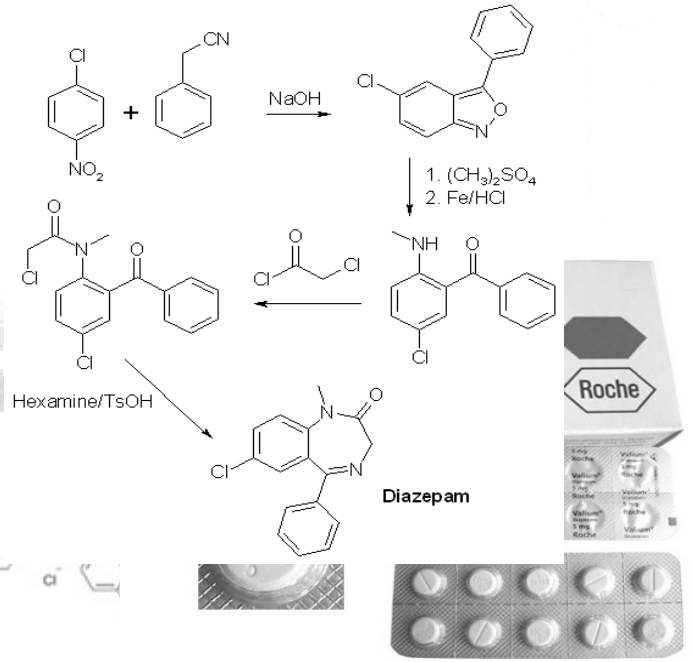
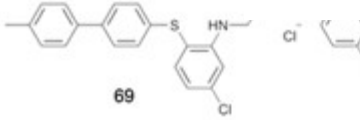
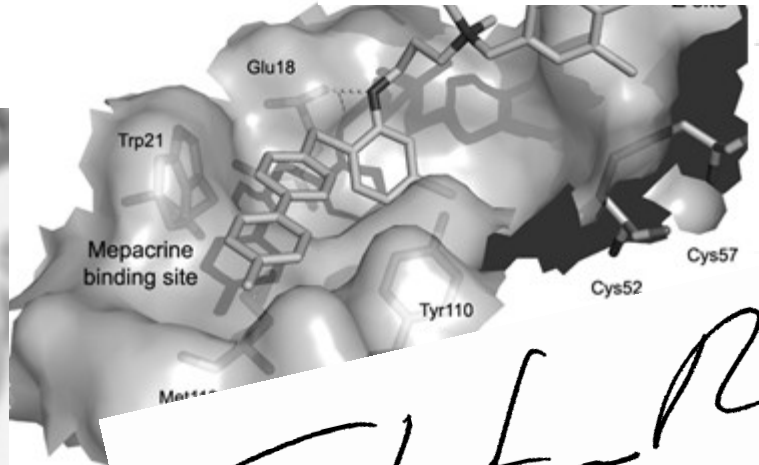
Chimica Farmaceutica







but we will never forget:

PHARMACODYNAMIC (PD) PROFILE

the study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of their actions and effects with their chemical structure.

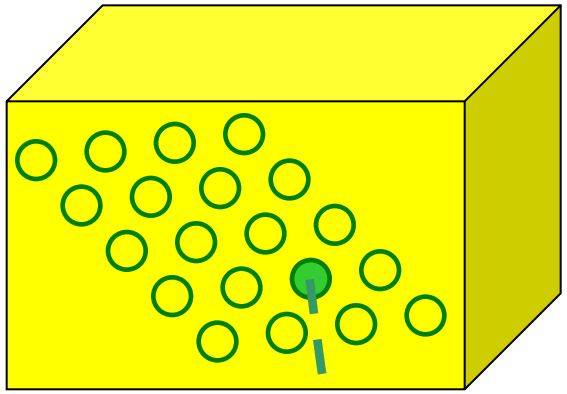
PHARMACOKINETIC (PK)/TOX PROFILE

The study of the process by which a drug is absorbed (A), distributed (D), metabolized (M), and eliminated (E) by the body.

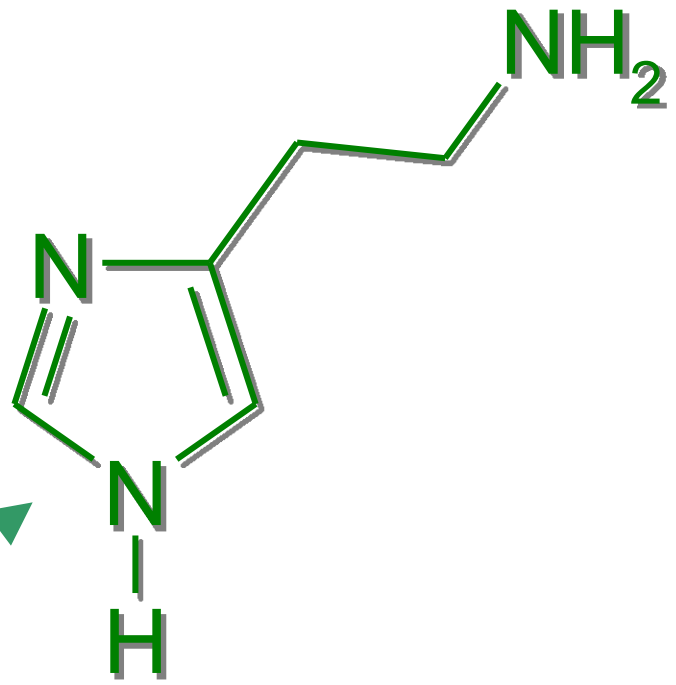
FORMULATION PROFILE

where PD and PK profiles are stored in a drug?

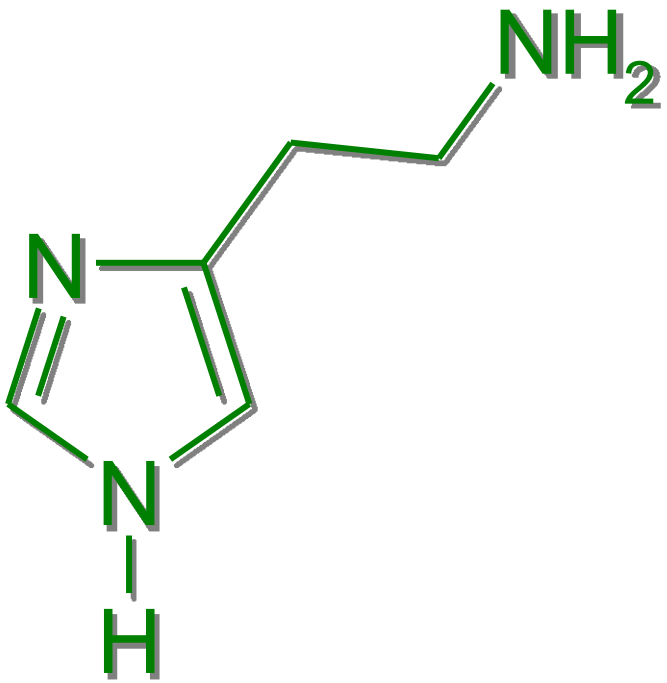
Chemical/Drug



Chemical Space

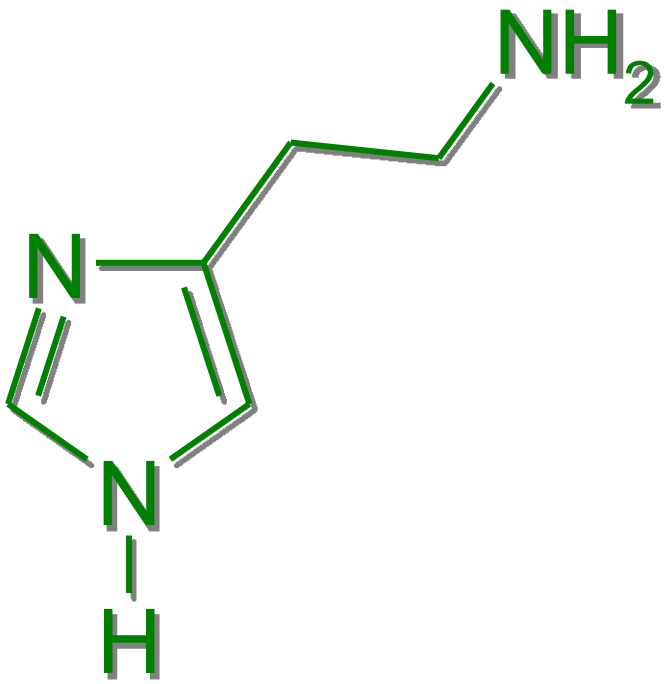


The first gold rule:



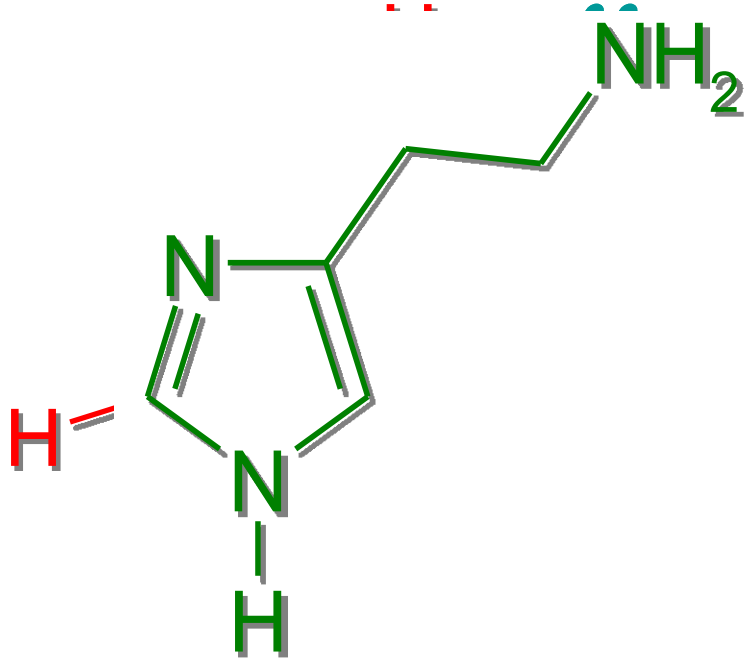
Identify the chemical class of belonging!!!

Please, we will never forget:



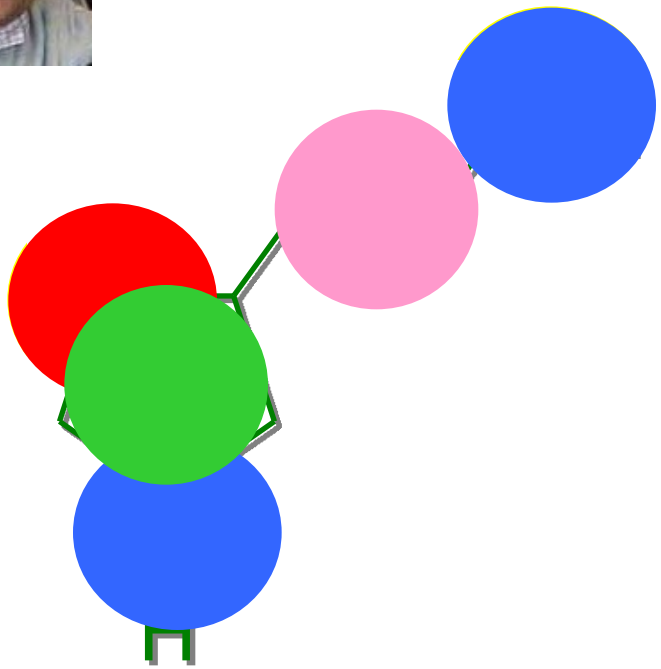
take the right distance from these representations!!!

First of all, please do not never forget the good orthography!



Of course this is our *slang!*

Good orthography means ability to recognize:



1. acid/base groups (*ionic bond)*;

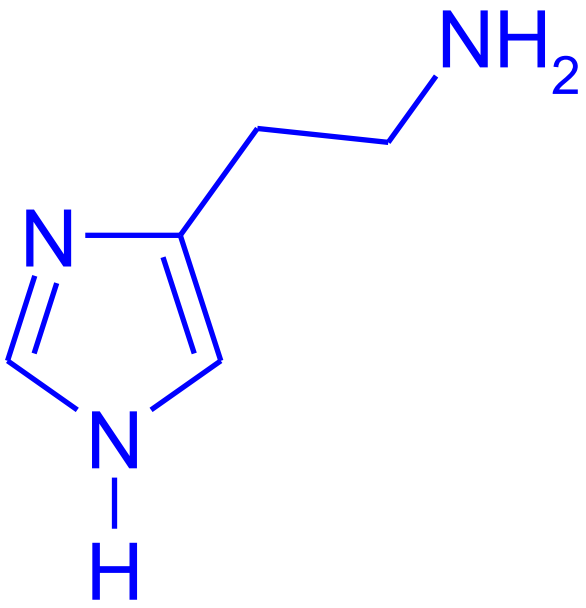
2. strong bond dipoles (*H-bond, dipole-dipole, charge-dipole…)*;

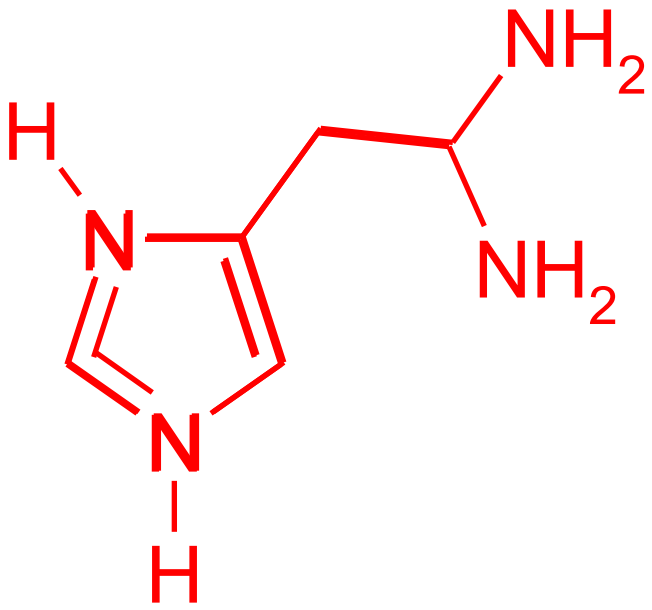
3. *π bonds (π-π interactions, charge-π, …)*;

4. weak bond dipoles (*dipole-dipole as van der Waals interactions*);

Do you remember:

1. pKa scale of acidity
2. hydrogen bond strength
3. aromaticity rule (4n+2)
4. bond dipole moment





1. acid/base groups (*ionic bond*);

2. Strong bond dipoles (*H-bond, dipole-dipole, charge-dipole…*);

3. π *bonds* (π-π *interactions, charge-*π*, ..)*;

4. Weak bond dipoles (*dipole-dipole as van der Waals*);

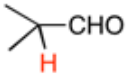
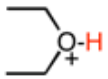
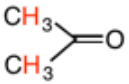
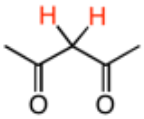
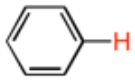
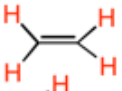
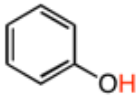
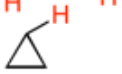
5. Tautomers (*tautomeric equilibrium and tautomer stability*);

6. Conformers (*conformational equilibrium and conformer stability*);

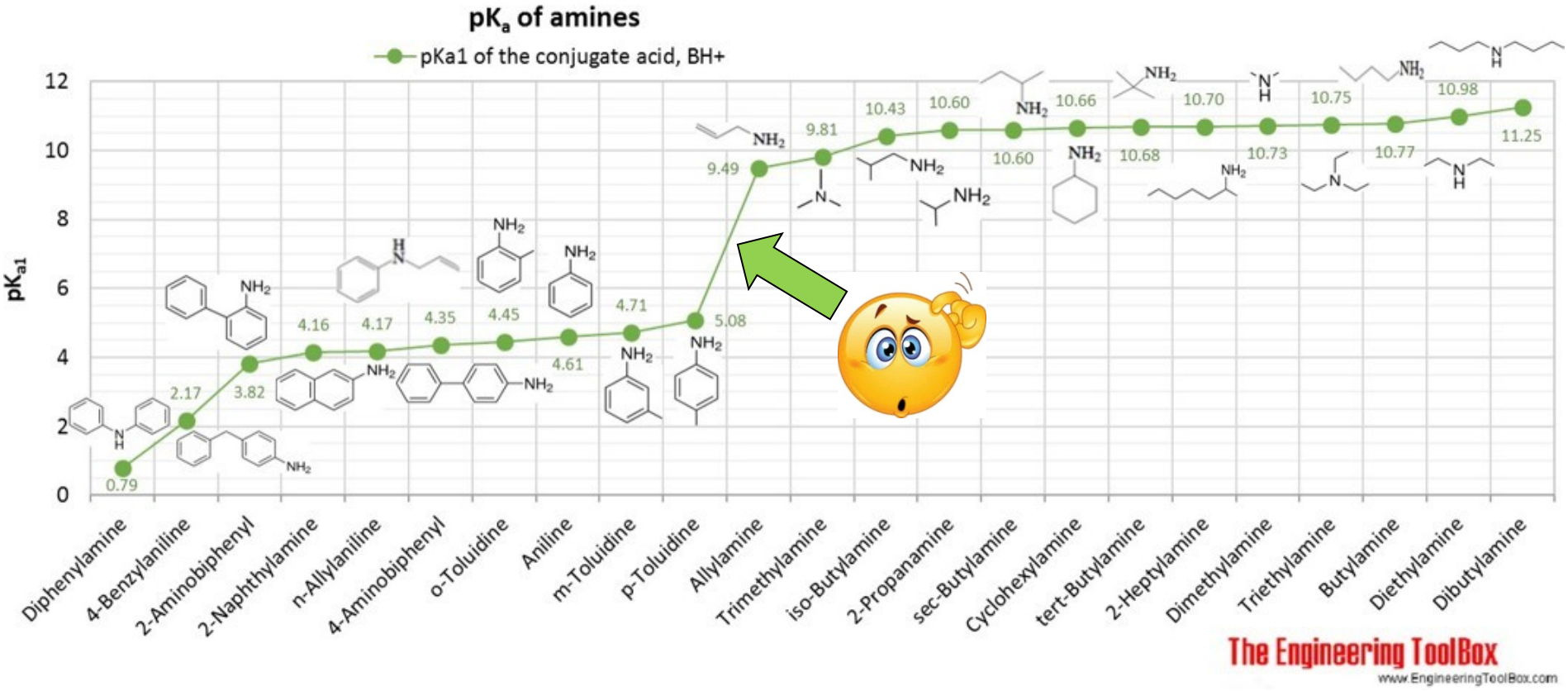
7. Stereochemistry (chiral centers)

8. Chemical reactivity;

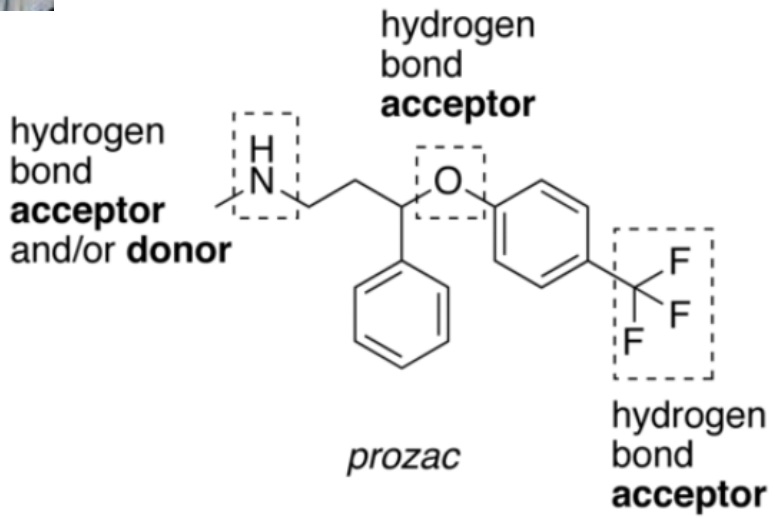
Just in case:

Brønsted Acids	pK_a	Brønsted Acids	pK_a
$CH_3C{\equiv}N^+\text{-}H$	-10	$CH_3COCH_2CO_2R$	11
HI	-10		15.5
HBr	-9	CH_3OH	15.5
$(CH_3)_2C{=}O^+\text{-}H$	-7.2	HOH	15.7
HCl	-7	C_2H_5OH	15.9
$(CH_3)_2^+S\text{-}H$	-5.4	$(CH_3)_3COH$	18
	-3.6		20
$C_2H_5^+OH_2$	-2.4	$(CH_3)_2SO_2$	23
H_3O^+	-1.7	$CH_3CO_2C_2H_5$	25
CF_3CO_2H	0.2	$CH_3C{\equiv}N$	25
HF	3.18	$HC{\equiv}CH$	25
CH_3CO_2H	4.76	NH_3	35
H_2S	7.0	$C_2H_5NH_2$	35
	9	$CH_3CH{=}CH_2$	38
NH_4^+	9.25		43
HCN	9.40		44
	10.0		46
CH_3NO_2	10.2		
C_2H_5SH	10.5	CH_4, C_2H_6	~50

This will be crucial for us during all our course!!!



