Quantitative Structure-Activity Relationships (QSAR)

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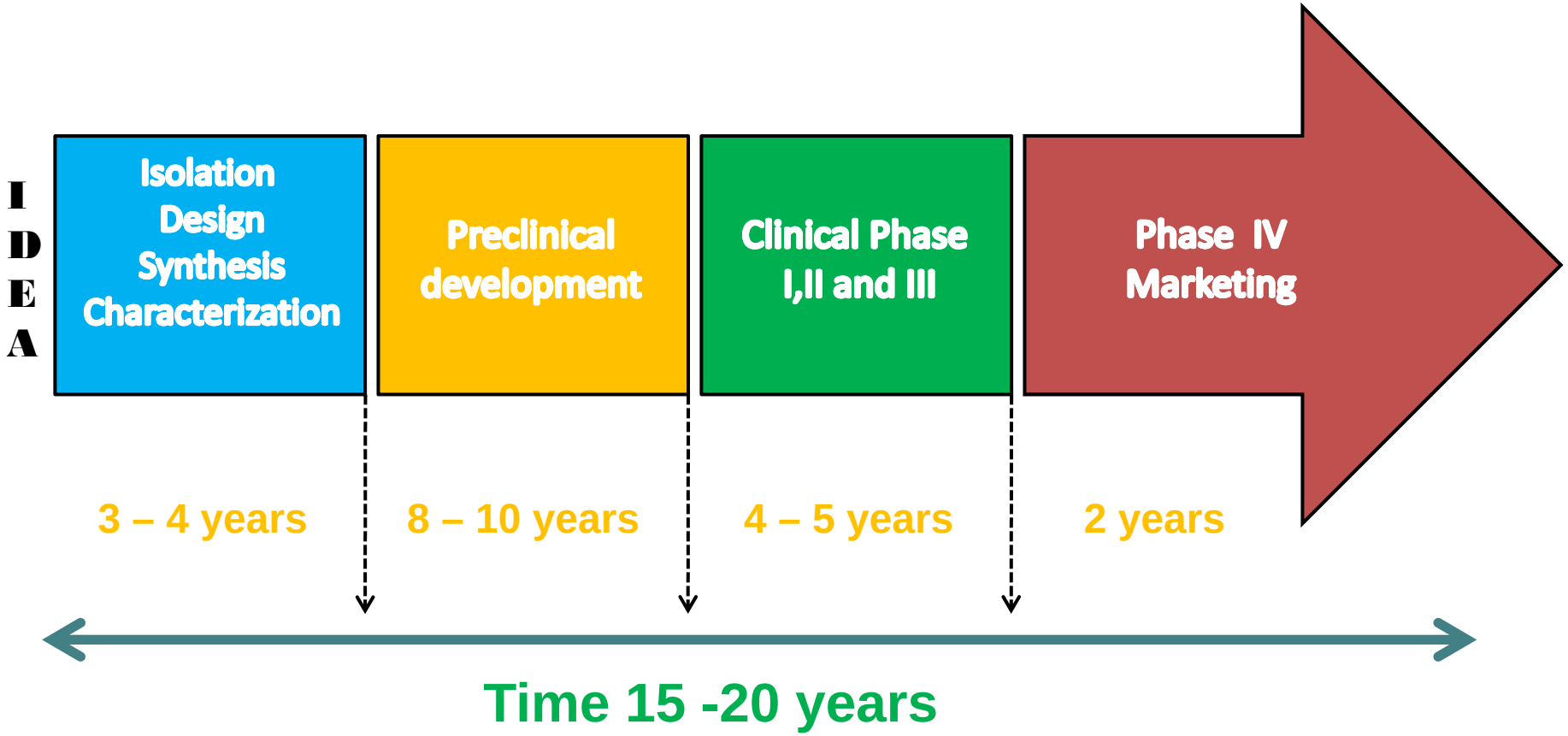
$$f(\text{biological activity}) = \text{electronic} + \text{hidrophobic} + \text{steric effects}$$

Quantitative structure-activity relationships (QSAR) represent an attempt to correlate structural or property descriptors of compounds with activities. These physicochemical descriptors, which include parameters to account for hydrophobicity, topology, electronic properties, and steric effects, are determined empirically or, more recently, by computational methods. Activities used in QSAR include chemical measurements and biological assays. QSAR currently are being applied in many disciplines, with many pertaining to drug design and environmental risk assessment.



Cost: 600 – 800 million dollars per molecule

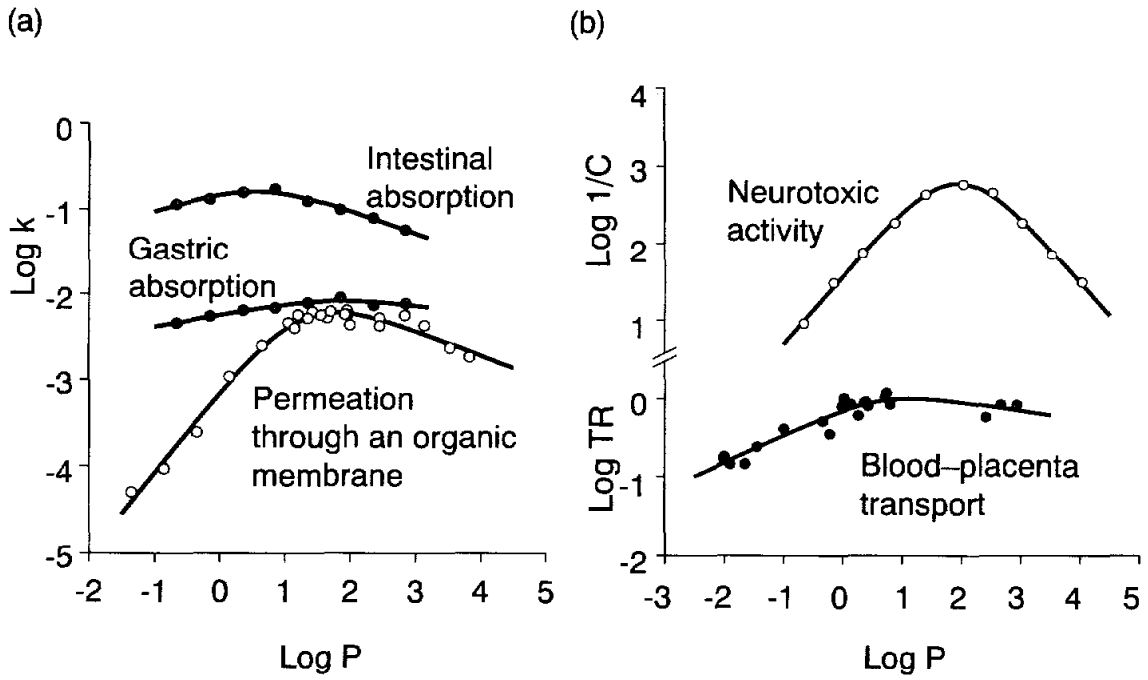
The objectives of QSAR

What can be achieved by correlation analysis?

Very much depends on the quality and quantitiy of data analyzed.

- ✓Prediction of Activity
- ✓Diagnosis of Mechanism
- ✓Classification
- ✓Optimization
- ✓Refinement of Synthetic Targets
- ✓Reduction and Replacement of Animals

Make drugs only as lipophilic as absolutely necessary



(a) The permeation of barbiturates form an aqueous phase through an organic membrane into another organic phase follows a nonlinear dependence on the lipophilicity of the compounds. Similar dependences are observed for the gastric and intestinal absorption rates of carbamates in the rat and for other absorption processes.

(b) The blood-brain barrier is permeable only for compounds with a certain lipophilicity. The neurotoxic activities of a series of homologous alcohols shows a nonlinear lipophilicity dependence, with a maximum near log P=2. The blood-placenta barrier shows a similar but slightly less pronounced lipophilicity dependence for a group of chemically different drugs

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Advantages and limitations of QSAR

- **As an instrument for prediction**

Estimation of physicochemical properties using substituent constants
Reduction of the number of compounds to be synthesized
Faster detection of the most favourable compound
Avoidance of synthesis of compounds with same activity

- **As a diagnostic instrument**

Information on possible types of interaction forces
Information on the 'nature' of the receptor
Information on the mechanism of action

- **Detection of exceptions (outliers)**

Modelos Estadísticos

Φ = *f* (constitution)

- **Hansch**

$$\text{Log } (1/C) = k_1\pi + k_2\sigma + k_3 Es + k_4$$

$$\text{Log } (P_x/P_H) = \pi$$

ATOMIC OR MOLECULAR PROPERTIES

- **Análisis Free-Wilson (1964)**

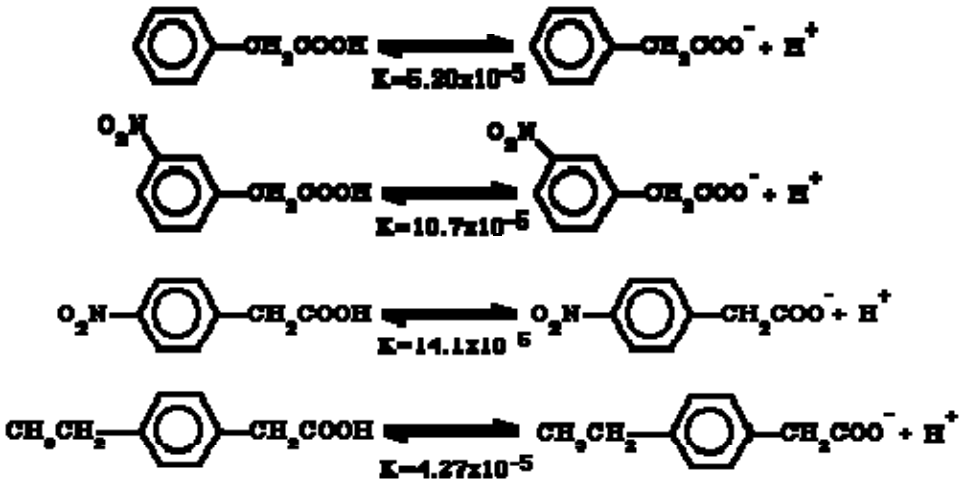
$$BA = \Sigma A_{ij} * S_{ij} + k$$

STRUCTURAL CHARACTERISTICS

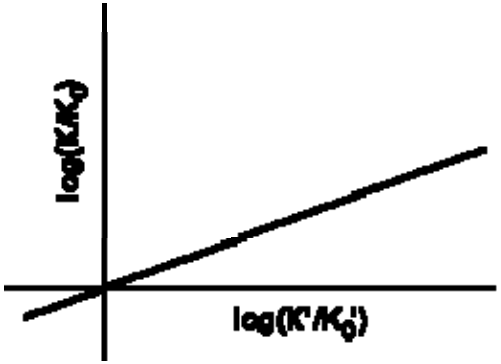
- **Fujita y Ban (1971)**

Combination of Hansch and Free-Wilson analysis

Substitution of BA by log (1/C) ⇒ LFER



Electron-withdrawal by the nitro group increases dissociation, with the effect being less for the meta than for the para substituent, just as was observed with benzoic acid. The electron-donating ethyl group decreases the equilibrium constant, as would be expected.



Example of a graph for a linear free energy relationship. K_0 or $K_{0'}$ represent equilibrium constants for unsubstituted compounds and K or K', for substituted compounds. Values for the abscissa are calculated from the dissociation constants of unsubstituted and substituted benzoic acid. Values for the ordinate are obtained from another organic acid or base with identical patterns of substitution, in this case phenylacetic acid.

$$\log \frac{K}{K_0} = \rho \log \frac{K'}{K_0'}$$

$$\log \frac{K}{K_0} = \rho\sigma$$

Modelos Estadísticos

$\Phi = f$ (constitution)

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$$\text{Log } (P_x/P_H) = \pi$$

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Representative list of common descriptors used in quantitative structure–property relationship (QSAR) studies

Solubility
Molar solubility (S)
Mole fraction solubility (X)
Activity coefficients (Log γ_w)
Hildebrand solubility paramters (δ_H)

Lipophilic
Log Po/w
Log D
Rm (TLC)
Log k', LogK_w (RPLC)
Hansch substituent constant (π)
Rekker's fragmental constant (f)

Electronic
Ionization constant (pKa)
Hammett constant (δ)
Taft polar constant (δ^*)
Taft inductive and resonance components (δ_1, δ_R)
Dipole moments
Hydrogen bonding parameters

Steric
Taft steric parameter (Es)
Molar refractivity (MR)
Parachor
Charton steric parameter (ν)
van der Waal's parameters

Constitutional
Total number of atoms
Number of individual types of atoms
Total number of bonds
Number of individual types of bonds
Number of rings
Molecular weight
Average atomic weight

Topological
Wiener index (W)
Randic indices
Kier and Hall connectivity indices (^{X})
Kier shape indices
Kier flexibility index
Balaban index (J)
Information content (IC) indices
Kappa shape indices
Topological complexities
Eccentric connectivity index
Detour index

Geometrical
Principle moments of inertia
Molecular volume
Molecular surface area
Shadow indices
Solvent accessible molecular surface area
Gravitation index

Electrostatic
Maximum and minimum partial charges in the molecule
Polarity paramters
Charged partial surface area (CPSA) descriptors

Quantum-Chemical
Charge distribution-related descriptors
HOMO-LUMO energies
Orbital electron densities
Superdelocalizabilities
Atom–atom polarizabilities
Molecular polarizabilities
Quantum molecular energies

Miscellaneous
Chemical shifts: ^1H, ^{13}C (δ_{ppm})
IR frequencies (ν)
Surface tension

Physicochemical and biological properties employed in quantitative structure-property relationship (QSAR) studies

Physicochemical

Organoleptic properties
Boiling point
Dissociation constant
Viscosity
Melting point
Molar volume
Diffusion coefficient
Partition coefficient
- Octanol–water
- Air–water

Reactivity
Release characteristics
Solubility
Stability
Transportability
Vapour pressure
Chromatographic retention time and response factors

Biological

Activity
Acute toxicity (LD50)
Alkylating profile (with DNA)
Bioconcentration
Biodegradation
Carcinogenicity
Chronic toxicity
Inhibitor constant
Metabolic profile
Michaelis constant
Mutagenicity
Penetration through skin
Pharmacokinetics
Receptor binding

Statistical and non-statistical techniques employed in quantitative structure-property relationship (QSAR) studies

- Multiple linear regression analysis (MLRA)
- Free–Wilson analysis
- Cluster analysis
- Pattern recognition
- Factor analysis
- Discriminant analysis
- Principal component analysis (PCA)
- Partial least square (PLS) analysis
- Comparative molecular field analysis (CoMFA)
- Artificial neural networks (ANN)
- Evolutionary algorithms, such as genetic function approximation (GFA)

Regression Analysis

- **Mathematically exact procedure** for the treatment of data with experimental errors (cf. mean value, standard devation).

