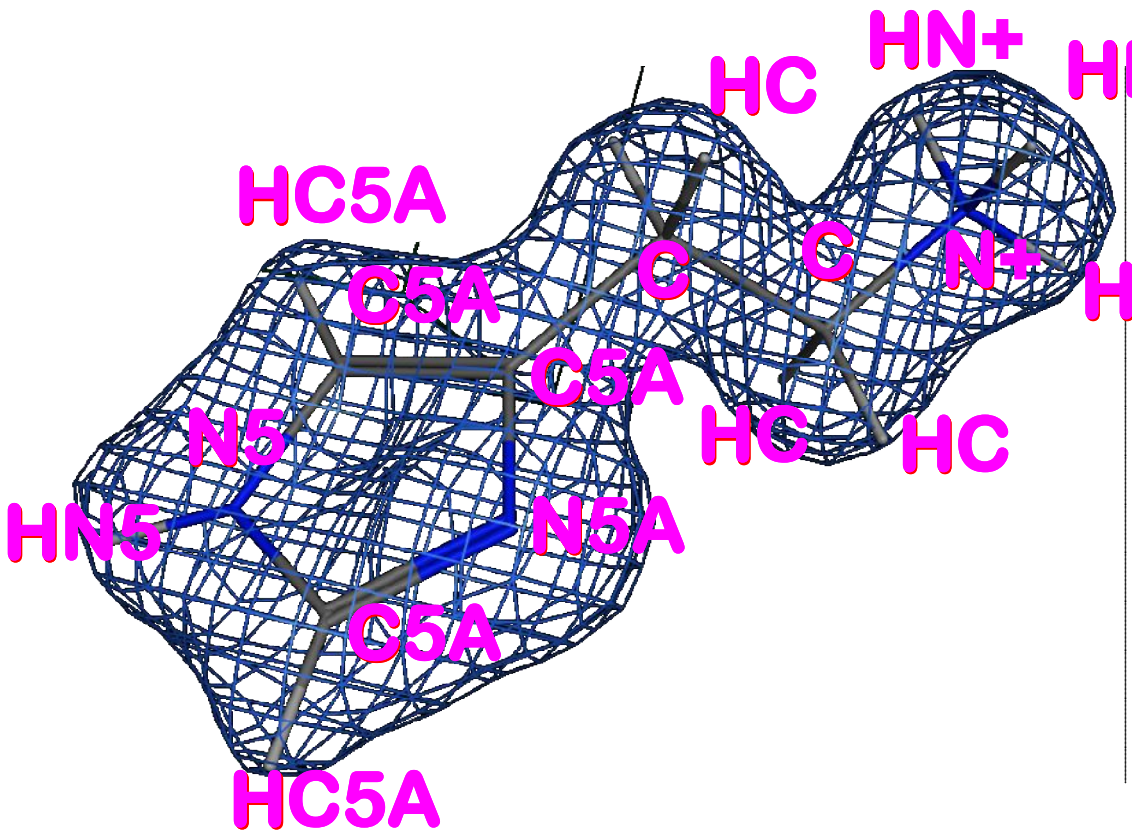
First of all… let's convert!





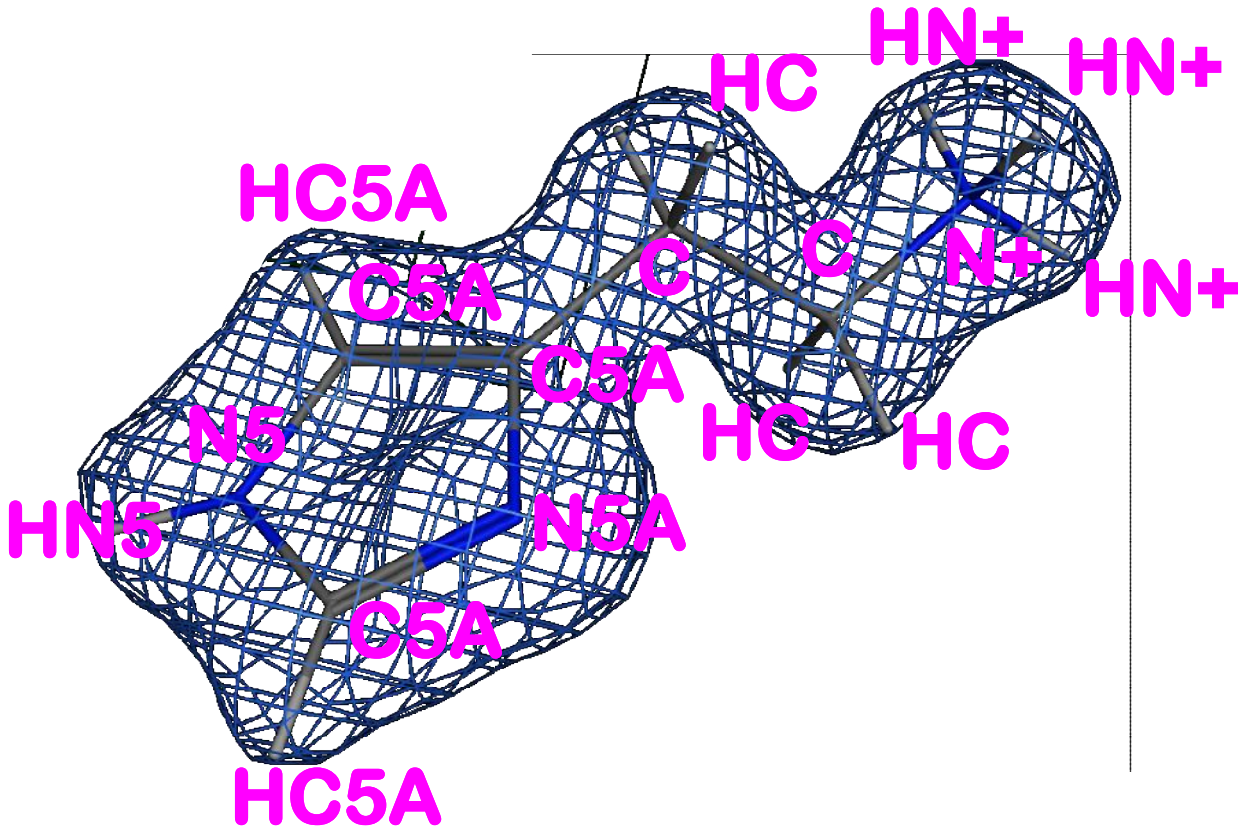
How? But learning from crystallographer, of course!

1. From what we observe, we learn.



ATOM	ATOM-TYPE
HN+	HN+
H	HC
N	HC5A
HN+ C	N+
	N5A
	N5
	C
	C5A

1. From what we observe, we learn.



DISTANCES (Å):

HN+ - N+ = 1.03

HC – C = 1.10

HC5A – C5A = 1.08

HN5 – N5 = 1.01

N+ - C = 1.46

C – C = 1.52

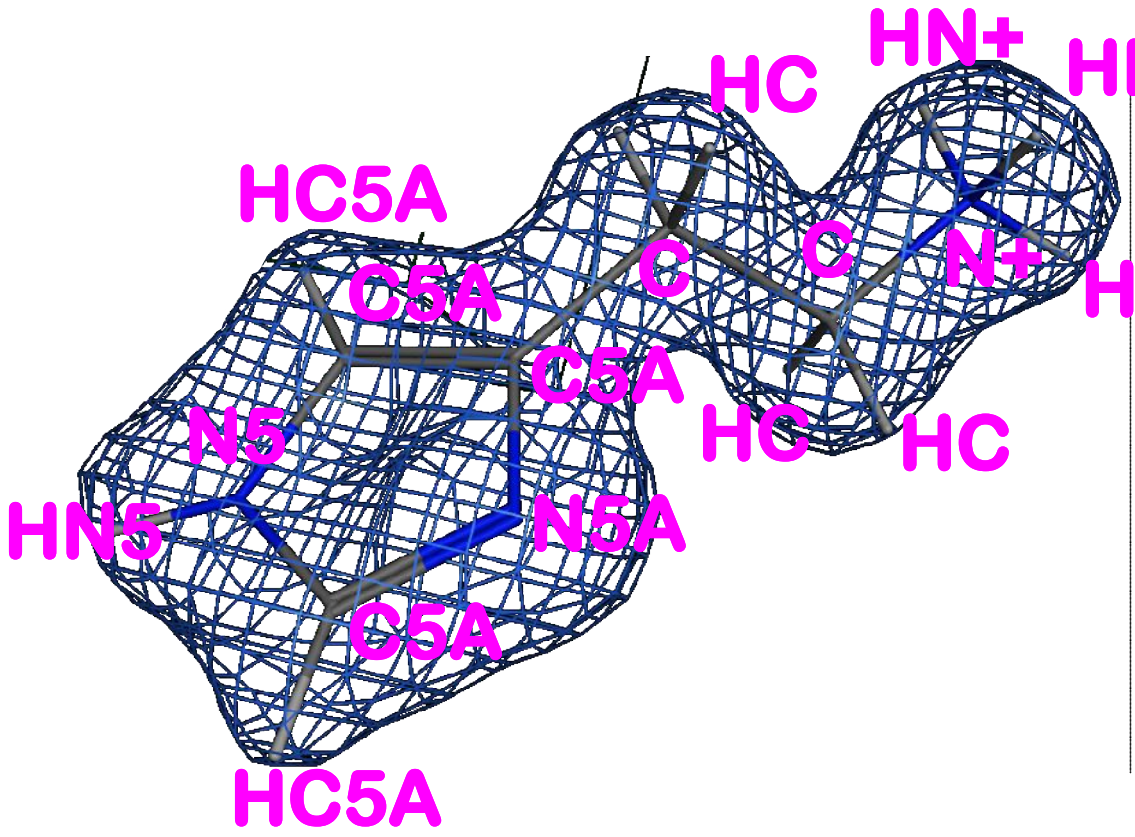
C – C5A = 1.51

C5A – C5A = 1.38

C5A – N5A = 1.35

C5A – N5 = 1.35

1. From what we observe, we learn.



ANGLES (°):