Just in case:



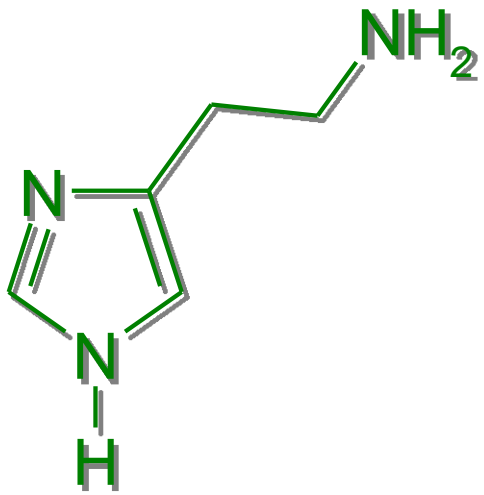
F−H ··· :F (38.6 kcal/mol)
O−H ··· :N (6.9 kcal/mol)
O−H ··· :O (5.0 kcal/mol)
N−H ··· :N (3.1 kcal/mol)
N−H ··· :O (1.9 kcal/mol)
HO−H ··· :OH_3^+ (4.3 kcal/mol)

Bond Dipole Moments

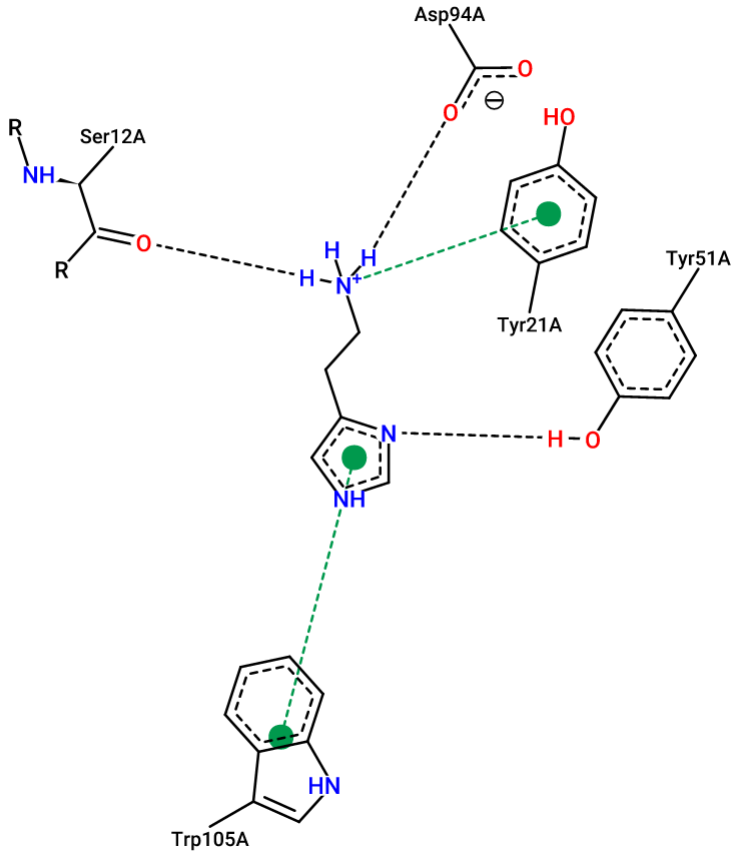
$\delta^+ \longrightarrow \delta^-$

Bond	Dipole Moment (D)
H-C	0.3
H-N	1.31
H-O	1.53
C-N	0.22
C-O	0.86
C-F	1.51
C-Cl	1.56
C-Br	1.48
C-I	1.29
C=O	2.4
CN (cyano)	3.6

The major difference between an organic chemist and a medicinal chemist

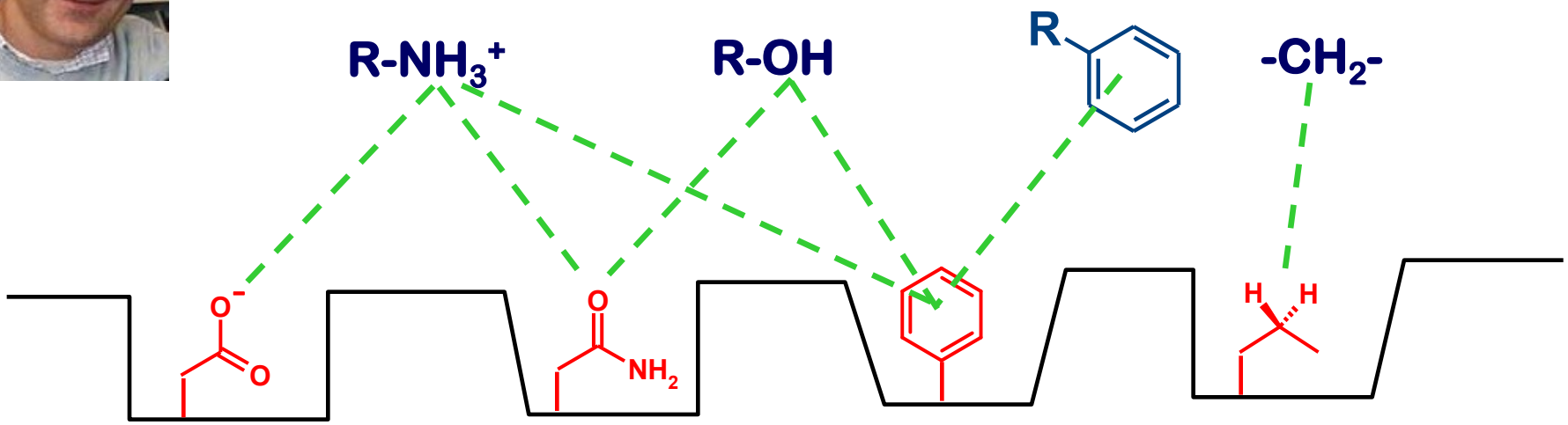


I'm like that and I have these properties



I'm like this and have these properties, and consequently I could recognize in this way …

From structure to interaction:



		(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

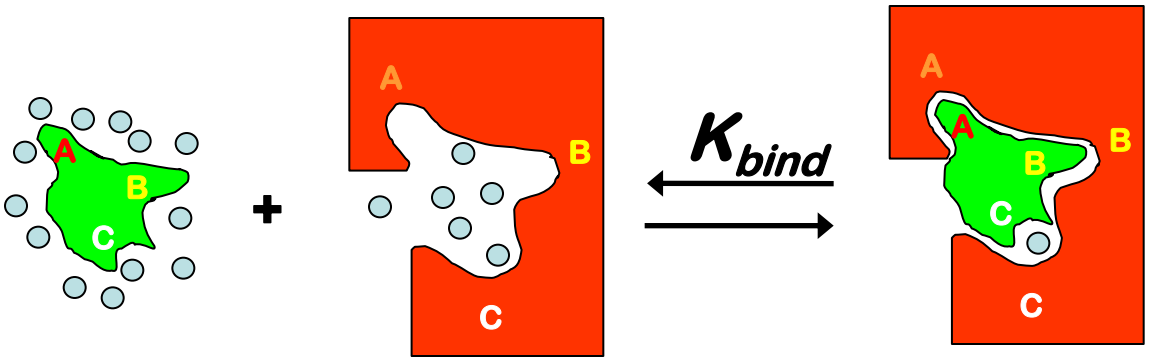
Possiamo pensare di tradurre qualitativamente

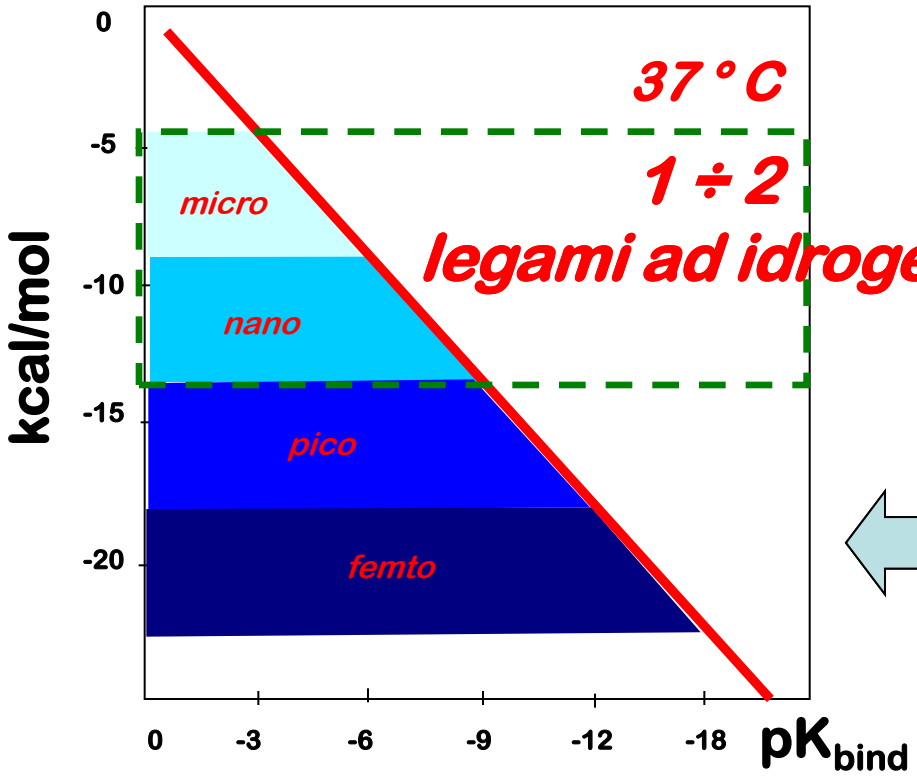
$$\Delta G^0_{bind} = \Delta G^0_e + \Delta G^0_h + \Delta G^0_s + \Delta G^0_{conf} + \Delta G^0_{solv}$$

in termini molecolari?

In un certo qual senso sì! Bisogna saper leggere dentro le strutture molecolari!

Dalla struttura all'interazione:



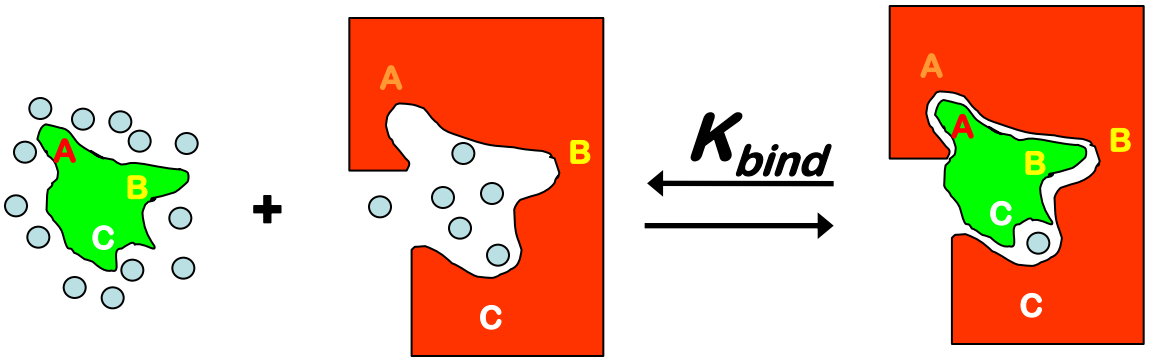


$$K_{bind} = e^{-\Delta G^0_{bind} / RT}$$

$$\Delta G^0_{bind} = -RT \ln K_{bind}$$

$$\Delta G^0_{bind} = RTpK_{bind}$$

Please, you will never forget:



Even if:

dipole-dipole interaction (van der Waals): $-\Delta G^0 \cong$ **0.5 ÷ 1**

remember that the unity is strength!

The only interaction that are able to shift the equilibrium to the right are those HYDROPHOBIC.

from structure to interaction…

Journal of
Medicinal
Chemistry
Perspective

J. Med. Chem. **2010,** *53,* 5061–5084 **5061**
DOI: 10.1021/jm100112j

A Medicinal Chemist's Guide to Molecular Interactions

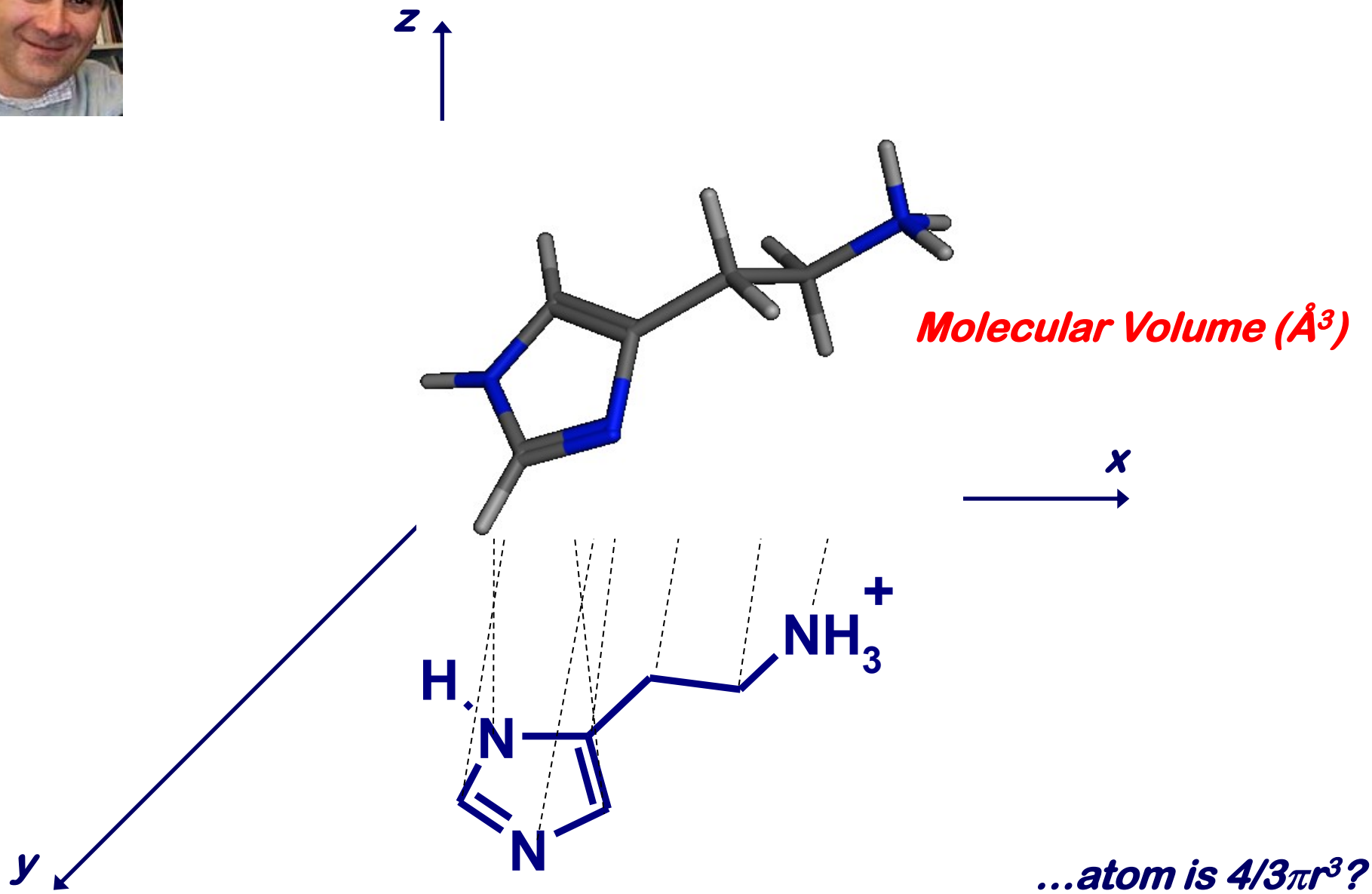
Caterina Bissantz, Bernd Kuhn, and Martin Stahl*

Discovery Chemistry, F. Hoffmann-La Roche AG, CH-4070 Basel, Switzerland

Received January 27, 2010

… a super paper!!!

the shadow of the reality:



Molecular Volume (Å³)

…atom is 4/3πr³?

