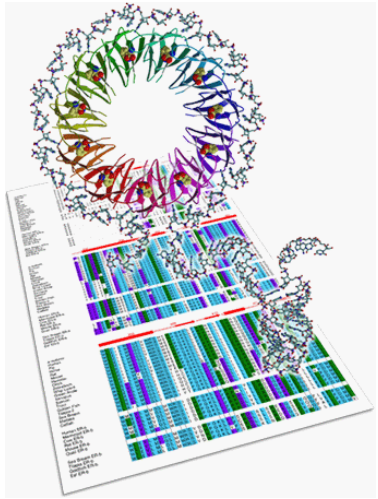
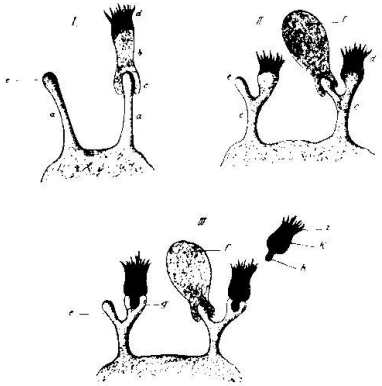
Escuela Complutense de Verano
Especialista en Bioinformática



Interacciones entre proteínas y pequeños ligandos (II)

Federico Gago
Departamento de Farmacología
Universidad de Alcalá, Madrid

"Corpora non agunt nisi fixata"



Paul Ehrlich
"Address in Pathology on Chemotherapeutics: Scientific Principles, Methods, and Results"
Lancet II, 445 (1913)

FORCES THAT DETERMINE LIGAND-RECEPTOR INTERACTIONS

Favourable forces

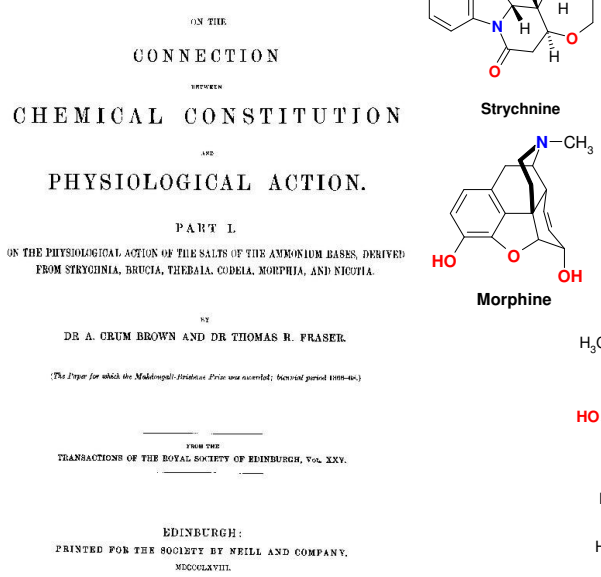
- ✓ electrostatic interactions
- ✓ hydrogen bonds
- ✓ hydrophobic effect
- ✓ van der Waals interactions
- ✓ desolvation of receptor and ligand

Unfavourable forces

- ✓ loss of translational and rotational entropy
- ✓ loss of internal rotations in ligand (*entropic*)
- ✓ loss of solvation energy of receptor and ligand (*enthalpic*)
- ✓ conformational changes in receptor

P. G. Strange *TiPS* 17, 238 (1996)

1st QSAR study:



ON THE

CONNECTION

BETWEEN

CHEMICAL CONSTITUTION

AND

PHYSIOLOGICAL ACTION.

PART I.

ON THE PHYSIOLOGICAL ACTION OF THE SALTS OF THE AMMONIUM BASES, DERIVED FROM STRYCHNIA, BRUCIA, THEBAIA, CODEIA, MORPHIA, AND NICOTIA.

BY

DR A. CRUM BROWN AND DR THOMAS R. FRASER.

(The Paper for which the Moldengall-Fothergill Prize was awarded; triennial period 1866-69.)

FROM THE

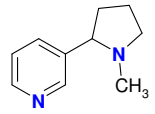
TRANSACTIONS OF THE ROYAL SOCIETY OF EDINBURGH, Vol. XXV.

EDINBURGH:

PRINTED FOR THE SOCIETY BY NEILL AND COMPANY.

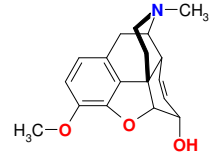
MDCCCLXVIII.

Strychnine

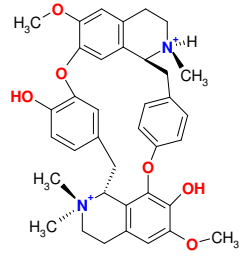


Nicotine

Morphine



Codeine



d-tubocurarine

Almost 100 years later:

"ρ–σ–π Analysis, A Method for the Correlation of Biological Activity and Chemical Structure"

C. Hansch & T. Fujita
J. Am. Chem. Soc. ***86***, 1616 (1964)

"A Mathematical Contribution to Structure-Activity Studies"

S. M. Free, Jr. & J. W. Wilson
J. Med. Chem. ***7***, 395 (1964)

Physiological activity $\Phi = f(C)$ (Brown & Fraser, 1868)

$\Delta\Phi = f(\Delta C)$

Biological activity = $f(a_i X_i, m)$ Linear Free Energy Relationships

$B.a. = \mu + \Sigma a_{ij} X_{ij}$ de novo model ($X_{ij} = 1, 0$)
μ = overall mean of b.a. values (Free & Wilson, 1964)

μ = b.a. of unsubstituted parent molecule (Fujita & Ban, 1971)

Biological activity = $\log(1/C) = k_1 (X_H) + k_2 (X_E) + k_3 (X_S) + \varepsilon$ parametric model
(Hansch & Fujita, 1964)

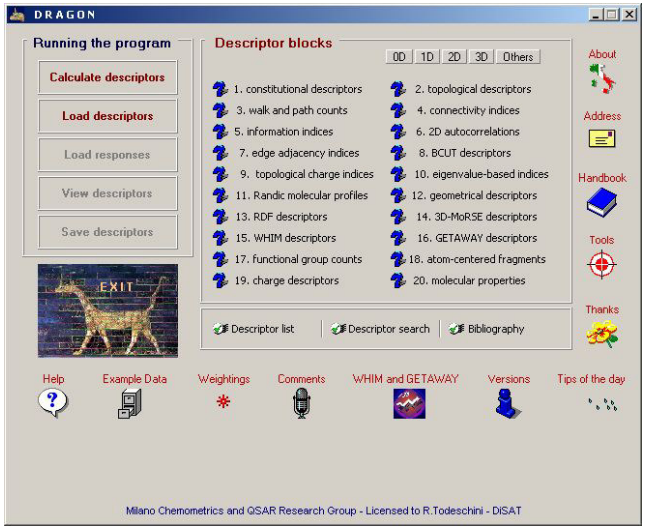
MOLECULAR PARAMETERS USED IN QSAR:

electronic: σ constants (ΔpKa values), NMR chemical shifts, atomic charges, MO indices, frontier orbital energies, superdelocalizability indices, electrostatic potential...

hydrophobic: π values (Δlog P values), HPLC log k'...

molecular shape/geometry: Taft's parameters, Kier's molecular connectivity indices, Verloop's sterimol parameters...

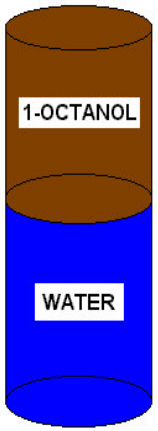
DRAGON 5 calculates 1,630 molecular descriptors



http://www.talete.mi.it/dragon.htm

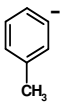
ID Block	Block description	Desc. No.
1	constitutional descriptors	48
2	topological descriptors	119
3	walk and path counts	47
4	connectivity indices	33
5	information indices	47
6	2D autocorrelations	96
7	edge adjacency indices	107
8	BCUT descriptors	64
9	topological charge indices	21
10	eigenvalue-based indices	44
11	Randic molecular profiles	41
12	geometrical descriptors	74
13	RDF descriptors	150
14	3D-MoRSE descriptors	160
15	WHIM descriptors	99
16	GETAWAY descriptors	197
17	functional group counts	152
18	atom-centred fragments	120
19	charge descriptors	14
20	molecular properties	29

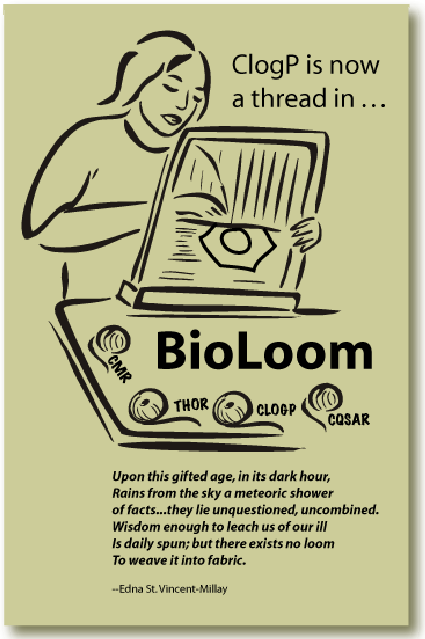
Hydrophobicity



Shake flask experiment

- **Measured as the Octanol / Water *Partition Coefficient* ($P_{o/w}$)**
- **Log P_A = Log $\left[\frac{[A]_{1\text{-octanol}}}{[A]_{water}}\right]$**
- **log P > 0 : lipid phase**
  log P < 0 : water phase

π_{CH_3} = logP  - logP 



BioByte

ClogP → BioLoom

calculates hydrophobic and molecular refractivity parameters via CLOGP & CMR

http://www.biobyte.com/bb/prod/bioloom.html

LogP **Interactive Analysis**

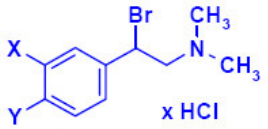
http://www.logp.com/

Interactive $LogK_{ow}$ (KowWin)

http://www.syrres.com/esc/est_kowdemo.htm

✓ calculates log P (octanol-water partition coefficient) and retrieve experimental log P data from an experimental database of 13,000 compounds.
✓ If experimental data is available, it is listed below the estimation.

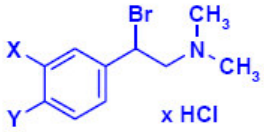
Antiadrenergic Activities of *meta*-, *para*-, and *meta,para*-Disubstituted *N,N*-Dimethyl-α-bromophenethylamines



meta	para	log 1/C	meta	para	log 1/C
H	H	7.46	Cl	F	8.19
H	F	8.16	Br	F	8.57
H	Cl	8.68	Me	F	8.82
H	Br	8.89	Cl	Cl	8.89
H	I	9.25	Br	Cl	8.92
H	Me	9.30	Me	Cl	8.96
F	H	7.52	Cl	Br	9.00
Cl	H	8.16	Br	Br	9.35
Br	H	8.30	Me	Br	9.22
I	H	8.40	Me	Me	9.30
Me	H	8.46	Br	Me	9.52

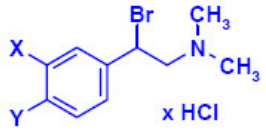
meta (X)	*para* (Y)	log 1/C obsd.	π	σ⁺	E_s^{meta}	log 1/C calc.	log 1/C calc.
H	H	7.46	0.00	0.00	1.24	7.82	7.88
H	F	8.16	0.15	-0.07	1.24	8.09	8.17
H	Cl	8.68	0.70	0.11	1.24	8.46	8.60
H	Br	8.89	1.02	0.15	1.24	8.77	8.94
H	I	9.25	1.26	0.14	1.24	9.06	9.26
H	Me	9.30	0.52	-0.31	1.24	8.87	8.98
F	H	7.52	0.13	0.35	0.78	7.45	7.43
Cl	H	8.16	0.76	0.40	0.27	8.11	8.05
Br	H	8.30	0.94	0.41	0.08	8.30	8.22
I	H	8.40	1.15	0.36	-0.16	8.61	8.51
Me	H	8.46	0.51	-0.07	0.00	8.51	8.36
Cl	F	8.19	0.91	0.33	0.27	8.38	8.34
Br	F	8.57	1.09	0.34	0.08	8.57	8.51
Me	F	8.82	0.66	-0.14	0.00	8.78	8.65
Cl	Cl	8.89	1.46	0.51	0.27	8.75	8.77
Br	Cl	8.92	1.64	0.52	0.08	8.94	8.94
Me	Cl	8.96	1.21	0.04	0.00	9.15	9.08
Cl	Br	9.00	1.78	0.55	0.27	9.06	9.11
Br	Br	9.35	1.96	0.56	0.08	9.25	9.29
Me	Br	9.22	1.53	0.08	0.00	9.46	9.43
Me	Me	9.30	1.03	-0.38	0.00	9.56	9.47
Br	Me	9.52	1.46	0.10	0.08	9.35	9.33