HN+ - N+ - HN+ = 107.1

HN+ - N+ - C = 111.8

HC - C - N+ = 108.2

HC - C - C = 111.4

C - C - C5A = 111.5

C - C5A - C5A = 126.2

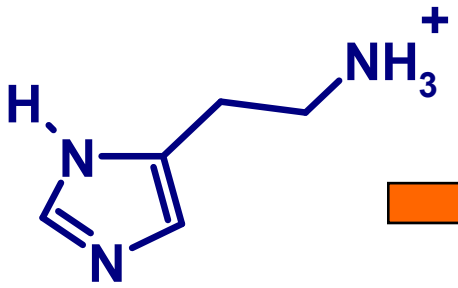
C5A - C5A - HC5A = 130.5

C5A - C5A - N5 = 107.2

C5A - N5 - C5A = 108.5

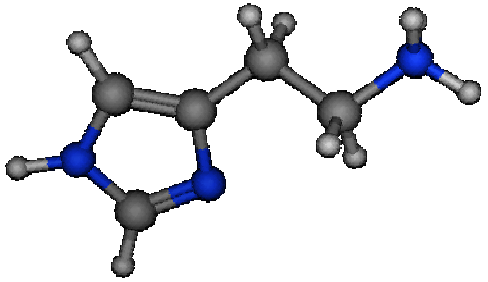
N5 - C5A - N5A = 108.7

2. … and ones learned, we can repeat!



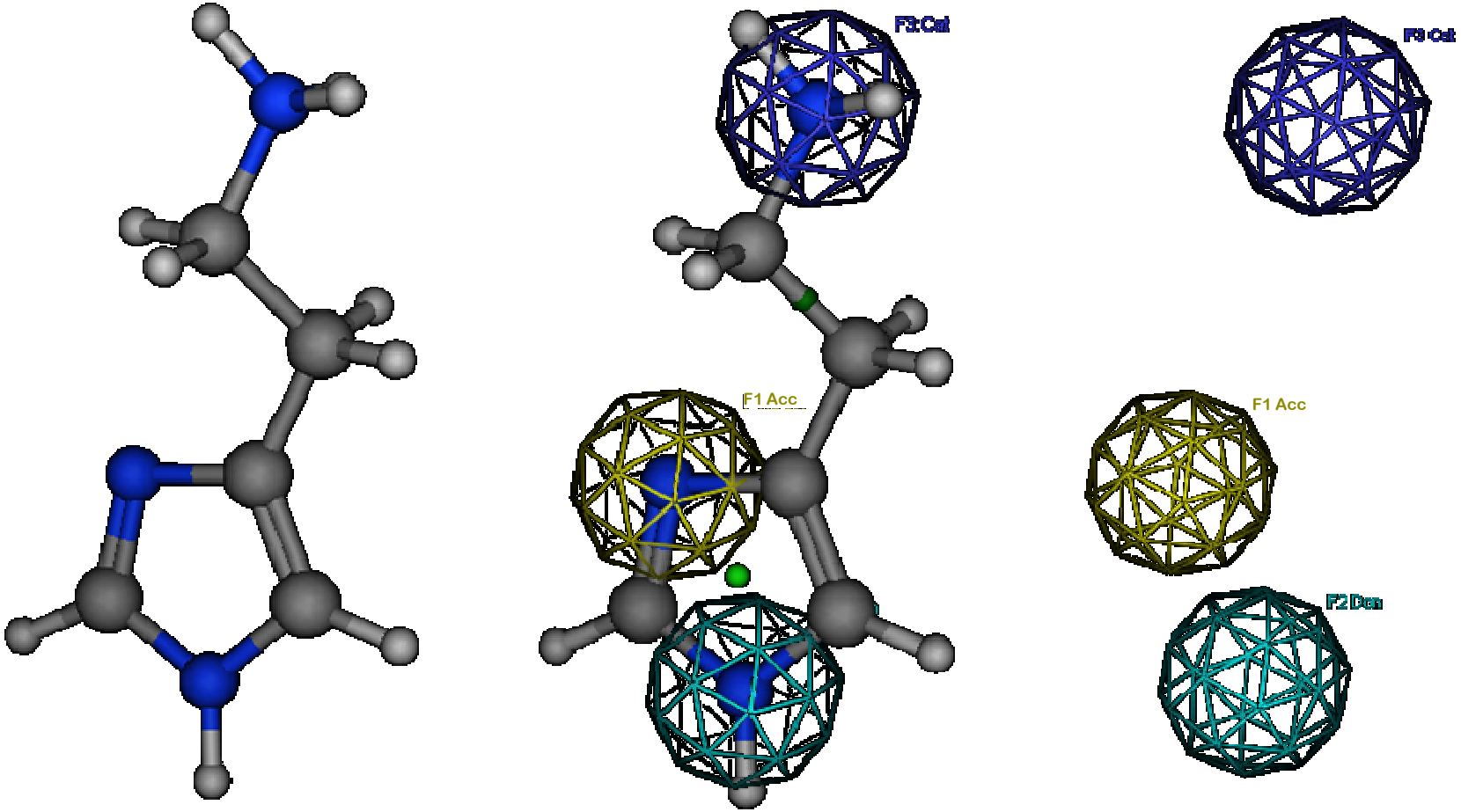
ATOM-TYPES

GEOMETRIC PROPERTIES TABLE

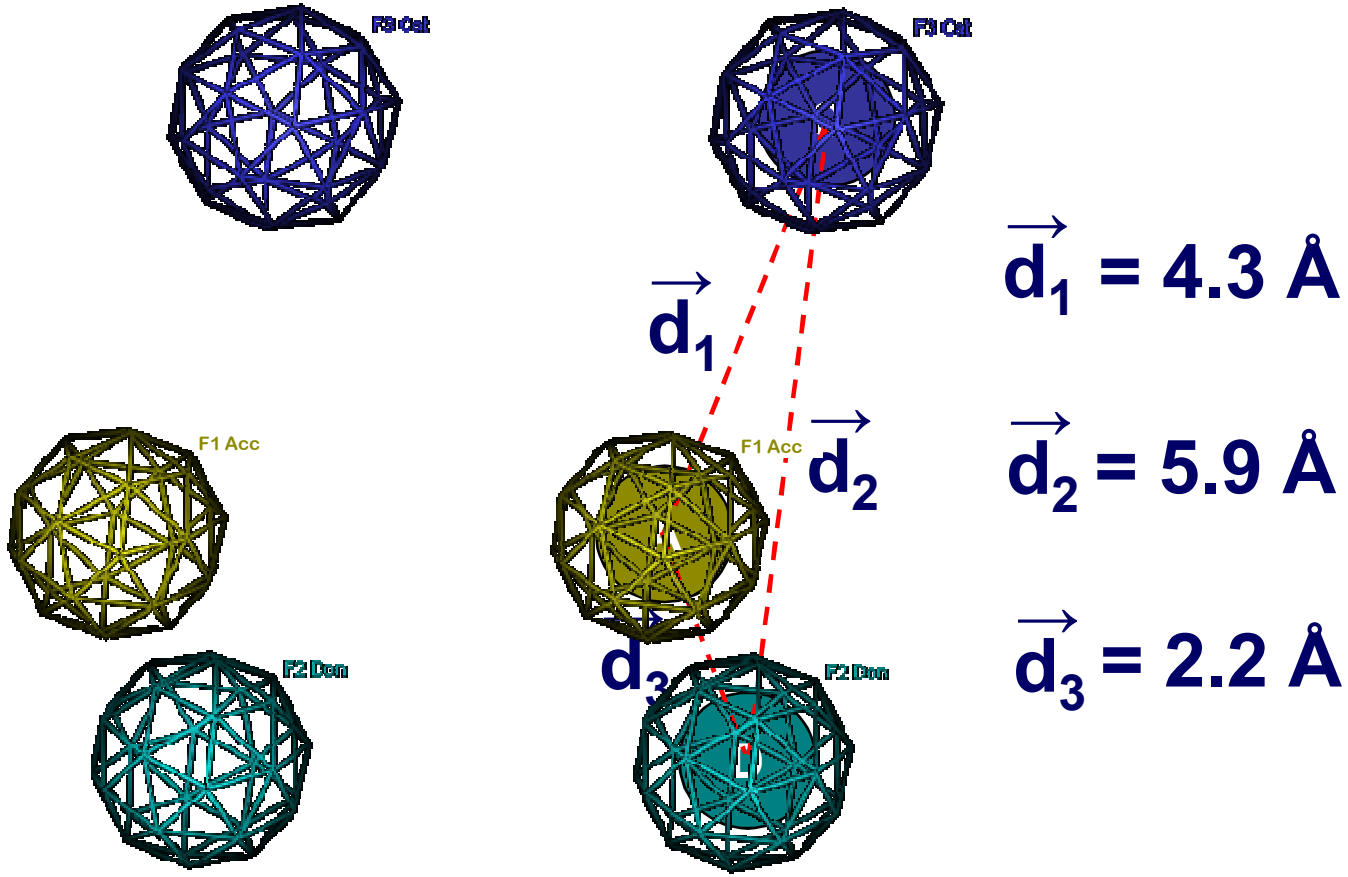


it will be a good conformation?