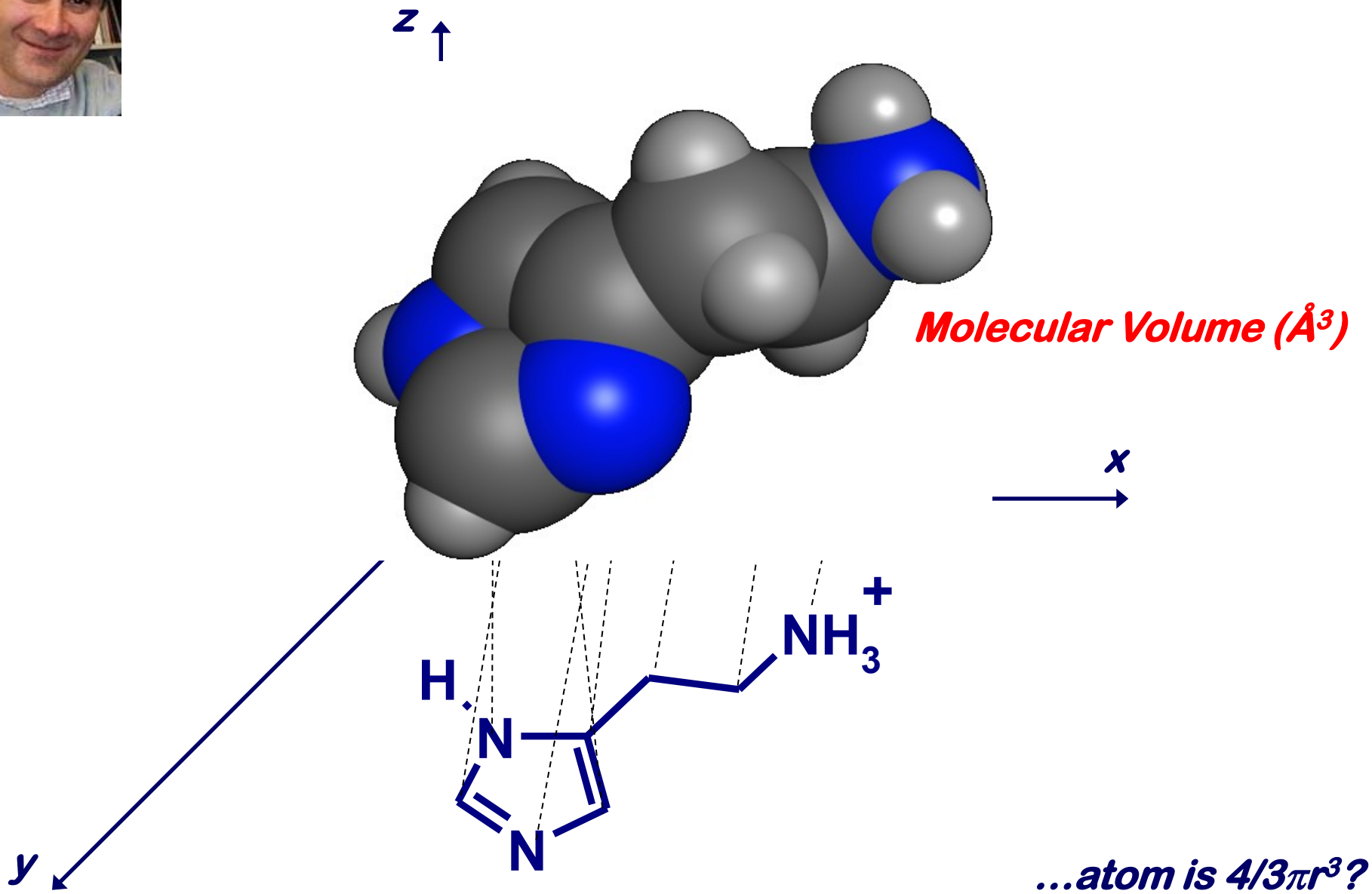
A quick refresh…

Element	radius (Å)
Hydrogen	1.20
Carbon	1.70
Nitrogen	1.55
Oxygen	1.52
Fluorine	1.47
Phosphorus	1.80
Sulfur	1.80
Chlorine	1.75
Copper	1.4

$$V_{vdW} = \frac{4}{3}\pi\ r_{vdW}^{3}$$

$$r_{vdW} = \sqrt[3]{V_{vdW}\ \frac{3}{4\pi}}$$

the shadow of the reality:



Molecular Volume (Å³)

…atom is 4/3πr³?

At this point measure the molecular size is easy…

Verloop A., Hoogenstraaten W., Tipker J. "Development and application of new steric substituent parameters in drug design." In Drug Design (Ed. Ariëns), vol.7, pp.165-207 (1976), New York: Academic Press.

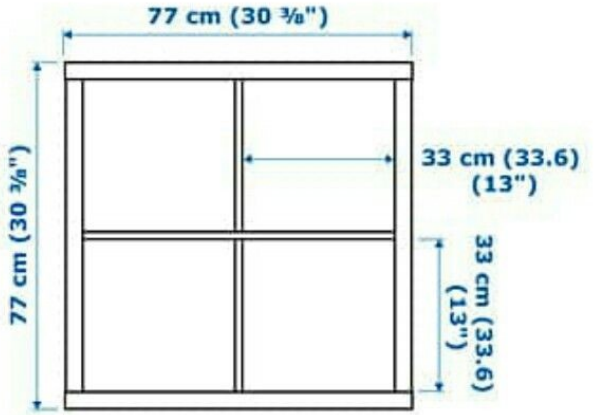
My favorite example:

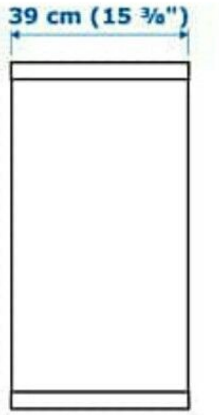
IKEA

CERCA UN PRODOTTO O UN SERVIZIO

NOVITÀ | OFFERTE | PRODOTTI | AMBIENTI | IDEE | RISTORANTE E BOTTEGA | DOVE SIAMO

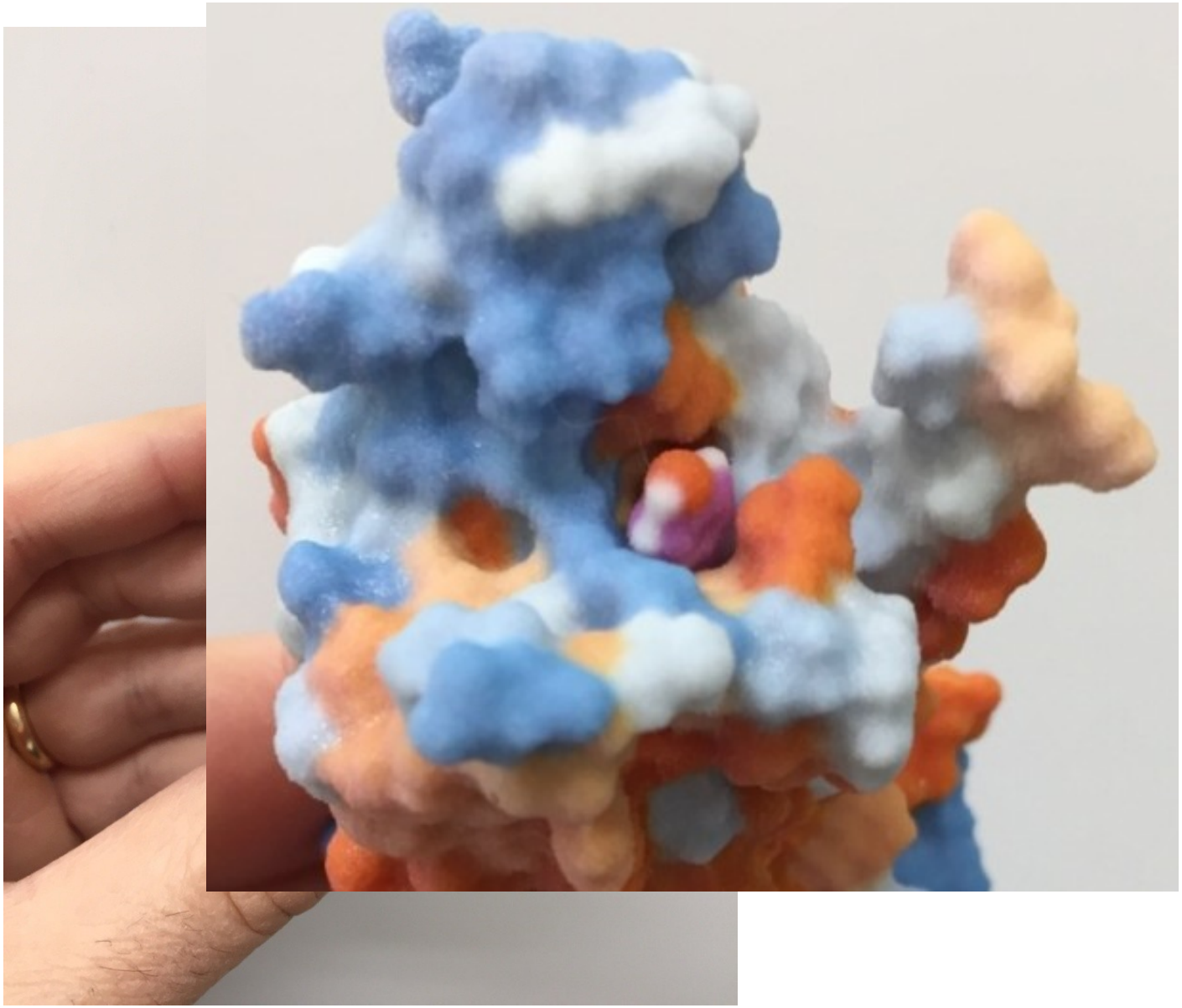
Home / Soggiorno / Scaffali



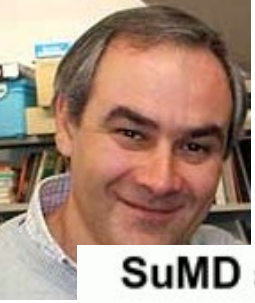


Credits: https://www.ikea.com/it/it/catalog/products/20275814/

Here is my first favorite example of PD concept:

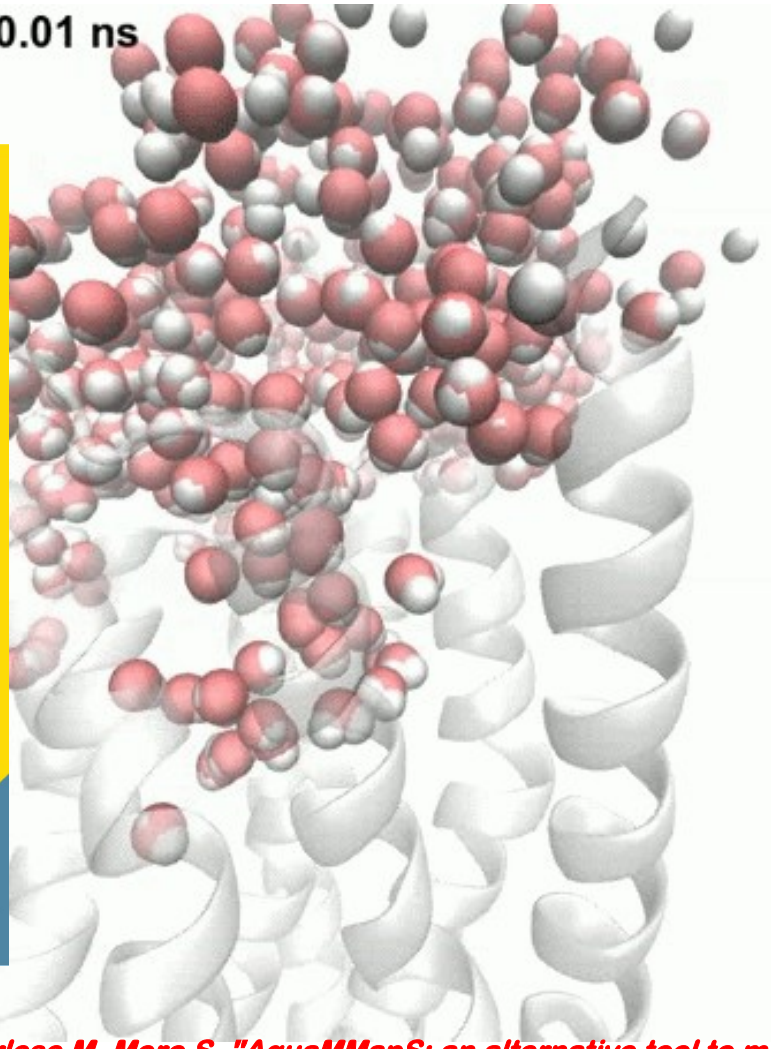


MMS Lab (2015): 3D printed model of the human A2A adenosine receptor co-crystallized its antagonist ZM 241385 (PDB entry: 4EIY)

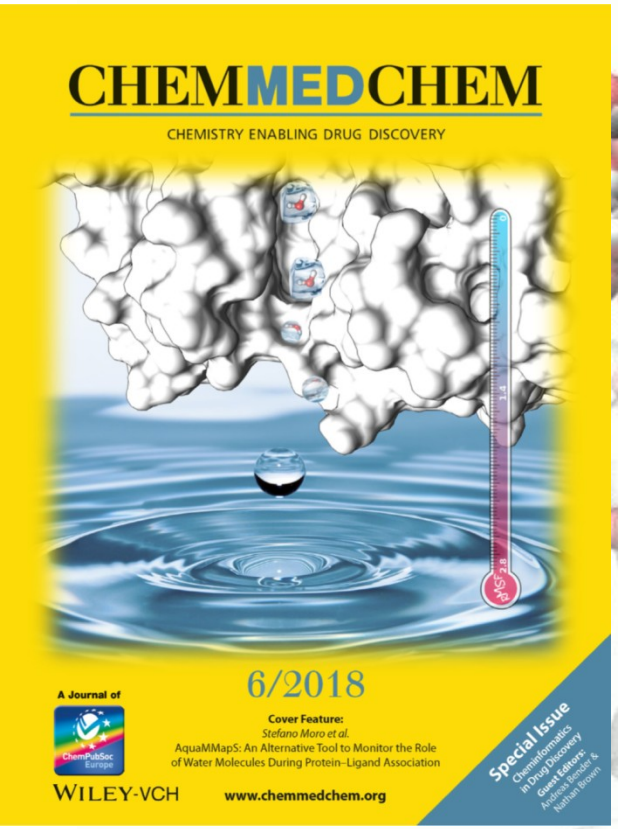


… and with some of you in a couple of years:

SuMD simulation time: 0.01 ns



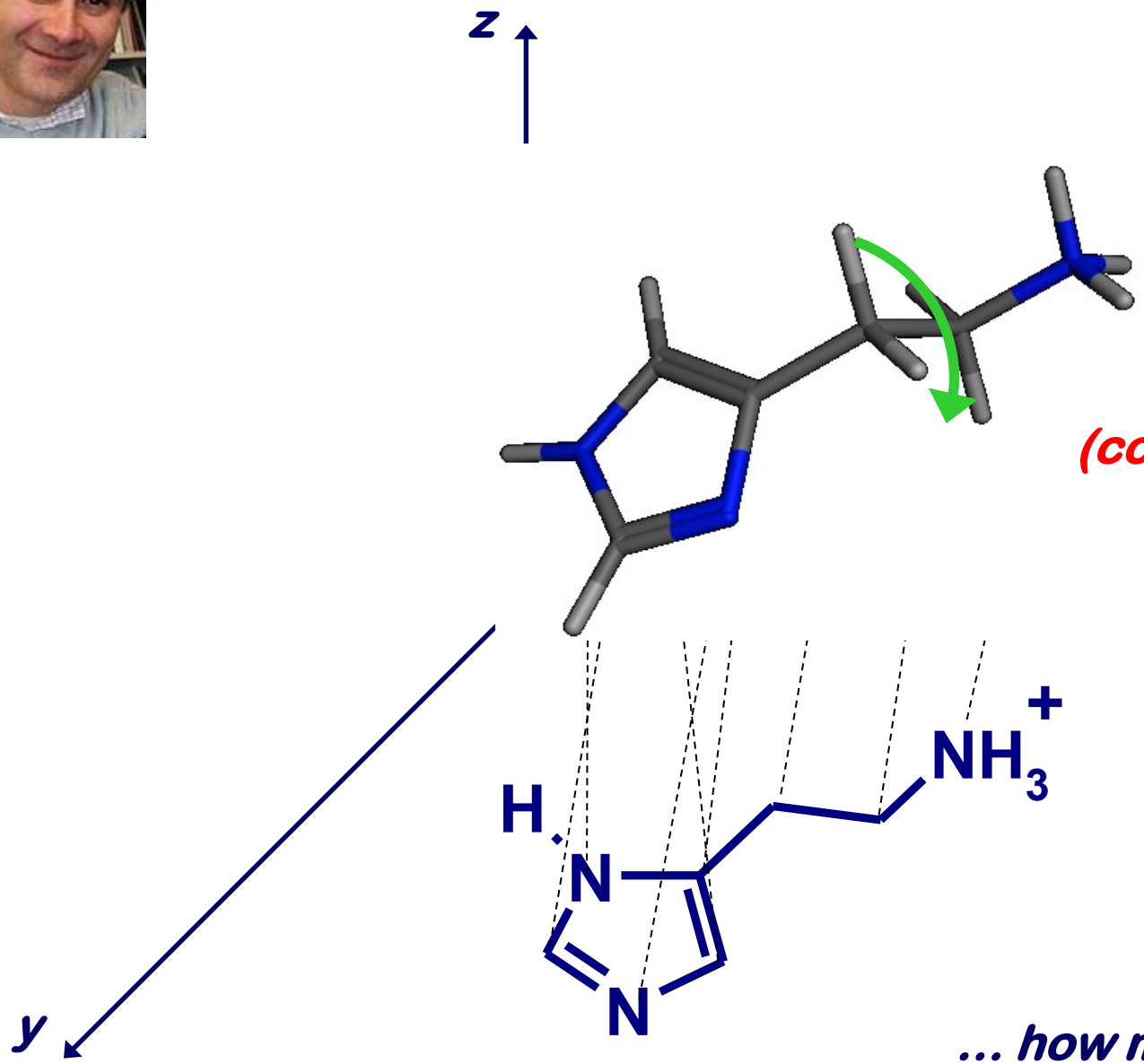
MMS
mms.dsfarm.unipd.it



Cuzzolin A, Deganutti G, Salmaso V, Sturlese M, Moro S. "AquaMMapS: an alternative tool to monitor the role of water molecules during protein-ligand association." ChemMedChem. 1, 1-13 (2018)

G. Deganutti *A. Cuzzolin*

the shadow of the reality:

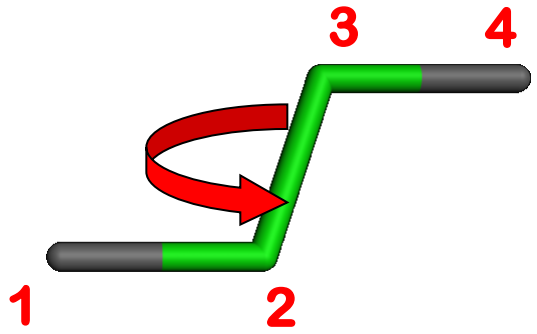


Rotatable bonds (conformer population)

… how many rotatable bond?