Minimization of the **sum of squared errors** (= squared deviations between y_i and y_{calc}) produces the **best fit** of the observed values to a certain model.

- **Regression analysis describes the relationship between:**
- **independent variables x_i** (definition: can be determined without experimental error), and
- **dependent variables y_i (contain experimental error).**

- **Hypothesis:** there is a significant relationship (95% level) between x_i and y_i values: **yes / no**

F test for overall significance

t tests for individual significances in multiple regression.

Formulas and Meaning of Statistical Parameters

Correlation coefficient r (relative quality of fit)

$$r^2 = 1 - \Sigma\Delta^2/S_{yy}$$

Standard deviation s (absolute quality of fit)

$$s^2 = \Sigma\Delta^2/(n - k - 1)$$

F test (Fisher value; level of statistical significance)

$$F = r^2.(n - k - 1)/(k.(1 - r^2))$$

Confidence intervals of $k_i \pm s.t.\sqrt{c_{ii}}$

C = molar concentration that causes a certain biological effect

Values of the regression coefficientes

Intervalo de confianza al 95 % de los coeficientes y de la constante

$$\text{Log } 1/C = 1.15\ (\pm 0.2)\ \pi - 1.46\ (\pm 0.4)\ \sigma + 7.82\ (\pm 0.2)$$

Logarithms of reciprocal values are the correct scaling

Lipophilicity parameter

Parámetro electrónico

Término constante

$$n = 22;\ R^2 = 0.945;\ s = 0.196;\ F = 78.6;\ R^2adj = 0.870$$

Number of compounds

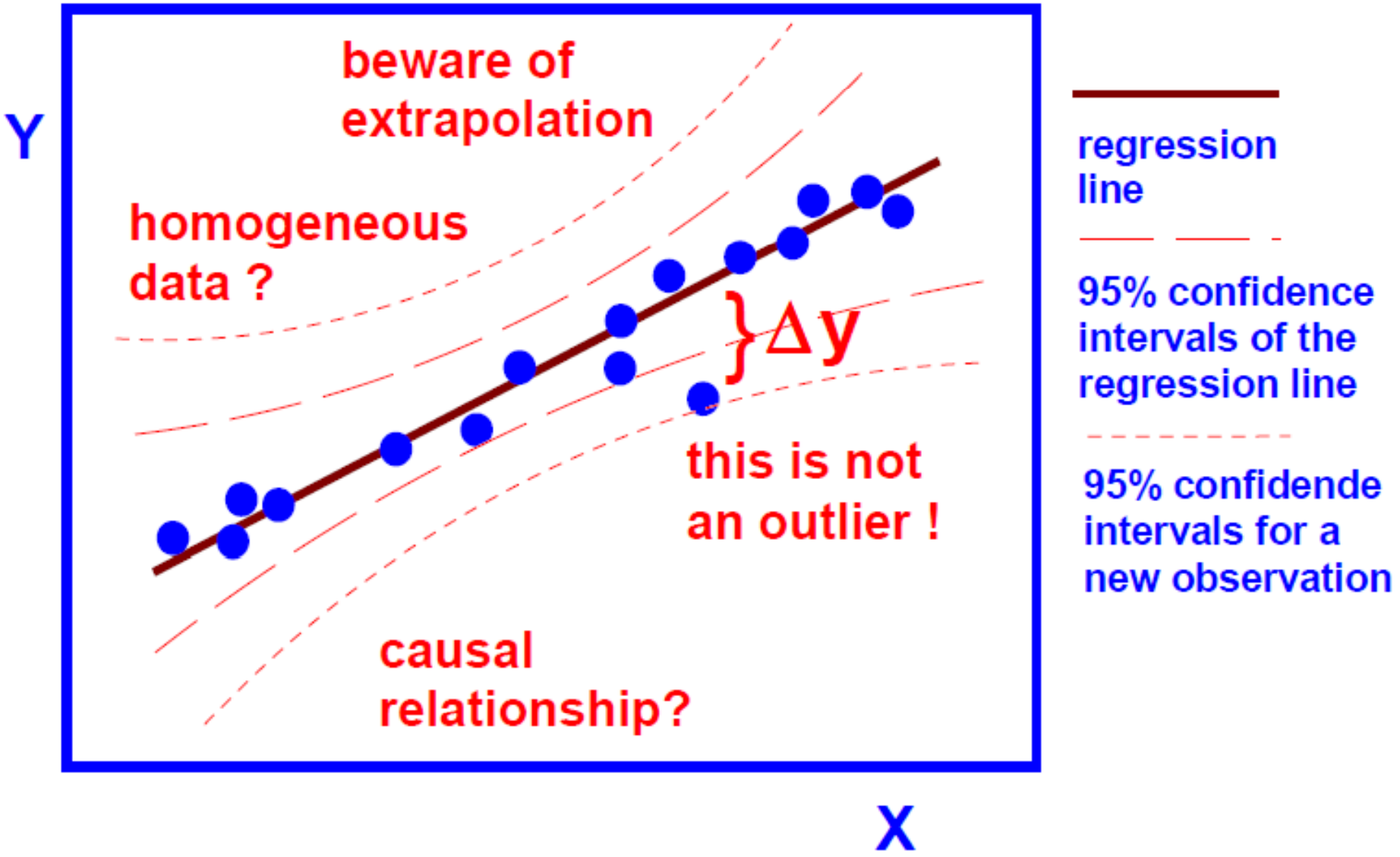
correlation coefficient r; measure of the relative queality of a model

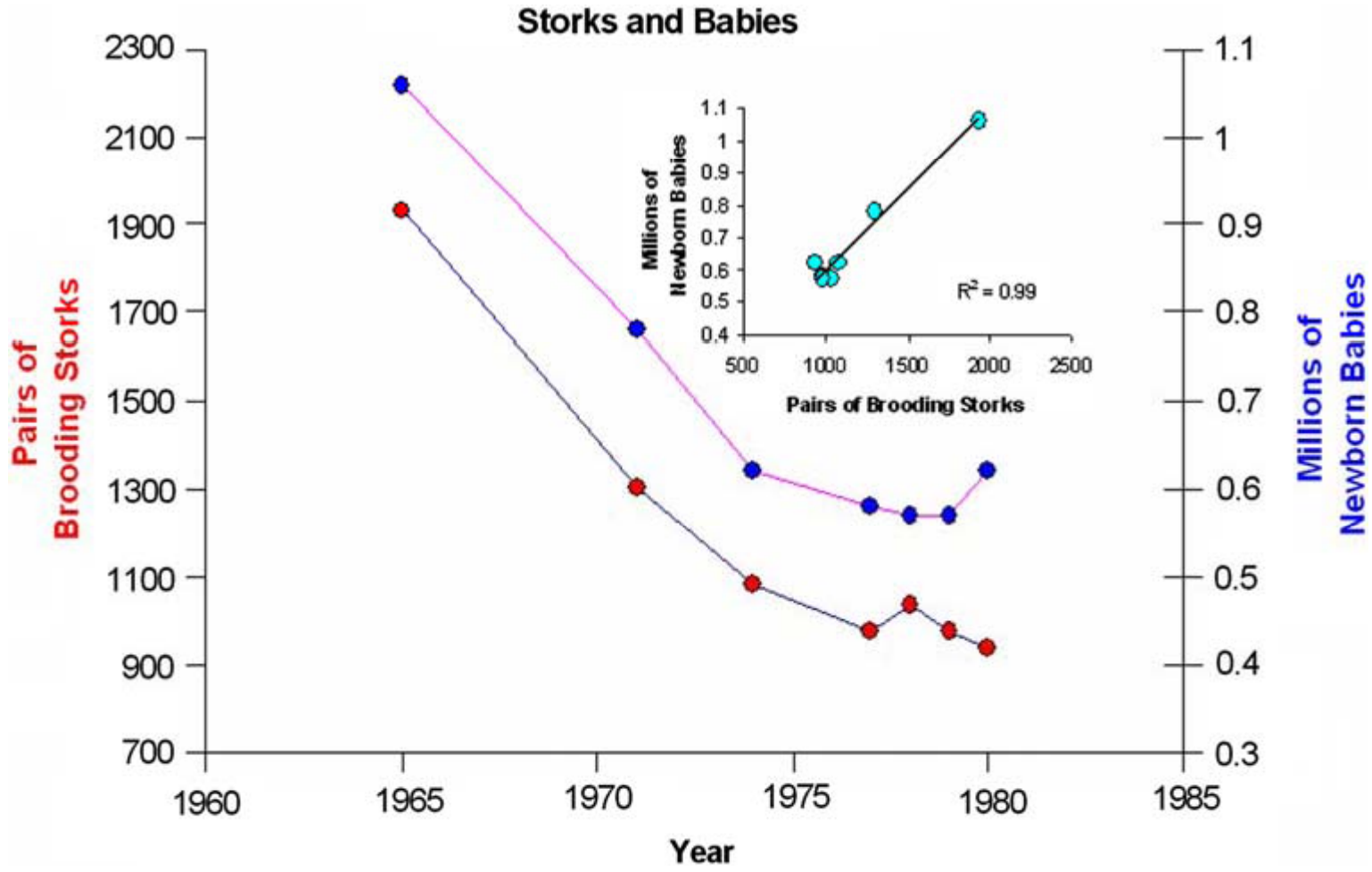
Standard deviation s; measure of the absolute quality of a model

Fisher value; measure of the statistical significance

R^2 adj = measure of internal predictivity.