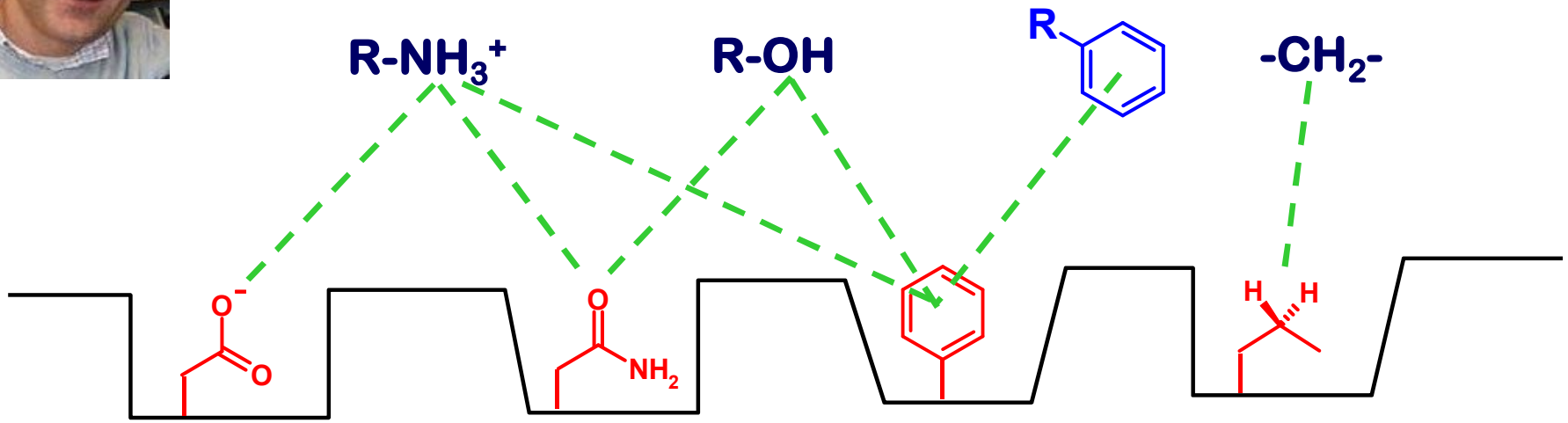
Pharmacophore definition:
2. *Pharmacophoric keys selections*



Pharmacophore definition:
3. *Interaction triangle*

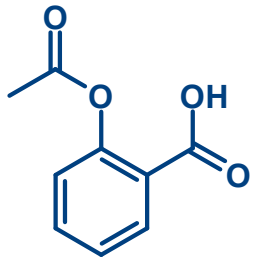


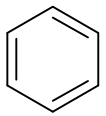
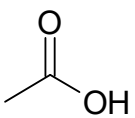
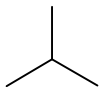
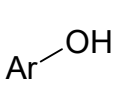
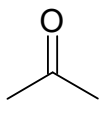
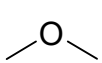
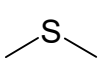
Do you remember…



		(kcal/mol)
charge-charge interaction (*ionic bond*):	$-\Delta G^0 \cong$	5 ÷ 10
charge-dipole interaction:	$-\Delta G^0 \cong$	1 ÷ 7
charge-π interaction:	$-\Delta G^0 \cong$	8 ÷ 10
hydrogen bond:	$-\Delta G^0 \cong$	1 ÷ 7
charge transfer interaction:	$-\Delta G^0 \cong$	1 ÷ 6
π-π interaction:	$-\Delta G^0 \cong$	1 ÷ 2
dipole-dipole interaction (van der Waals):	$-\Delta G^0 \cong$	0.5 ÷ 1

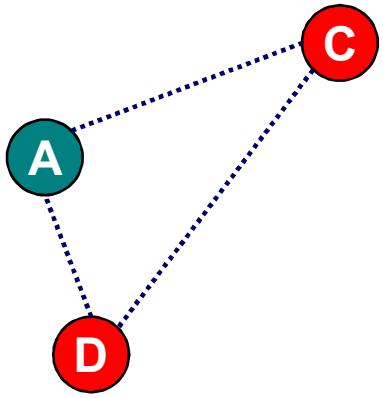
Pharmacophore definition:
4. From structural key to pharmacophoric key



							
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

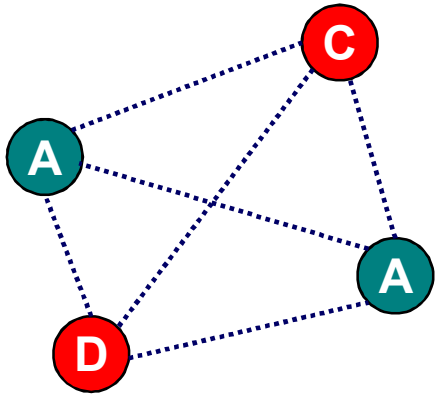
The triangle saga :



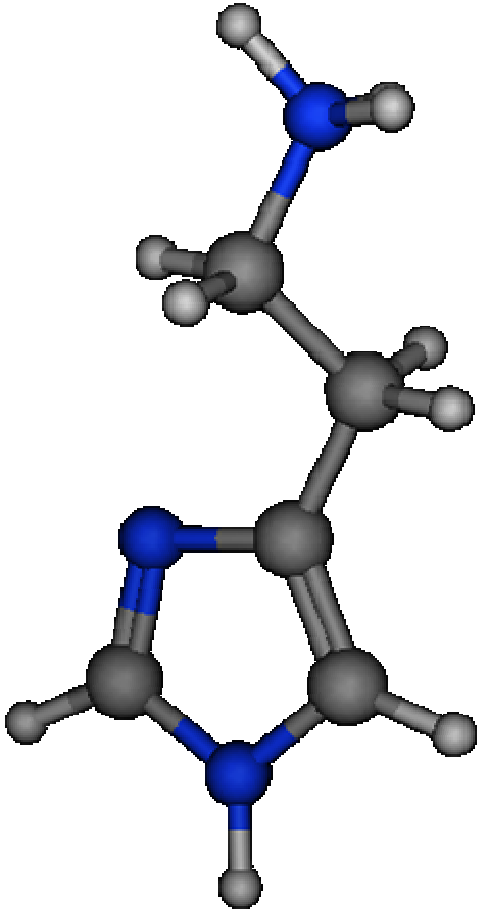
Any pharmacophoric triangle can be described as a three characters string: **ACD**

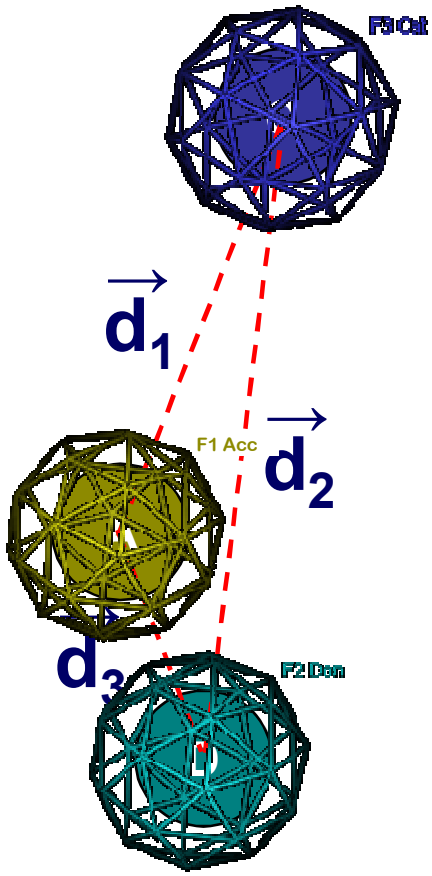
For any triangle we cal calculated numerical descriptors: **perimeter, sides length.**

Any polygons can be subdivided into a sum of triangles:



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

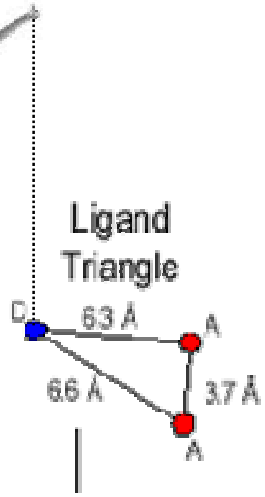


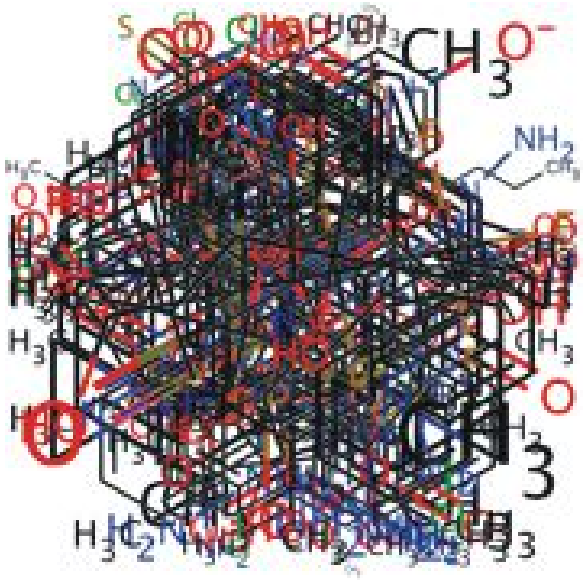


ACD 462 12

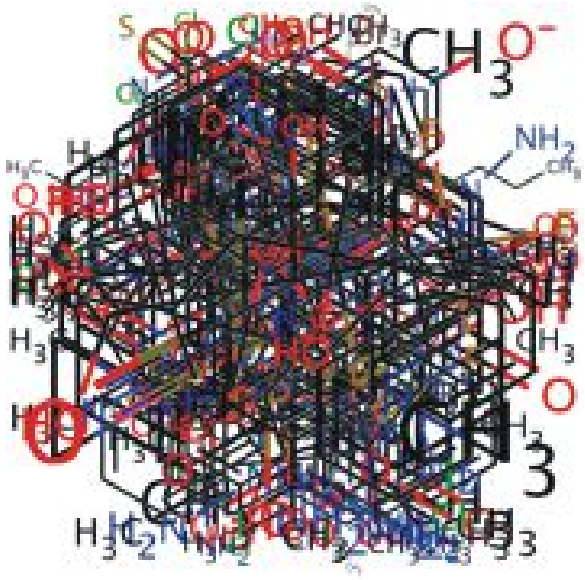
3D 2D 1D

Pharmacophore definition:
5. *Geometric hashing scheme*





What we need for a good fishing?



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

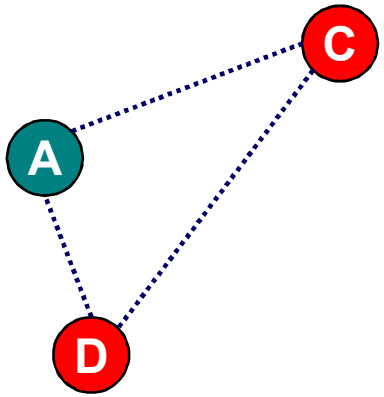
② generation of all plausible pharmacophoric hypothesis;

③ generation of all possible pharmacophoric triangles;

④ generation of all possible pharmacophoric strings.

a bit of combinatorial calculus:

Hypothesis: consider a pharmacophoric model with three plausible 'features' (interactors) how many pharmacophoric triangles can be generated?

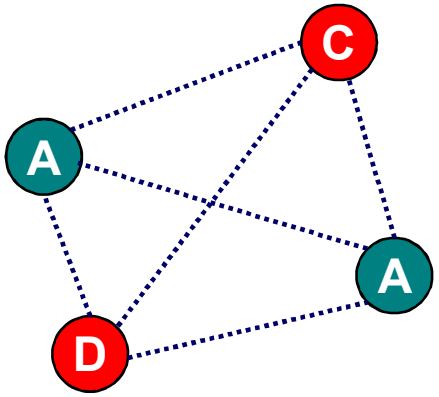


This is a "*simple disposition – without repetitions)*" of *n* elements grouped *k* per time:

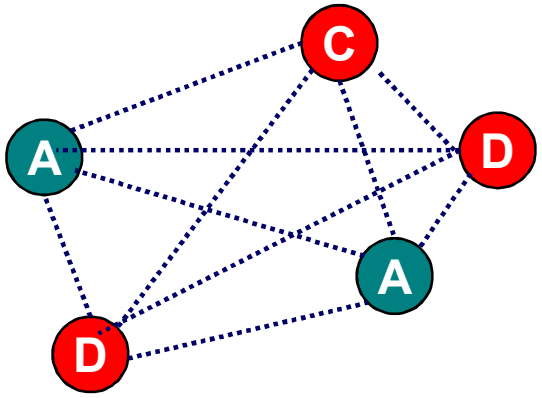
$$C_{3,3} = \frac{n!}{(n-k)!} = \frac{3!}{(3-3)!} = 6$$

a bit of combinatorial calculus:

Now is easier:

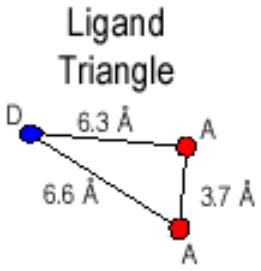


$$C_{4,3} = \frac{n!}{(n-k)!} = \frac{4!}{(4-3)!} = 24$$



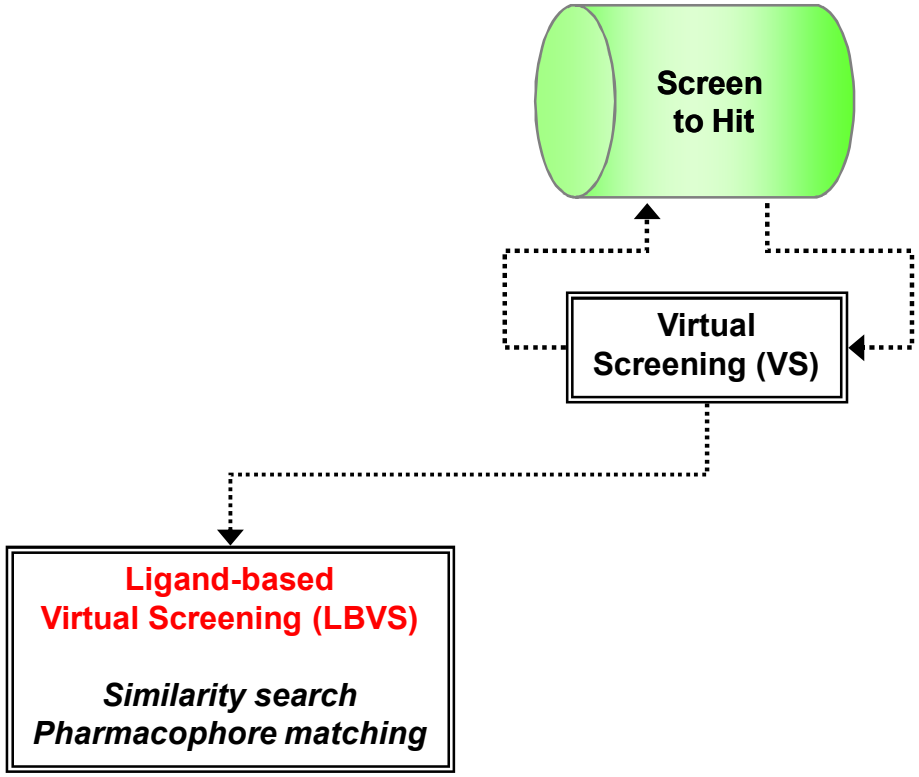
$$C_{5,3} = \frac{n!}{(n-k)!} = \frac{5!}{(5-3)!} = 60$$

Pharmacophore definition:
5. *Geometric hashing scheme*

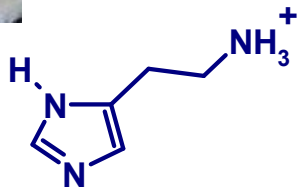


D = HBond Donor
A = HBond Acceptor
H = Hydrophobic Point

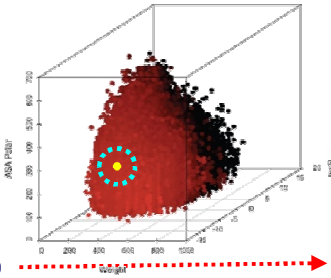
Here is a possible work-flow:



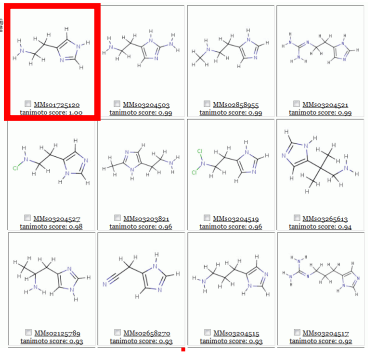
Here is a possible work-flow:

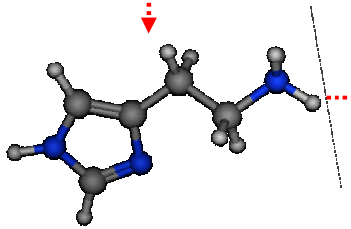


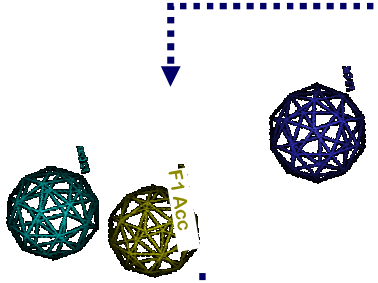
00001111100101010101010

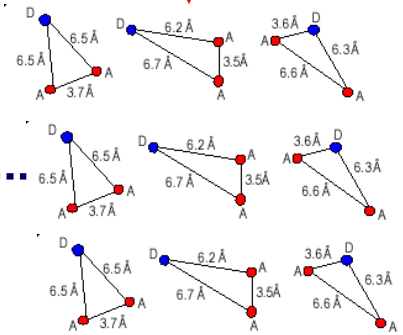


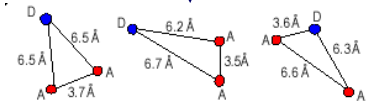
$$\frac{A \cap B}{A_{solo} + B_{solo} + A \cap B}$$

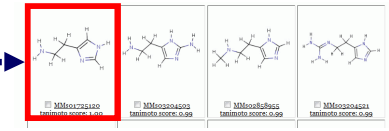












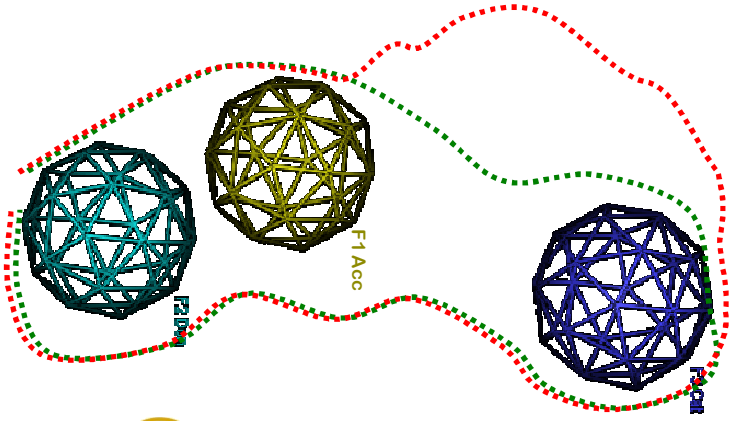
The real drama of pharmacophore fishing:

This fishing is inevitably rich of false positives!!!