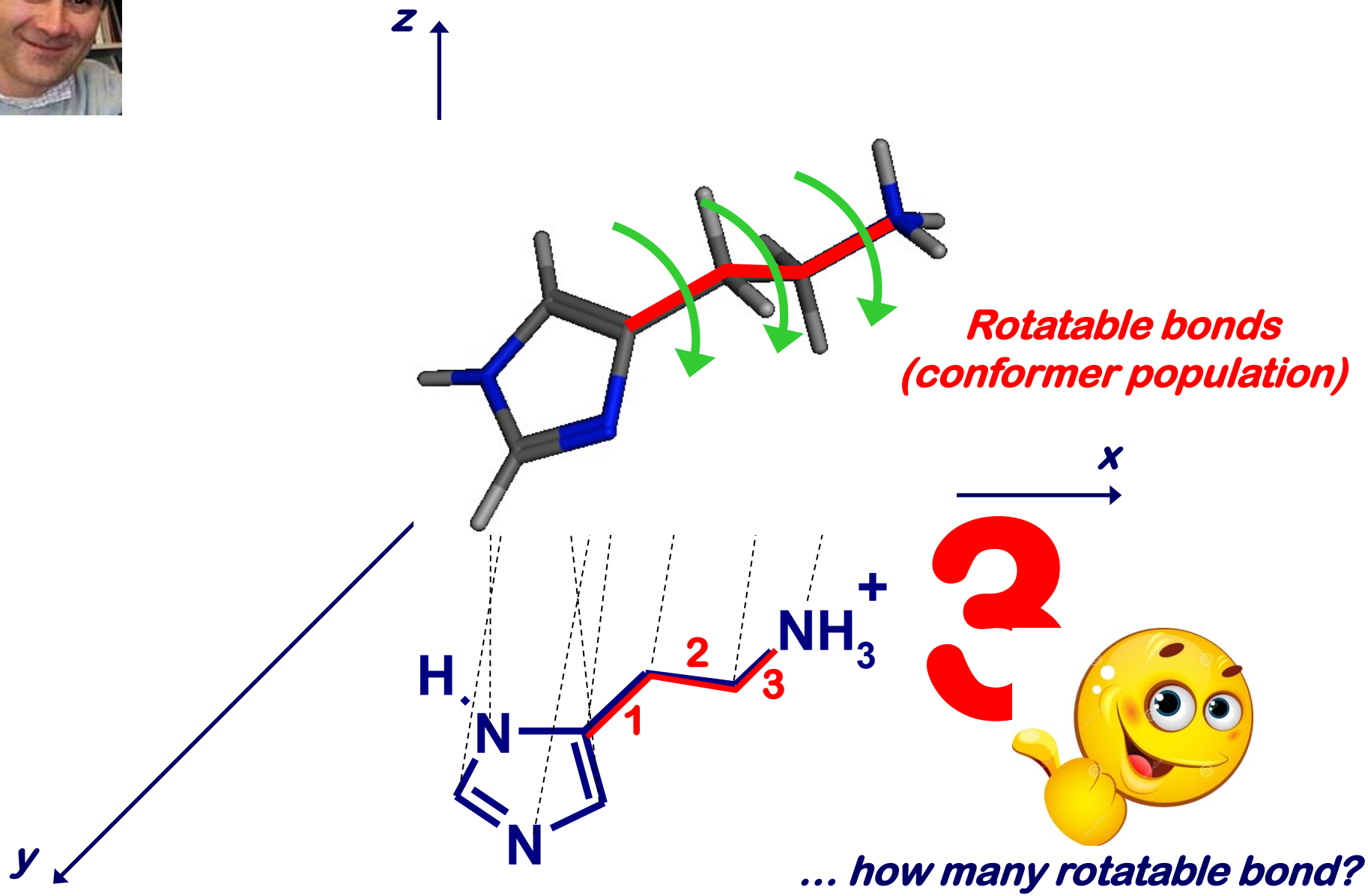
An easy way to determine *molecular rigidity*:

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!!!

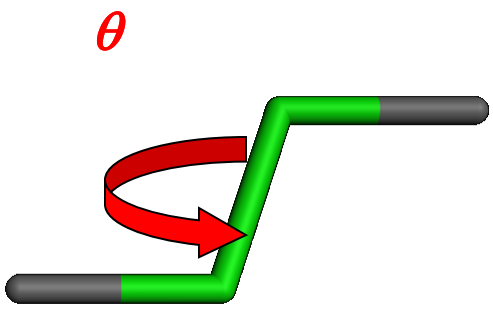
the shadow of the reality:

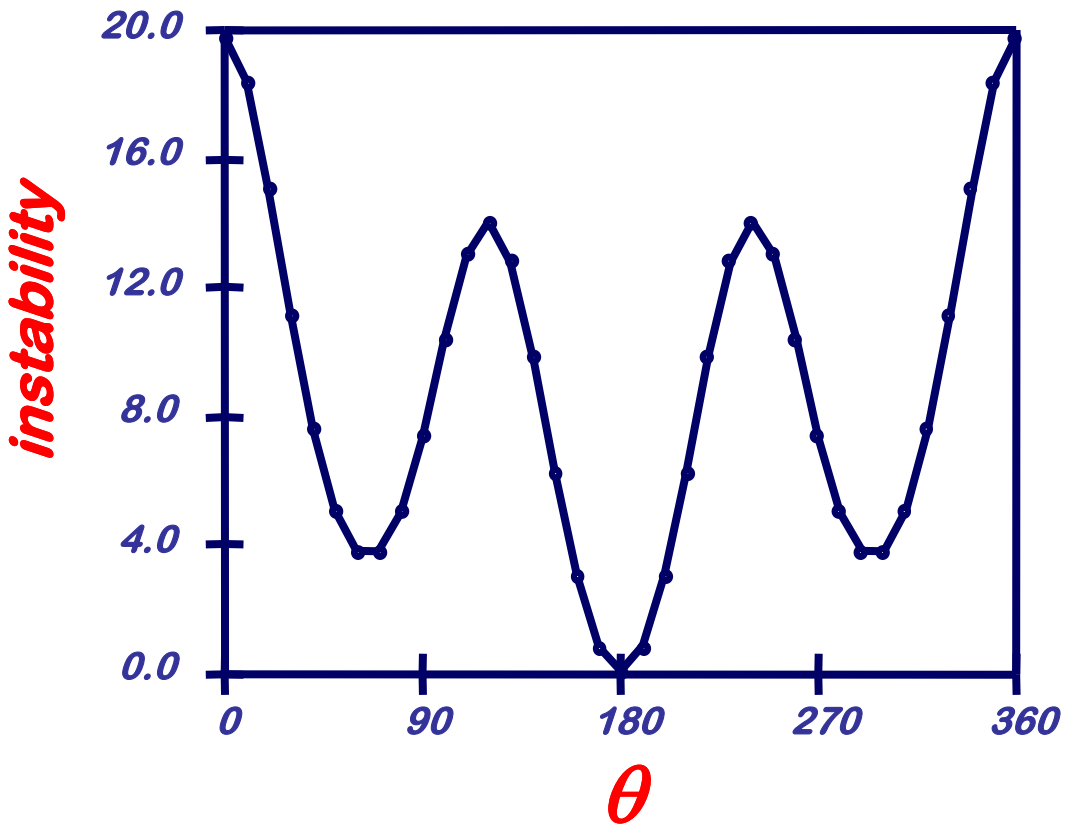


Rotatable bonds (conformer population)

… how many rotatable bond?

Few fundamental concepts:

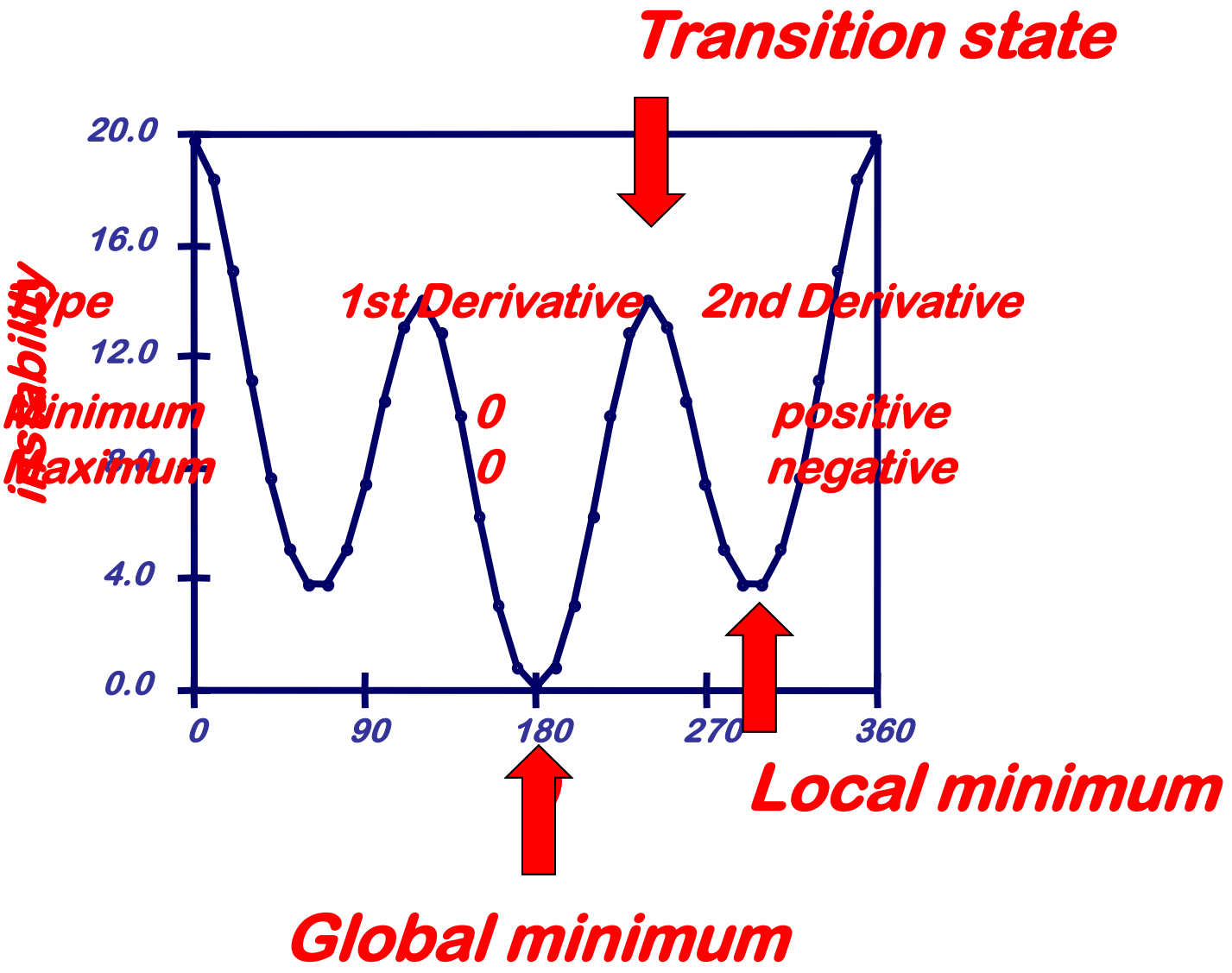




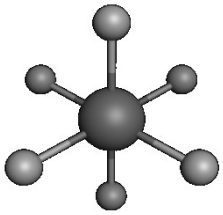
Conformers:

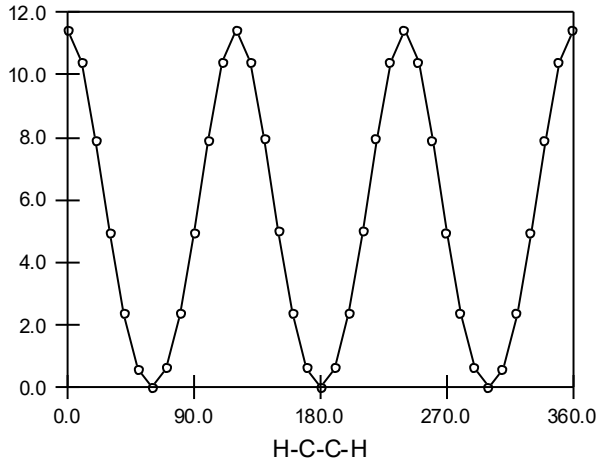
Structures differing only by rotation around one or more rotatable bonds.

Few fundamental concepts:

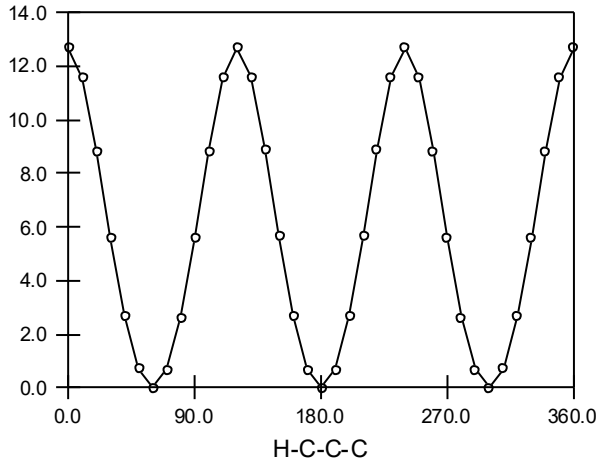


For a molecular system with N rotatable bonds, there are 3^N potential minima.

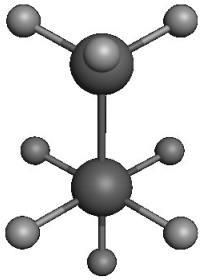


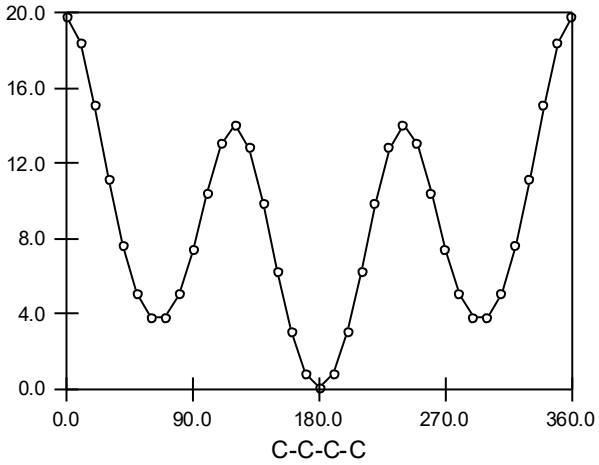


ethane

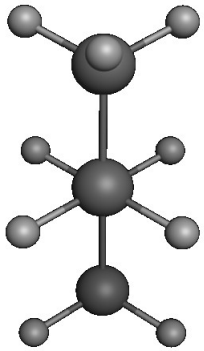


propane



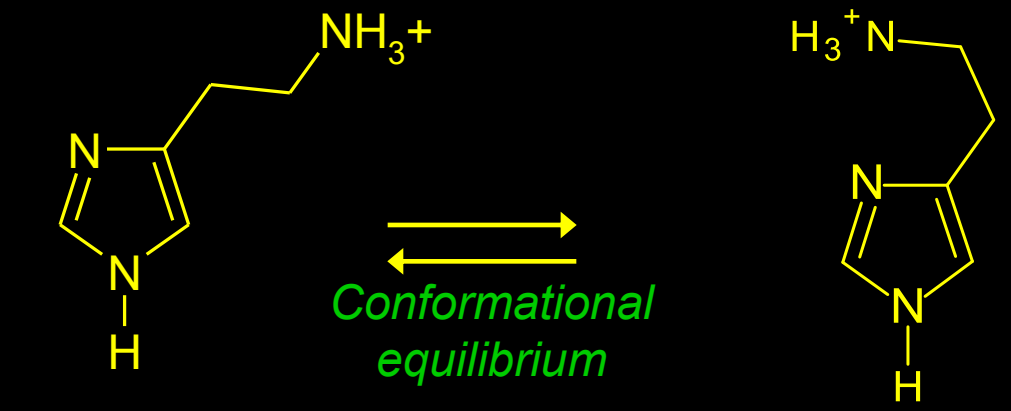


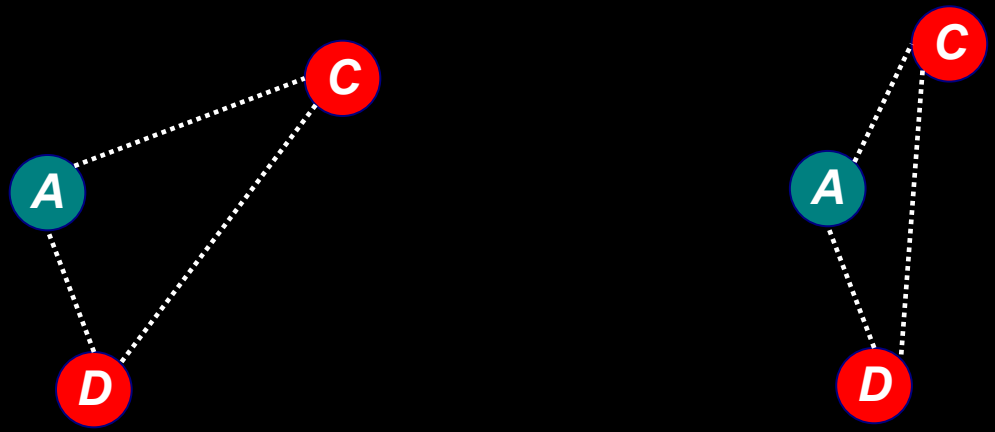
butane



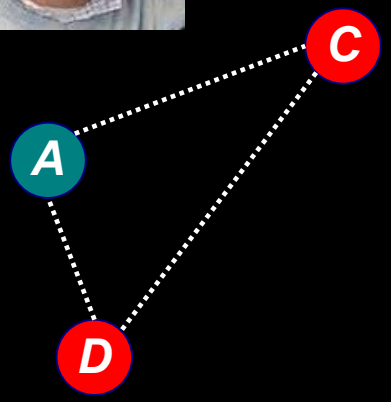
N = 1

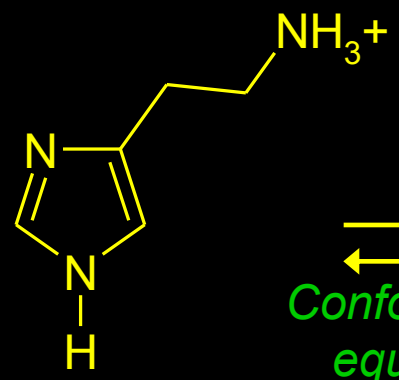
and this incredible consequence:



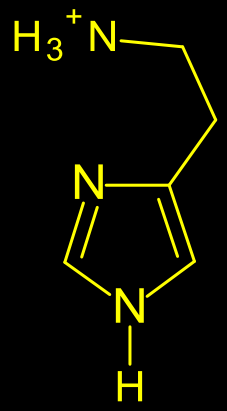


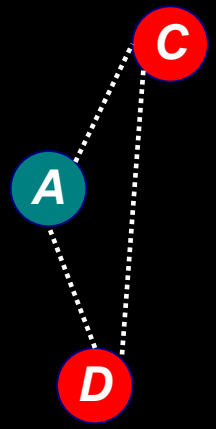
and the story is going on…



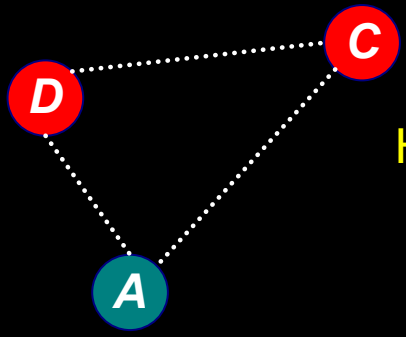


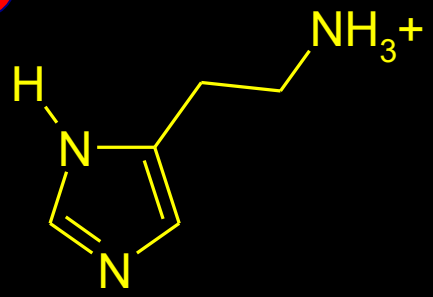
Conformational equilibrium





Tautomeric equilibrium





Do you remember these two concepts:

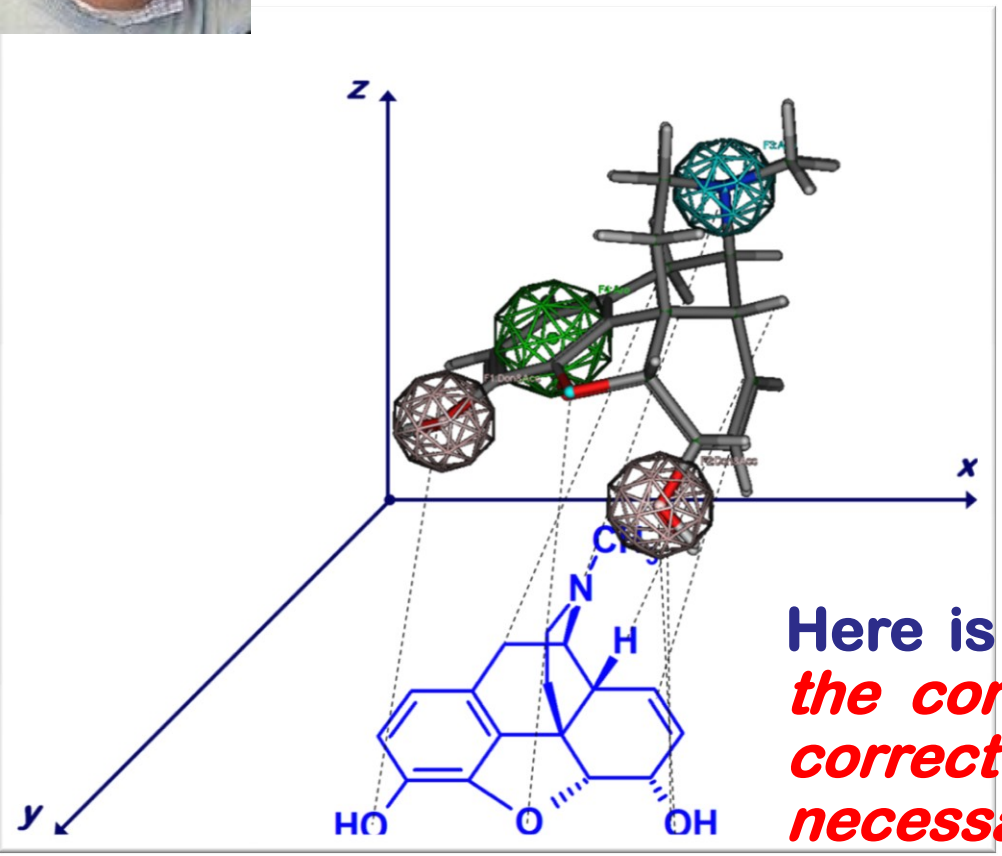
Stability *as a measure of the geometrical deformability of an object;*

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

the magic of the cycles!

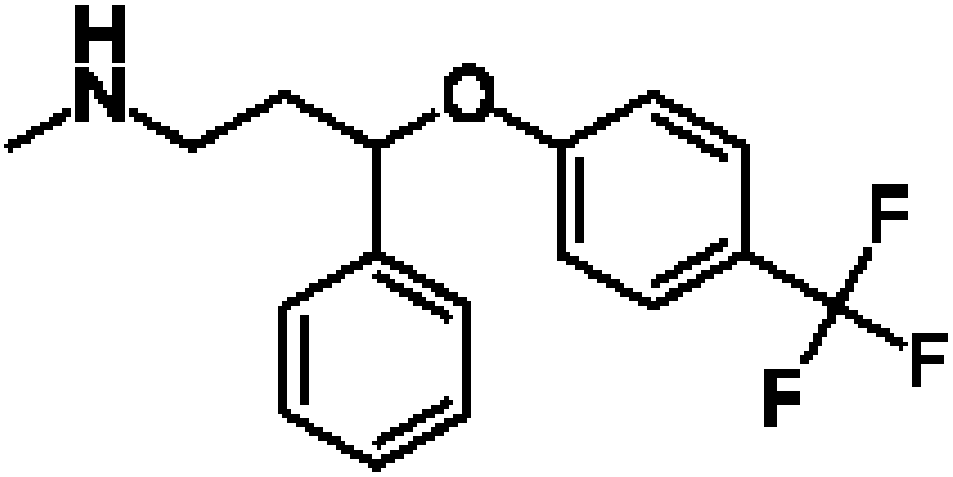
… how many rotatable bond?

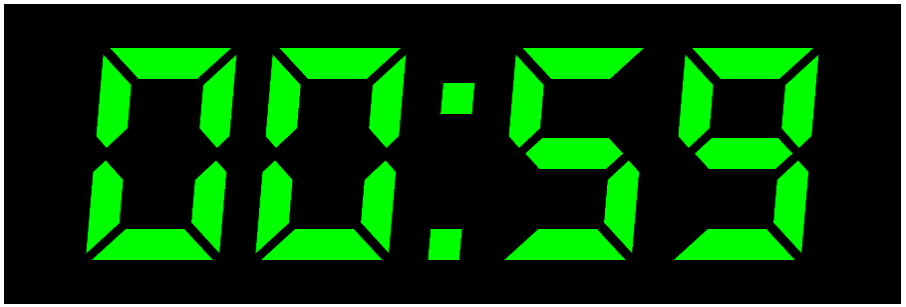
the magic of the cycles!



Here is the magic of cycles: *to place the correct functional groups, in the correct position in space for the time necessary to maximize the effect of the complementarity between the ligand and its recognition cavity (activity)*

Can we try again our little experiment?





1. Chemical class;
2. Functional groups;
3. Possible interaction scheme;
4. Guess pKa value;
5. Number of rotatable bonds;
6. Tautomers;
7. Chiral centers;
8. Chemical/enzinatic reactivity;
9. …

but we will never forget:

PHARMACODYNAMIC (PD) PROFILE

the study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of their actions and effects with their chemical structure.

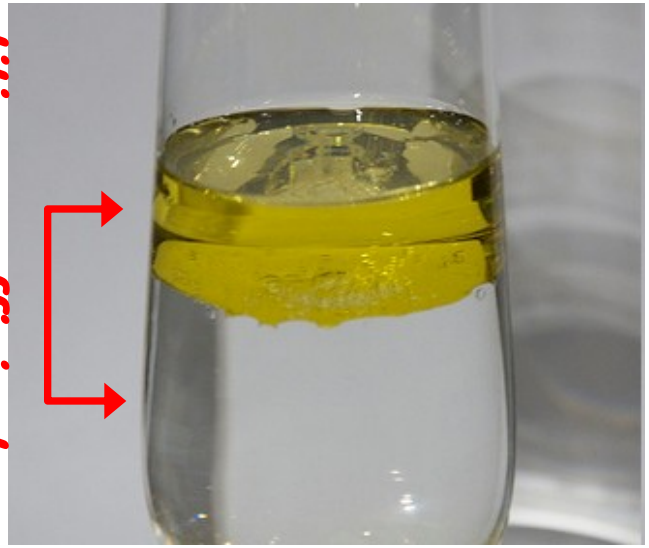
PHARMACOKINETIC (PK)/TOX PROFILE

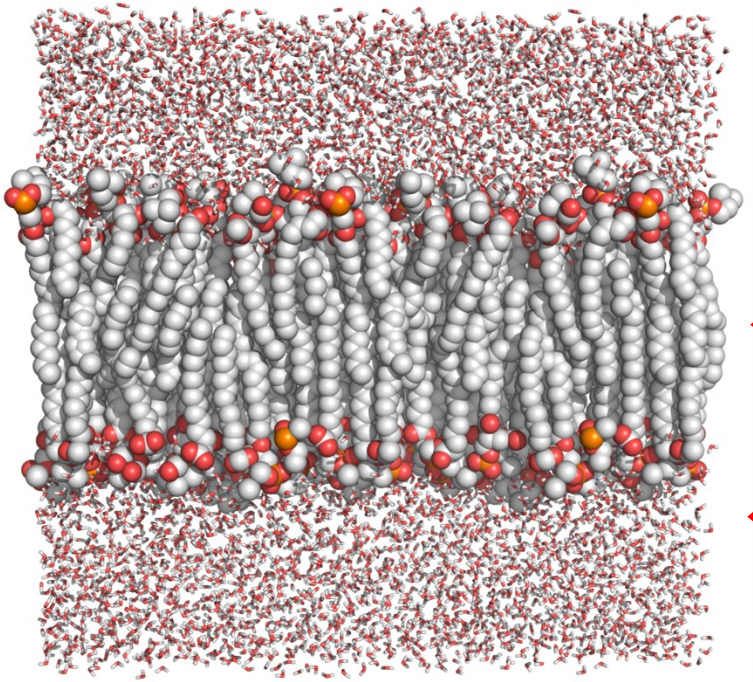
The study of the process by which a drug is absorbed (A), distributed (D), metabolized (M), and eliminated (E) by the body.

FORMULATION PROFILE

But you don't find a wonderful analogy?

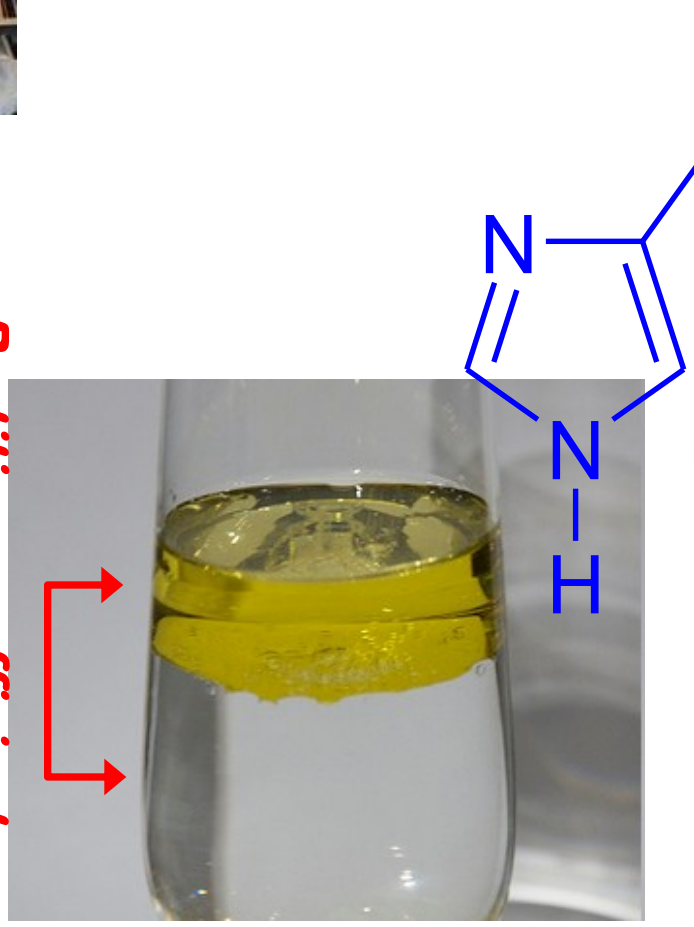
Partition coefficient



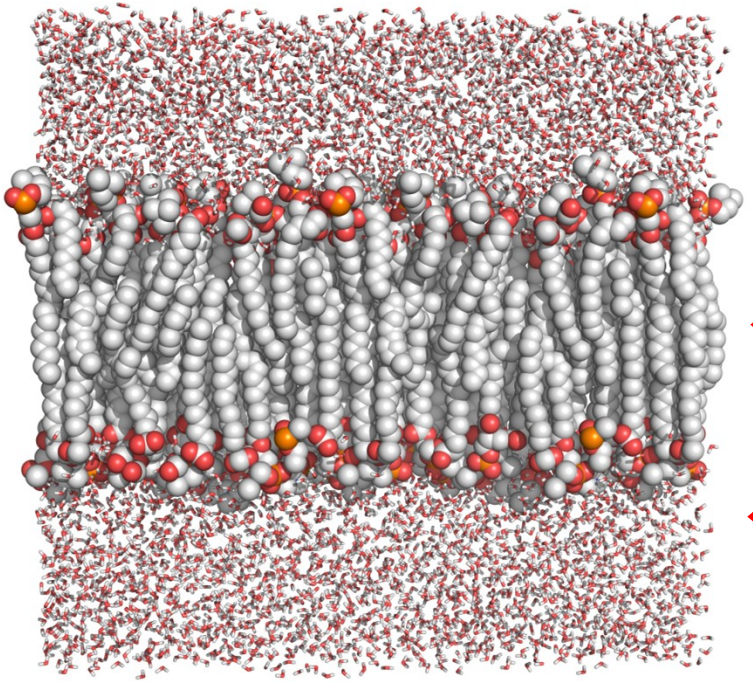


Thermodynamic solubility in H_2O (mg/ml)

But where are written these properties?

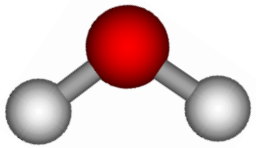


Partition coefficient

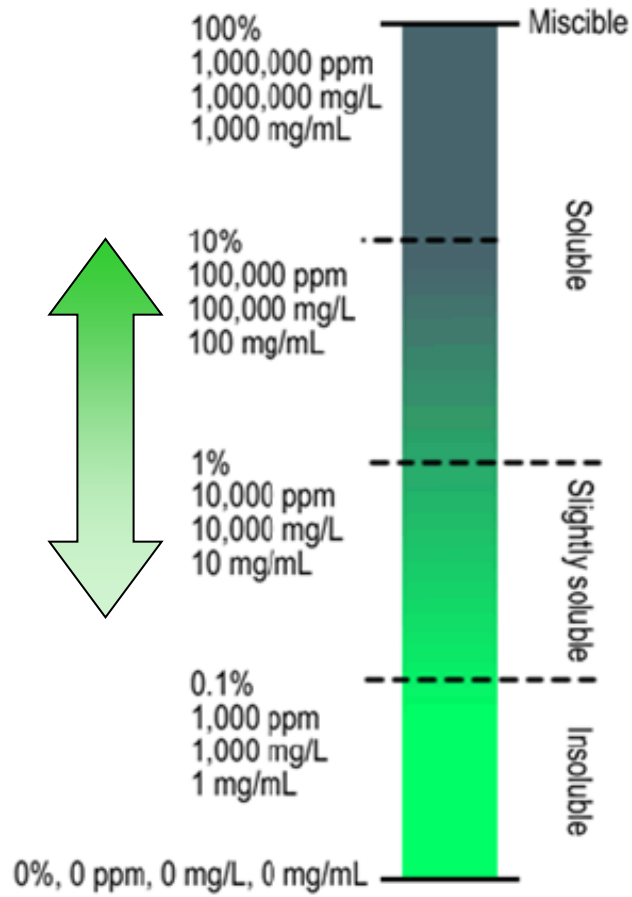


Thermodynamic solubility in H_2O (mg/ml)

Solubility in



" corpora non agunt nisi soluta "



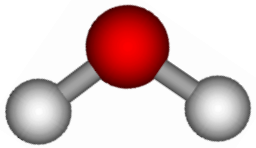
Chemical factors influencing solubility in H_2O:

***presence of ionisable groups** (depending upon pH)*

***hydrogen bonds** (donors/acceptors)*

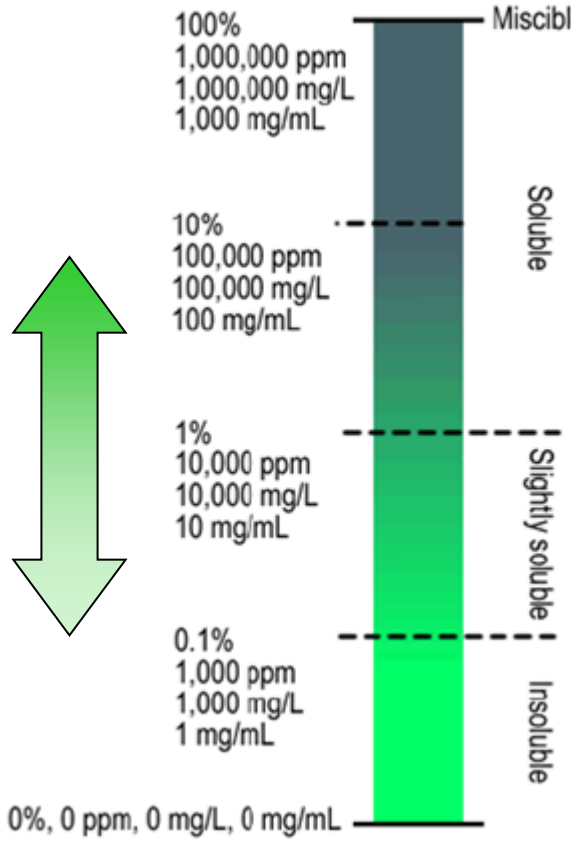
polarized functional groups

Solubility in



" corpora non agunt nisi soluta "

Dwayne Friesen



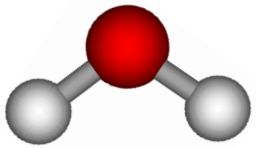
$$C/(N+O) \leq 3$$

$$3 < C/(N+O) < 5$$

$$C/(N+O) \geq 5$$

Applies to only neutral molecular and represents only a qualitative and approximate indication of water solubility of an organic compound!!!