Matrix for Hansch Analysis



meta (X)	*para* (Y)	log 1/C obs.	*meta*- F	Cl	Br	I	Me	*para*- F	Cl	Br	I	Me	log 1/C calc.
H	H	7.46											7.82
H	F	8.16						1					8.16
H	Cl	8.68							1				8.59
H	Br	8.89								1			8.84
H	I	9.25									1		9.25
H	Me	9.30										1	9.08
F	H	7.52	1										7.52
Cl	H	8.16		1									8.03
Br	H	8.30			1								8.26
I	H	8.40				1							8.40
Me	H	8.46					1						8.28
Cl	F	8.19		1				1					8.37
Br	F	8.57			1			1					8.60
Me	F	8.82				1		1					8.62
Cl	Cl	8.89		1					1				8.80
Br	Cl	8.92			1				1				9.02
Me	Cl	8.96				1			1				9.04
Cl	Br	9.00		1						1			9.05
Br	Br	9.35			1					1			9.28
Me	Br	9.22				1				1			9.30
Me	Me	9.30				1						1	9.53
Br	Me	9.52			1							1	9.51

Matrix for Free Wilson Analysis



Free Wilson Analysis, Results: μ = 7.82

Position	H	F	Cl	Br	I	Me
meta	0.00	-0.30	0.21	0.43	0.58	0.45
para	0.00	0.34	0.77	1.02	1.43	1.26

(n = 22; r = 0.97; s = 0.19)

Hansch Analyses, Results:

C. Hansch and E. J. Lien, Biochem. Pharmacol. 17, 709 (1968)

log 1/C = 1.221 π - 1.587 σ + 7.888

(n = 22; r = 0.918; s = 0.238)

A. Cammarata, J. Med. Chem. 15, 573 (1972)

log 1/C = 0.747 (±0.12) π_m - 0.911 (±0.25) σ_m + 1.666 (±0.12) r_v^{para} + 5.769

(n = 22; r = 0.961; s = 0.164)

Hansch Equations

log 1/C = 1.151 (±0.19) π - 1.464 (±0.38) σ⁺ + 7.817 (±0.19)

(n = 22; r = 0.945; s = 0.196; F = 78.63)

log 1/C = 1.259 (±0.19) π - 1.460 (±0.34) σ⁺ + 0.208 (±0.17) E_s^{meta} + 7.619 (±0.24)

(n = 22; r = 0.959; s = 0.173; F = 69.24)

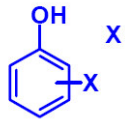
Free Wilson Equation

log 1/C = - 0.301 (±0.50) [m-F] + 0.207 (±0.29) [m-Cl] + 0.434 (±0.27) [m-Br] + 0.579 (±0.50) [m-I] + 0.454 (±0.27) [m-Me] + 0.340 (±0.30) [p-F] + 0.768 (±0.30) [p-Cl] + 1.020 (±0.30) [p-Br] + 1.429 (±0.50) [p-I] + 1.256 (±0.33) [p-Me] + 7.821 (±0.27)

(n = 22; r = 0.969; s = 0.194; F = 16.99)

Free Wilson Analyses

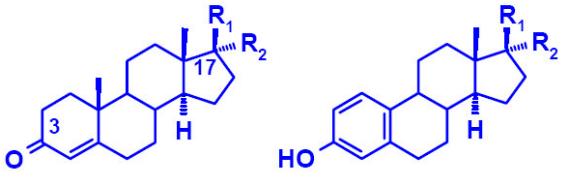
Antibacterial activity of phenols vs. *Staphylococcus aureus*



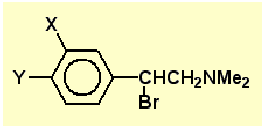
X = H, Cl

log 1/C = 0.503 (±0.13) [Cl] + 2.578
(n = 9; r = 0.960; s = 0.256; F = 83.06)

Corticosteroid-binding globulin affinities of steroids



log 1/CBG = 2.022 (±0.52) [4.5 >C=C<] + 5.186 (±0.36)
(n = 21; r = 0.882; s = 0.568; F = 66.41;
Q^2 = 0.726; s_{PRESS} = 0.630)



$$\log(1/ED_{50}) = -0.301[m\text{–F}] + 0.27[m\text{–Cl}] + 0.434[m\text{–Br}] + 0.579[m\text{–I}] + 0.454[m\text{–Me}] + 0.340[p\text{–F}] + 0.768[p\text{–Cl}] + 1.020[p\text{–Br}] + 1.429[p\text{–I}] + 1.256[p\text{–Me}] + 7.821$$

$$n = 22,\ r^2 = 0.94,\ s = 0.194,\ F = 17.0$$

A negative coefficient indicates that the presence of that group is unfavourable to activity.

A positive coefficient indicates that the presence of that group is favourable to activity.

The Squared Correlation Coefficient, R^2

Total Sum of Squares: $$TSS = \sum_{i=1}^{N} (y_i - \langle y \rangle)^2$$

Explained Sum of Squares: $$ESS = \sum_{i=1}^{N} (y_{calc,i} - \langle y \rangle)^2$$

Residual Sum of Squares: $$RSS = \sum_{i=1}^{N} (y_i - y_{calc,i})^2$$

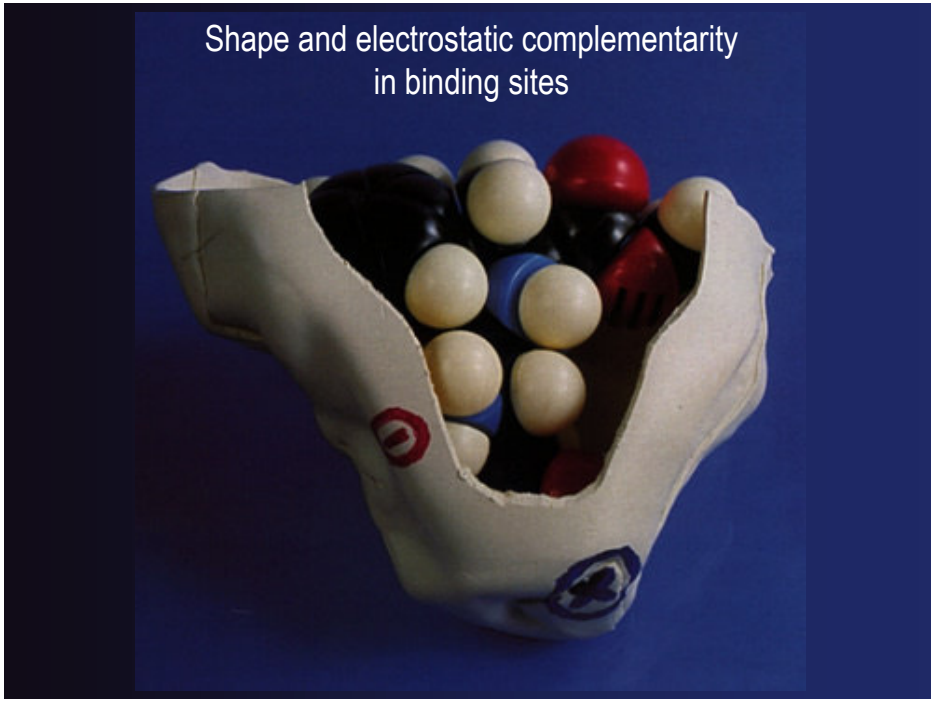
$$R^2 = \frac{ESS}{TSS} \equiv \frac{TSS - RSS}{TSS} \equiv 1 - \frac{RSS}{TSS}$$

"A QSAR Investigation of Dihydrofolate Reductase Inhibition by Baker Triazines Based Upon Molecular Shape Analysis"
A. J. Hopfinger
J. Am. Chem. Soc. 120, 7196 (1980)

"Molecular Graphics and QSAR in the Study of Enzyme-Ligand Interactions. On the Definition of Bioreceptors"
C. Hansch & T. E. Klein
Acc. Chem. Res. 19, 392 (1986)

"Comparative Molecular Field Analysis (CoMFA). 1. Effect of Shape on Binding of Steroids to Carrier Proteins"
R. D. Cramer, III, D. E. Patterson & J. D. Bunce
J. Am. Chem. Soc. 110, 5959 (1988)

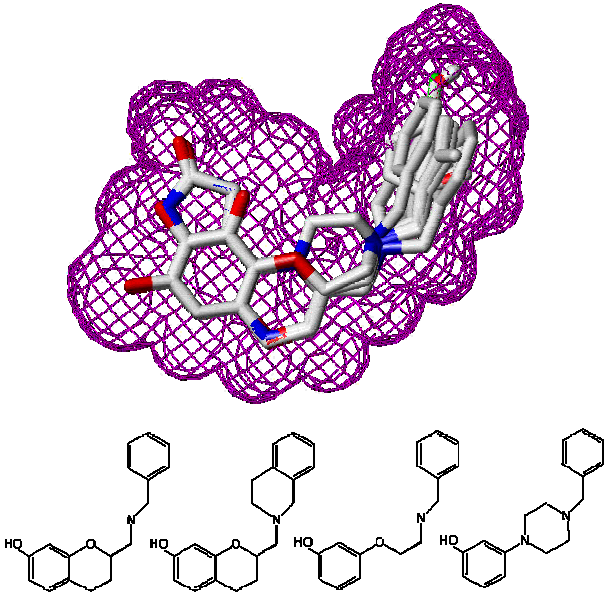
"Prediction of Drug Binding Affinities by Comparative Binding Energy Analysis"
A. R. Ortiz, M. T. Pisabarro, F. Gago & R. Wade
J. Med. Chem. 38, 2681 (1995)



3D QSAR

- Can use 3D fingerprint descriptors
- Often involves direct comparison of molecules, e.g. overlap of fields
- Requires method of aligning molecules in 3D (molecular superposition)
- As well as being used predictively, some 3D QSAR can be used to build a “pharmacophore” which describes the features in common

Alignment of structures in 3D

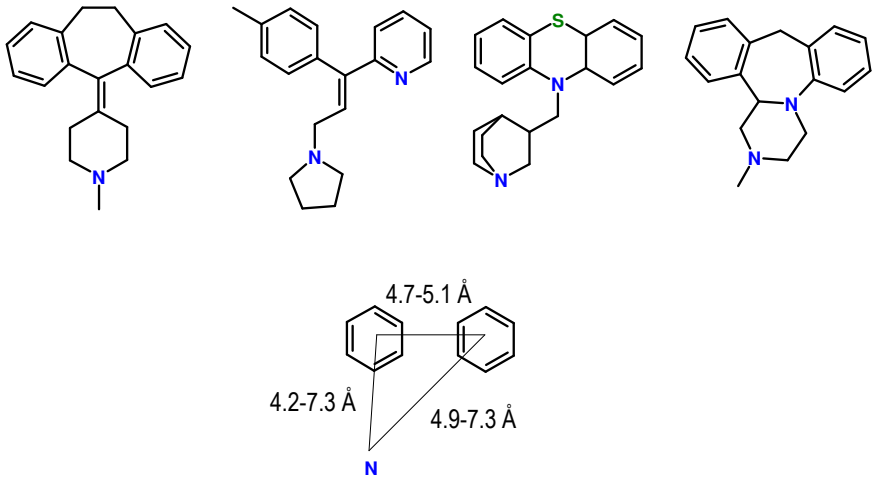


Molecular Superposition and Pharmacophore Detection

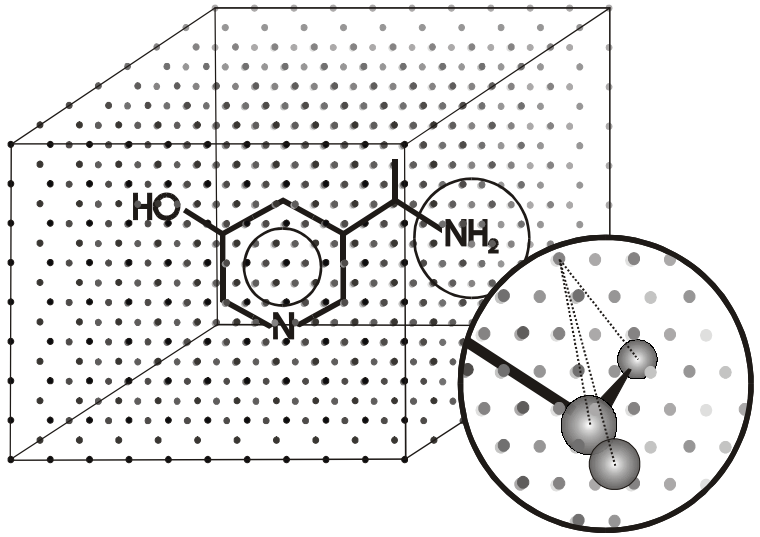
- Superimpose several molecules in 3D
- Calculate similarity between molecules
- Visualize molecular similarity
- Build a model of activity
- Pharmacophore model generation
- Infer how molecule might bind to protein

Usually employed in cases when no protein structure is available for docking studies

Simple pharmacophore for an H_1 antihistamine



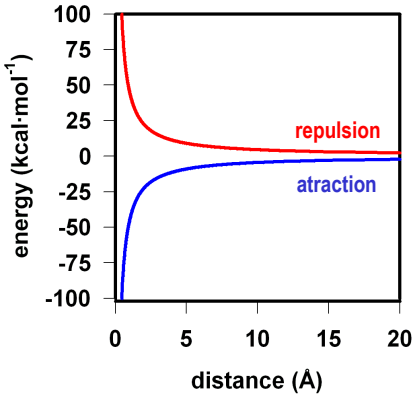
Introducing the 3rd dimension: 3D QSAR (CoMFA)