Regression Analysis - A Common QSAR Tool





J Comput Aided Mol Des (2008) 22:81–89

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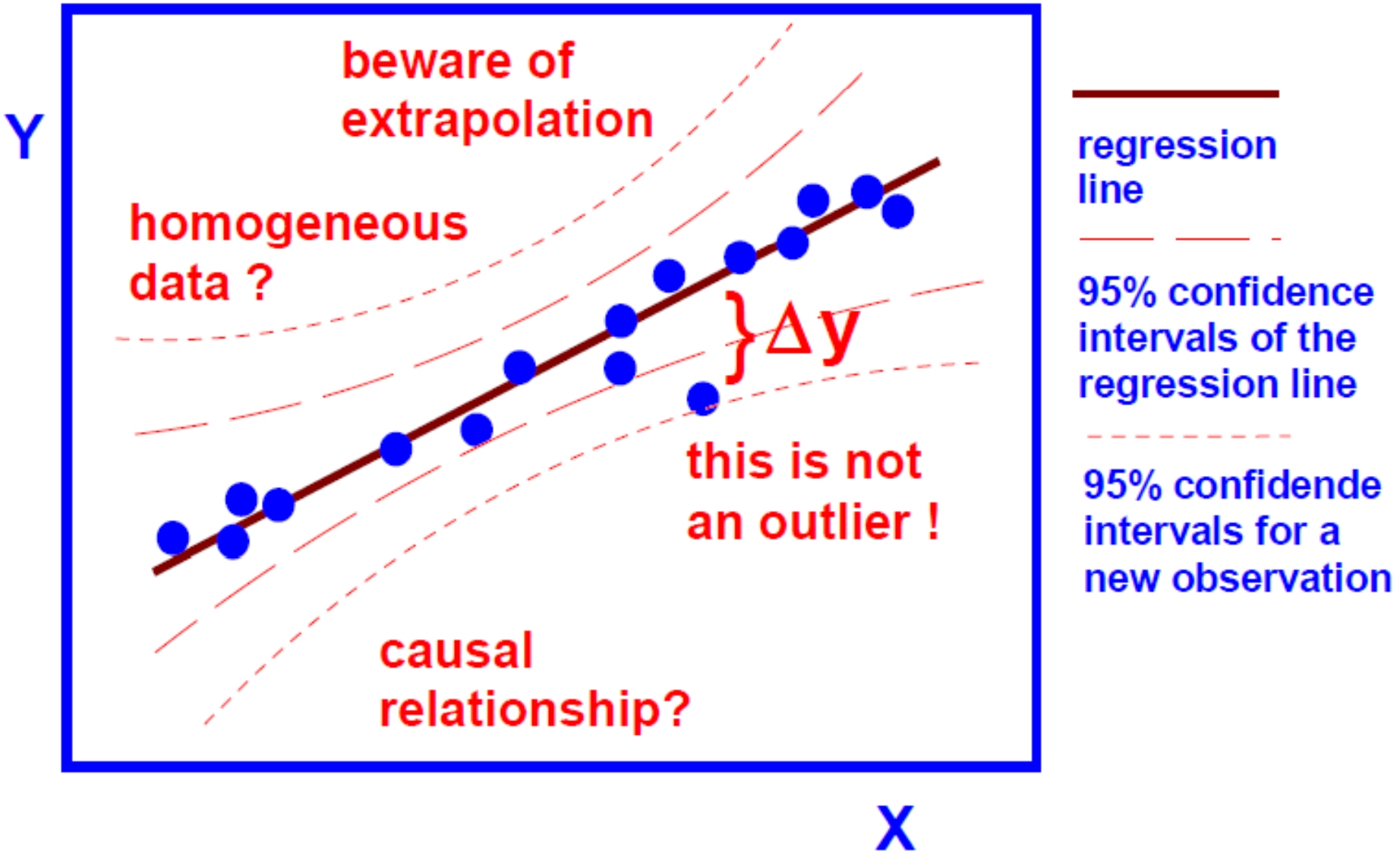
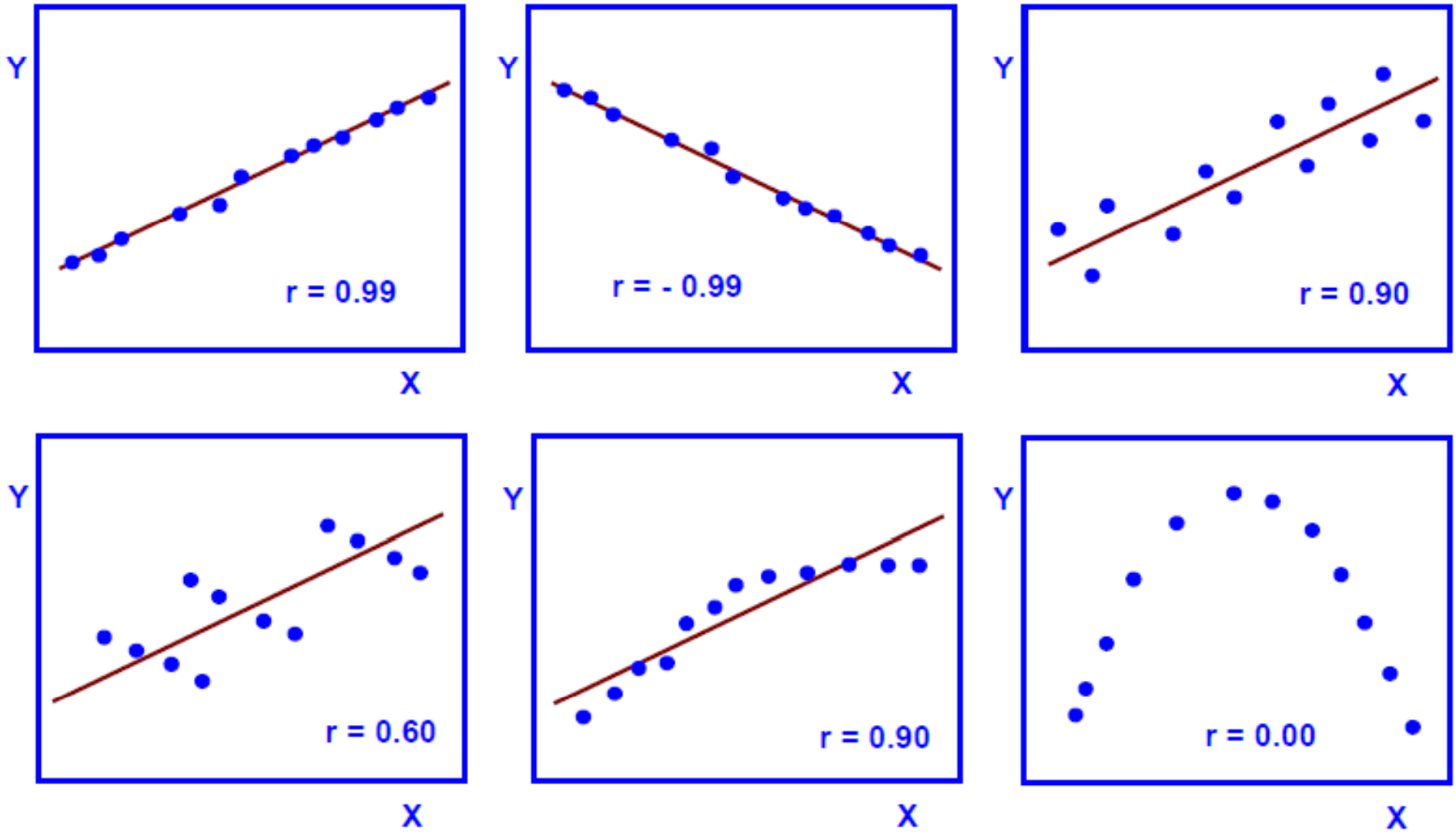


The most important is a graphical analysis of the data!



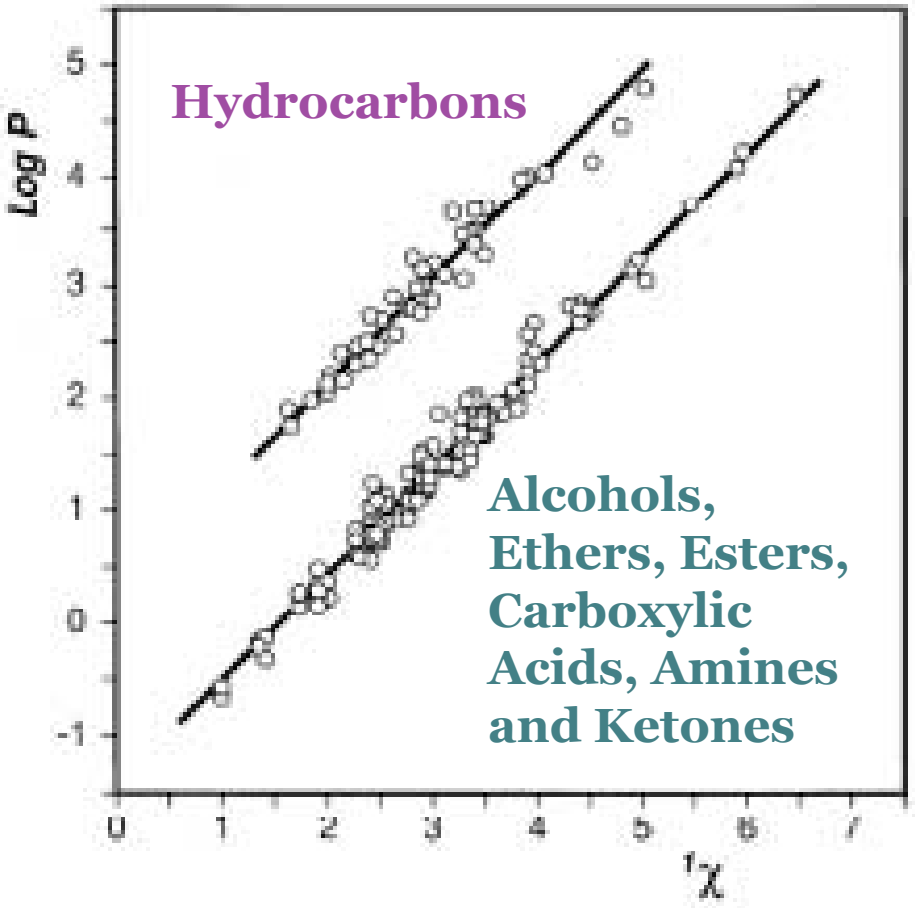
A Diagram Tells You More Than Thousand Equations

183 Hydrocarbons, Alcohols, Ethers, Esters, Carboxylic Acids, Amines and Ketones

MR *vs.* $^{1}\chi$	*r = 0.908; s = 0.380; F = 855.26*
MR *vs.* $^{2}\chi^{v}$	*r = 0.826; s = 0.419; F = 389.58*
log P *vs.* $^{1}\chi$	*r = 0.719; s = 0.632; F = 193.36*
log P *vs.* $^{2}\chi^{v}$	*r = 0.635; s = 0.574; F = 122.33*

Log P = 0.941 (±0.02) $^{1}\chi$ - 1.693 (±0.05) I + 0.244 (±0.08)
(n = 183; r = 0.990; s = 0.150; F = 4,633)

A diagram tells you more than thousand equations



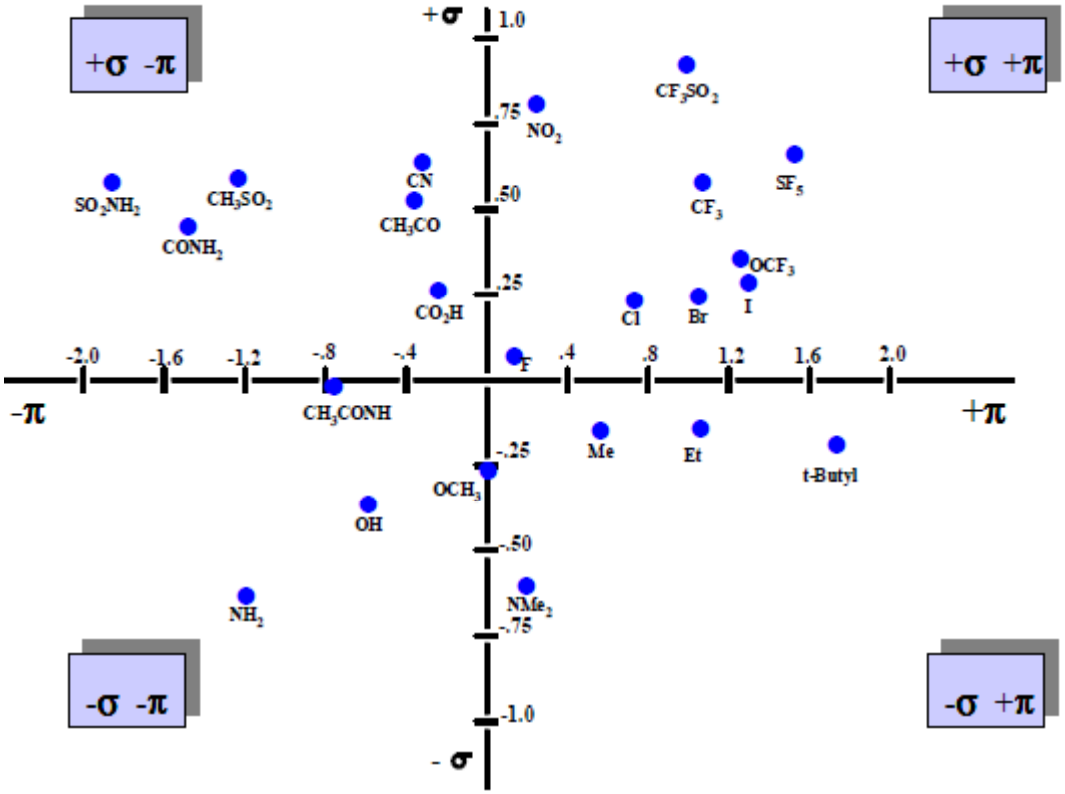
Log P vs. $^1\chi$ and I

Log P = 0.941 (±0.02) $^1\chi$ - 1.693 (±0.05) I + 0.244 (±0.08)

n = 183
r = 0.990
s = 0.150
F = 4,633

Anil K. Saxena, Quant. Struct.-Act. Relat. 14, 142-150 (1995)

Craig Diagram (P. Craig, J. Med. Chem. 14, 680 (1971))