Solubility in



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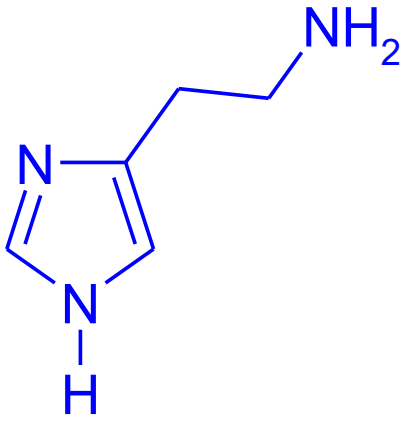
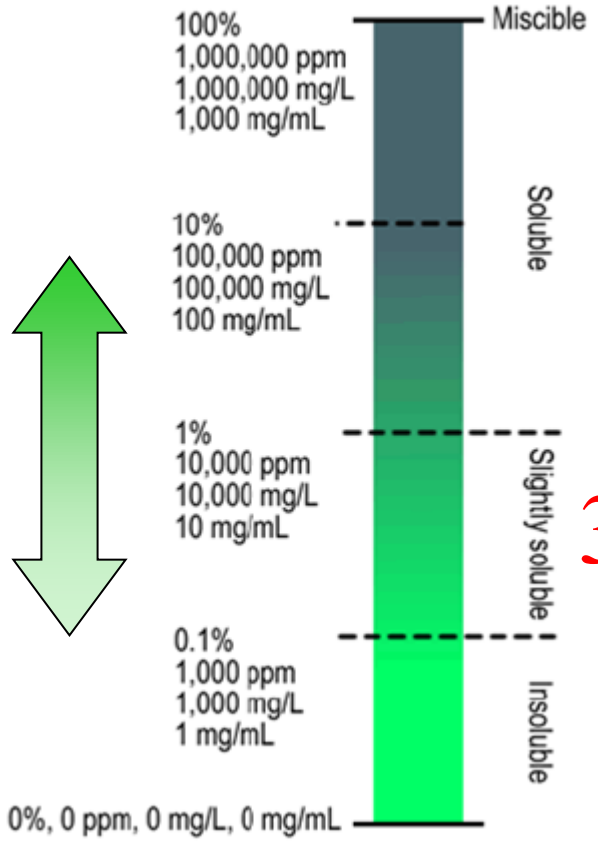


$C_5H_9N_3$



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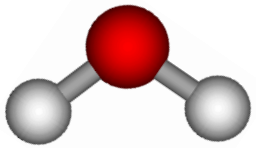

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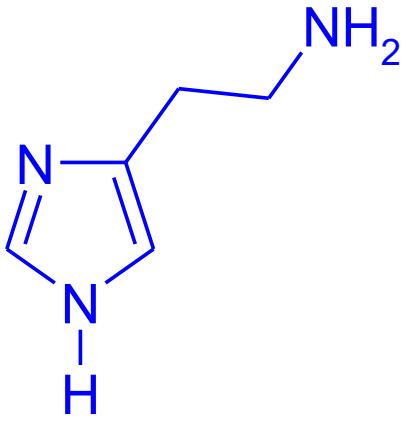

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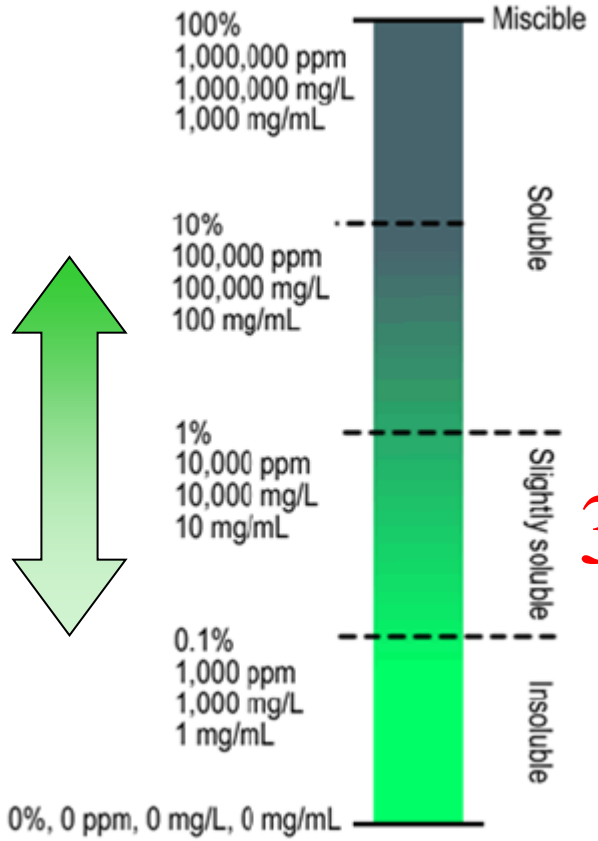

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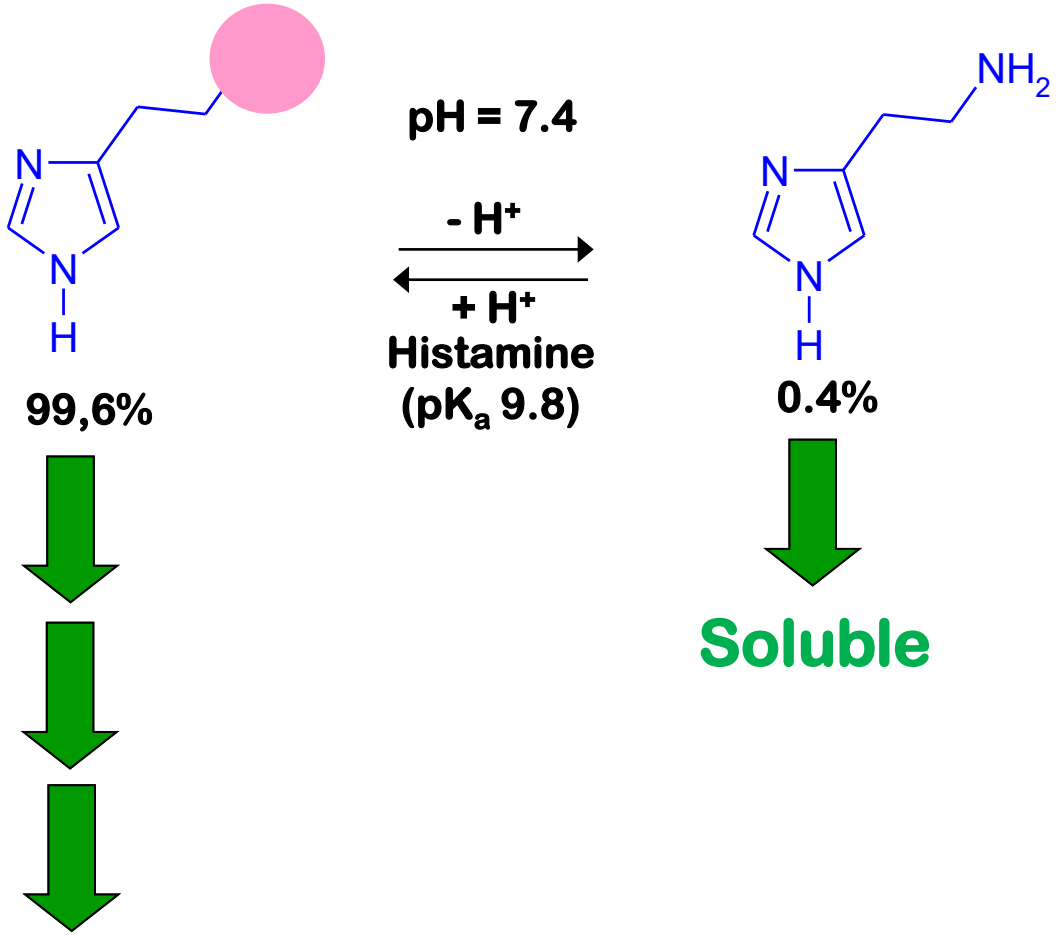
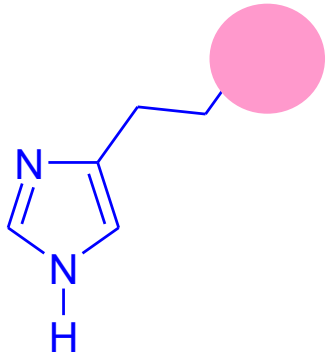
The first crucial pharmaceutical difference!



but…

Solubility Prediction



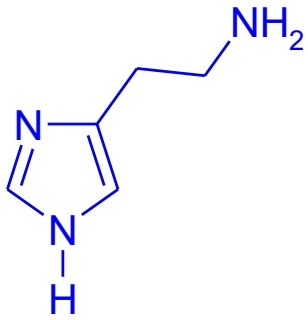
99,6%

pH = 7.4

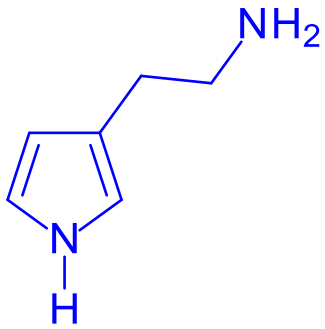
$- H^+$

$+ H^+$

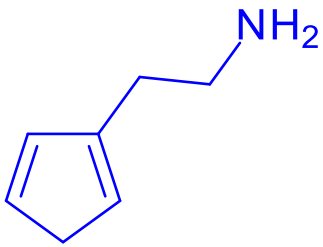
Histamine (pK_a 9.8)



1.7



3

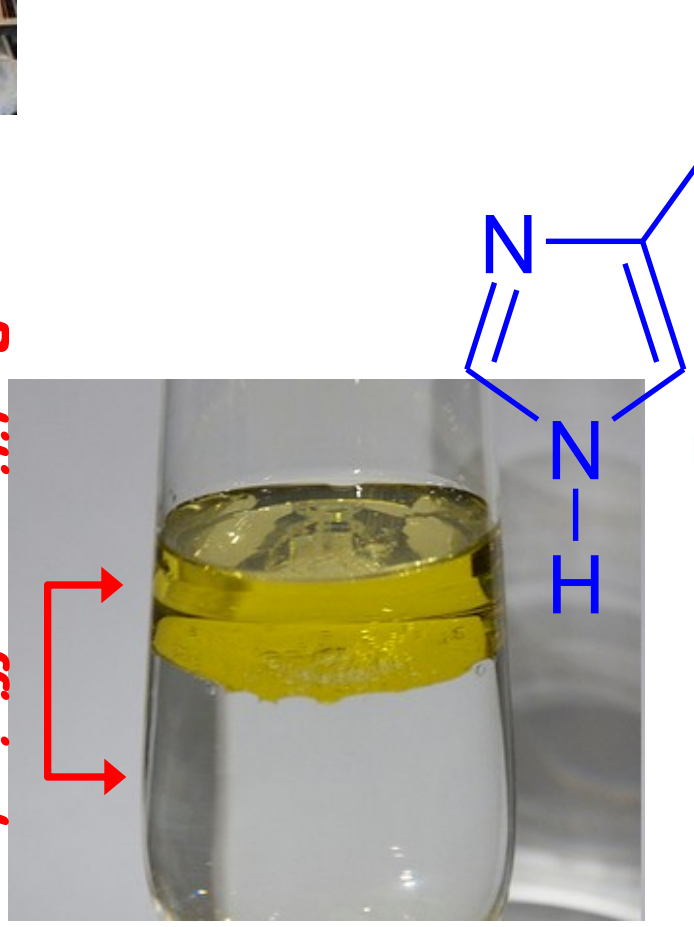


0.4%

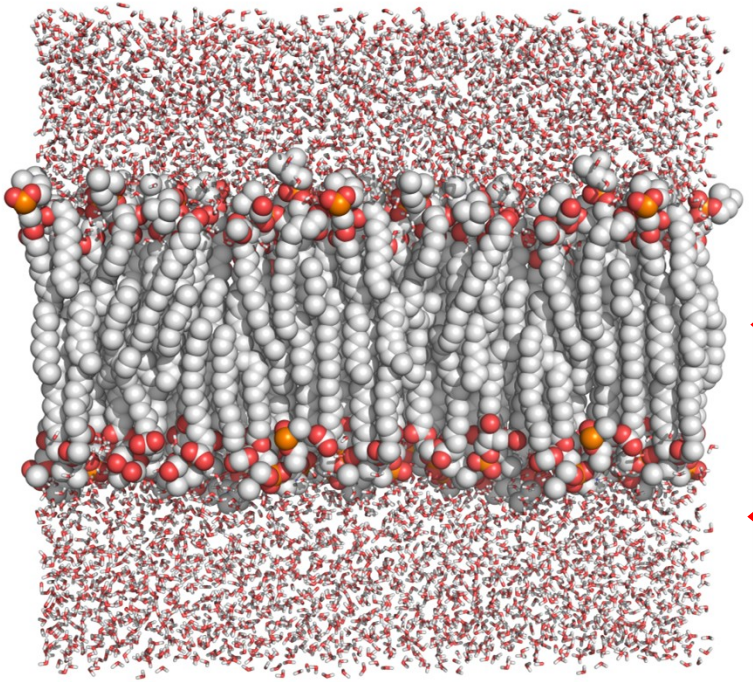
7

soluble

But where are written these properties?



Partition coefficient

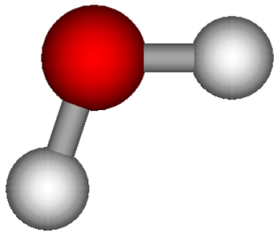


Thermodynamic solubility in H_2O (mg/ml)

A very simple definition:

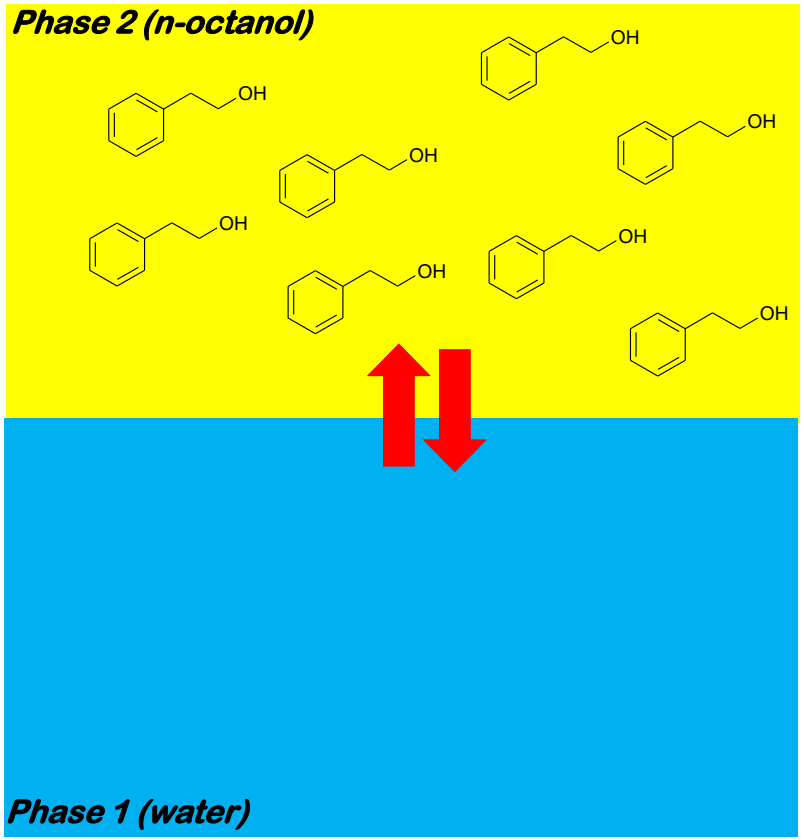
In organic chemistry, we have a family of compounds characterized by bonds with $\Delta EN \cong 0$

HYDROCARBONS

and they are surely  phobics!!!

Hydrophobicity and partition coefficient

$$\mu_{(phase2)} = \mu^0_{(phase2)} - RT \ln\left[C_{(phase2)}\right]$$



$$\mu_{(phase1)} = \mu^0_{(phase1)} - RT \ln\left[C_{(phase1)}\right]$$

At the equilibrium:

$$\mu_{(phase1)} = \mu_{(phase2)}$$

$$\mu^0_{(phase1)} - RT \ln\left[C_{(phase1)}\right] = \mu^0_{(phase2)} - RT \ln\left[C_{(phase2)}\right]$$

$$\mu^0_{(phase1)} - \mu^0_{(phase2)} = RT \ln\left[C_{(phase1)}\right] - RT \ln\left[C_{(phase2)}\right]$$

$$\mu^0_{(phase1)} - \mu^0_{(phase2)} = RT \ln\left[\frac{C_{(phase1)}}{C_{(phase2)}}\right]$$

$$\left[\frac{C_{(phase1)}}{C_{(phase2)}}\right] = P$$ **Partition coefficient**

Hydrophobicity and partition coefficient

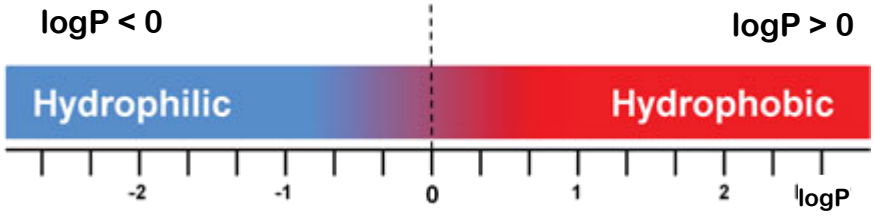
$$\left[\frac{C_{(phase1)}}{C_{(H_2O)}}\right] = P$$

Partition coefficient

We can define: "*hydrophobic*" a compound with P > 1;
"*hydrophilic*" a compound with P < 1.

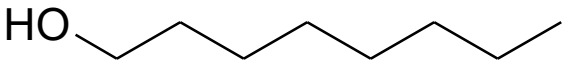
$$\log\left[\frac{C_{(phase1)}}{C_{(H_2O)}}\right] = \log P$$

We can define: "*hydrophobic*" a compound with logP > 0;
"*hydrophilic*" a compound with logP < 0.



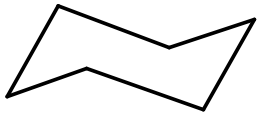
Hydrophobicity and partition coefficient

How we can choose the second phase:



***n*-octanol**

- immiscible in water even if 27% of water dissolves in it… so the first region of hydration of the solute is preserved;
- UV transparent;
- Low vapor pressure.