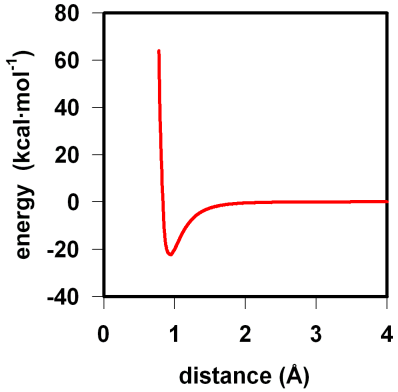


NON-BONDING TERMS

$$E_{electrostatic} = \frac{1}{4\pi\pi_0\varepsilon}\sum_{ij}\frac{q_i q_j}{r_{ij}}$$

$$E_{Lennard-Jones} = \sum_{ij}\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}$$





CoMFA

- Stands for Comparative Molecular Field Analysis
- Uses fields to optimize overlay of multiple structures based on features related to binding:
  - Electrostatics
  - Sterics
  - Hydrophobics
- Finds commonality in the fields, and correlates with activity
- Requires that structures be manually or automatically aligned
- Can be used predictively or for visualization
- Integrates with SYBYL

http://www.tripos.com/sciTech/inSilicoDisc/strActRelationship/qsar.html

CoMFA Features

- Develop quantitative structure-activity relationships
- Predict the properties and activities of untested molecules
- Compare different QSAR models statistically and visually
- Optimize the properties of a lead compound
- Validate models of receptor binding sites
- Generate hypotheses about the characteristics of a receptor binding site
- Prioritize compounds for synthesis or screening
- Determine key structural requirements for high affinity receptor ligands

THE ESSENCE OF 3D-QSAR IS:

* select a group of molecules, each possessing a measured biological response

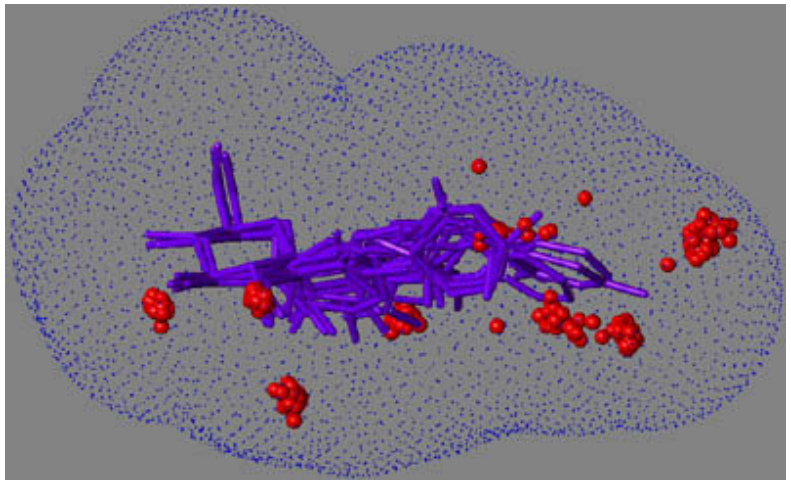
* align molecules according to some predetermined orientation rules

* calculate a set of spatially dependent parameters for each molecule determined in the receptor space surrounding the aligned series

* derive a function that relates each molecule's spatial parameters to their respective biological property

* establish self-consistency and predictive ability of the derived function

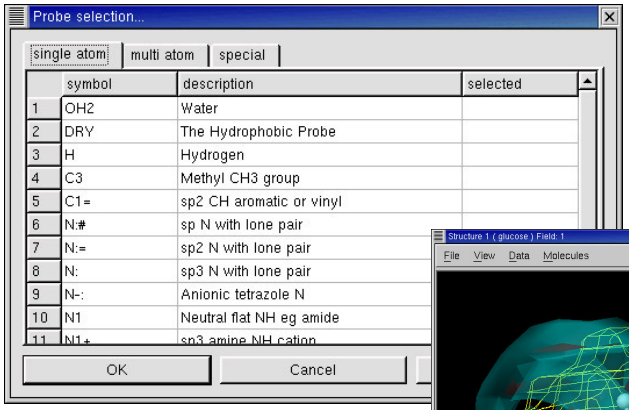
Green & Marshall, *TiPS 16, 285 (1995)*

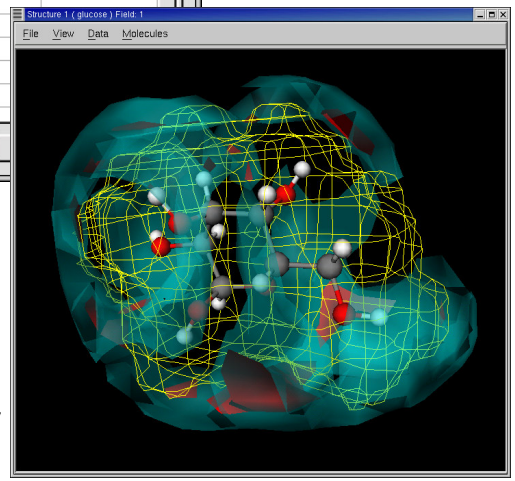


Manuel Pastor, Gabriele Cruciani, Kimberly Watson

"A strategy for the incorporation of water molecules present in a ligand binding site into a 3D QSAR analysis"

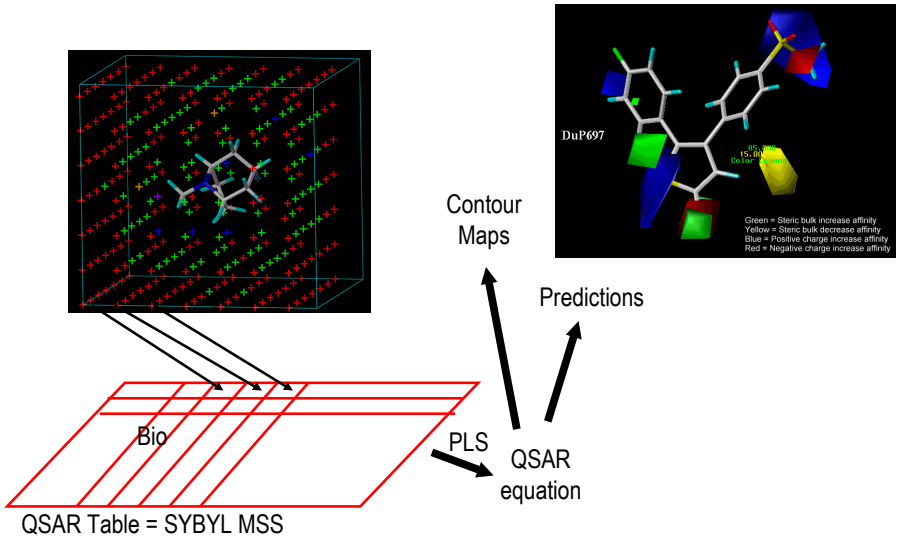
J.Med.Chem. 40, 4089-4102 (1997)





http://www.moldiscovery.com/

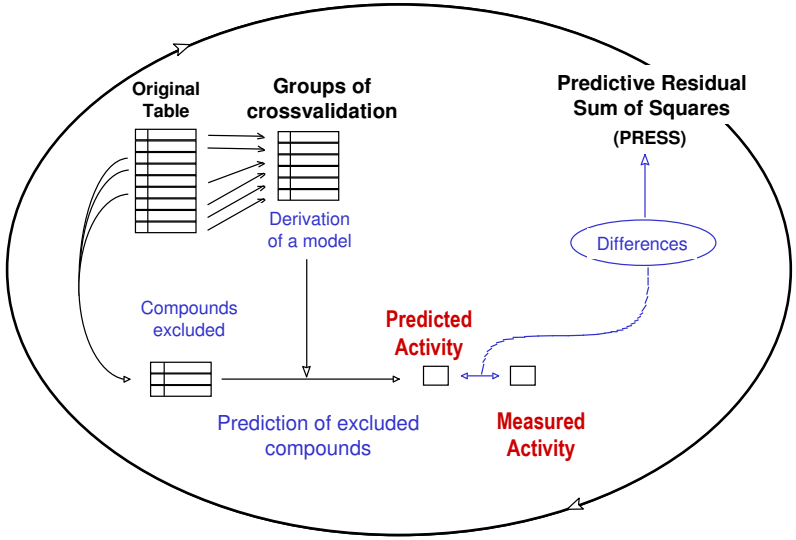
CoMFA is a (3D-Q)SAR method



PCA and PLS

- *Principal Component Analysis* may be used to pre-select principal components (i.e. the descriptors which account for the most variance in the independent variables), which are then used instead of the original descriptors in the equations
- *Partial Least Squares* is a method which also takes into account the variance in the dependent variable to derive coefficients that weigh the importance of each contribution to the differences in activity.

Cross-validated PLS analyses



Performance

Standard Deviation of Error in Predictions:

$$SDEP = \sqrt{\frac{\sum_{i=1}^{N}(Yexp(i) - Ypred(i))^2}{N}} = \sqrt{\frac{PRESS}{N}}$$

Correlation Coefficient in Cross-Validation:

$$Q^2 = 1 - \left[\frac{\sum(Yexp(i) - Ypred(i))^2}{\sum(Yexp(i) - \langle Yexp \rangle)^2}\right]$$

TRADITIONAL QSAR Disadvantages:	3D-QSAR Advantages:
- Congeneric series	- Mixed series
- Missing physicochemical parameter values	- No parameters must be estimated
- Lack of 3D structural information	- 3D structural information included
- Results expressed only as a numerical equation	- Results can be graphically displayed in 3D
- Collinearity of parameters must be avoided	- Energy fields can be collinear
- Inadequate description of steric effects	- Good description of steric effects
- Inadequate description of hydrogen bonding	- Good description of hydrogen bonding

K. H. Kim, in *'3D QSAR in Drug Design. Theory, Methods and Applications'* (1993)

TRADITIONAL QSAR Advantages:	3D-QSAR Disadvantages:
- Simplicity and speed	- More complicated to run
- No bioactive conformation required	- A bioactive conformation must be assumed
- No alignment needed	- Superposition rules and alignment problems
- May extrapolate into unexplored region with care	- Difficult to extrapolate into unexplored regions
- Results summarized in a simple equation	- Results not usually summarized in an equation
- Useful information is provided by the coefficients in the correlation equation	- Less useful information from the coefficients obtained in the correlation equation
- No weighting of parameters is necessary	- Many adjustable parameters involved
- Simple use of indicator variables	- Use of indicator variables is not straightforward

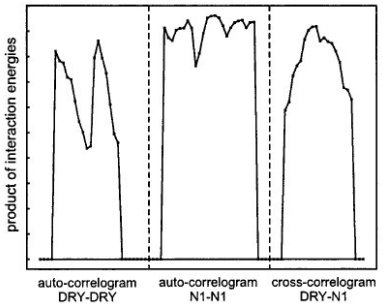
K. H. Kim, in *'3D QSAR in Drug Design. Theory, Methods and Applications'* (1993)

J. Med. Chem. **2000**, *43*, 3233−3243

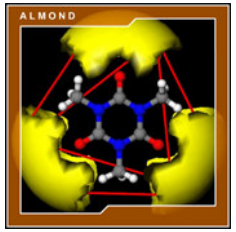
GRid-INdependent Descriptors (GRIND): A Novel Class of Alignment-Independent Three-Dimensional Molecular Descriptors

Manuel Pastor,† Gabriele Cruciani,*,† Iain McLay,§ Stephen Pickett,§ and Sergio Clementi†

Laboratory on Chemometrics, Department of Chemistry, University of Perugia, Via Elce di Sotto 10, 06123 Perugia, Italy, and CADD Department, Rhone-Poulenc Rorer, Dagenham, Essex RM10 7XS, U.K.