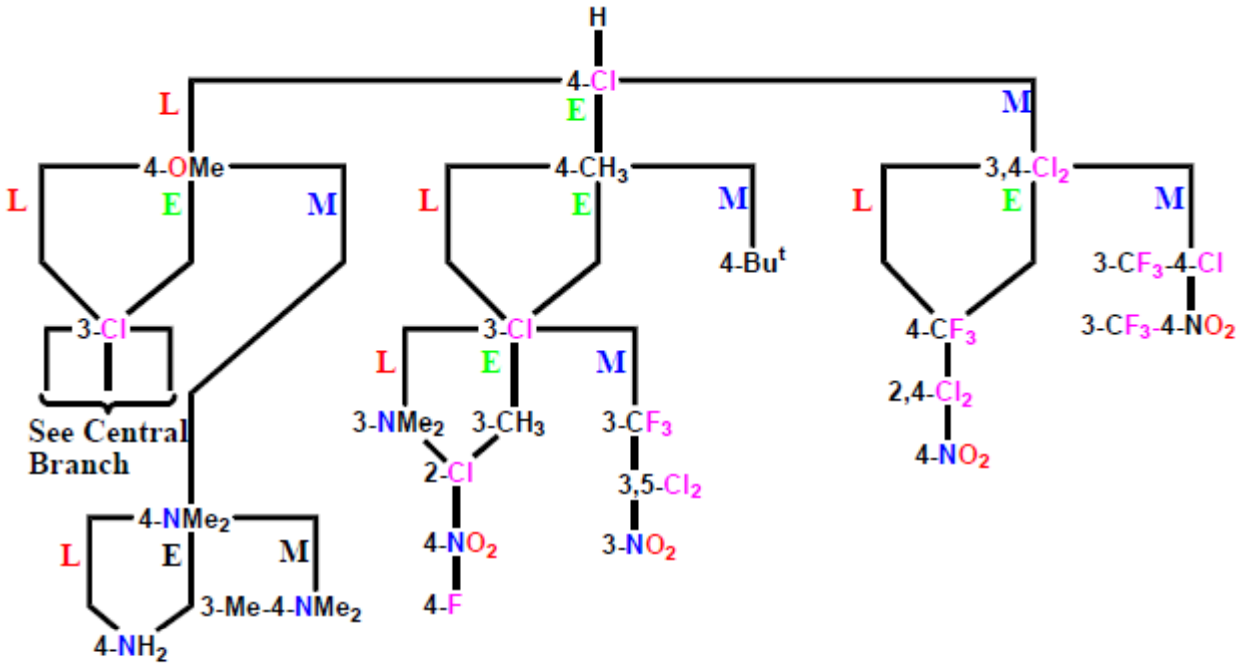
Allows an easy identification of suitable substituyents for QSAR analysis.

- Two relevant properties should be incluyed
- Selection of a substituent per quadrant in order to guarantee the orthogonality.
- Selection of a suitable range of values per properties

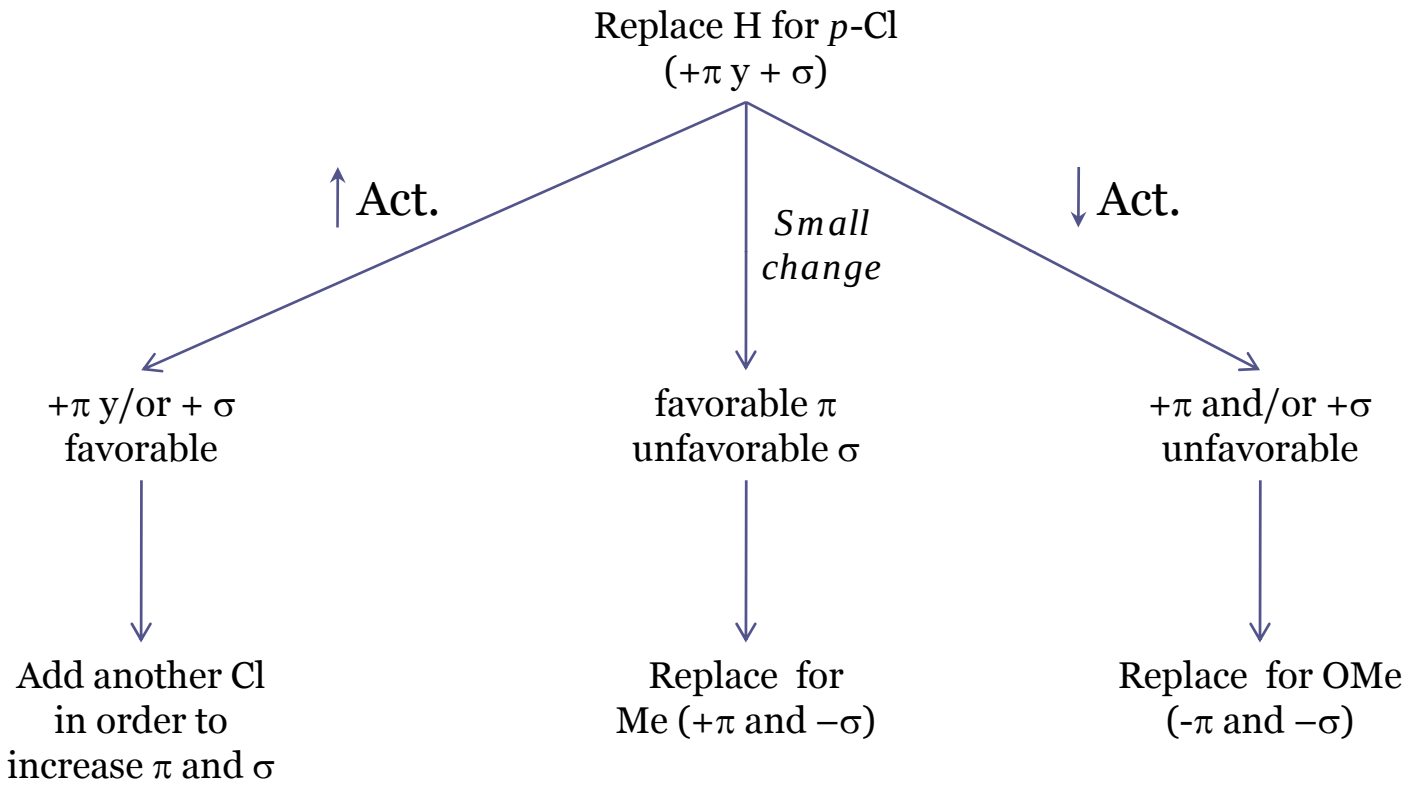
Topliss scheme J. Topliss, J. Med. Chem. 15, 1007 (1972)

Employed to decide the suitable substituents to optimize the products one by one when the synthesis is complex and slow

Example: aromatic substituents

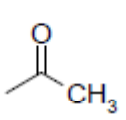
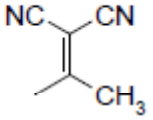
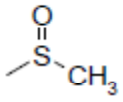
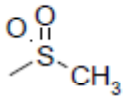
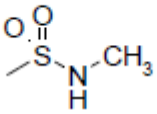
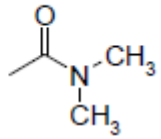


Topliss scheme



Additional possible changes are suggested on the basis of π, σ and steric effects variations

Bio-isosters

Sustituyente						
π	-0.55	0.40	-1.58	-1.63	-1.82	-1.51
σ_p	0.50	0.84	0.49	0.72	0.57	0.36
σ_m	0.38	0.66	0.52	0.60	0.46	0.35
MR	11.2	21.5	13.7	13.5	16.9	19.2

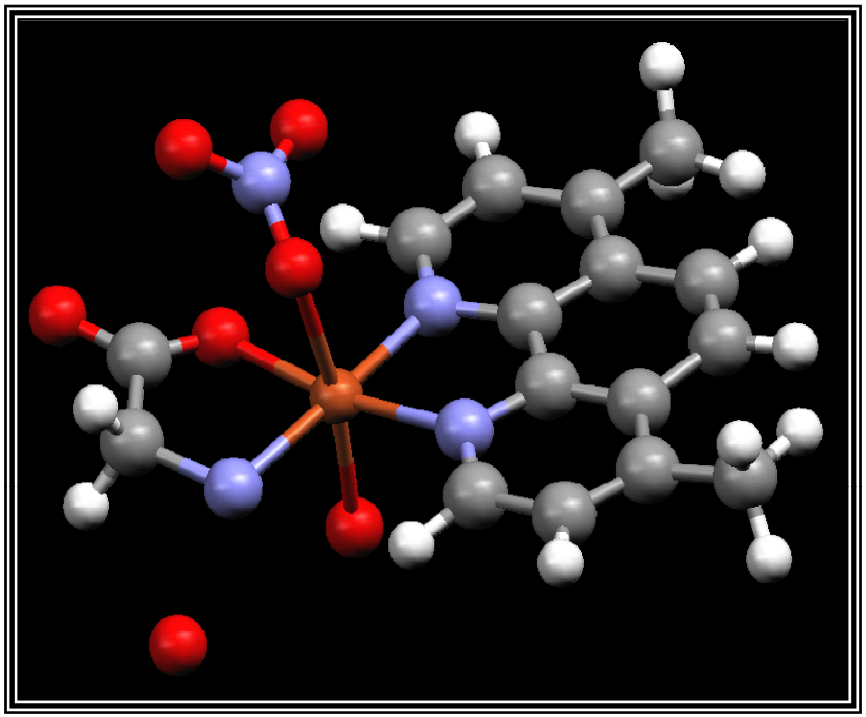
Groups with similar physical or chemical properties which produce broadly similar biological properties to a chemical compound.

The purpose of exchanging one bioisostere for another is to enhance the desired biological or physical properties of a compound without making significant changes in chemical structure.

Reduce toxicity or modify the activity of the lead compound, and may alter the metabolism of the lead.

Also is possible to choose bioisosters based on the most important property.

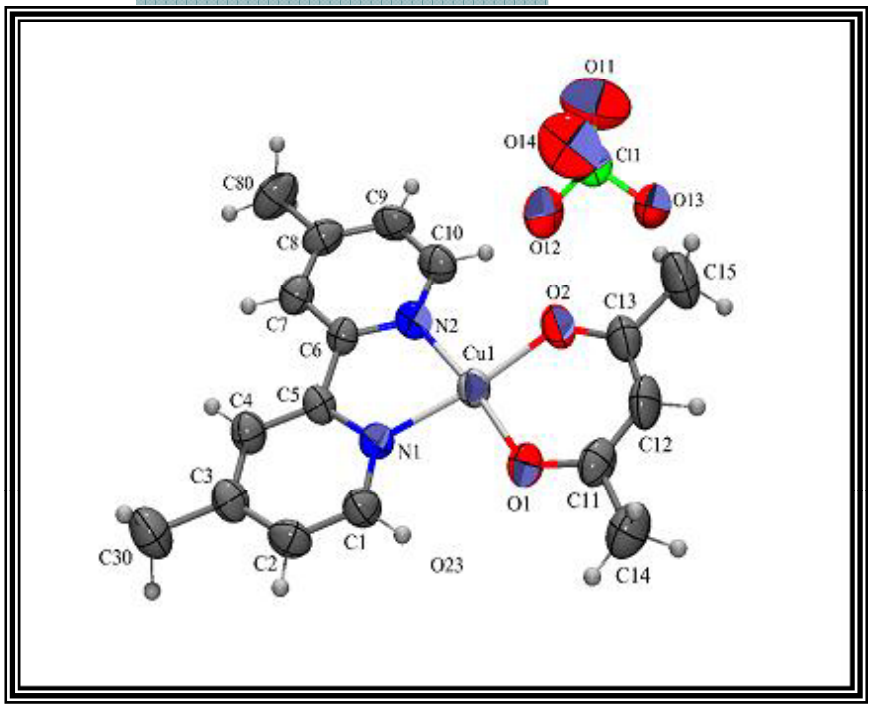
(ej. COMe y SOMe have similar $\sigma\pi$; SOMe y SO2Me have similar π)