Generally speaking, there may be many compounds that have a common pharmacophoric hypothesis but, at the level of their recognition site, they miss the proper topological complementarity (shape and volume).

The real drama of pharmacophore fishing:

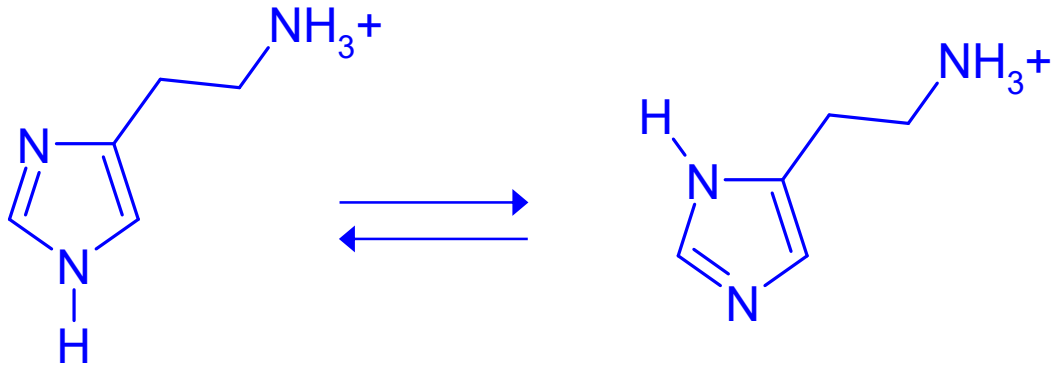
This fishing is inevitably rich of false positives!!!



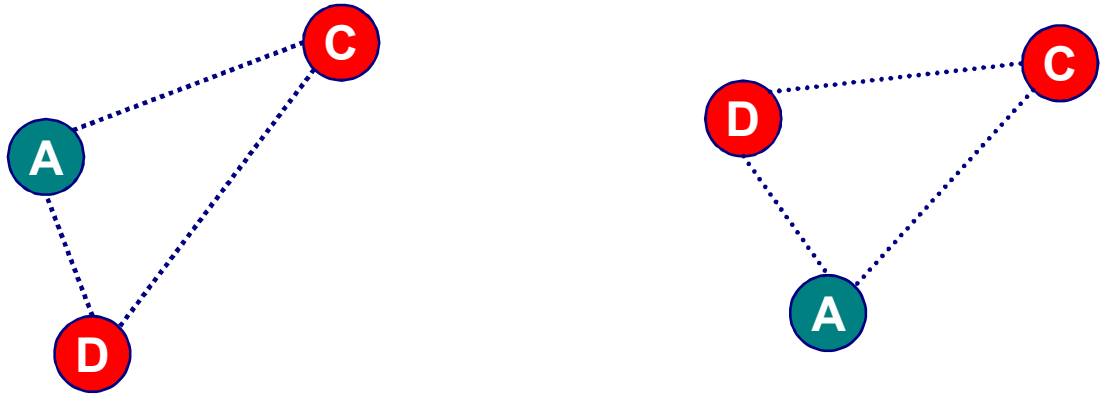
..... interactions shape/volume

..... interactions shape/volume

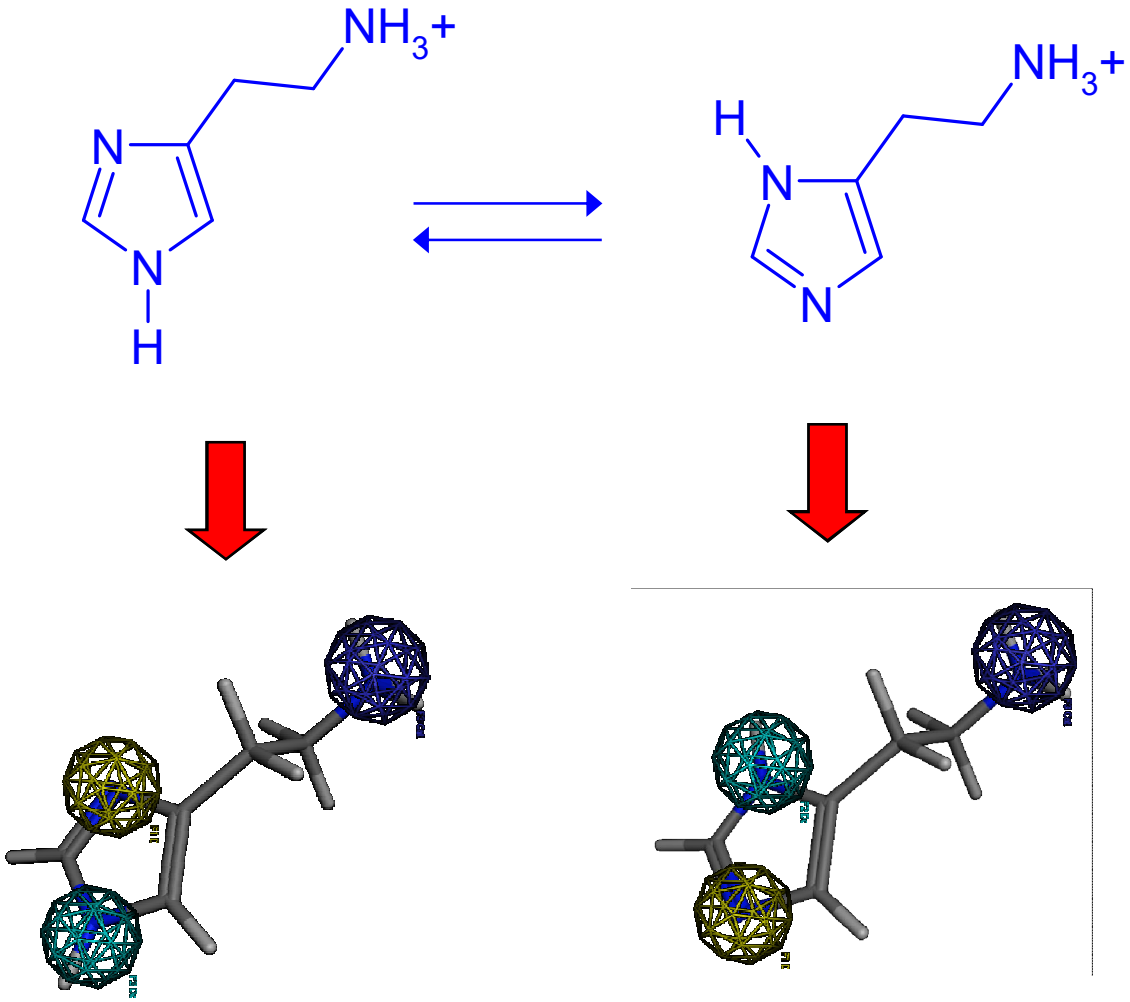
… and if I deal with more than ONE pharmacophore hypothesis?



do you remember this equilibrium?



My warm suggestion is to build up more that ONE pharmacophore hypothesis!