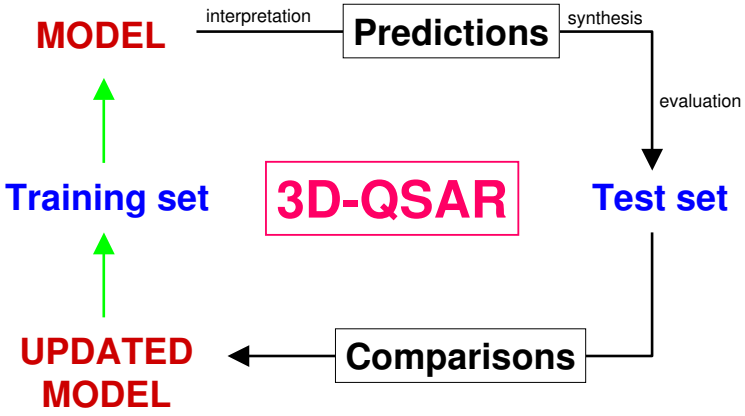


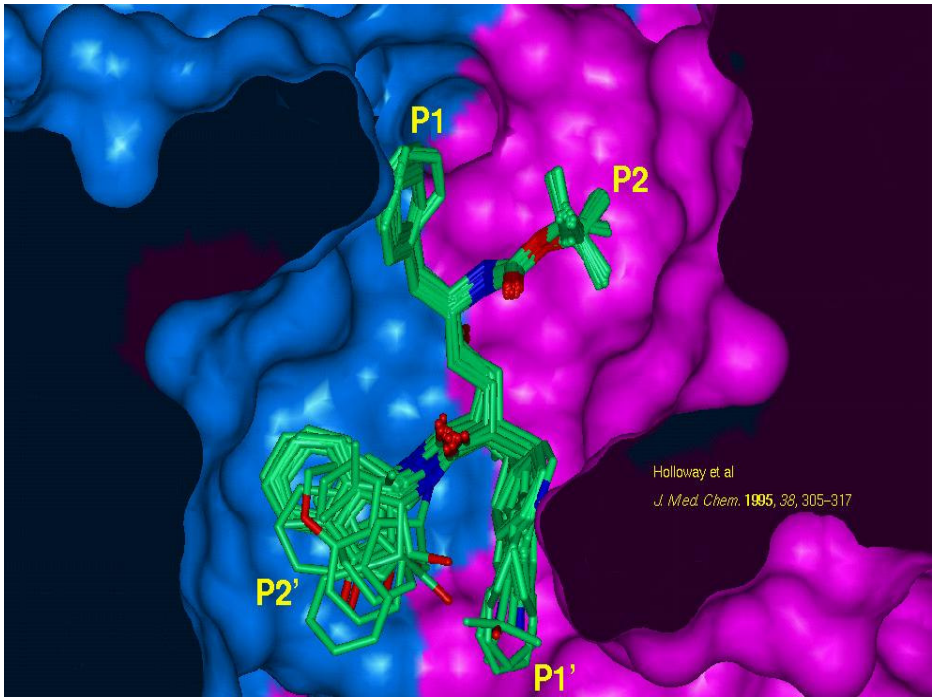
ALMOND



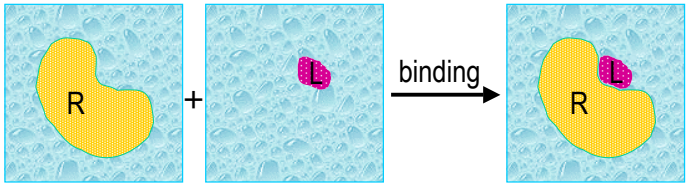
Molecular Discovery

http://www.moldiscovery.com/

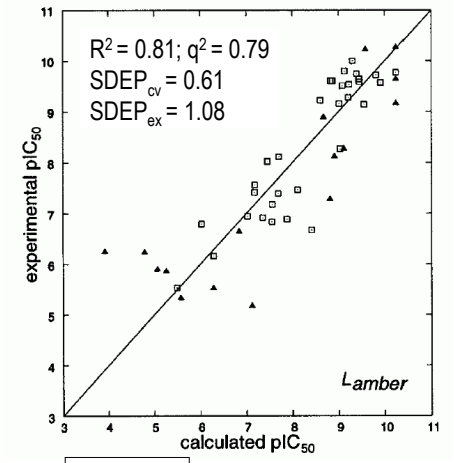


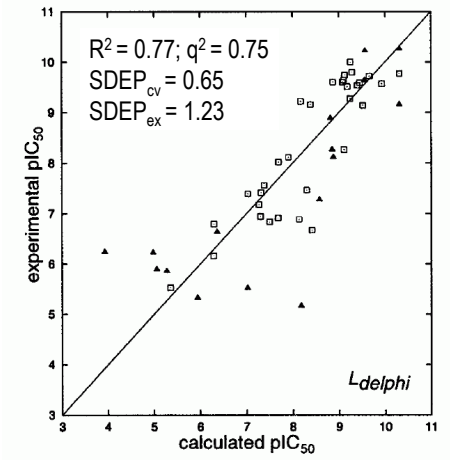


ENERGETICS OF COMPLEX FORMATION



$$\Delta E_{binding} = E_{LR} - (E_R + E_L)$$





C. Pérez, M. Pastor, A. R. Ortiz & F. Gago
J. Med. Chem. ***41***, 836 (1998)

Linear regression analysis:

Activity = a (E_{inter}) + *b*

Comparative Binding Energy

(COMBINE)

Análisis Comparativo de Energías de Unión

Comparative Molecular Field Analysis

(CoMFA)

Análisis Comparativo de Campos Moleculares

MODELLING PHASE

REFINEMENT STAGE

ENERGY CALCULATION AND PARTITIONING / MATRIX PRETREATMENT

MODEL DERIVATION

unbound receptor (R)

n unbound ligands (L)

n (R:L) complexes

energy minimization

n refined (R:L) complexes

desolvation energy terms (?)

$\Delta U = E_{LR} - (E_L + E_R)$ → energy decomposition

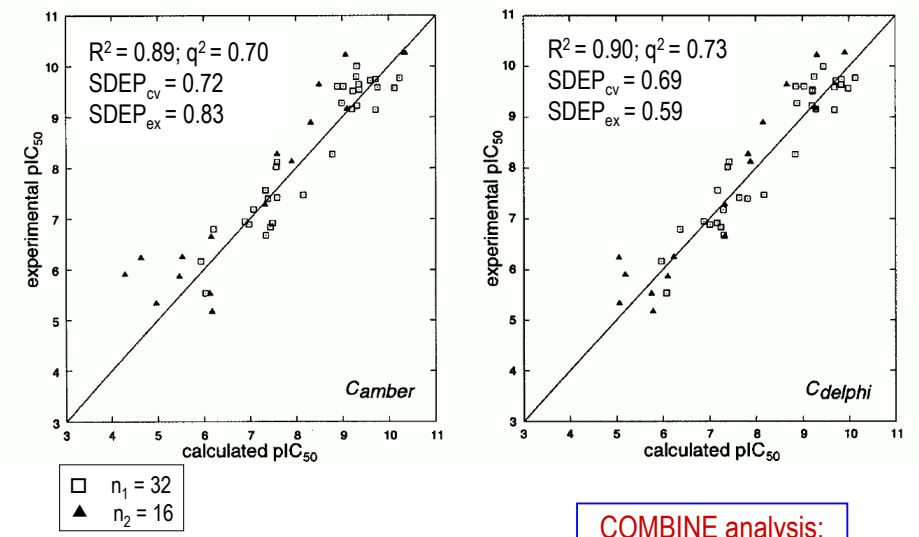
Activity = $\sum_{i=1}^{n} w_i \Delta u_i^{sel} + C$

Principal Component Analysis (PCA)

Partial Least Squares (PLS)

MODEL VALIDATION:
- cross-validation
- permutation of activity data (*scrambling*)
- random numbers

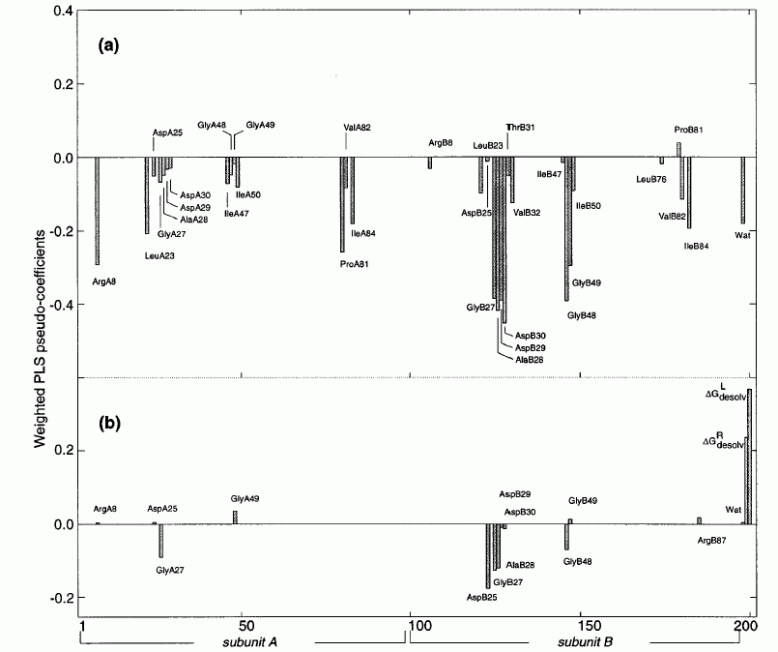
PREDICTIONS: error assessment

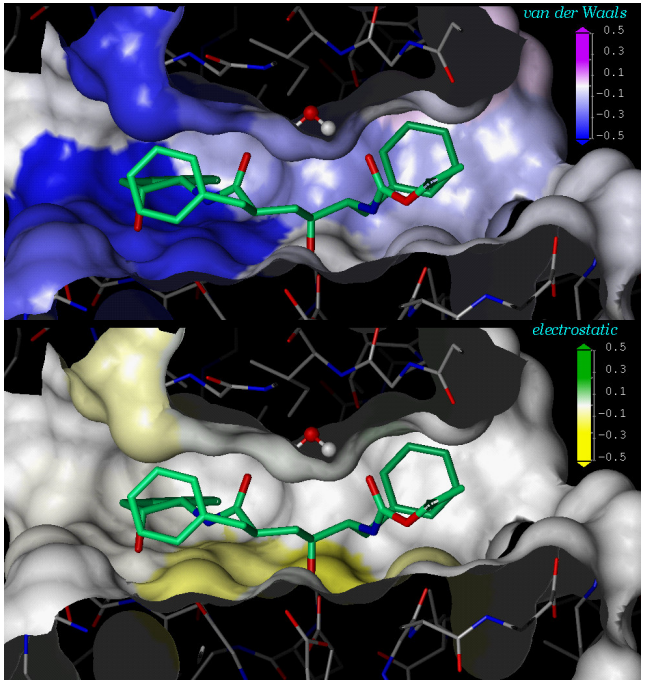


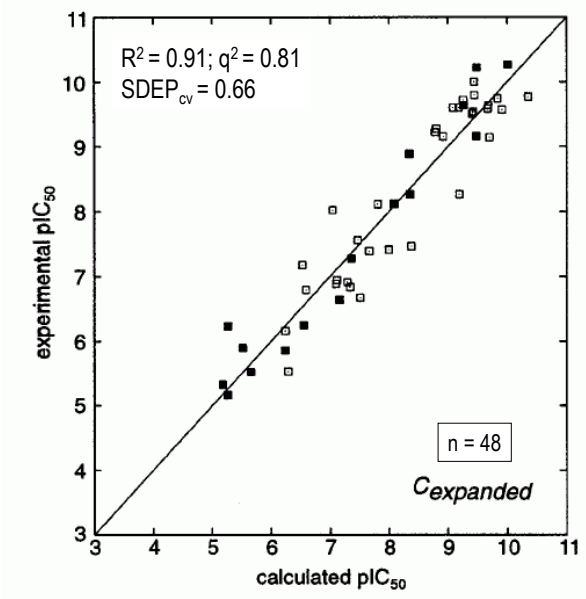
C. Pérez, M. Pastor, A. R. Ortiz & F. Gago
J. Med. Chem. ***41***, 836 (1998)

COMBINE analysis:

$$\sum_{i=1}^{n} w_i \Delta u_i^{sel} + C$$







Combinatorial Chemistry & High Throughput Screening, 2001, *4*, 627-642 627

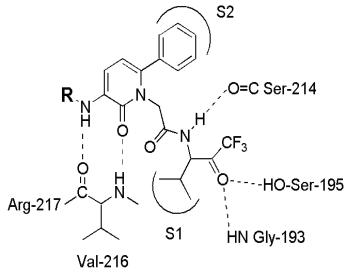
Comparative Binding Energy (COMBINE) Analysis of HumanNeutrophil Elastase Inhibition by Pyridone-containing Trifluoromethylketones

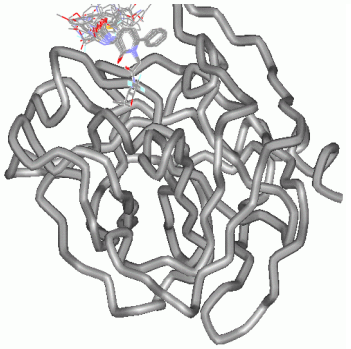
Carmen Cuevas,[†] Manuel Pastor,[#] Carlos Pérez[†] and Federico Gago[*]

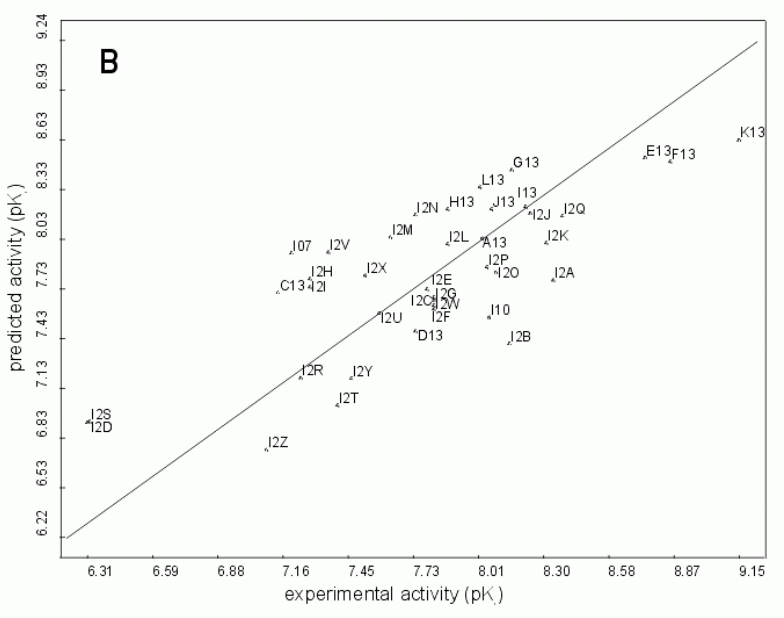
Departamento de Farmacología, Universidad de Alcalá, E-28871 Alcalá de Henares, Madrid, Spain