Casiopeína II-gly

[Cu(4,7-dimetil-1,10-fenantrolina)(gli)]NO_3

Acta Cryst. (**1993**), C49, 890-893



Casiopeína III-Ia

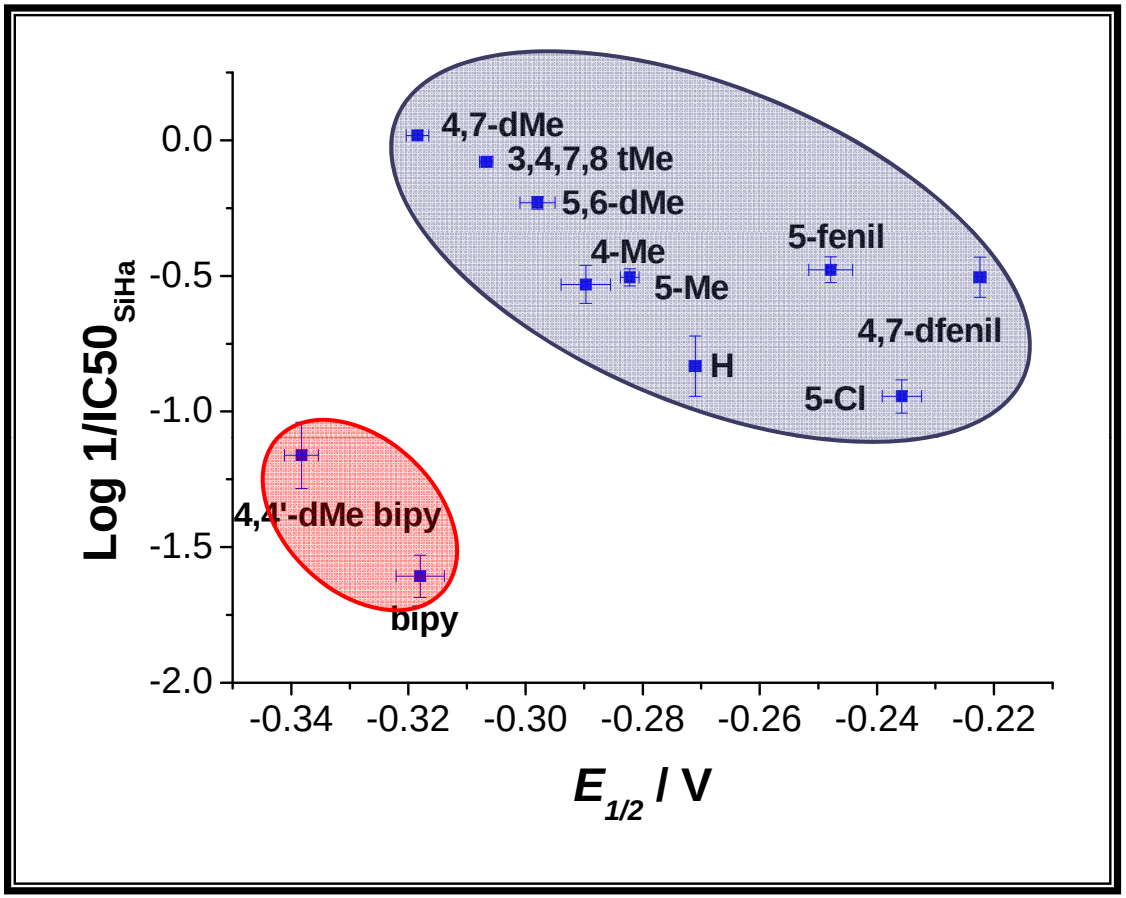
[Cu(4,4'-dimetil-2,2'-bipiridina)(acac)]NO_3

J. Journal of Inorganic Biochemistry 98 (**2004**) 1045-1053.

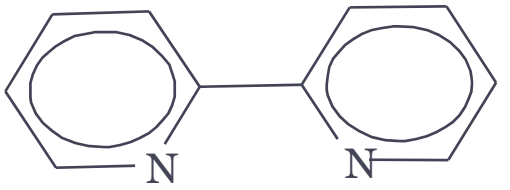
f(biological activity) = Electronic + Hidrofobic + Steric effects

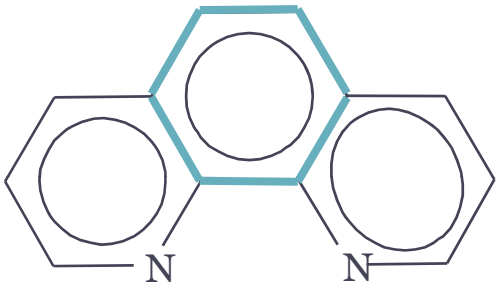
f(antiproliferative activity) = $E_{1/2}$ + Log $D_{o/w}$ + ?

INFLUENCIA DEL LIGANTE DIIMINA.



Actividad antiproliferativa del grupo de complejos con ligante secundario acetilacetonato en la linea celular SiHa (Log 1/IC50 SiHa) contra $E_{1/2}$ para el par *CuI/CuII* estandarizado contra el par Ferroceno/Ferricinio.





Variable indicadora $I_{N\text{-}N}$

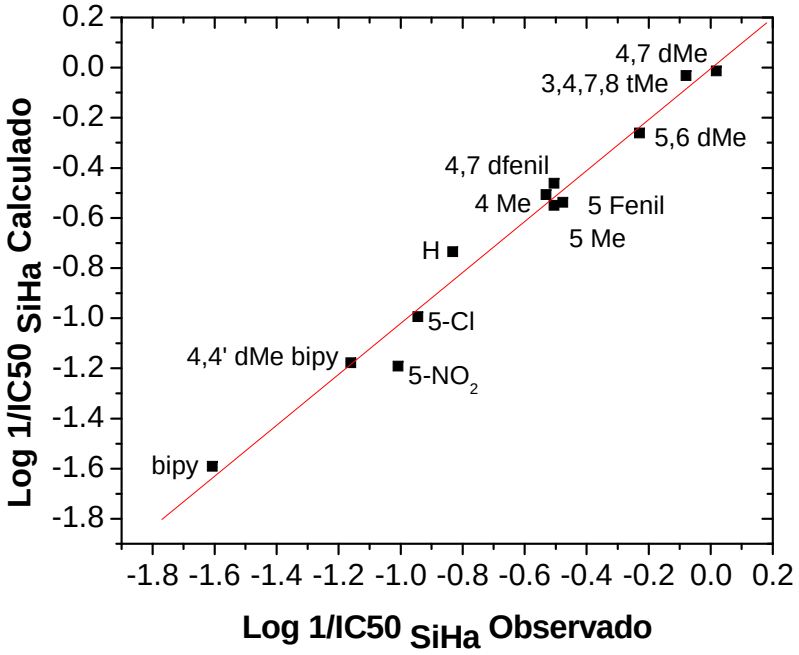
Fenantrolina = 1

Bipiridinas = 0

Influencia del ligante diimina

$$\text{Log } 1/IC50_{\text{SiHa}} = -4.94(\pm 0.56) + 1.35(\pm 0.11)\boldsymbol{I}_{\boldsymbol{N\text{-}N}} - 0.72(\pm 0.09)pE_{1/2} + 0.39(\pm 0.07)\ \text{Log D}$$

$$R^2 = 0.9893,\ R^2_{adj} = 0.9847,\ sd = 0.0597,\ F = 214.87,\ n = 11$$



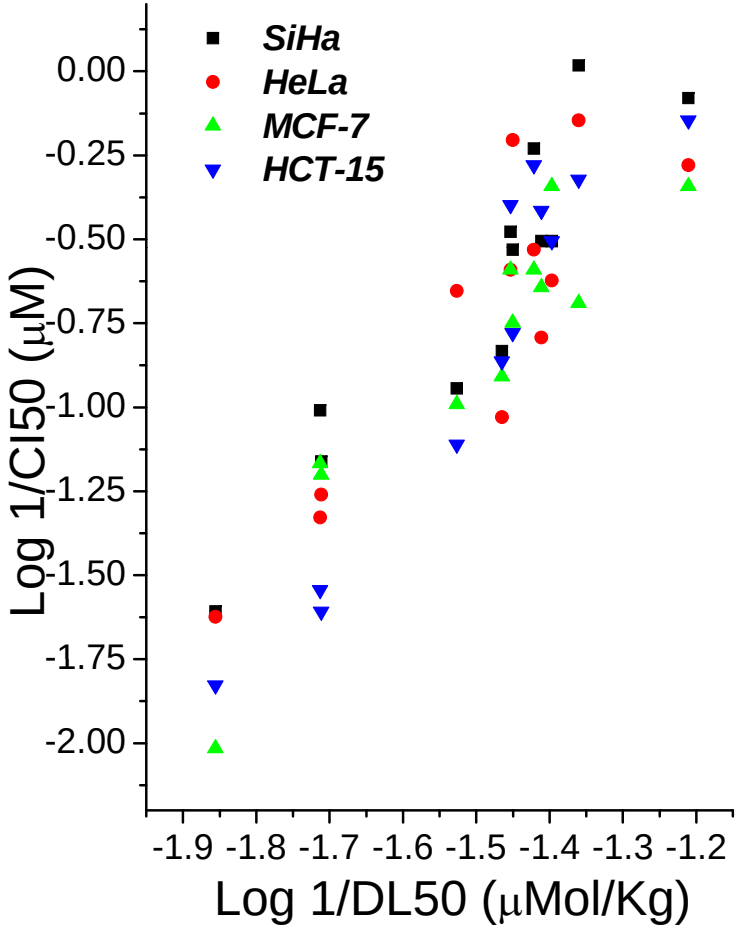
Log 1/IC50 SiHa calc =
1.01599 Log 1/IC50 SiHa obs – 0.00468

R = 0.9894
Sd = 0.0739
N = 12
P < 0.0001

Influencia del ligante diimina

Log 1/C	Intercept	$I_{N\text{-}N}$	$pE_{1/2}$	Log D	n = 11
HeLa	-3.78(±1.71)	+1.19(±0.41)	-0.47(±0.33)	+ 0.23(±0.26)	R^2= 0.8262, R^2_{adj} = 0.7517, sd = 0.2263, F = 11.09,
SiHa	-4.94(±0.56)	+ 1.35(±0.11)	- 0.72(±0.09)	+ 0.39(±0.07)	R^2= 0.9893, R^2_{adj}= 0.9847, sd = 0.0597, F = 214.87,
MCF-7	-3.37(±1.31)	+ 1.08(±0.32)	- 0.40(±0.25)	+ 0.42(±0.20)	R^2= 0.9046, R^2_{adj}= 0.8636, sd = 0.1742, F = 22.11, n = 11
HCT-15	-4.57(±1.18)	+ 1.49(±0.29)	- 0.59(±0.23)	+ 0.39(±0.18)	R^2 = 0.9449, R^2_{adj}= 0.9212, sd = 0.1565, F = 39.98, n=11
DL50	-2.63(±0.49)	+ 0.47(±0.12)	– 0.17(±0.09)	+ 0.11(±0.07)	R^2 = 0.9373, R^2_{adj}= 0.9104, sd = 0.0519, F = 34.87,

TOXICIDAD AGUDA (DL50) Vs. CONCENTRACIÓN INHIBITORIA 50 (CI50)



Toxicidad aguda (DL50 (μmol/kg) en ratones macho ICR.) vs. Concentración inhibitoria (IC50 (μM)) en HeLa, SiHa, MCF-7 y HCT-15: $IC50_{línea\ celular} = mLD50 + b$. (R), Coeficiente de correlaciónt; (SD), Desviación estándar; (n), numero de puntos en la curva; y (P), Valor de P para la prueba *t* de pendiente = 0.

Cell line	*m*	*b*	R	SD	n	P
HeLa	0.72	-14.78	0.96	3.73	12	<0.0001
SiHa	0.64	-13.68	0.92	4.54	12	<0.0001
MCF-7	0.41	- 5.64	0.95	1.54	11	<0.0001
HCT-15	1.31	-29.46	0.98	4.08	12	<0.0001

Regresar

Influencia del ligante diimina

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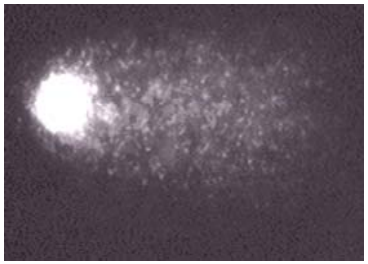
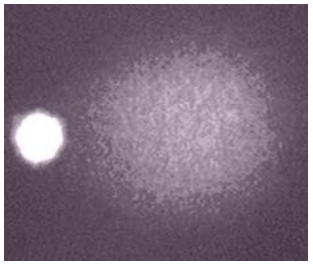
HeLa	-3.78(±1.71)	+1.19(±0.41)	-0.47(±0.33)	+ 0.23(±0.26)	R^2= 0.8262, R^2_{adj} = 0.7517, sd = 0.2263, F = 11.09,
SiHa	-4.94(±0.56)	+ 1.35(±0.11)	- 0.72(±0.09)	+ 0.39(±0.07)	R^2= 0.9893, R^2_{adj}= 0.9847, sd = 0.0597, F = 214.87,
MCF-7	-3.37(±1.31)	+ 1.08(±0.32)	- 0.40(±0.25)	+ 0.42(±0.20)	R^2= 0.9046, R^2_{adj}= 0.8636, sd = 0.1742, F = 22.11, n = 11
HCT-15	-4.57(±1.18)	+ 1.49(±0.29)	- 0.59(±0.23)	+ 0.39(±0.18)	R^2 = 0.9449, R^2_{adj}= 0.9212, sd = 0.1565, F = 39.98, n=11
DL50	-2.63(±0.49)	+ 0.47(±0.12)	– 0.17(±0.09)	+ 0.11(±0.07)	R^2 = 0.9373, R^2_{adj}= 0.9104, sd = 0.0519, F = 34.87,