What we are still orphans:

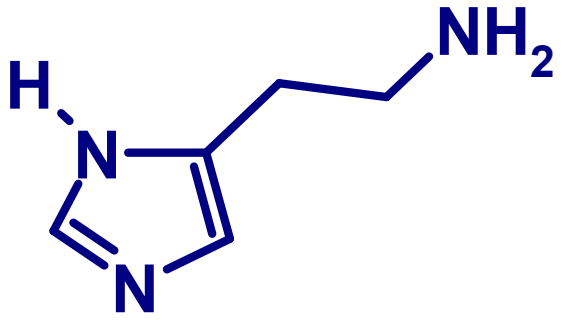
- Virtualize molecular topology (shape and volume);

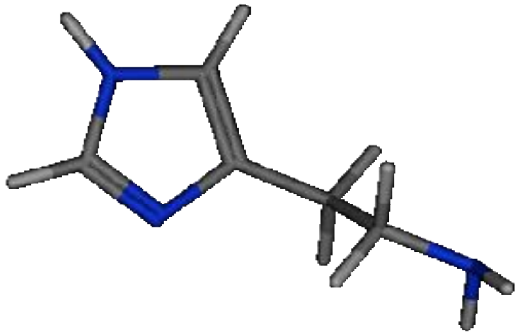
- Virtualize the generation of alternative conformers;

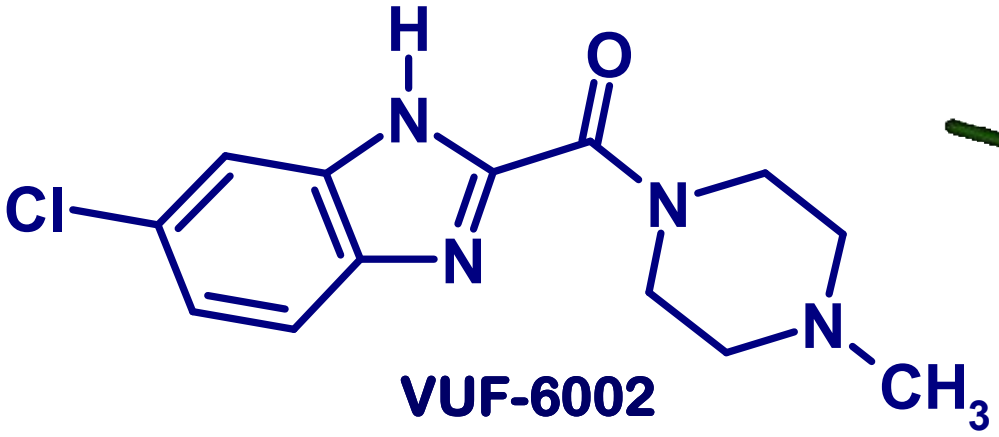
- Virtualize the evaluation of the stability of each conformer.


TITLE
“Progettazione e Sviluppo di un Farmaco”
DIRECTOR
Stefano Moro
CAMERA
Chimica e Tecnologia Farmaceutiche
DATE
SCENE
TAKE

Ed ecco un'altra interessante applicazione! Immaginiamo che:







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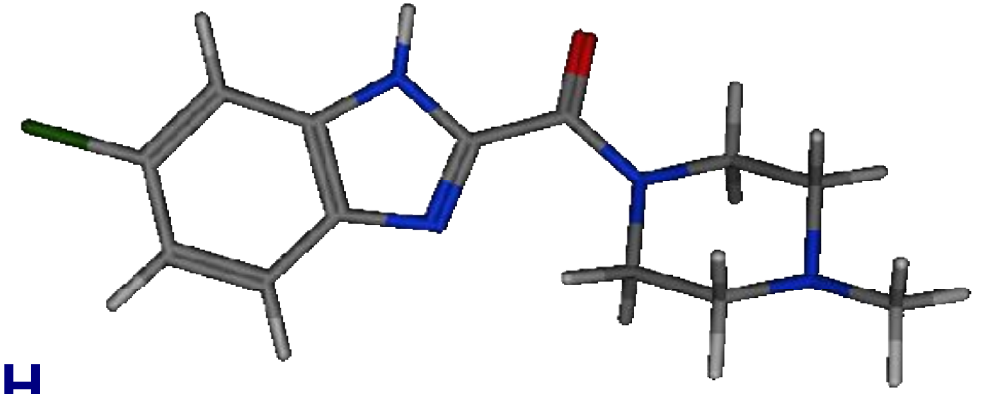
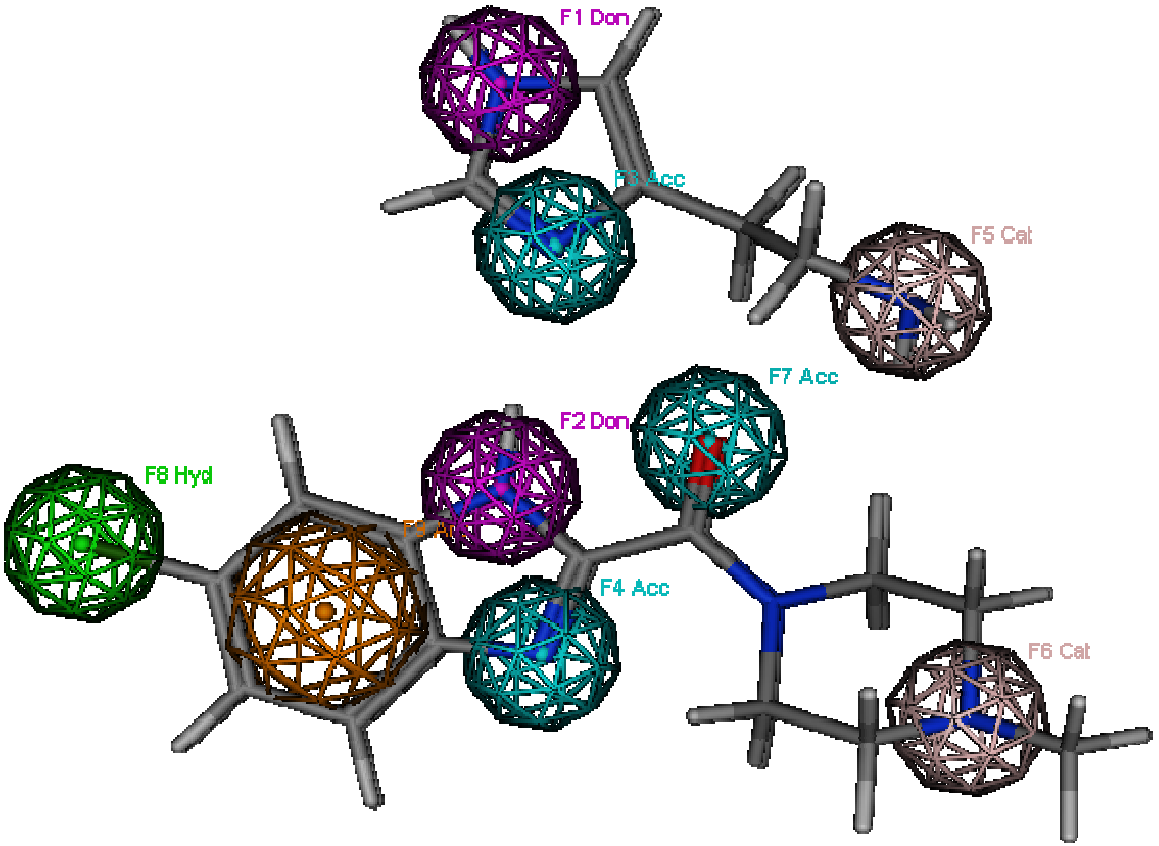
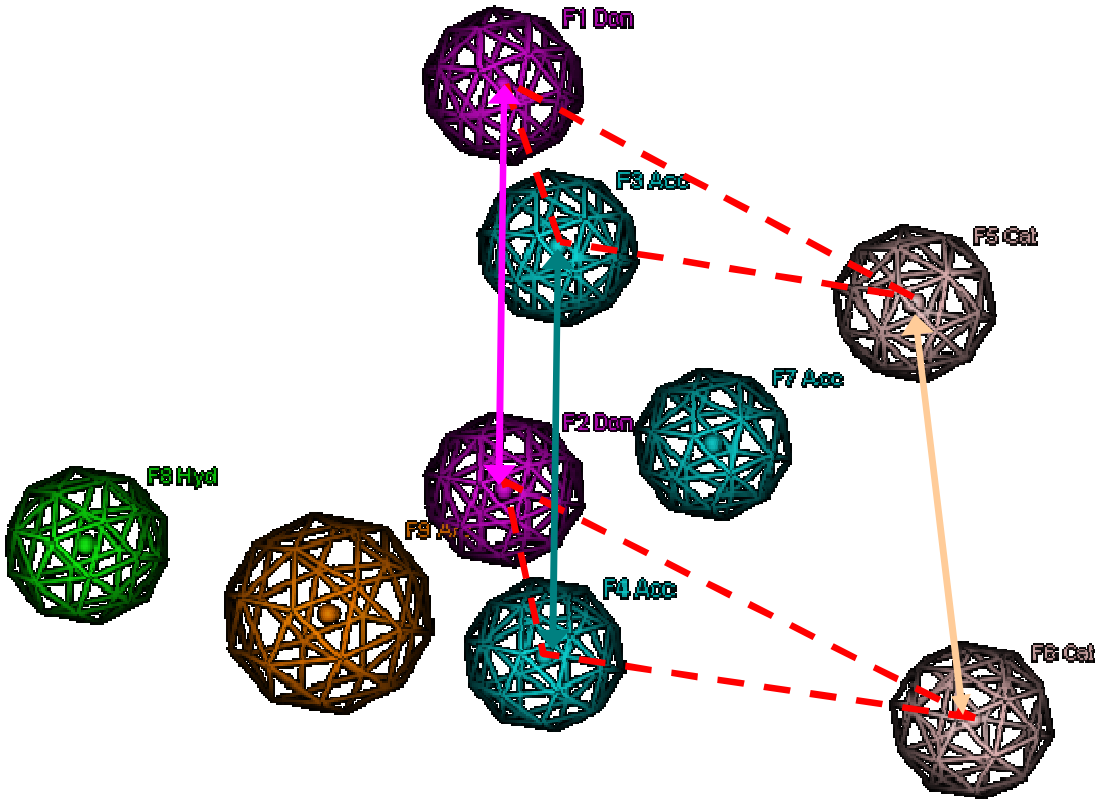