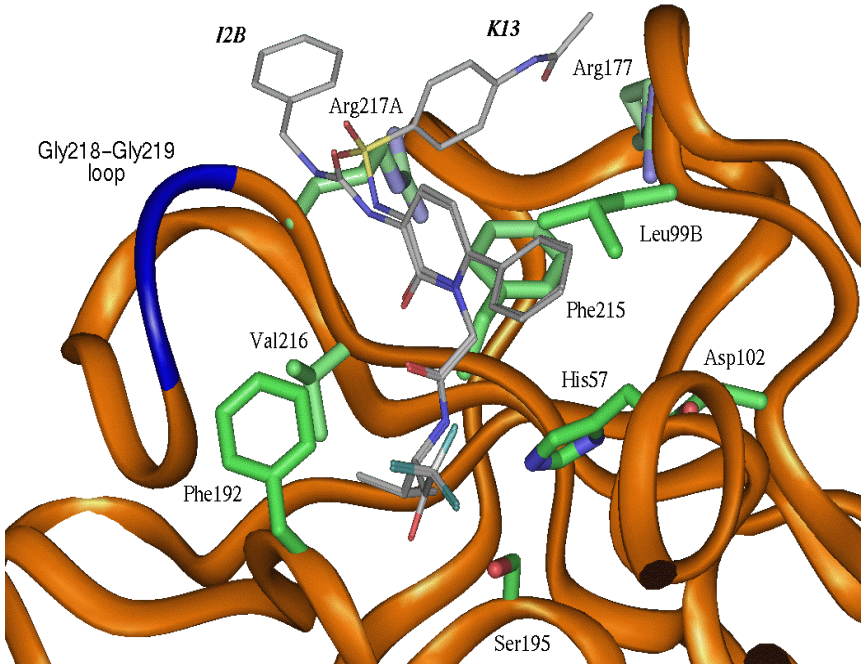
[†] *Present address: Pharma Mar S.A., Cantoblanco, 28760 Tres Cantos, Madrid, Spain*

[#] *Present address: Departament de Ciències Experimentals i de la Salut, Universitat Pompeu, Fabra, Dr. Aiguader 80, E-08003 Barcelona, Spain*





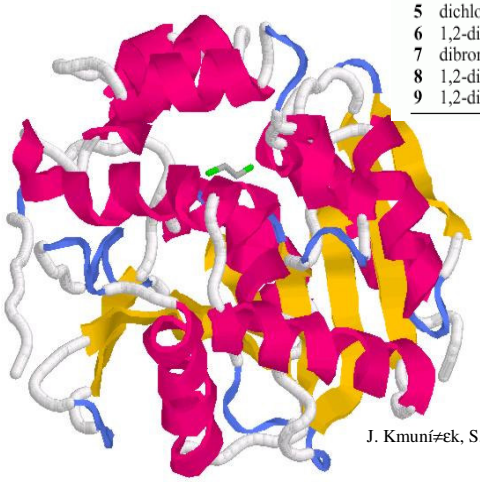


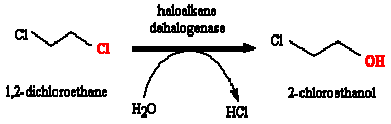


Haloalkane dehalogenase from *Xanthobacter autotrophicus* GJ10

Table 1: Steady-State Dissociation Constants of Haloalkane Dehalogenase[a]

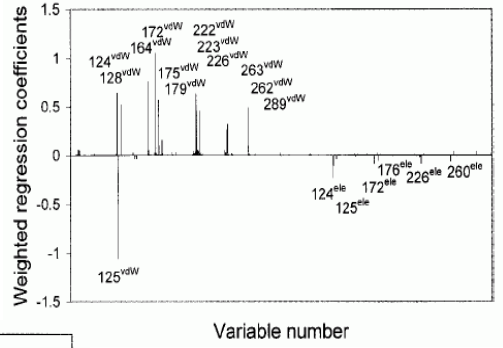
	compound	log K_m (mM)		compound	log K_m (mM)
1	1-chlorobutane	0.34	10	1,2-dibromopropane	0.11
2	1-chlorohexane	0.15	11	2-chloroethanol	2.60
3	1-bromobutane	−1.22	12	2-bromoethanol	1.04
4	1-bromohexane	−0.52	13	epichlorohydrine	1.68
5	dichloromethane	2.00	14	epibromohydrine	0.34
6	1,2-dichloroethane	−0.28	15	2-chloroacetonitrile	0.80
7	dibromomethane	0.38	16	2-bromoacetonitrile	−0.31
8	1,2-dibromoethane	−2.00	17	2-chloroacetamide	2.00
9	1,2-dichloropropane	1.11	18	2-bromoacetamide	1.30

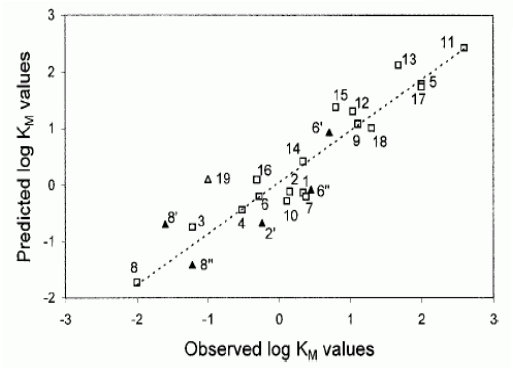




J. Kmuní≠ek, S. Luengo, F. Gago, A.R. Ortiz, R.C. Wade & J. Damborsk | ***Biochemistry***, 40, 8905-8917 (2001)

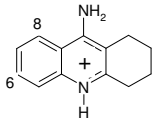
Selected energy contributions in the best COMBINE model



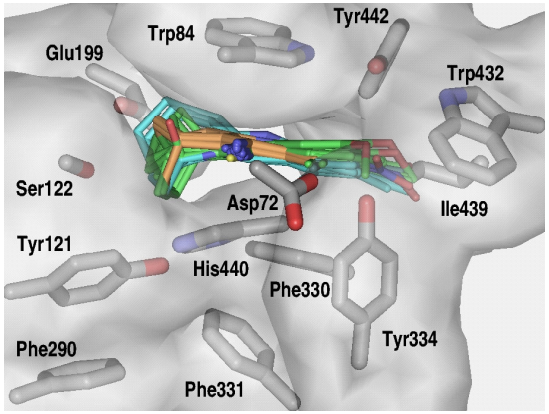


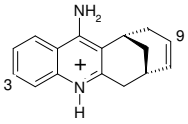
- □ training set
- ▲ prediction set
- ' Phe172Trp mutant enzyme
- " Trp175Tyr mutant enzyme
- △ new substrate + Phe172Trp mutant enzyme

Modulation of Binding Strength in Active Site Inhibitors of Acetylcholinesterase Studied by Comparative Binding Energy (COMBINE) Analysis

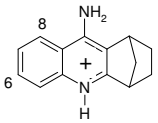


16 tacrines

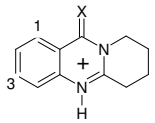




7 huprines

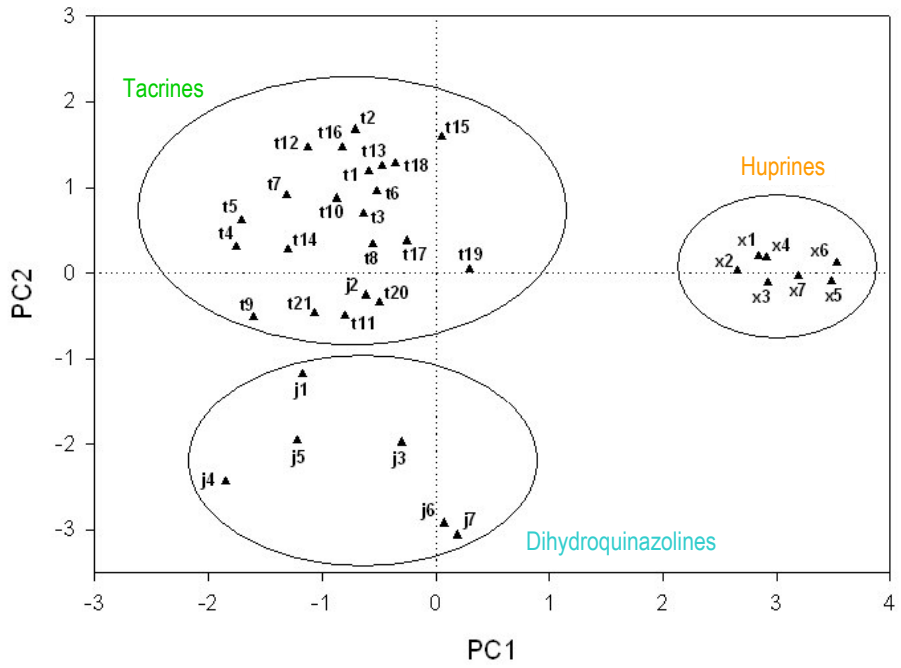


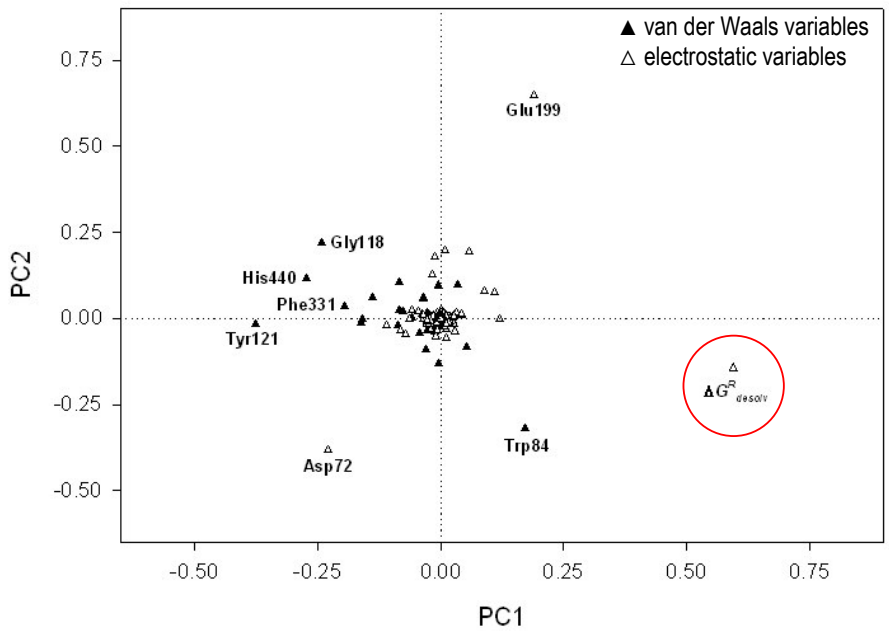
5 1,4-methylenetacrines



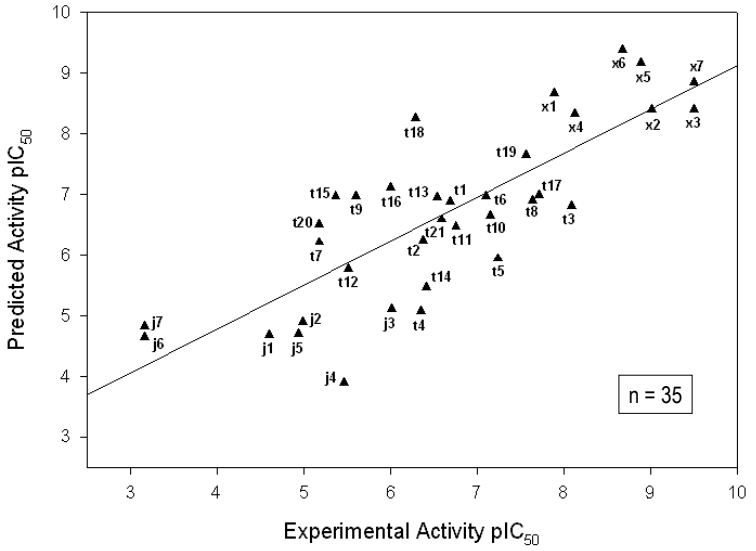
7 dihydroquinazolines

Martín-Santamaría, S.; Muñoz-Muriedas, J.; Luque, F.J.; Gago, F. ***J. Med. Chem.*** 47, 4471-4482 **(2004)**