Daño oxidante al ADN

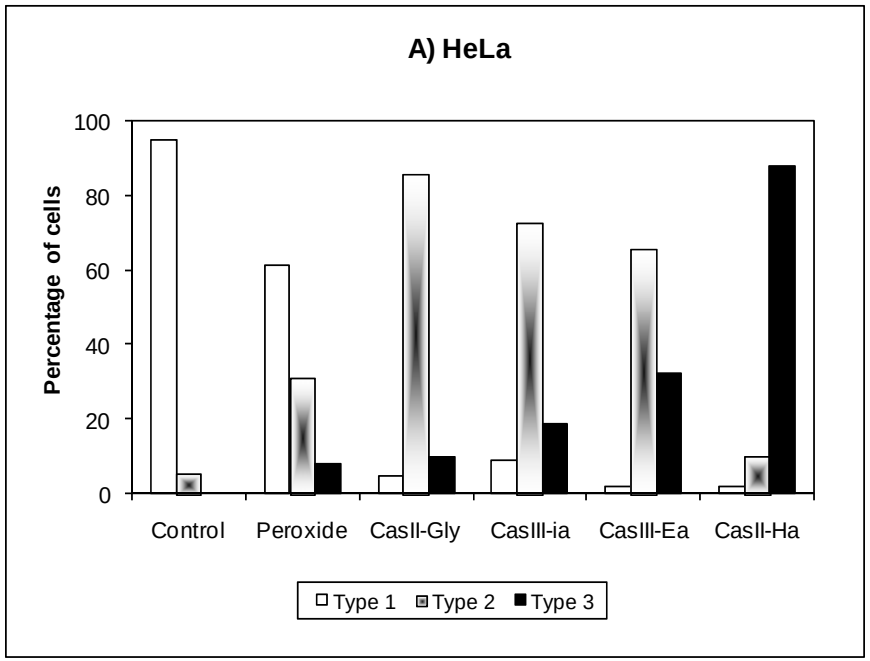
Tipo 1
Nucloid

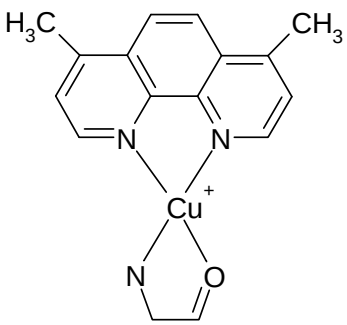


Tipo 2
clasic comet

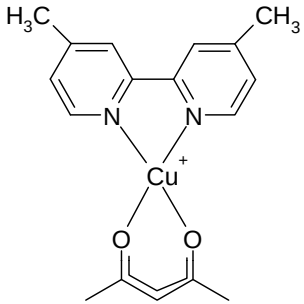


Tipo 3
apoptotic comet

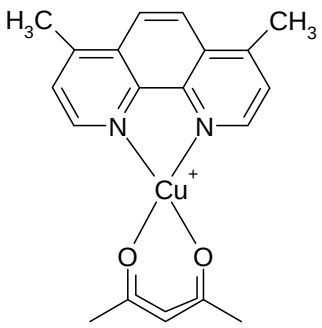




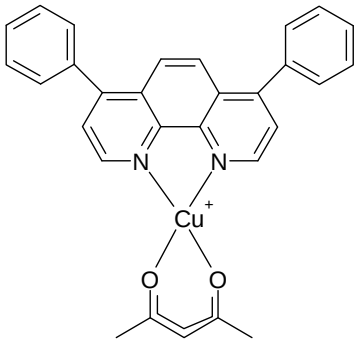
Cas II-



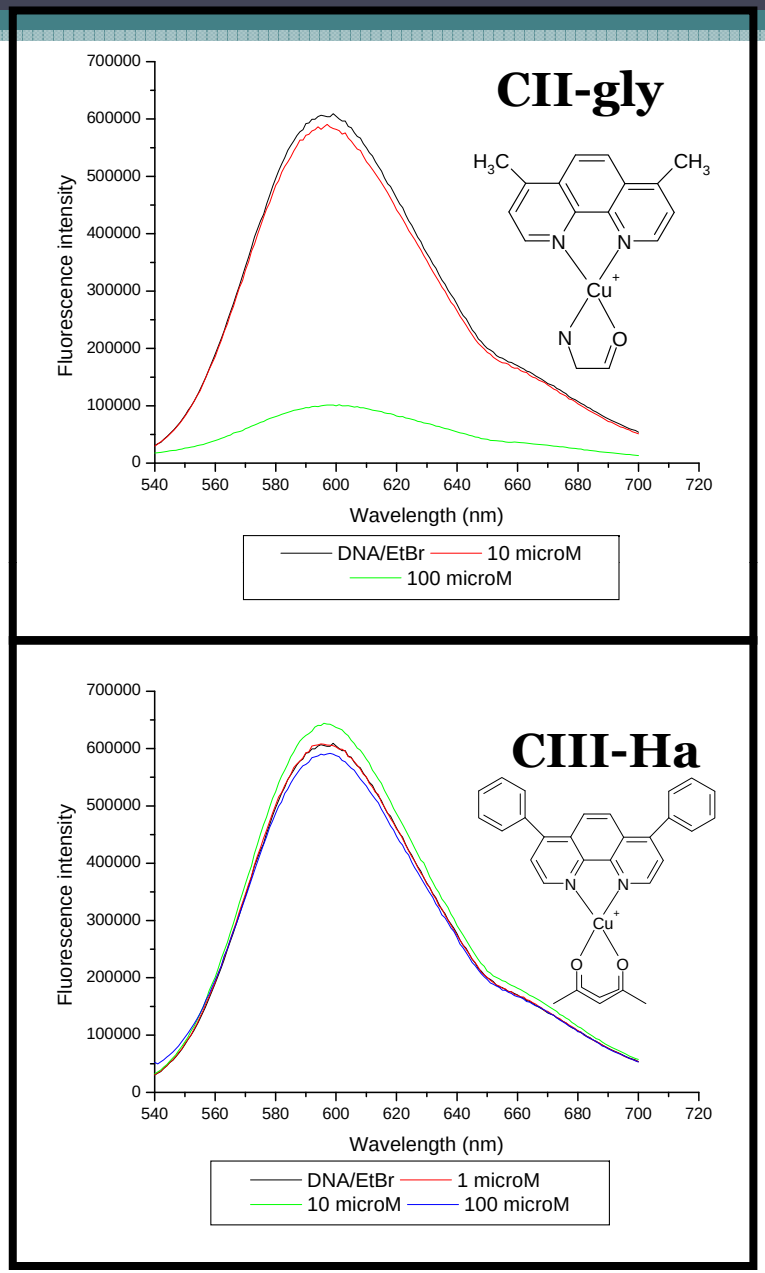
Cas III-ia

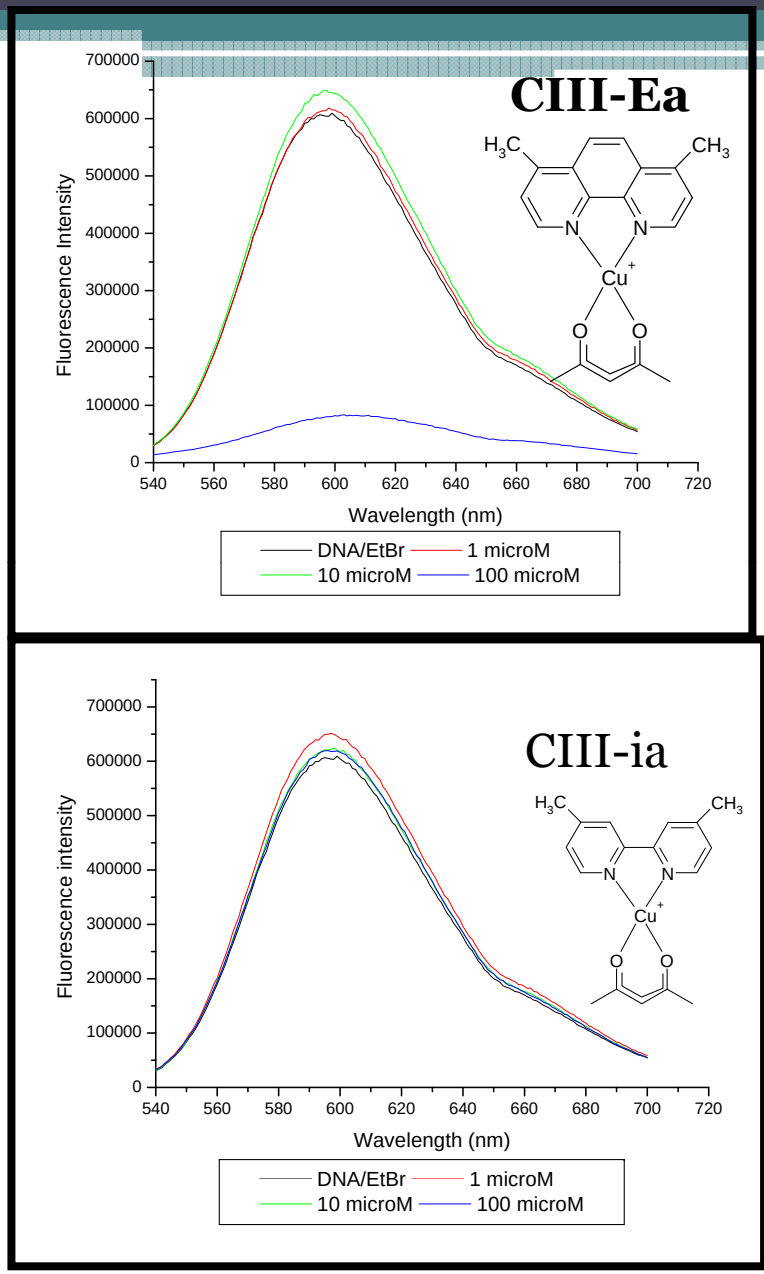


Cas III-Ea



Cas III-





ADN 20 microg/ml; Et Br 1 microM; Excitation 526; detection 540-700;
Dr. Jorge H. Serment Guerrero.

Influencia del ligante diimina

Log 1/C	Intercept	$I_{N\text{-}N}$	$pE_{1/2}$	Log D	n = 11
HeLa	-3.78(±1.71)	+1.19(±0.41)	-0.47(±0.33)	+ 0.23(±0.26)	R^2= 0.8262, R^2_{adj} = 0.7517, sd = 0.2263, F = 11.09,
SiHa	-4.94(±0.56)	+ 1.35(±0.11)	- 0.72(±0.09)	+ 0.39(±0.07)	R^2= 0.9893, R^2_{adj}= 0.9847, sd = 0.0597, F = 214.87,
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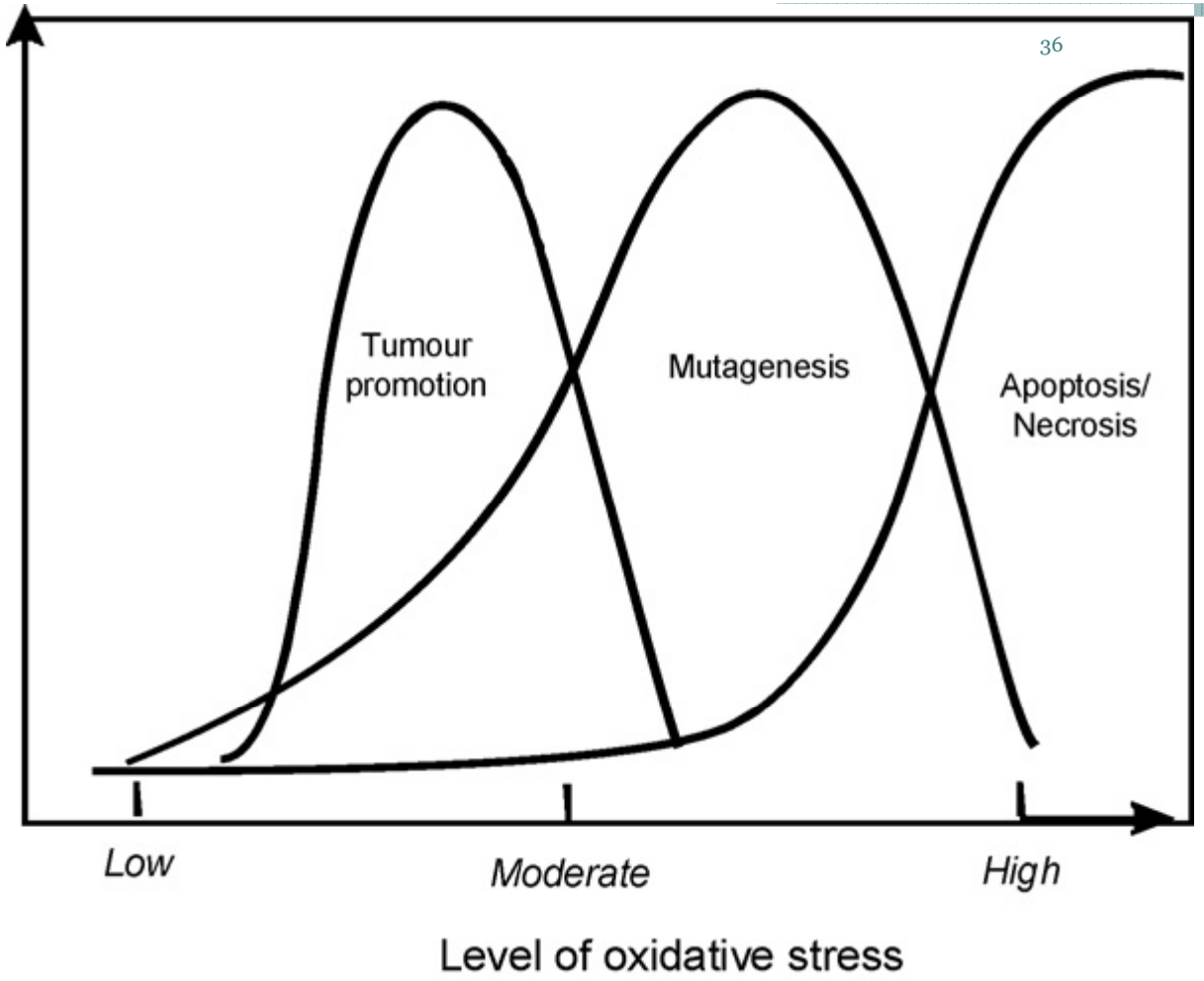