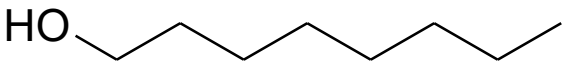
cyclohexane

Immiscible in water and very low amount of water dissolves in it… so also the first region of hydration of the solute is lost.
The differences between the logP values in *n*-octanol and cyclohexane is a measure of the de-hydration energy of a solute.

Do you see any similarity?

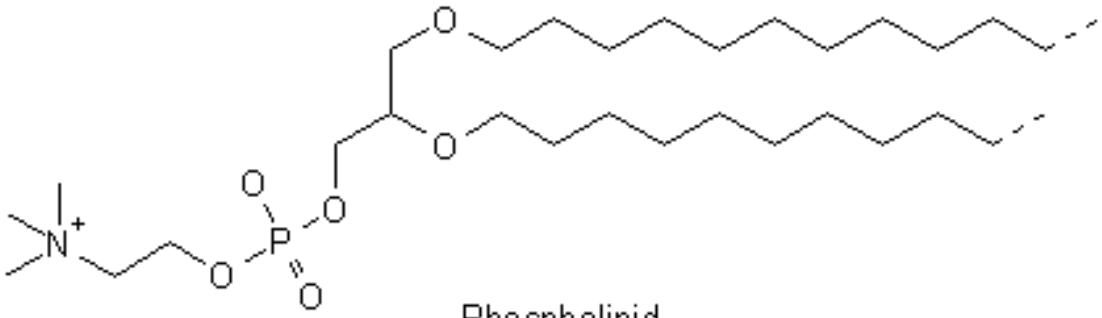
…in addition to this?

How we can choose the second phase:

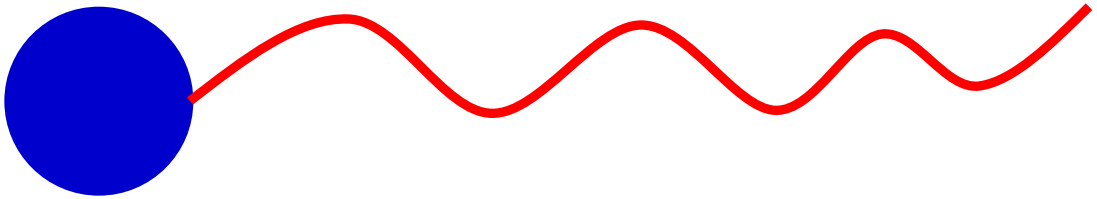


***n*-octanol**

- **"Similarity" with biological membrane;**



Phospholipid



Lipinski's "Rule of Five"

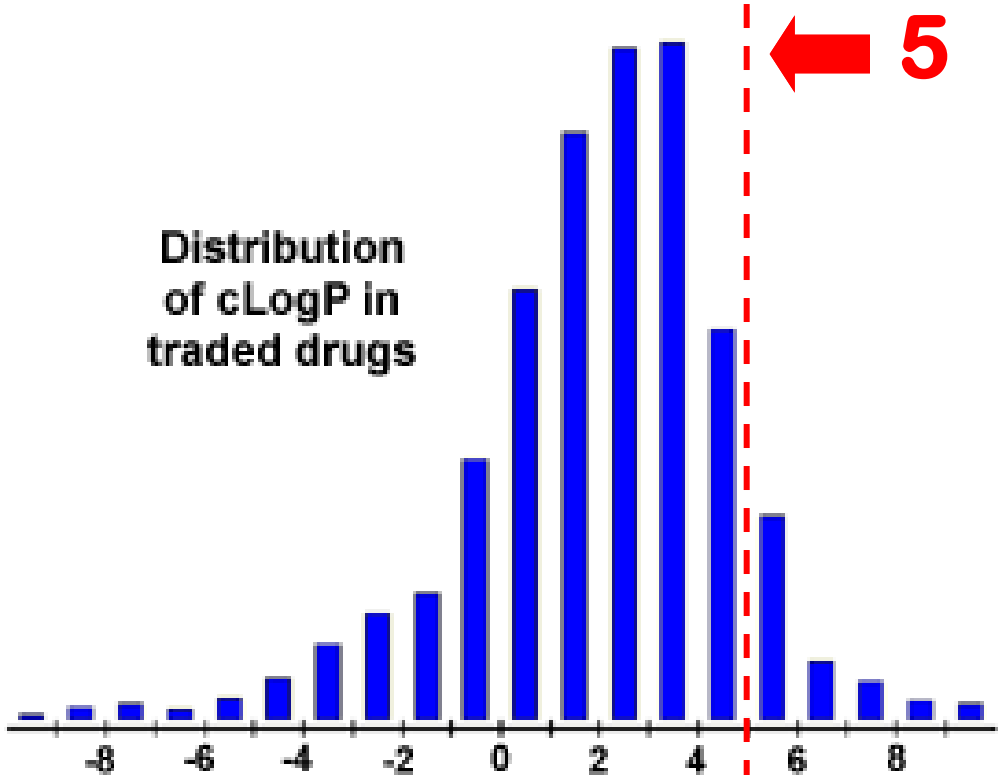
Poor absorption or permeation, if …

- **Number of H-bond donors > 5 (OH & NH)**
- **Number of H-bond acceptors > 10 (O & N)**
- **Molecular weight > 500**
- **log *P* > 5**

Lipinski et al., Adv. Drug Deliv. 23 (1997) 3.

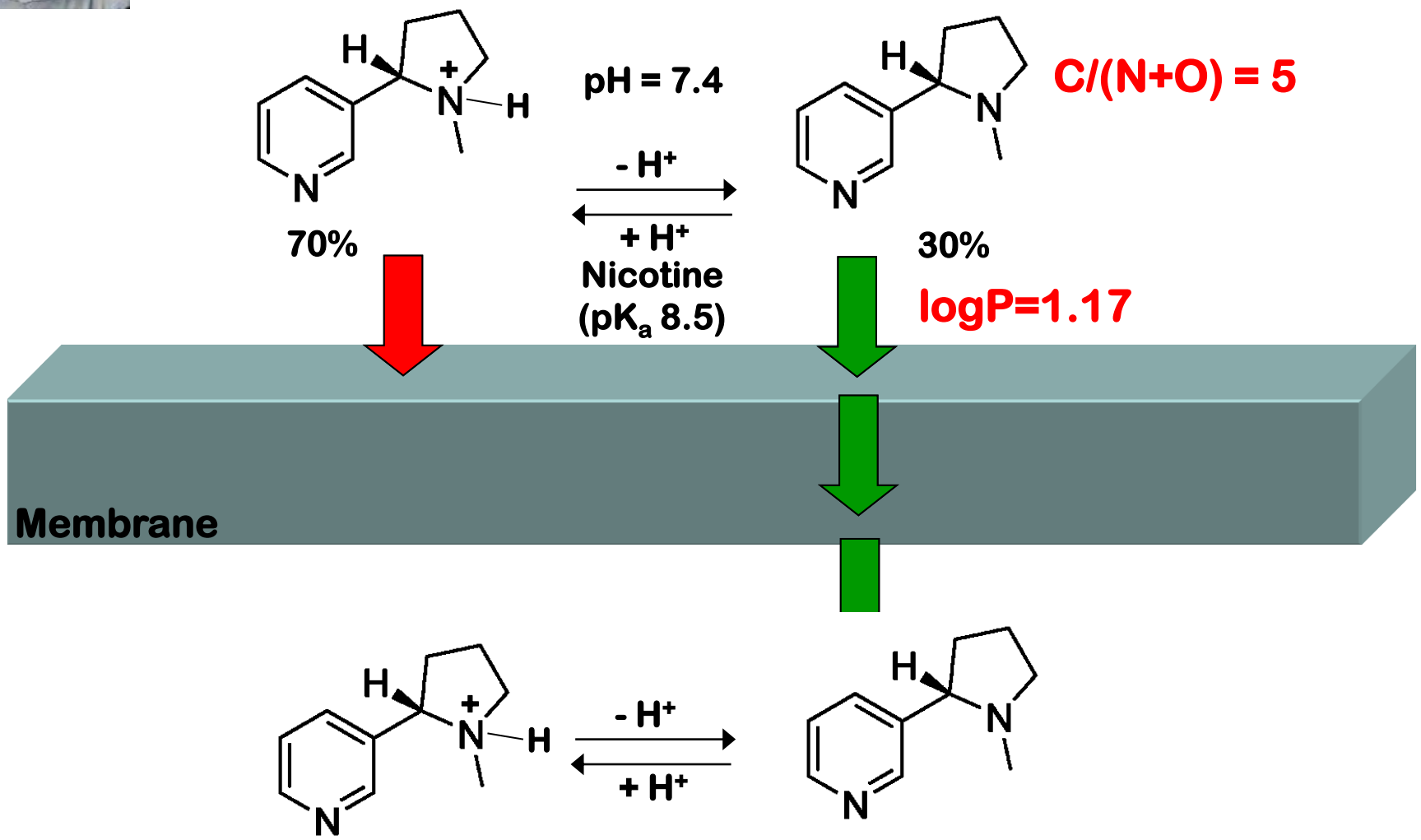
N.B. Like all rules they are there to be broken and a number of exceptions exist. I have personally worked on a couple of well-absorbed drugs which broke this rule but as a general guide it works well. Remember that you may have charge in your molecule so that LogD(7.4) or LogD(5.5) is really the important parameter rather than Log P. Keeping LogD(7.4) around 2 seem generally good advice. Manipulating the pKa can be a way of improving a molecule.

Hydrophobicity and partition coefficient



It has been shown for compounds to have a reasonable probability of being well *orally absorb* their logP value must not be greater than 5.0. The distribution of calculated logP values of more than 3000 drugs on the market underlines this fact (see diagram).

The first crucial pharmaceutical difference!



The fragments method of Hansch-Fujita.

(J. Am. Chem. Soc. 1964, 86, 5175)

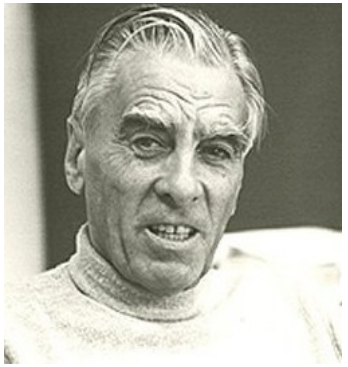
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POMONA COLLEGE, CLAREMONT, CALIF.]

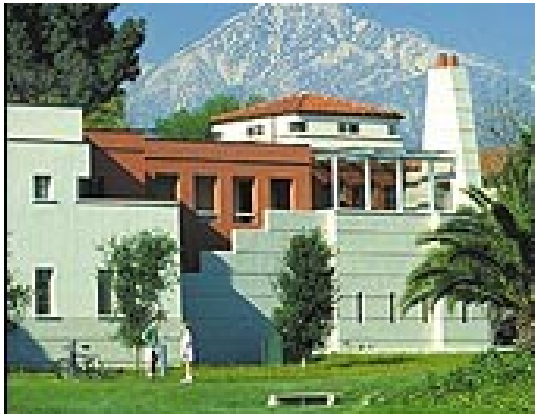
A New Substituent Constant, π, Derived from Partition Coefficients

BY TOSHIO FUJITA,[1a] JUNKICHI IWASA,[1b] AND CORWIN HANSCH

RECEIVED FEBRUARY 19, 1964

The partition coefficients between 1-octanol and water have been determined for 203 mono- and disubstituted benzenes. From these values a substituent constant, π, has been calculated for 67 functional groups. The constant π is defined as: $\pi = \log P_X - \log P_H$ where P_X is the partition coefficient of a derivative and P_H is that of the parent compound. π has been derived for many of the functions from eight different systems: benzene, nitrobenzene, aniline, phenol, benzyl alcohol, benzoic acid, phenylacetic acid, and phenoxyacetic acid. It is found that, although π varies continuously for a given function depending on its electronic environment, the range over which it varies is not great. In certain of the systems, π-values are related by a simple linear expression.





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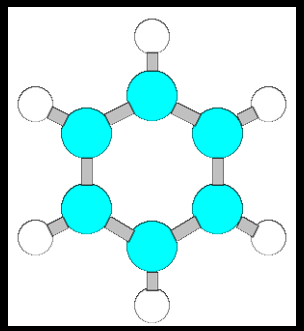
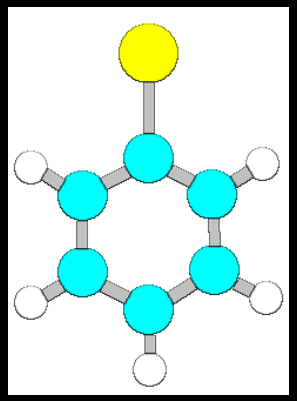
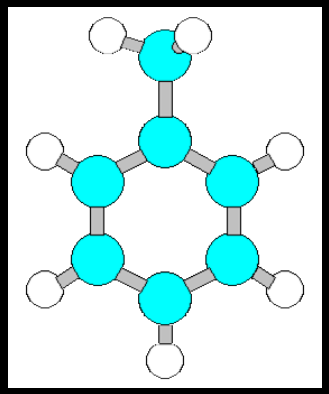
The hydrophobic constant of substituent, π



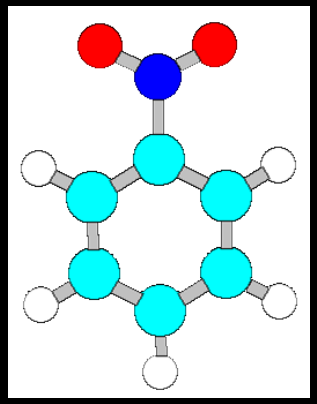
log P = 2.13



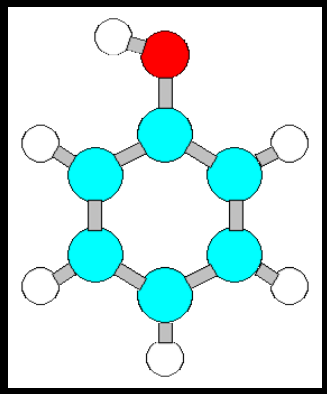
log P = 2.99



log P = 2.69



log P = 1.85



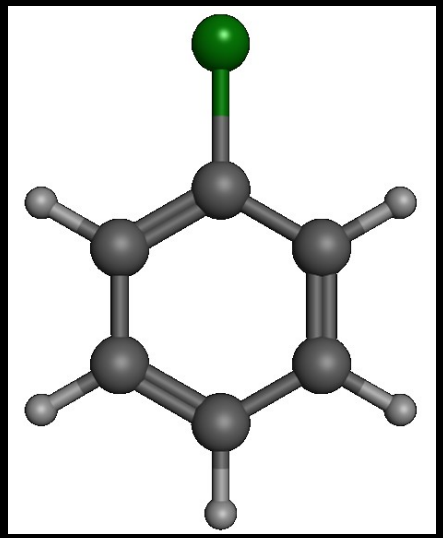
log P = 1.48

$$\pi_X = \log P_{C_6H_5X} - \log P_{C_6H_6}$$

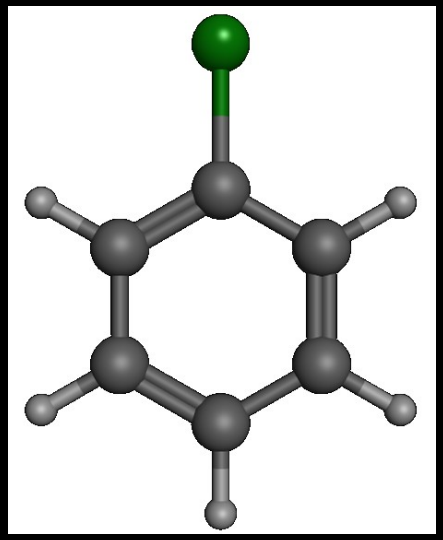
$\pi_{Br} = 0.86$ $\pi_{CH_3} = 0.56$ $\pi_{NO_2} = -0.28$ $\pi_{OH} = -0.67$

The hydrophobic constant of substituent, π

Substituent	π aromatic
F	0.14
Cl	0.71
Br	0.86
I	1.12
OH	-0.67
OCH_3	-0.02
SCH_3	0.61
CN	-0.57
COOH	-0.28
$COOCH_3$	-0.01
$COCH_3$	-0.55
NH_2	-1.23
$N(CH_3)_2$	-0.28
NO_2	-0.28
CH_3	0.56

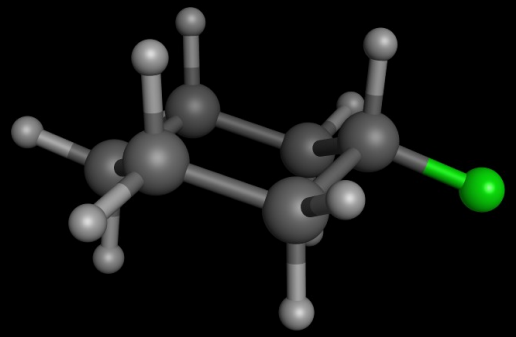


The hydrophobic constant of substituent, π



Ref. benzene
log P = 2.13

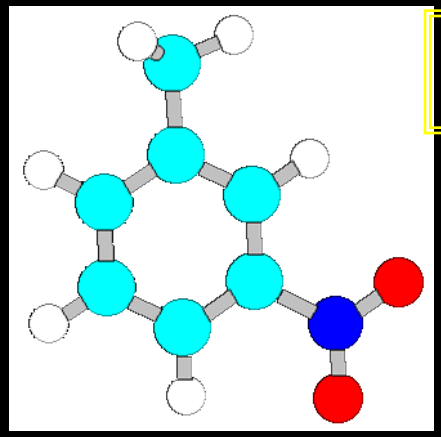
Substituent	π aromatic
F	0.14
Cl	0.71
Br	0.86
I	1.12
OH	-0.67
OCH_3	-0.02
SCH_3	0.61
CN	-0.57
COOH	-0.28
$COOCH_3$	-0.01
$COCH_3$	-0.55
NH_2	-1.23
$N(CH_3)_2$	-0.28
NO_2	-0.28
CH_3	0.56



Ref. cyclohexane
log P = 3.44

The additive rule:

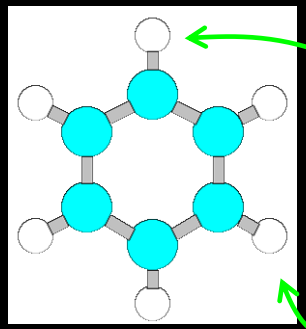
It works? Just check together:



log P : 2.45

IMPRESSIVE!!!!!

log P $_{calculated}$ (ClogP):



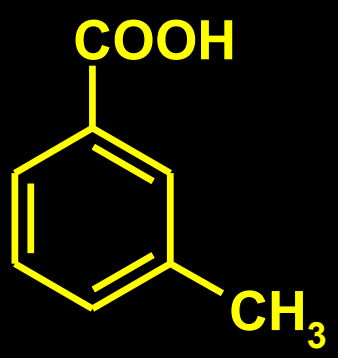
lop $P_{C_6H_6}$ = 2.13

π_{CH_3} = 0.56

π_{NO_2} = -0.28

2.41

The hydrophobic constant of substituent, π



...

log P 1.80 log P 2.30 log P 2.40

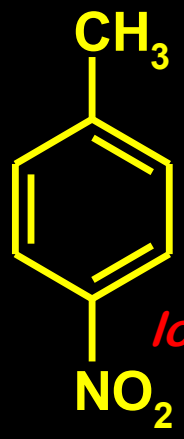
Clog P 1.61 Clog P 2.14 Clog P 2.38

...not too bad!!!