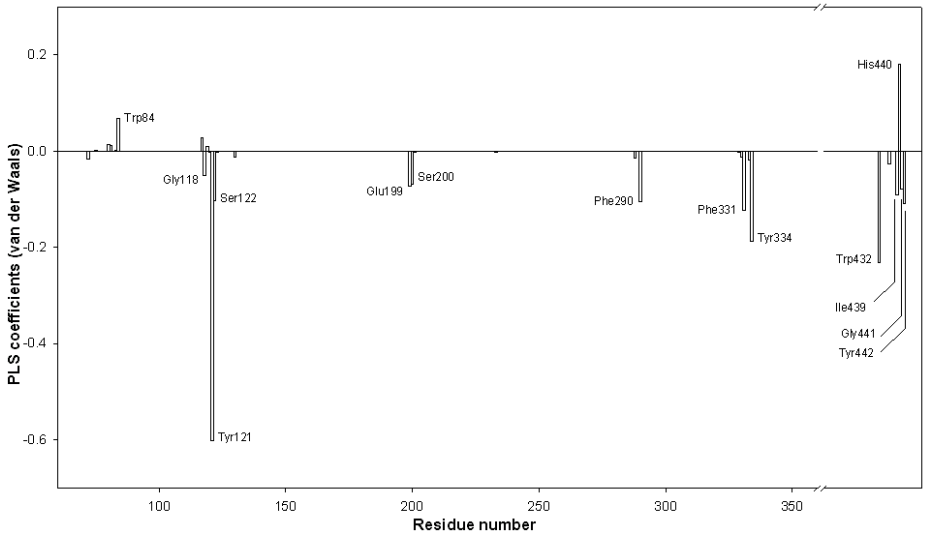




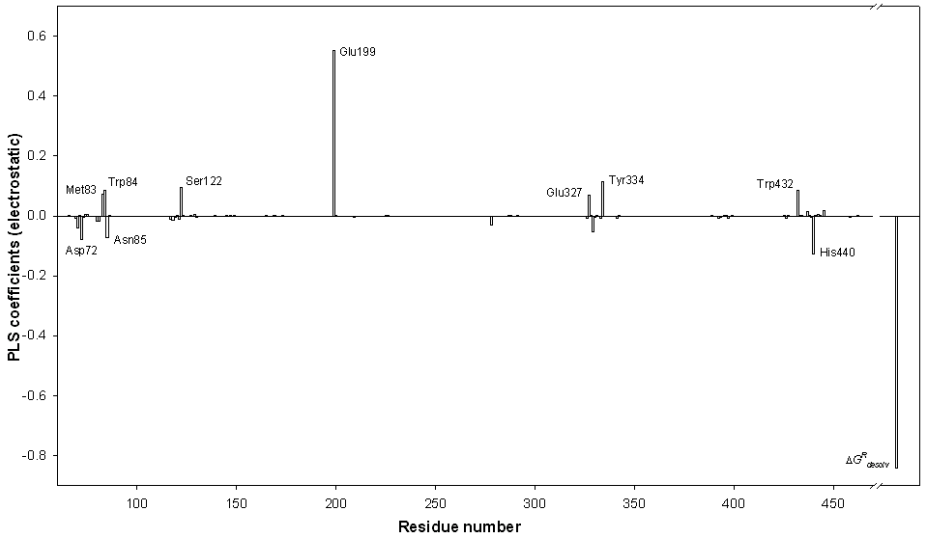
Cross-validation of the COMBINE model: Q^2 = 0.76, SDEP = 0.78 log units



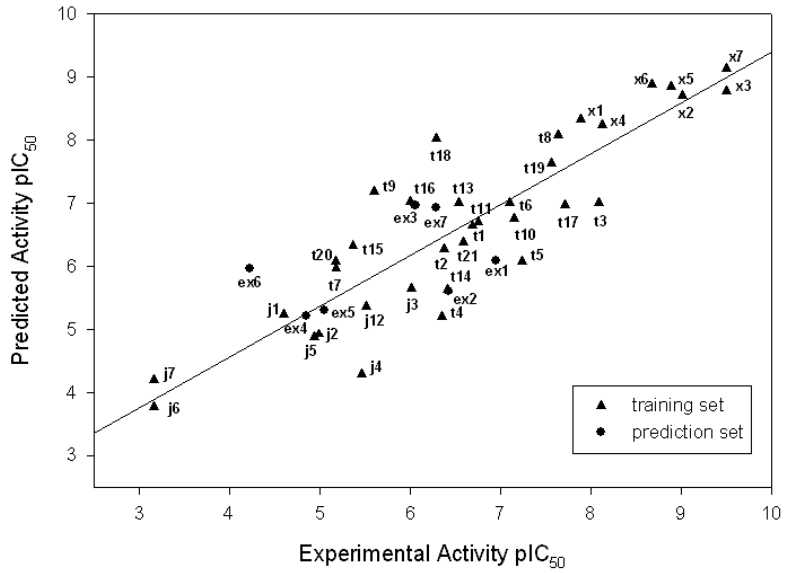
Normalized PLS coefficients (van der Waals)



Normalized PLS coefficients (electrostatic)



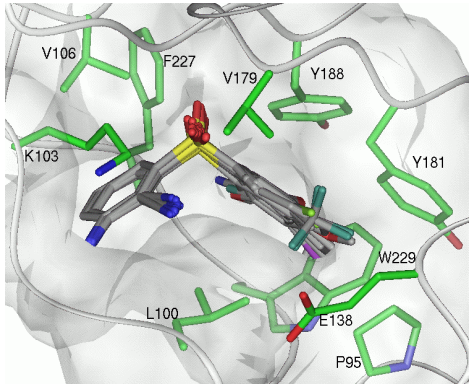
Predictive ability* of the COMBINE model: SDEP = 0.93 log units

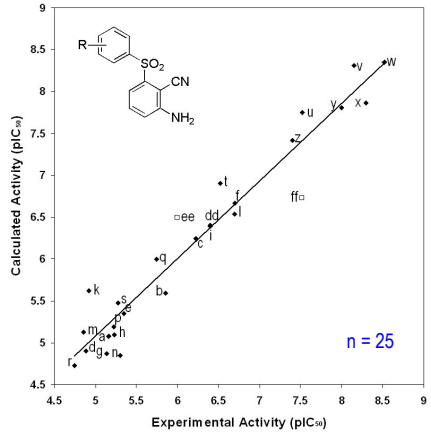


* seven 9-amino-1,2,3,4-tetrahydroacridine derivatives

Chemometrical Identification of Mutations in HIV-1 Reverse Transcriptase Conferring Resistance or Enhanced Sensitivity to Arylsulfonylbenzonitriles

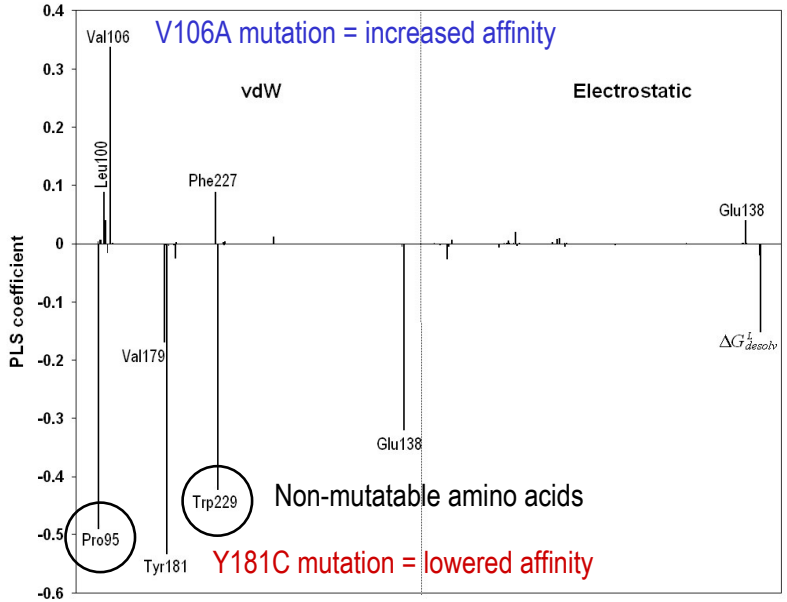
$r^2 = 0.95$; $q^2 = 0.89$; SDEP = 0.40 (3 PC)





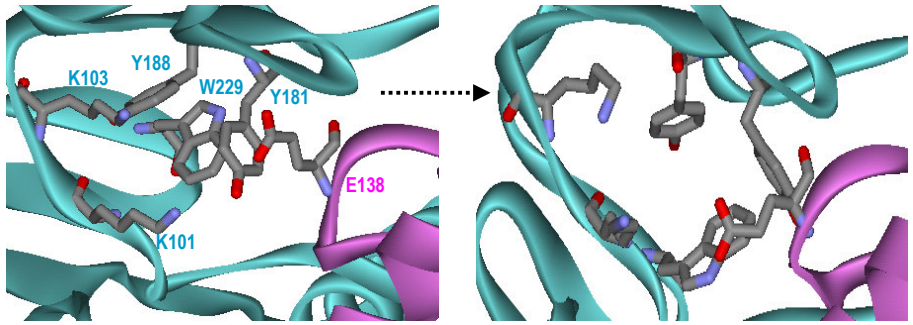
Fátima Rodríguez-Barrios & Federico Gago
Journal of the American Chemical Society, 126(9): 2718-2719 (2004)

$r^2 = 0.959$ $q^2 = 0.851$ (n= 27; 4 PC)



Apo enzyme

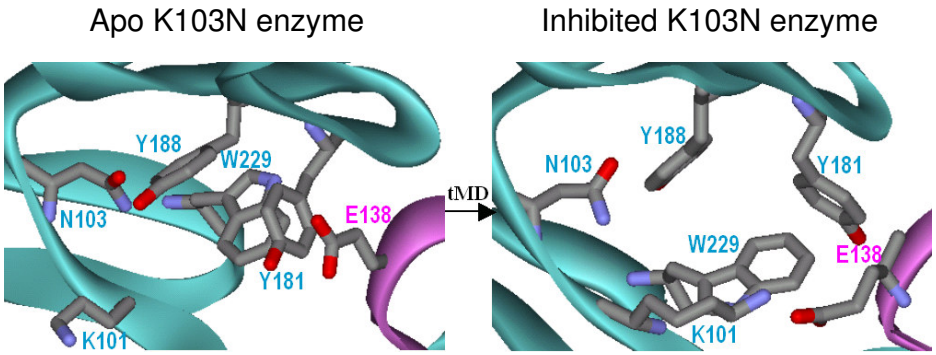
Inhibited enzyme



Targeted molecular dynamics

$$E = 0.5\, k_r\, N\, (\text{rmsd} - \text{trmsd})^2$$

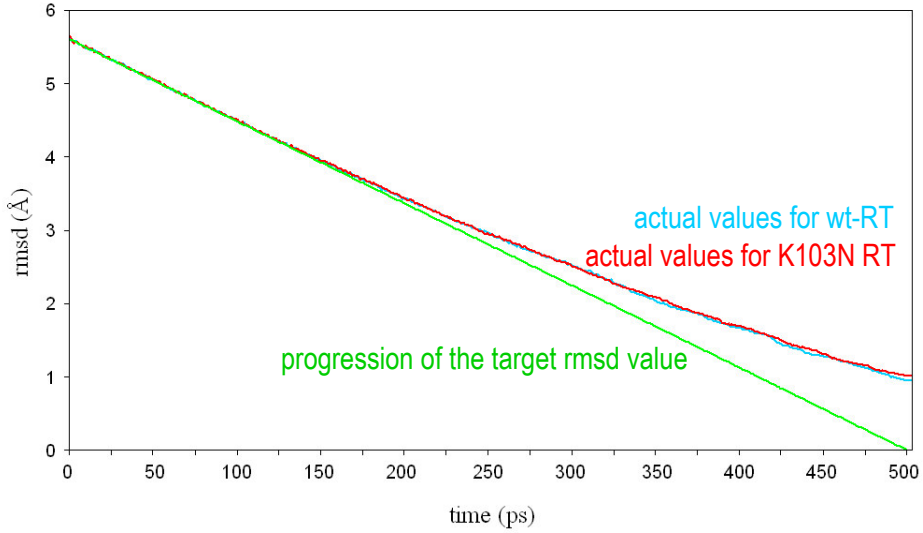
Understanding the basis of resistance in the irksome Lys103Asn HIV-1 reverse transcriptase mutant through targeted molecular dynamics simulations