M. Valko et al. / The International Journal of Biochemistry & Cell Biology 39 (2007) 44–84

J.M. Matés, F.M. Sánchez-Jiménez / The International Journal of Biochemistry & Cell Biology 32 (2000) 157-170

Reacción de Fenton y Ciclo de Haber Weiss

Reacción de Fenton

$$Cu^{1+} + H_2O_2 \rightarrow Cu^{2+} + OH^{\bullet} + OH^-$$

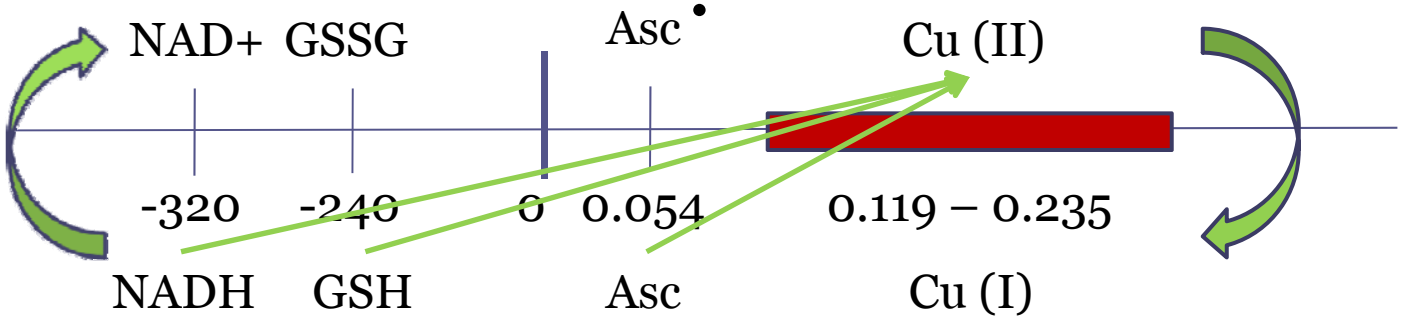
Ciclo Haber Weiss

$$H_2O_2 + OH^{\bullet} \rightarrow H_2O + O_2^{\bullet -} + H+$$

$$Cu^{2+} + O_2^{\bullet -} \rightarrow Cu^{1+} + O_2$$

$$Cu^{1+} + H_2O_2 \rightarrow Cu^{2+} + OH^{\bullet} + OH^-$$

$$H_2O_2 + O_2^{\bullet -} \rightarrow O_2 + OH^{\bullet} + OH^-$$



IUPAC Compendium of Chemical Terminology 2003

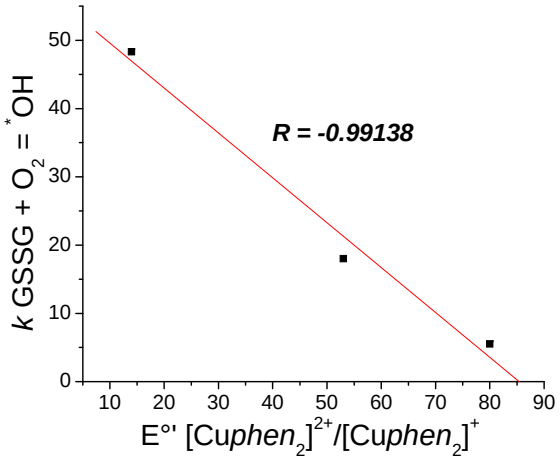
Cinética para reacciones catalizadas por complejos de cobre y potenciales de oxido-reducción para la pareja Cu(II)/Cu(I).

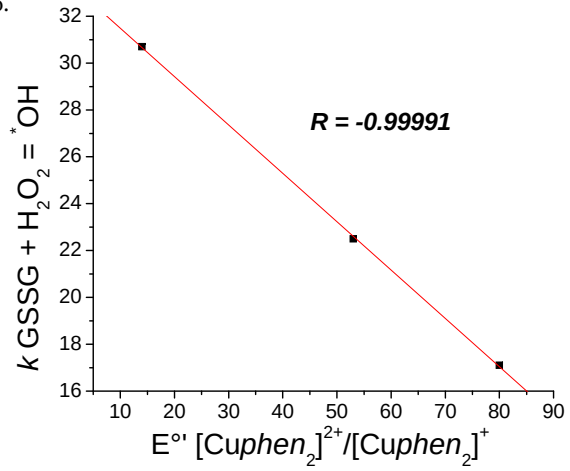
phen	GSH + O_2 [a]	GSH + H_2O_2 [a]	E°' *Cuphen*$_2^{2+}$ [b]	$E_{1/2}$ *acac Complexes* [c]	$E_{1/2}$ *gly Complexes* [c]
	k_0, mol $L^{-1}min^{-1}$ x 10^6	k_2, $mol^{-1}min^{-1}$		mV *vs*. NHE	
H	**5.52**	**17.1**	**321**	**186**	**198**
4,7-diMe	**48.3**	**30.7**	**255**	**139**	**147**
5,6-diMe	**18**	**22.5**	**294**	**159**	**165**

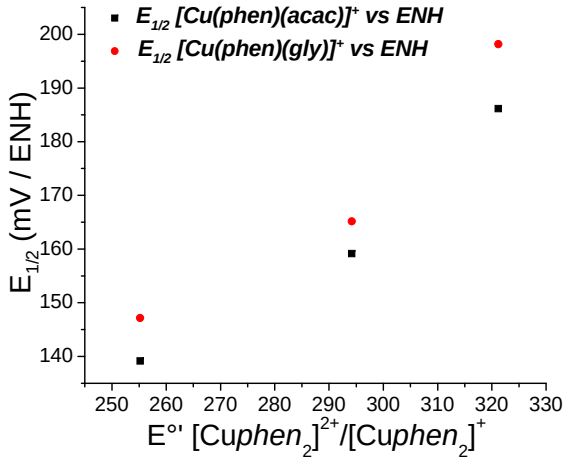
[a] constante de velocidad condicionada a 25°C para la oxidación de GSH por O_2 y H_2O_2 [*T.M. Florence, J Inorg Biochem 28 (1986) 33-37.*]

[b] Potencial de oxido reducción para los complejos cobre (II) bis-fenantrolina. Los valores originales contra el electrodo estándar de calomel (SCE) [*G. Sanna, M.I. Pilo, M.A. Zoroddu, S. R., S. and Mosca, Inorganica Chimica Acta 208 (1993) 153-158.* se convirtieron en mV vs. electrodo normal de hidrógeno (SHE) empleando el valor de 241.2 mV vs. SHE para SCE

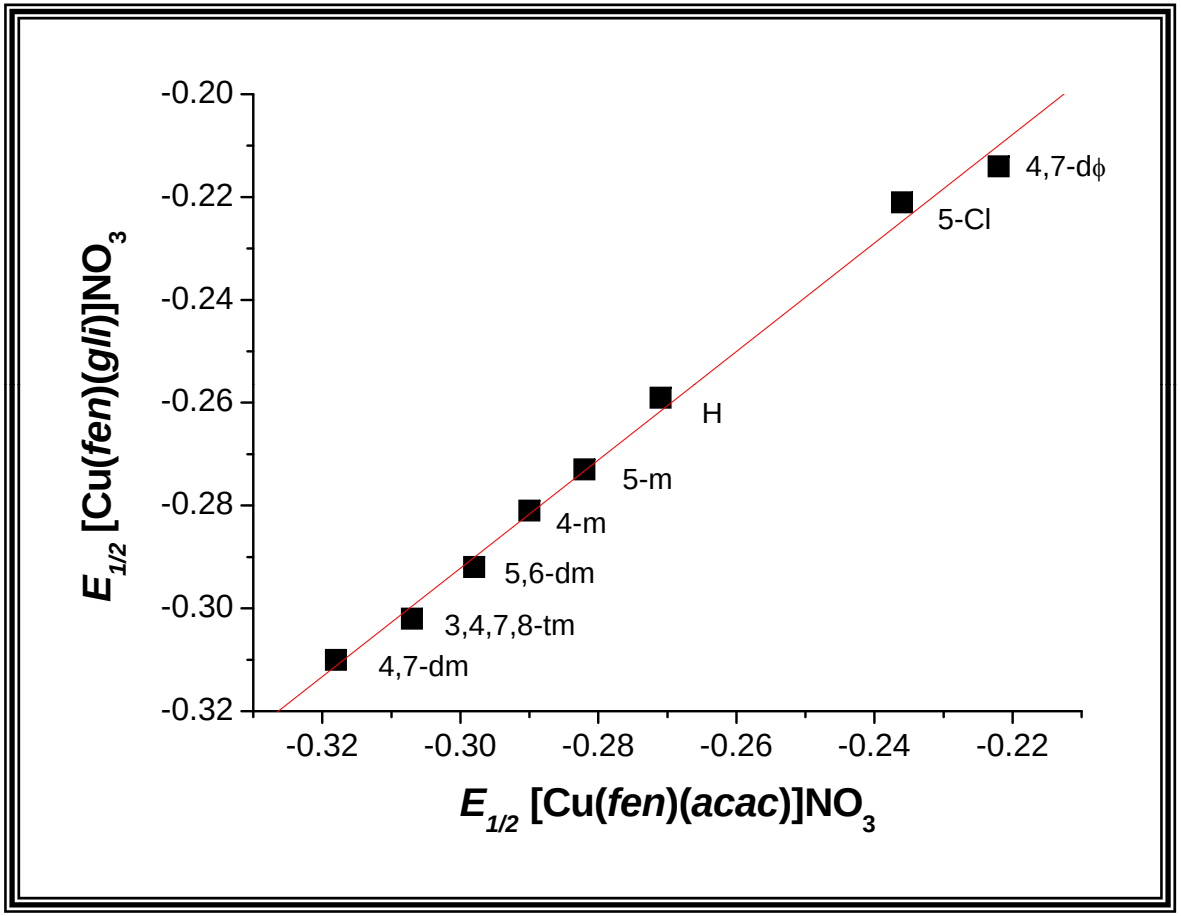
[c] Los potenciales de media onda para los grupos de complejos acetilacetonato y glicinato fueron convertidos en mV. Vs SCE empleando el valor experimental de la pareja ferroceno/ferricinio (Fc/Fc^+) vs. SCE seguido de la conversión en mV vs SHE tal y como se hizo en b.







$E_{1/2}$ *complejos gly*= 1.05 $E_{1/2}$ *complejos acac* + 0.02
R^2 = 0.9973, sd = 0.00284, N = 8



$E_{1/2}$ para el par redox *CuI/CuII* reportados en Voltz (V) contra el par Ferroceno/Ferricinio (Fc/Fc+) de los complejos [Cu(*phen*)(*acac*)]+ *Vs* [Cu(*phen*)(*gly*)]+.