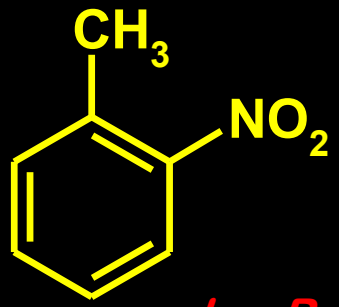
The hydrophobic constant of substituent, π

But not so good…

log P 2.45

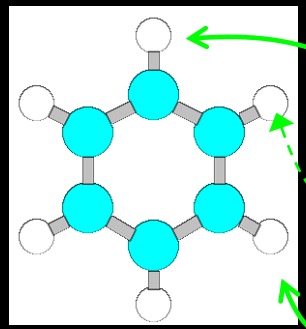


log P 2.42



log P 2.30

log P *calculated* (ClogP):



lop $P_{C_6H_6}$ = 2.13

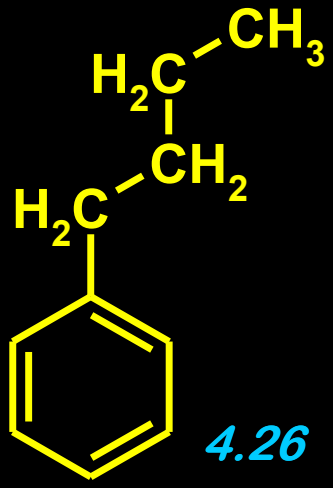
π_{CH_3} = 0.56

π_{NO_2} = -0.28

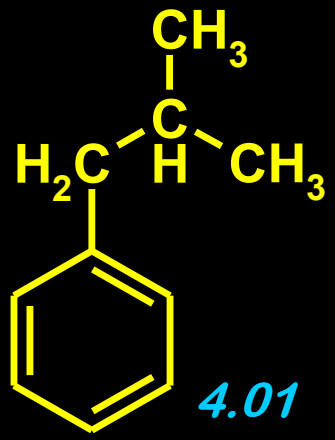
2.41 ?

The hydrophobic constant of substituent, π

again…



4.26



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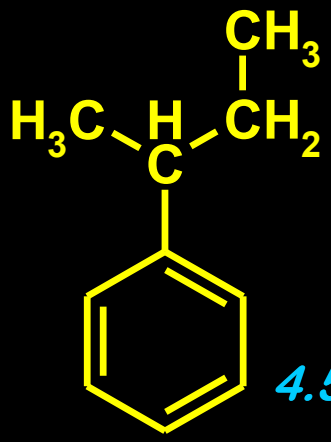

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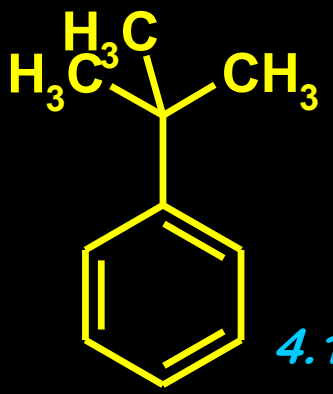
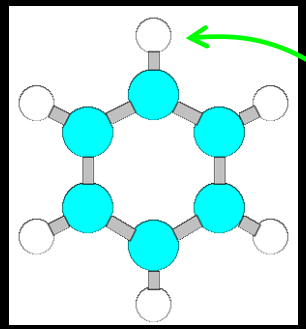


4.11

log P calculated (ClogP):



lop $P_{C_6H_6}$ = 2.13

4 x π_{CH_3} = 2.24

4.37

?

Corwin… we have a problem!

Here is how he fixed the problem… as an engineer usually done introduction the magic correction factors !!!

Remember: a correction factor is any mathematical adjustment made to a calculation to account for deviations in either the sample or the method of measurement.

The hydrophobic correction factors, $\Delta\pi$

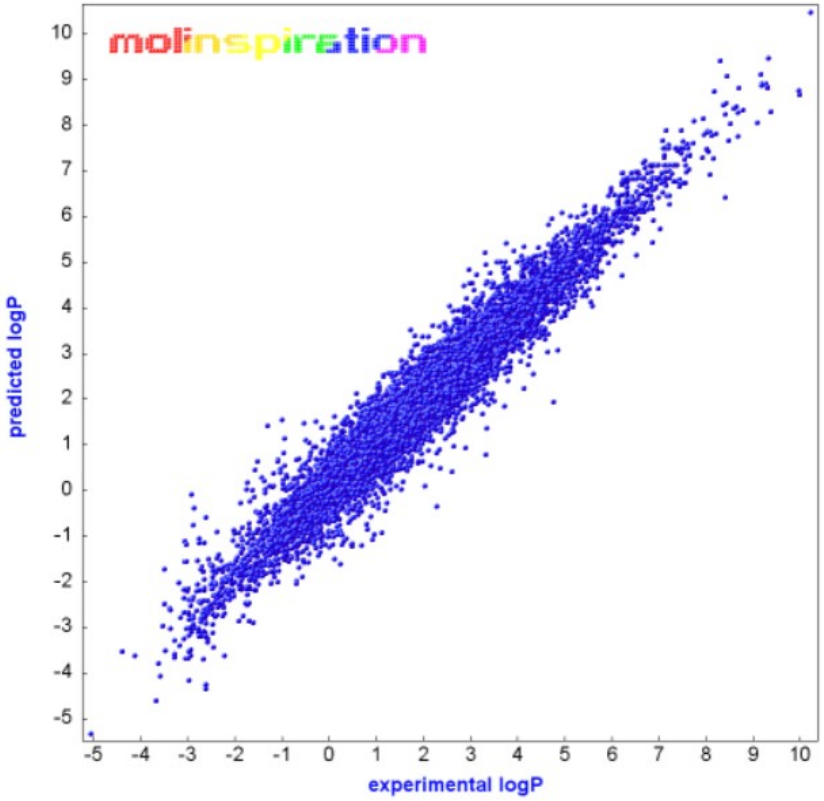
- Branched carbon chain ($\Delta p = -0.20$);
- Double bond ($\Delta p = -0.30$);
- Intra-molecular H-bond ($\Delta p = 0.65$);
- Ring condensation ($\Delta p = -0.20$)
- …

Finally the log P calculated by Hansch-Fujita:

$$Clog\ P = log\ P_{ref} + \Sigma\ \pi_{Xi} + \Sigma\ \Delta\pi$$

Nowadays, are these methods reliable?

… you decide!!!



n = 12'202, r^2 = 0.944, r = 0.972, stdev = 0.428, mae = 0.328

credits: https://www.molinspiration.com/cgi-bin/properties

ClogP… a wonderfully precious molecular descriptor!

Nowadays, these methods are reliable… and freely available!!!

https://molinspiration.com/cgi-bin/properties

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Calculation of Molecular Properties and Bioactivity Score

Enter SMILES

Clear

or draw molecule below

JSME Molecular Editor by Peter Ertl and Bruno Bienfait

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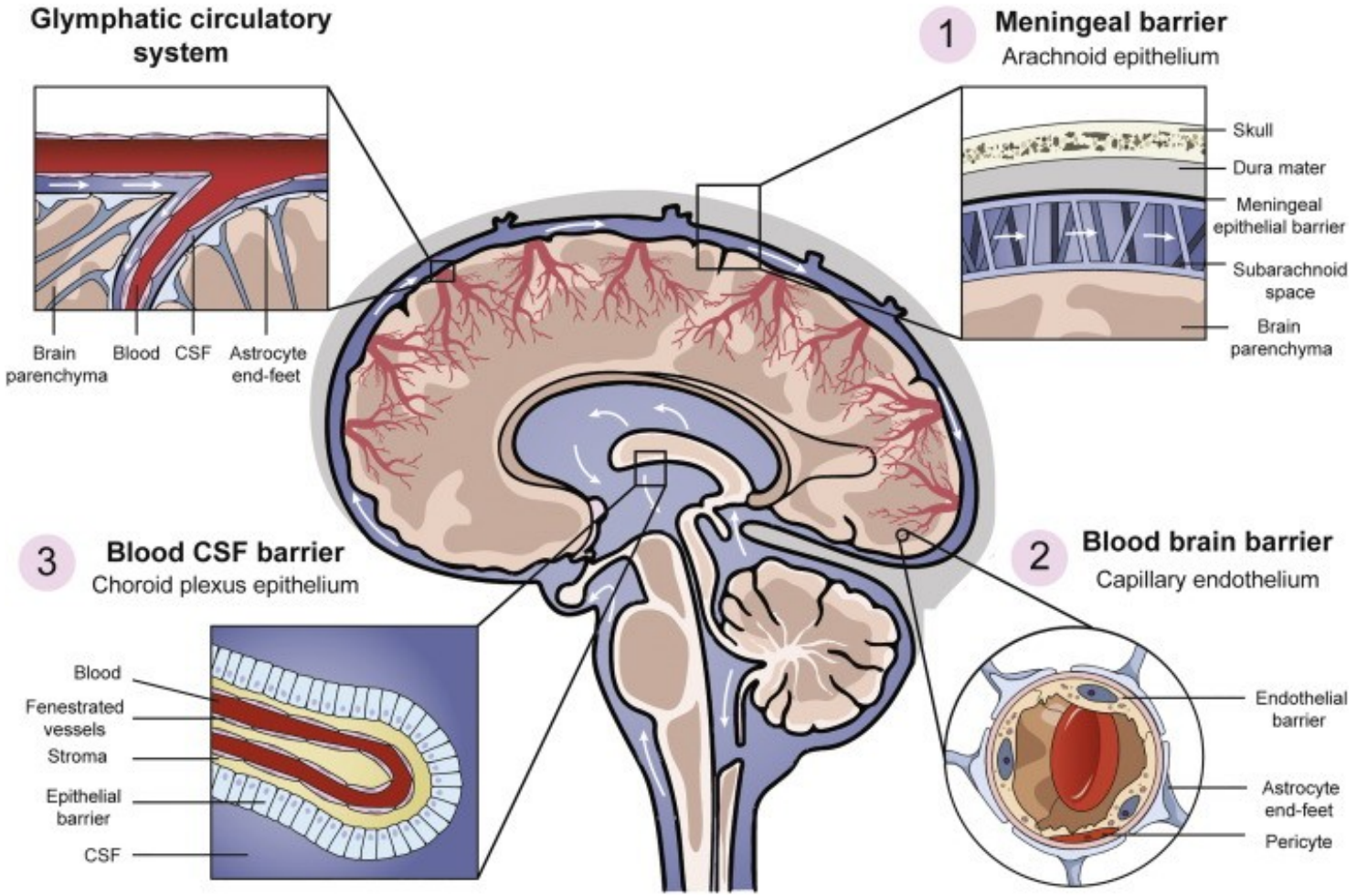
Beyond Lipinski's "Rule of Five"

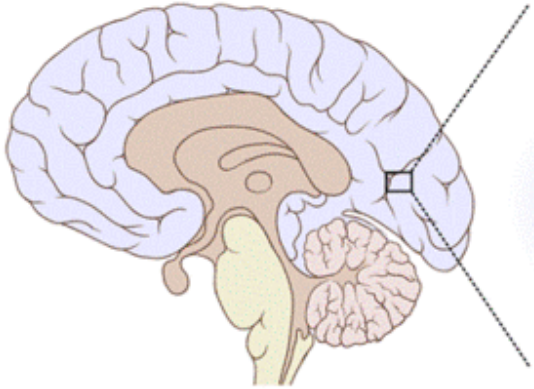
Organization of brain barriers:

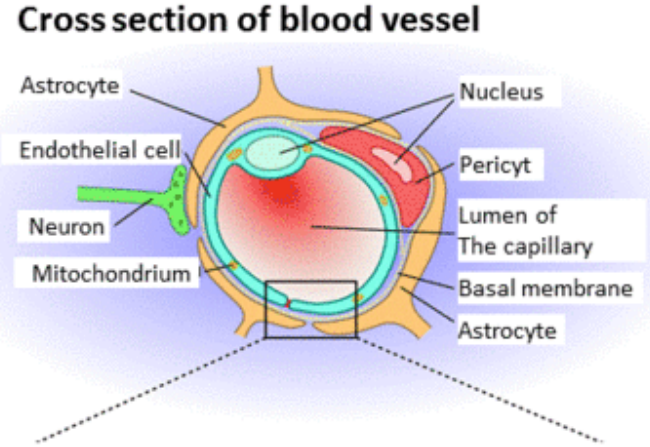


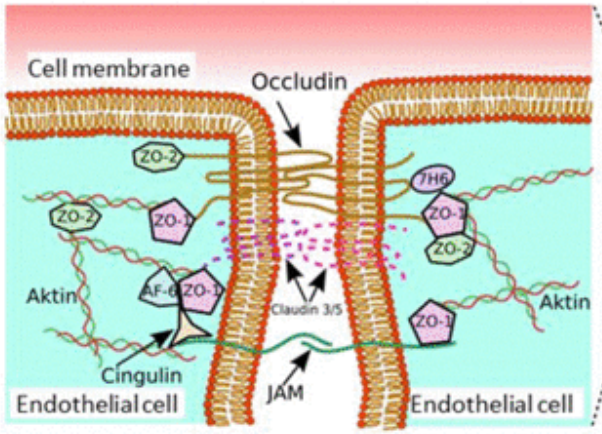
credits: https://www.sciencedirect.com/science/article/abs/pii/S1568997217301052/

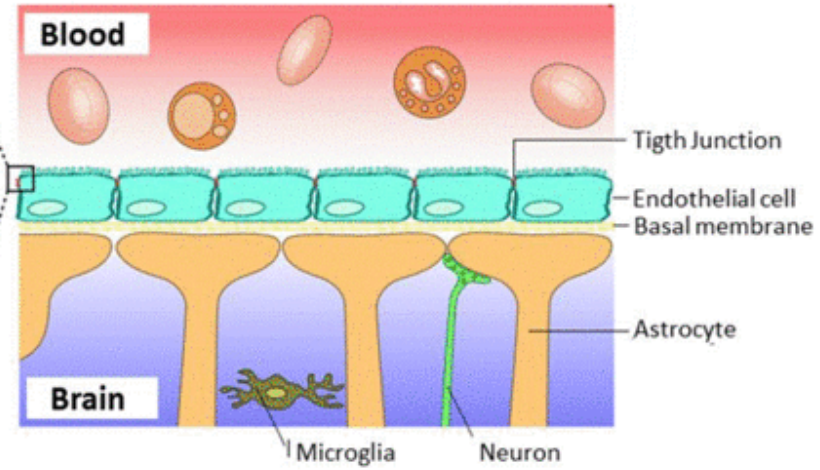
Beyond Lipinski's "Rule of Five"

Pathways across the blood–brain barrier









credits: https://www.emf.ethz.ch/en/knowledge/topics/health/blood-brain-barrier/

Beyond Lipinski's "Rule of Five"

Pathways across the blood–brain barrier

Lipophilicity: $0 \leq logP \leq 3$

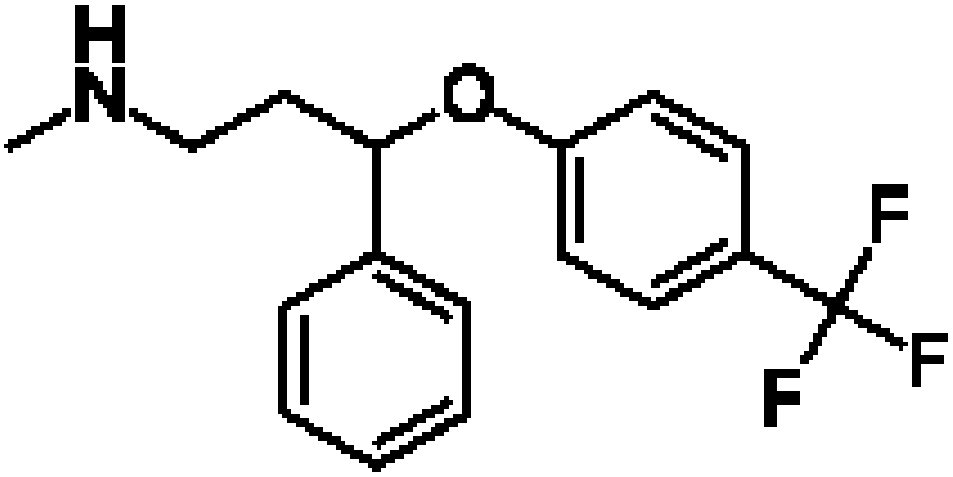
Molecular weight: < 450

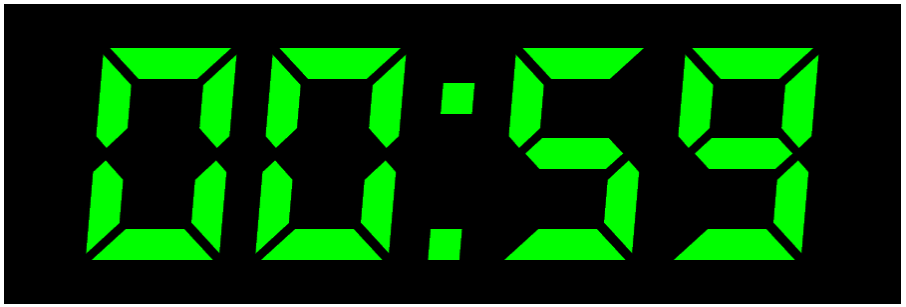
Polar surface area (PSA): $60 \div 90$ Å^2

Hydrogen bonding (O + N): ≤ 5

Charge: $4 \leq pKa \leq 10$

Can we try again our little experiment?





1. Chemical class;
2. Functional groups;
3. Possible interaction scheme;
4. Guess pKa value;
5. Number of rotatable bonds;
6. Tautomers;
7. Chiral centers;
8. Chemical/enzimatic reactivity;
9. Guess water solubility;
10. Guess logP;
11. Guess BBB permeation;
12. …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