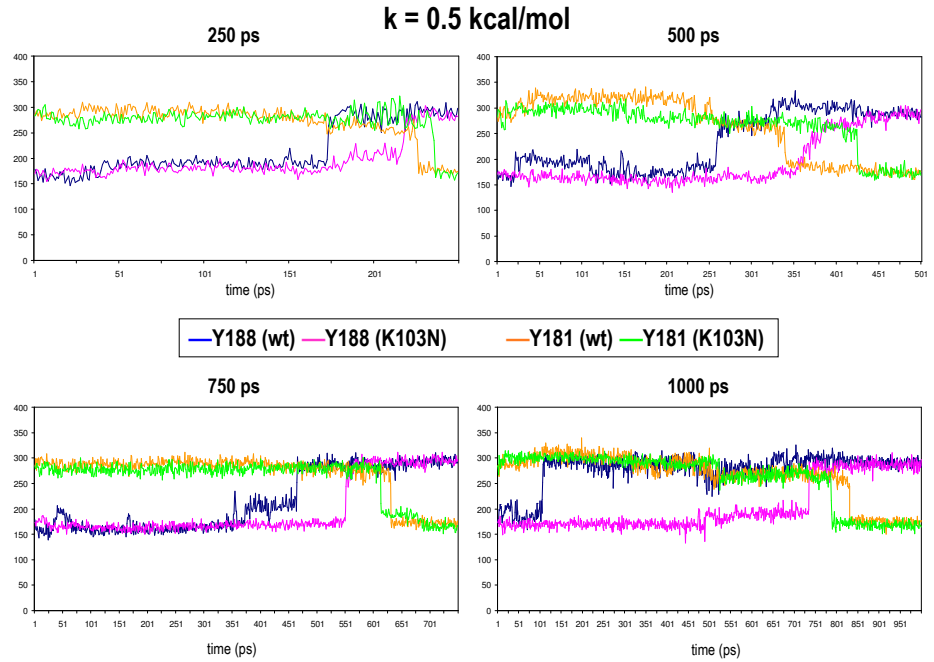


Rodríguez-Barrios, F.; Gago, F. "Understanding the basis of resistance in the irksome Lys103Asn HIV-1 reverse transcriptase mutant through targeted molecular dynamics simulations" ***Journal of the American Chemical Society***, 126(47): 15386-15387 **(2004)**

Time evolution of the mass-weighted root-mean-square deviation (rmsd) of all the atoms in the simulated structures compared to the reference structures

(force constant = 0.5 kcal mol^{-1} $Å^{-2}$)



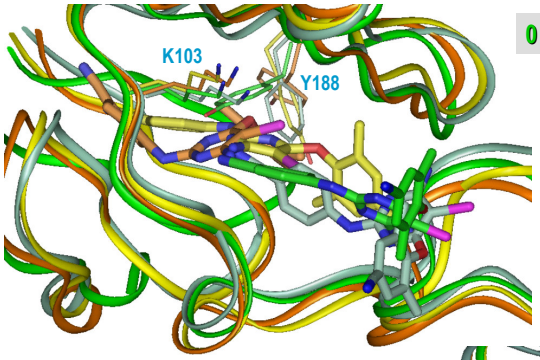


Sensitivity (μM) of HIV-1 RT to different NNRTIs

Compound	Wild-type	K103N
Nevirapine	0.39 ± 0.085	≥ 10
Delavirdine	0.25 ± 0.085	7.0 ± 0.28
TSAO-m^3T	0.85 ± 0.085	8.5 ± 0.57
Emivirine (MKC-442)	0.059 ± 0.011	2.1 ± 0.21
Thiocarboxanilide (UC-781)	0.036 ± 0.014	0.83 ± 0.62
PETT (MSK-076)	0.002 ± 0.001	0.007 ± 0.0005
Quinoxaline (GW867)	0.017 ± 0.008	0.43 ± 0.035
Capravirine (AG/1549)	0.005 ± 0.001	0.004 ± 0.001
Efavirenz	0.004 ± 0.002	0.14 ± 0.064
Etravirine (TMC-125)	0.029 ± 0.014	0.032 ± 0.015
ddGTP	0.037 ± 0.002	0.016 ± 0.003
PFA (foscarnet)	5.4 ± 0.49	2.5 ± 0.74

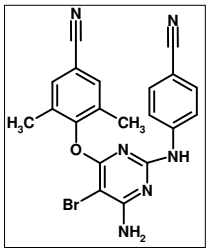
50% inhibitory concentration or compound concentration required to inhibit recombinant HIV-1 RT by 50%.
Template/primer: (poly)rC·(oligo)dG; radiolabeled substrate: [^{3}H]dGTP.

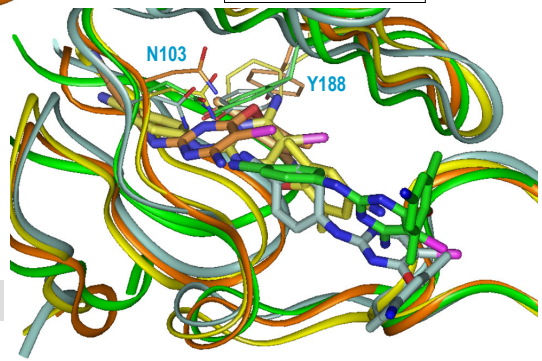
Balzarini et al. (2004)



0 ps → 250 ps → 290 ps → 500 ps

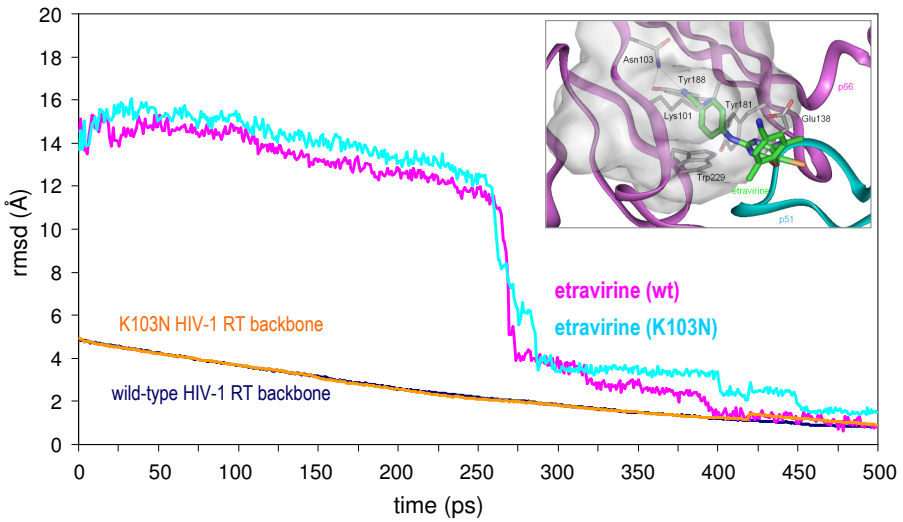
ETRAVIRINE





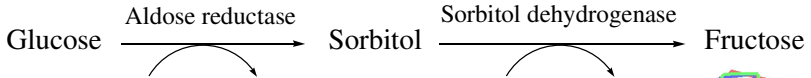
0 ps → 250 ps → 290 ps → 500 ps

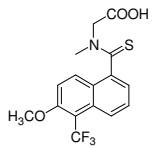
Time evolution of the mass-weighted root-mean-square deviation (rmsd) along the simulation time



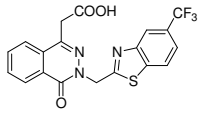
Rodríguez-Barrios, F.; Balzarini, J.; Gago, F. "The molecular basis of resilience to the effect of the Lys103Asn mutation in non-nucleoside HIV–1 reverse transcriptase inhibitors studied by targeted molecular dynamics simulations"
Journal of the American Chemical Society, 127(20): 7570-7578 **(2005)**

Inhibición de la Aldosa Reductasa como Diana para Prevenir las Complicaciones Diabéticas

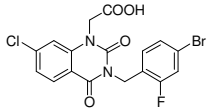




Tolrestat



Zopolrestat



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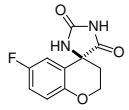
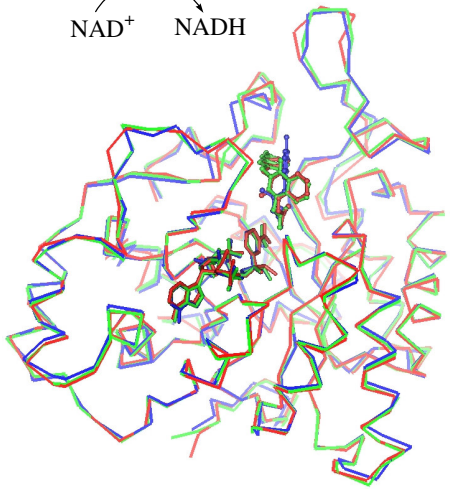
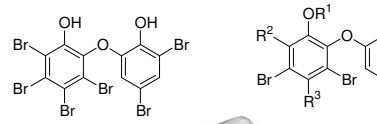


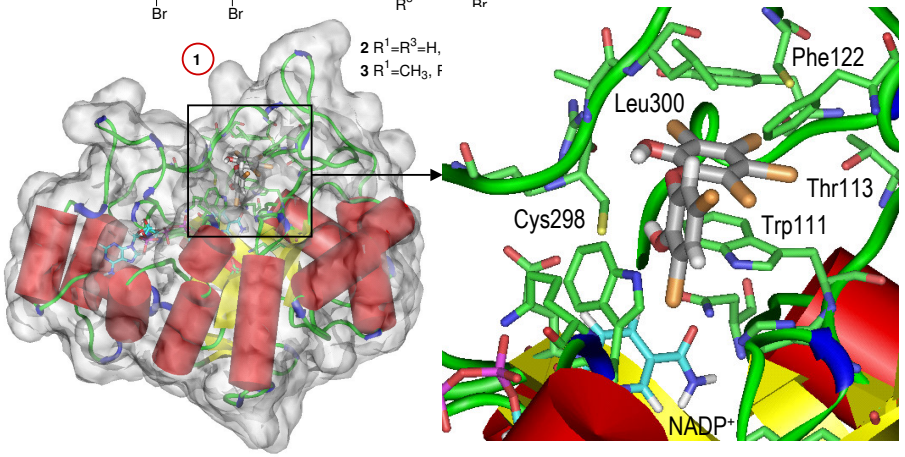
Sorbinil



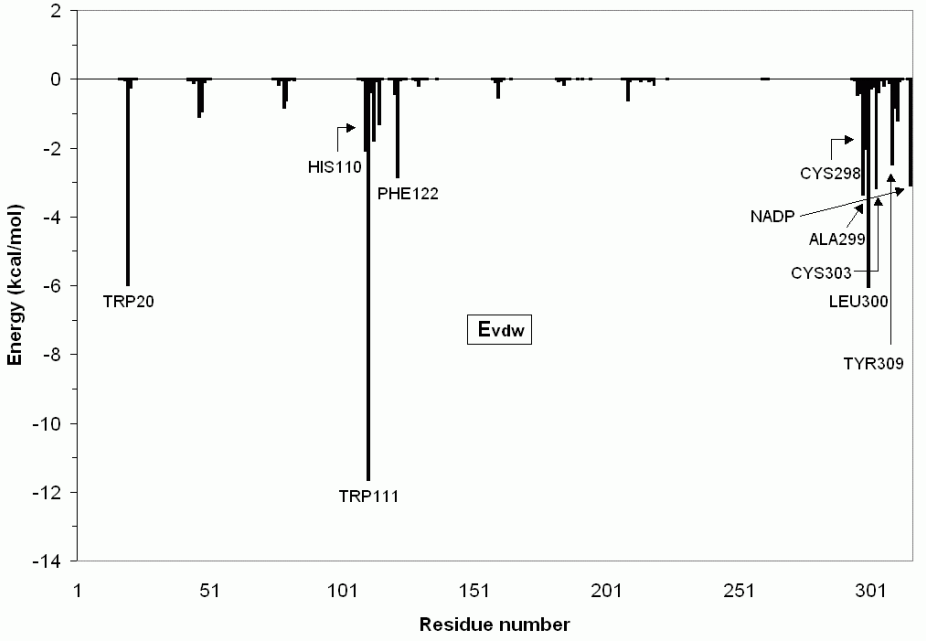
Synthesis, Activity, and Molecular Modeling Studies of Novel Human Aldose Reductase Inhibitors Based on a Marine Natural Product

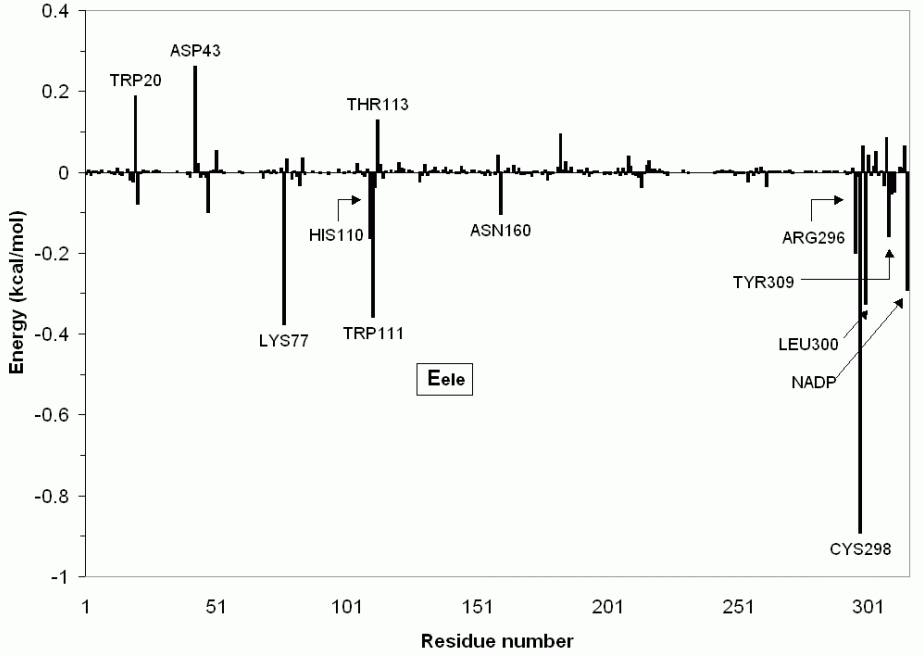


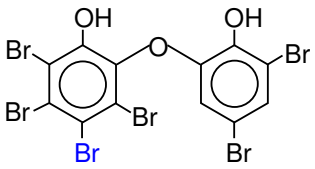
2 R^1=R^3=H,
3 R^1=CH_3, F



de la Fuente, J.A.; Manzanaro, S.; G. de Quesada, T.; Reymundo, I.; Luengo, S.M.; Gago, F. ***J. Med. Chem.*** 46: 5208-5221 **(2003)**