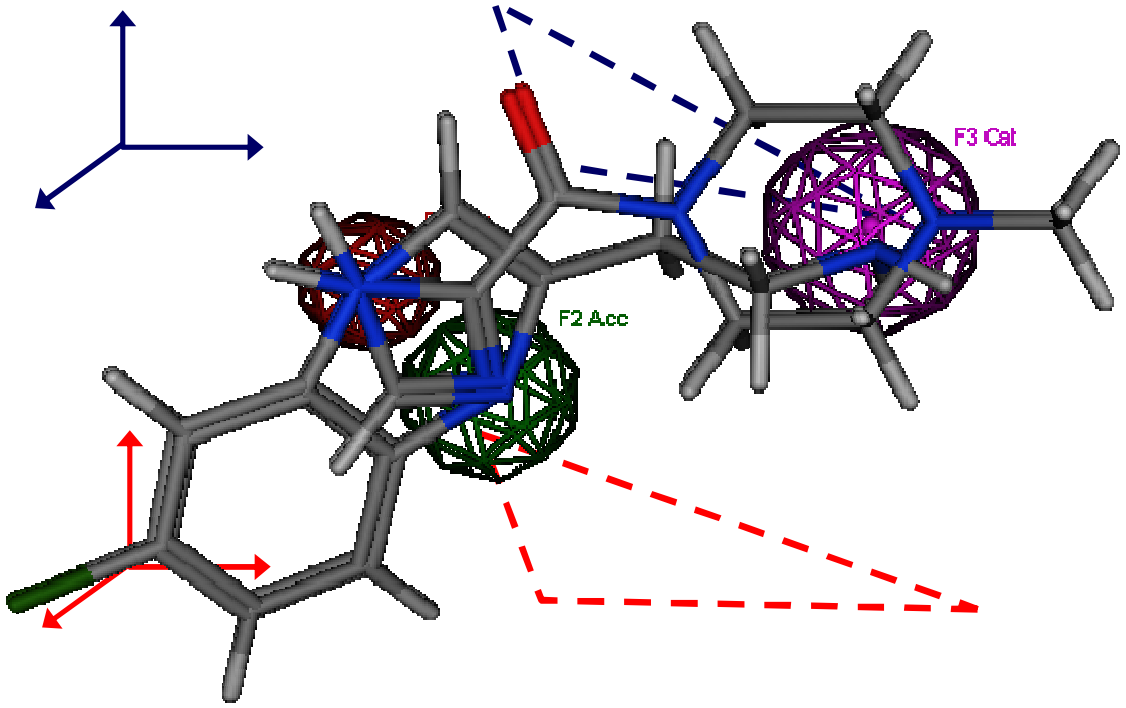
Sovrapponiamo?



Identifichiamo gli interattori



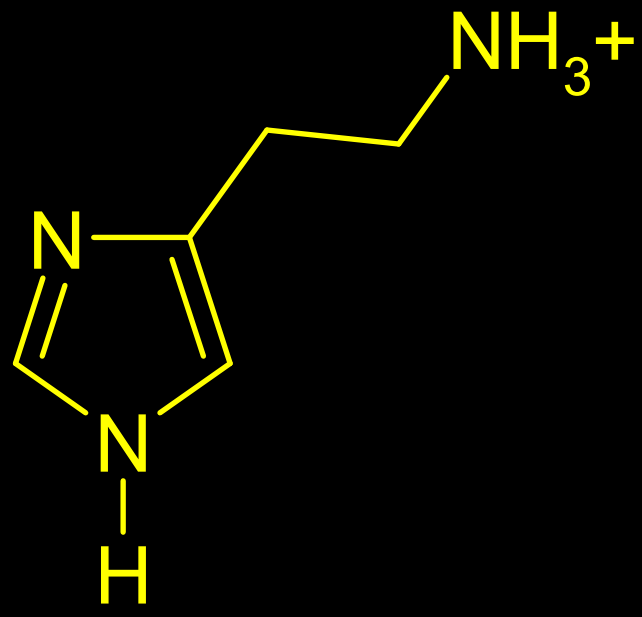
Identifichiamo i triangoli farmacoforici
Identifichiamo le distanze da “minimizzare”
Minimizziamo!



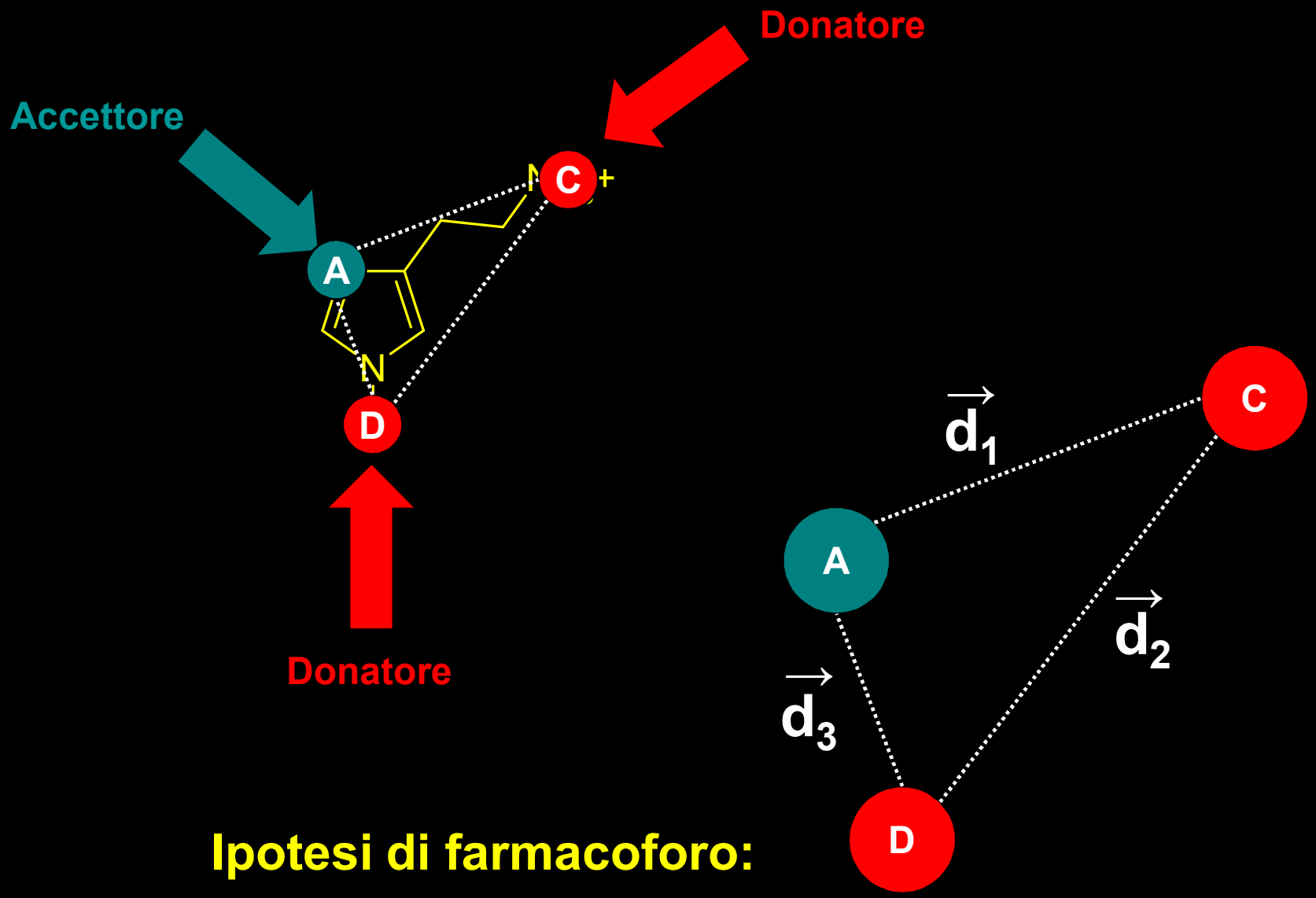
Uniformiamo il sistema di riferimento
Roto-trasliamo affinchè le distanze farmacoforiche hanno raggiunto il loro minimo di intensità
Sovrapposto!!!

Provocazione n. 1 :

Sareste in grado di proporre un ragionevole modello farmacoforico per la struttura molecolare qui sotto riportata?

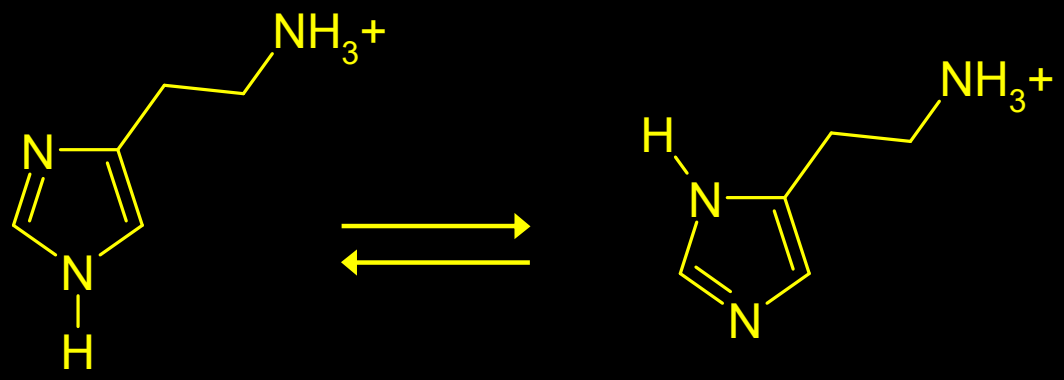


… beh, proviamo a definirlo?