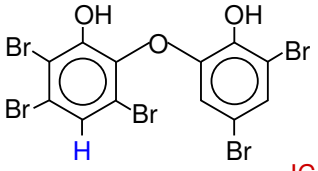




IC_{50} = 6.4 ± 1.1 μM

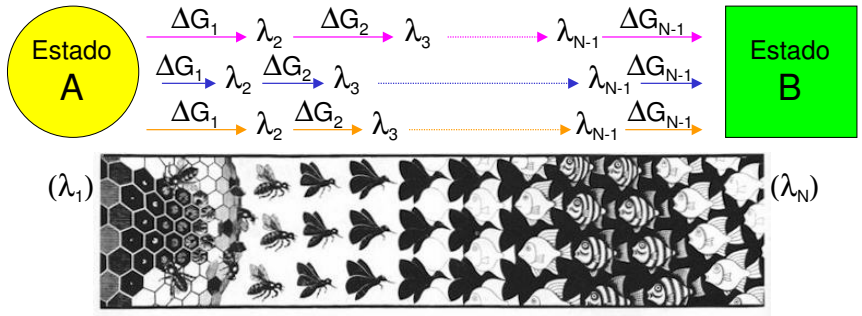
Metamorfosis
Magia de Escher"

Perturbación Energía Libre
"Alquimia Computacional"



IC_{50} = 25%

Perturbación Energía Libre

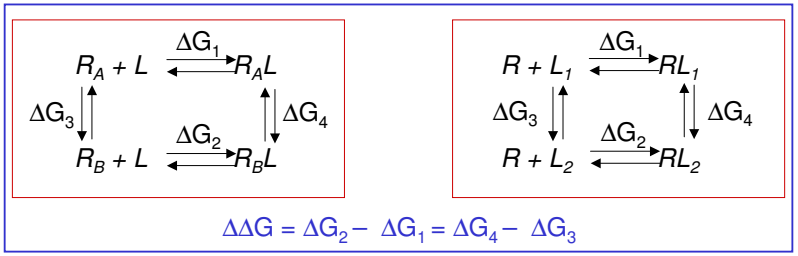


$$\Sigma\Delta G_i \text{ (ruta 1)} = \Sigma\Delta G_i \text{ (ruta 2)} = \Sigma\Delta G_i \text{ (ruta 3)}$$

$$G(\lambda) = -\,k\,T\,\ln\,\Delta(\lambda)$$

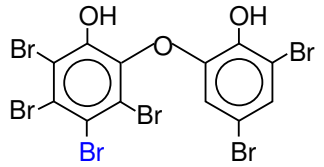
$$\Delta G_{BA} + \Delta G_{AB} = 0$$

Ciclos termodinámicos

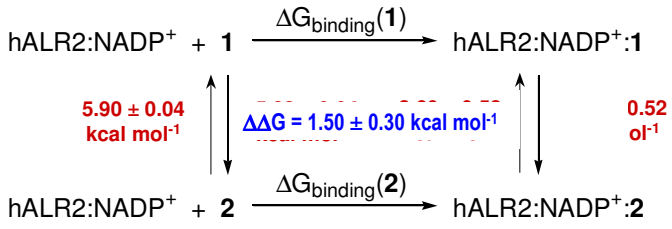


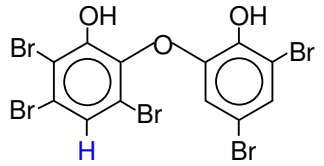
✓ La energía libre es una función termodinámica de estado: con tal de que el sistema cambie de forma reversible, el cambio en energía libre, ΔG, será independiente de la ruta.

✓ Si los procesos no físicos se simulan en condiciones idénticas, se pueden cancelar los errores inherentes a esta aproximación.



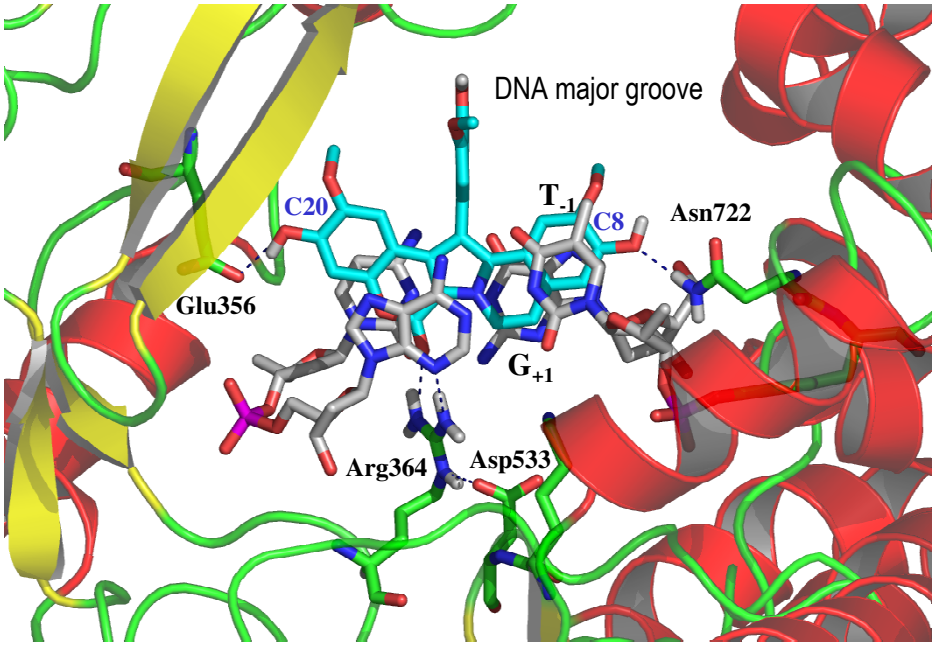
IC_{50} = 6.4 ± 1.1 μM



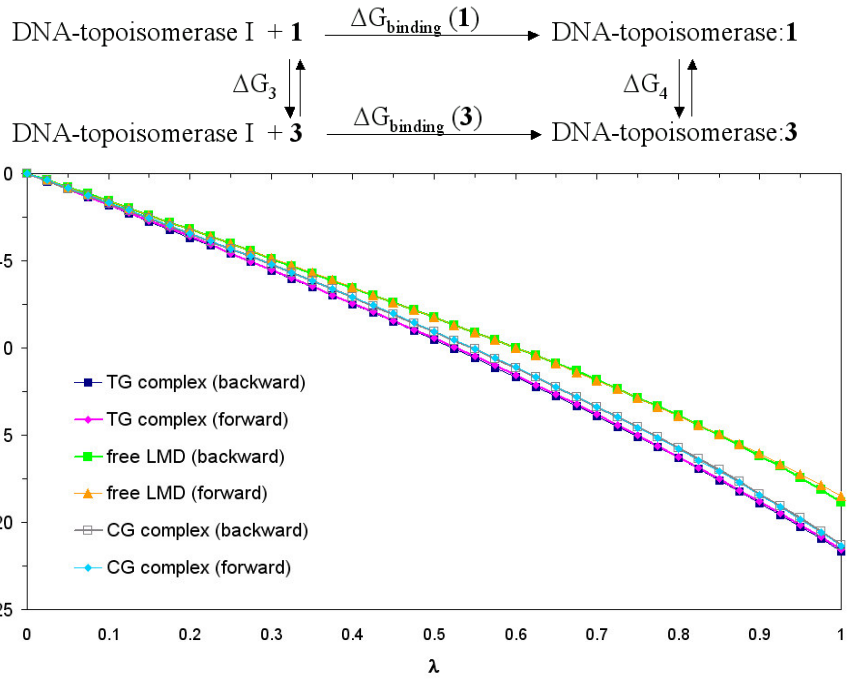


IC_{50} = 25%

de la Fuente et al. ***J. Med. Chem.*** 46(24): 5208-5221 **(2003)**

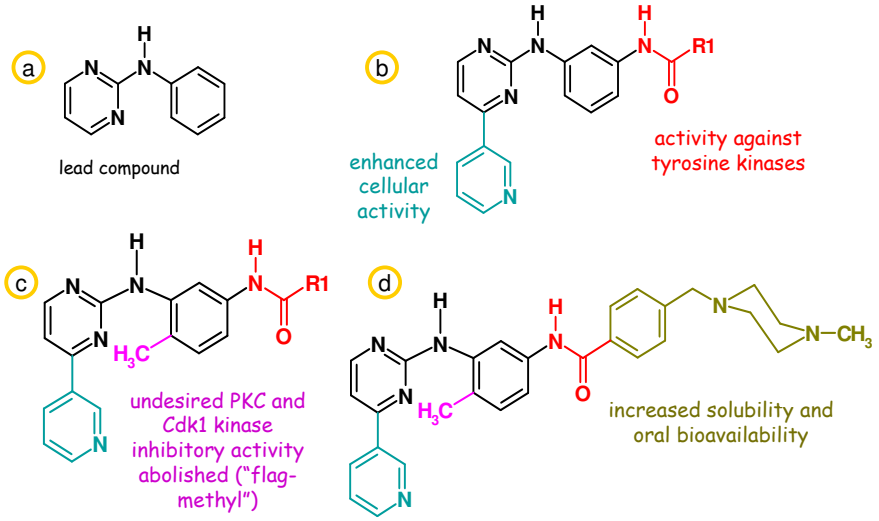


Marco, E.; Laine, W.; Tardy, C.; Lansiaux, A.; Iwao, M.; Ishibashi, F.; Bailly, C.; Gago, F. "Molecular determinants of topoisomerase I poisoning by lamellarins: comparison with camptothecin and structure-activity relationships" ***J. Med. Chem.*** 48(11): 3796-3807 **(2005)**

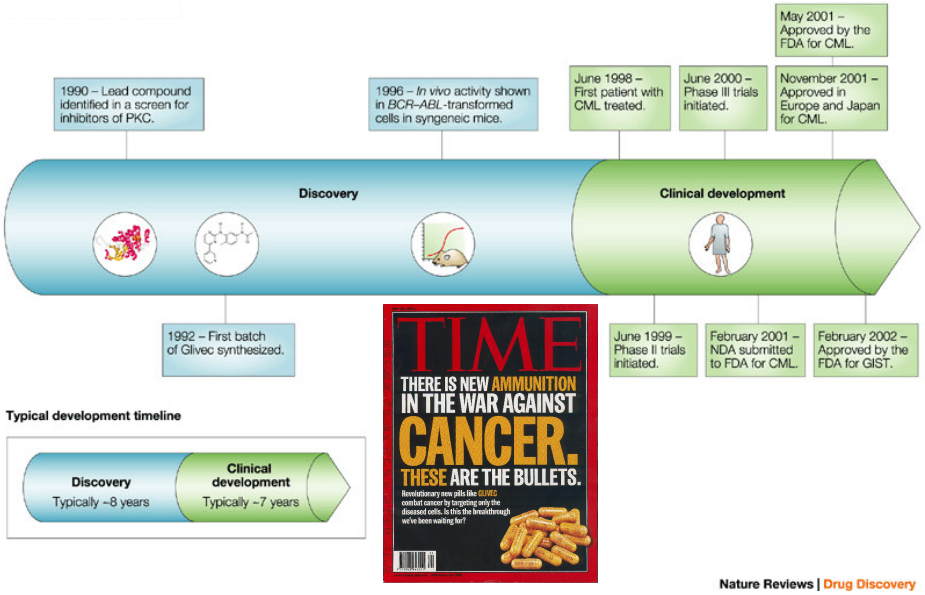


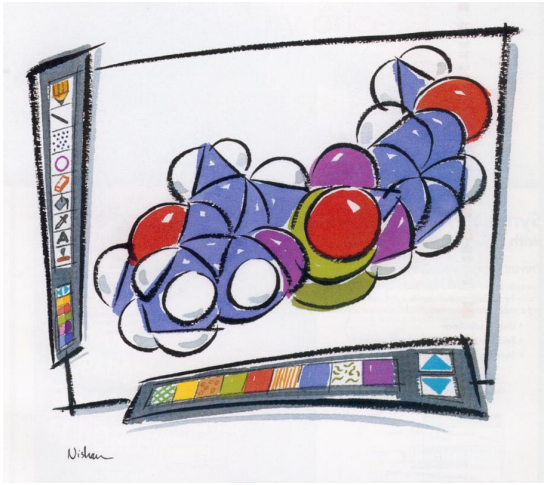
Glivec (STI571/ Imatinib):

a rationally developed, targeted anticancer drug



Glivec development timeline





PREGUNTAS, POR FAVOR

E-mail: federico.gago@uah.es