Ipotesi di farmacoforo:

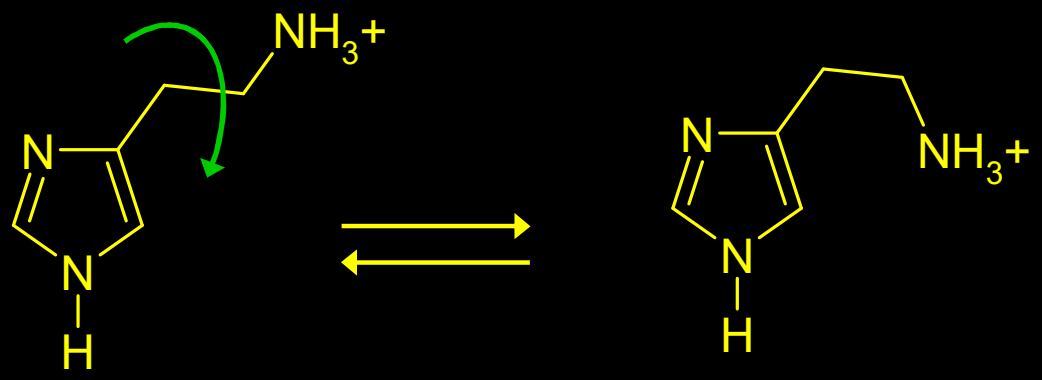
… siamo proprio sicuri?



ci ricordiamo dell'equilibrio tautomerico?!?!

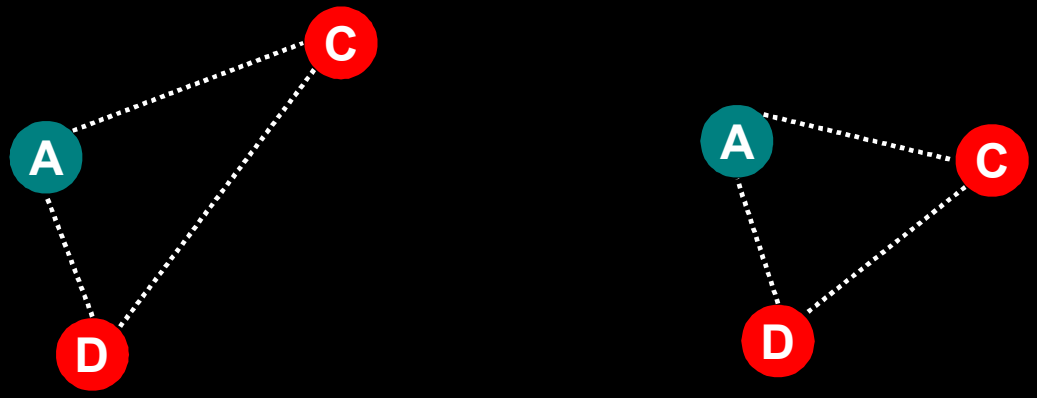
ed il farmacoforo allora?

… siamo tranquilli?

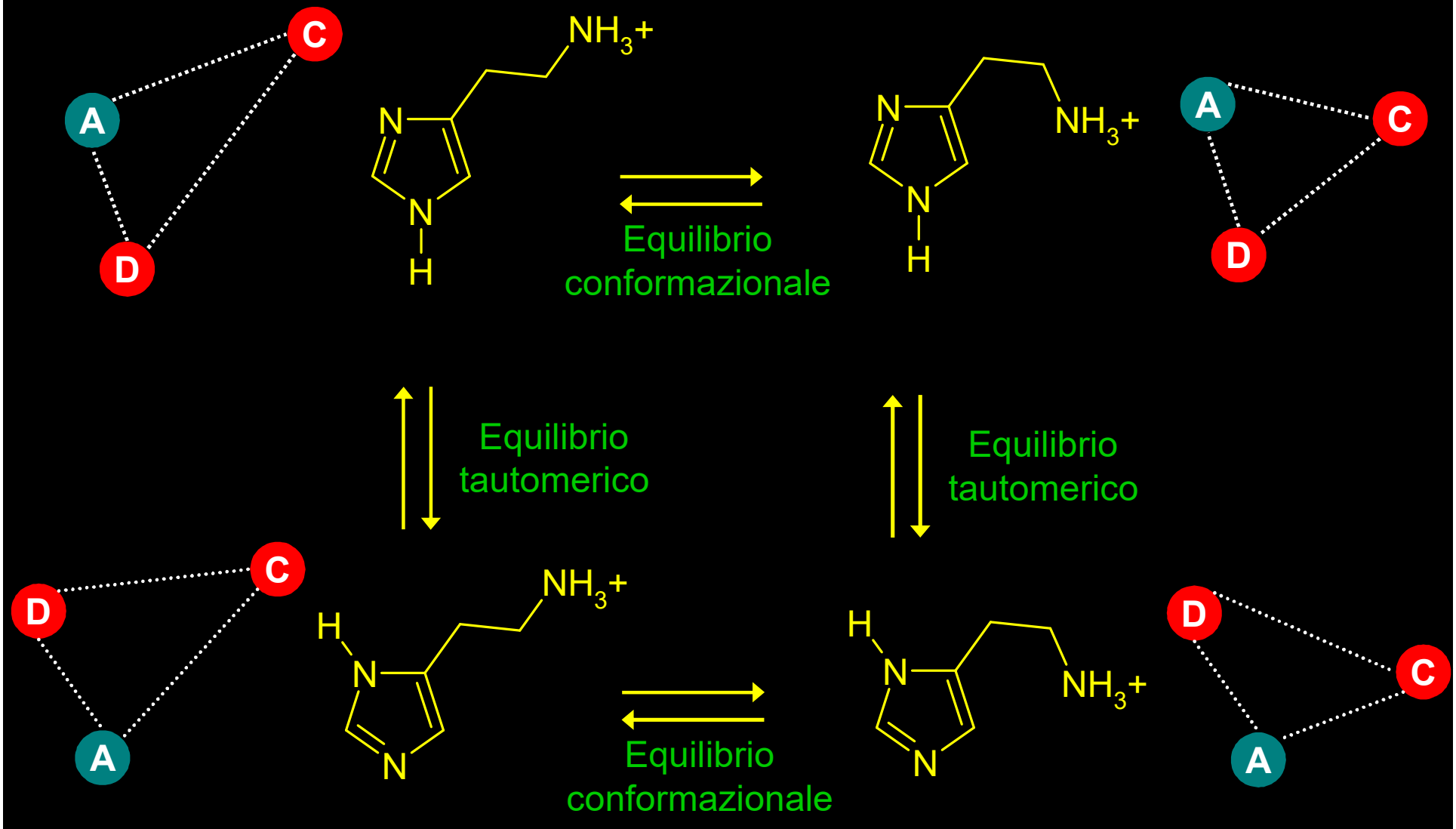


ci ricordiamo dell'equilibrio conformazionale?!?!

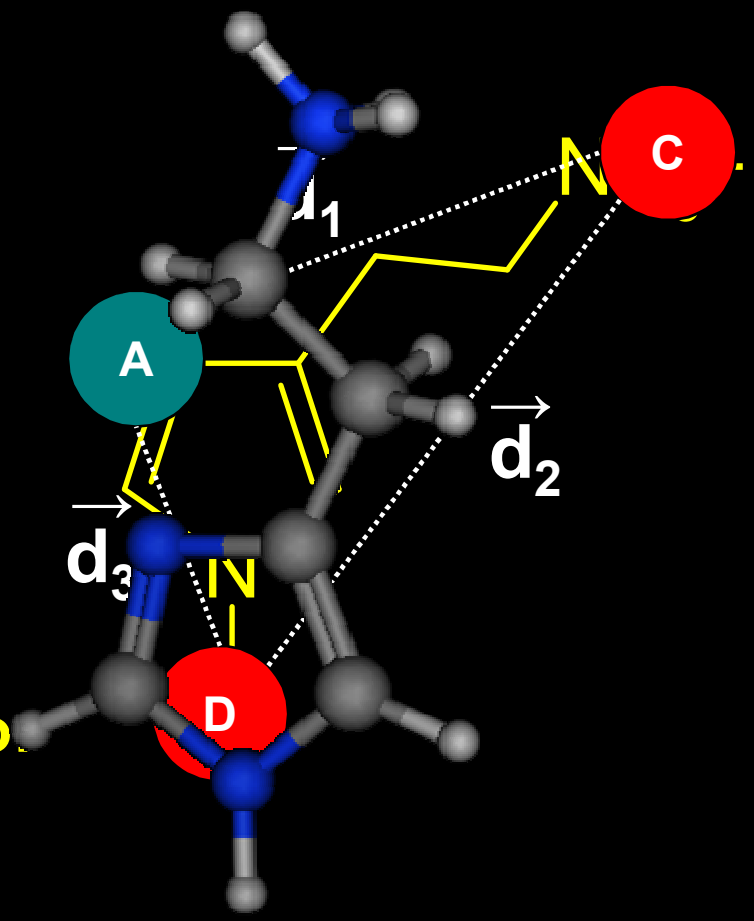
e quindi?



… ma quanti farmacofori abbiamo?



… capito il problema, però?



3D

Ipotesi di farmacoforo