Regresar

Cinética para reacciones catalizadas por complejos de cobre y potenciales de oxido-reducción para la pareja Cu(II)/Cu(I).

phen	GSH + O_2 [a]	GSH + H_2O_2 [a]	E°' *Cuphen*$_2^{2+}$ [b]	$E_{1/2}$ *acac Complexes* [c]	$E_{1/2}$ *gly Complexes* [c]
	k_0, mol $L^{-1}min^{-1}$ x 10^6	k_2, $mol^{-1}min^{-1}$		mV *vs*. NHE	
H	**5.52**	**17.1**	**321**	**186**	**198**
4,7-diMe	**48.3**	**30.7**	**255**	**139**	**147**
5,6-diMe	**18**	**22.5**	**294**	**159**	**165**

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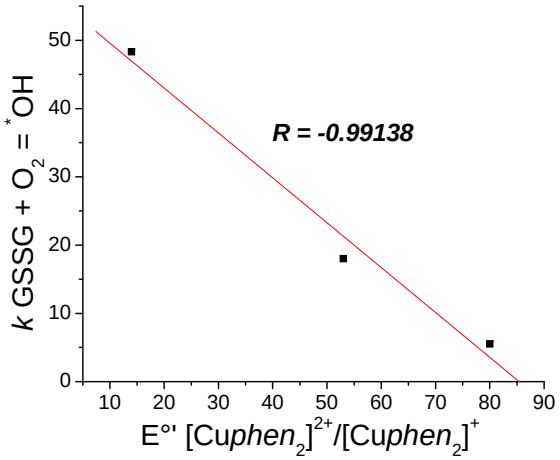
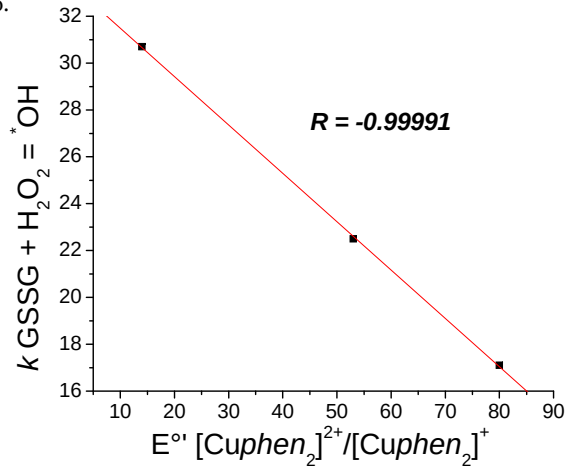
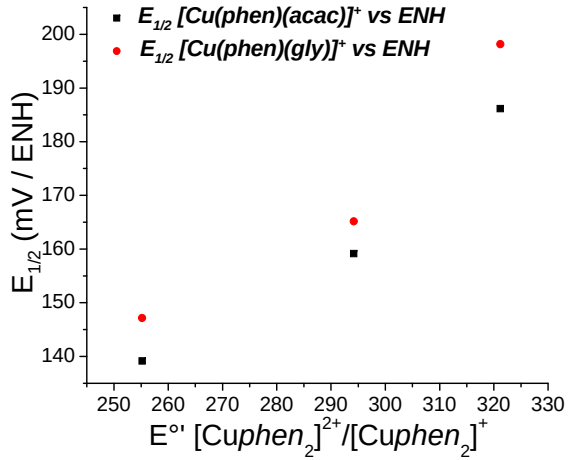






QSAR's empleando solamente descriptores teóricos.

Log 1/IC50 $_{MCF\text{-}7}$=

-3.37(±1.31) + 1.08(±0.32)$\boldsymbol{I_{N\text{-}N}}$ - 0.40(±0.25)$pE_{1/2}$ + 0.42(±0.20)Log D

-2.87(±0.55) + 0.70(±0.25) $\boldsymbol{I_{N\text{-}N}}$ + 0.19(±0.11)$pKa_{\boldsymbol{N\text{-}N}}$ + 0.16(±0.09)$CLog\ P_{\boldsymbol{N\text{-}N}}$

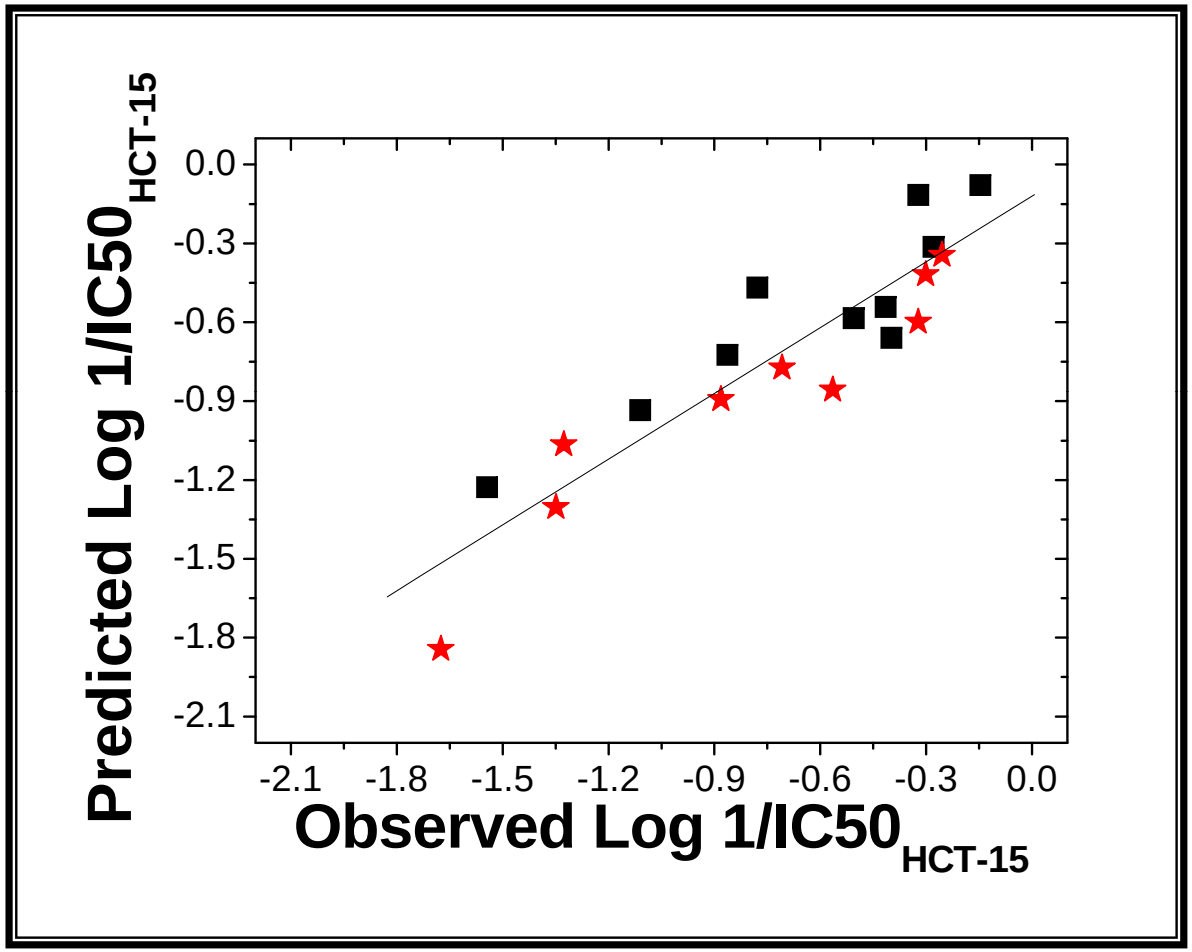
R^2= 0.9046, R^2_{adj}= 0.8636, sd = 0.1742, F = 22.11, n = 11

R^2= 0.9269, R^2_{adj}=0.8956, sd = 0.1557, F = 29.59, n = 11

QSAR's empleando solamente descriptores teóricos.

Log 1/C	Intercept	$I_{N\text{-}N}$	$pE_{1/2}$ / pKa	Log D / $CLogP_{N\text{-}N}$	n = 11
HeLa	-3.78 (±1.71) -2.94 (±0.72)	+1.19 (±0.41) + 0.73 (±0.30)	- 0.47 (±0.33) + 0.31 (±0.14)	+ 0.23 (±0.26) + 0.31 (±0.14)	R^2= 0.8262, R^2= 0.8348
SiHa	-4.94 (±0.56) -3.11 (±0.54)	+ 1.35 (±0.11) + 0.82 (±0.23)	- 0.72 (±0.09) + 0.35 (±0.10)	+ 0.39 (±0.07) ----------	R^2= 0.9893, R^2= 0.9218
MCF-7	-3.37 (±1.31) -2.87 (±0.55)	+ 1.08 (±0.32) + 0.70 (±0.25)	- 0.40 (±0.25) + 0.19 (±0.11)	+ 0.42 (±0.20) + 0.16 (±0.09)	R^2= 0.9046, R^2= 0.9269
HCT-15	-4.57 (±1.18) -3.81 (±0.61)	+ 1.49 (±0.29) + 1.04 (±0.26)	- 0.59 (±0.23) + 0.43 (±0.12)	+ 0.39 (±0.18) ----------	R^2 = 0.9449, R^2 = 0.9325
DL50	-2.63 (±0.49) -2.44 (±0.14)	+ 0.47 (±0.12) + 0.30 (±0.06)	– 0.17 (±0.09) + 0.12 (±0.03)	+ 0.11 (±0.07) + 0.03 (±0.02)	R^2 = 0.9373, R^2 = 0.9811

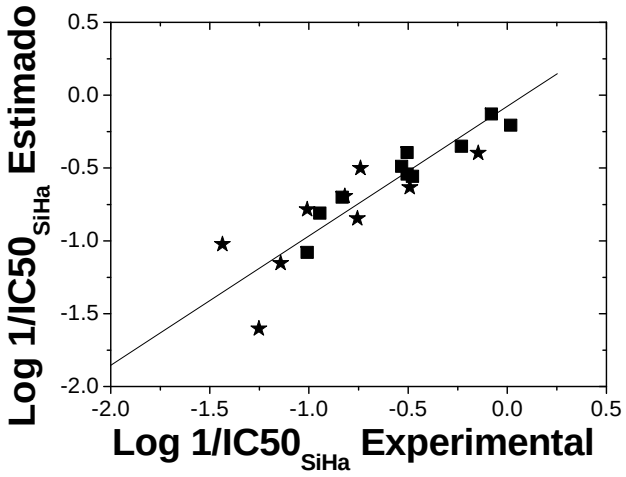
Influencia del ligante secundario



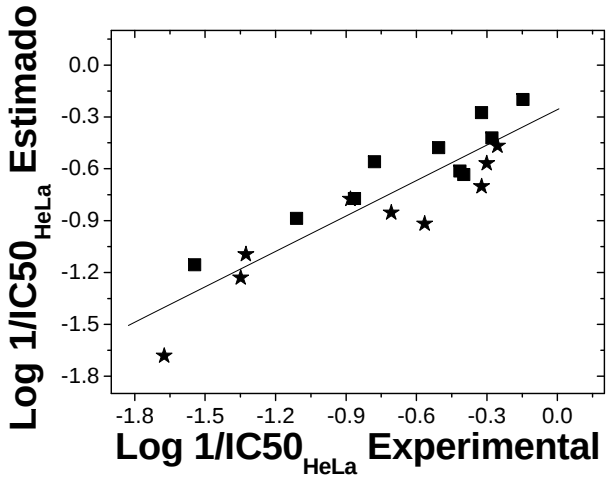
- Log 1/IC50 $_{HCT-15}$ = -3.74(±0.60) - 0.57(±0.13) $pE_{1/2}$ + 0.16(±0.06) ΣCLog P

  R^2= 0.8342, R^2adj= 0.8134, sd = 0.2050, F = 40.24, n = 19

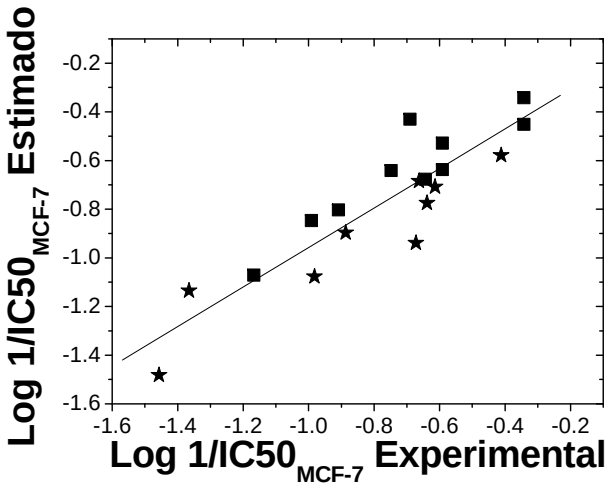
A


Log 1/IC50SiHa Estimado
Log 1/IC50SiHa Experimental
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.0
-1.5
-1.0
-0.5
0.0
0.5

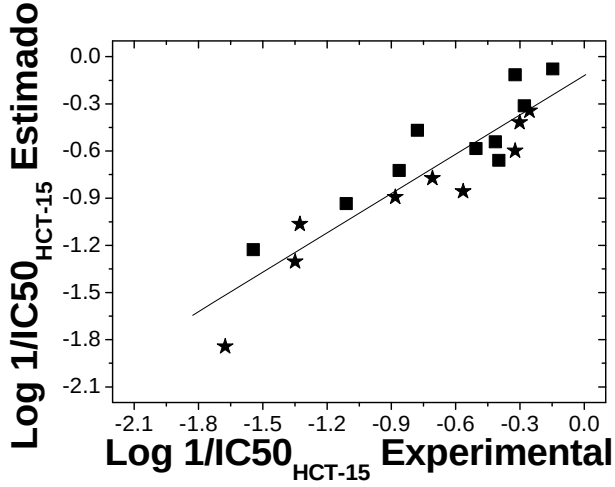
B


Log 1/IC50HeLa Estimado
Log 1/IC50HeLa Experimental
0.0
-0.3
-0.6
-0.9
-1.2
-1.5
-1.8
-1.8
-1.5
-1.2
-0.9
-0.6
-0.3
0.0

C


Log 1/IC50MCF-7 Estimado
Log 1/IC50MCF-7 Experimental
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
-1.6
-1.4
-1.2
-1.0
-0.8
-0.6
-0.4
-0.2

D


Log 1/IC50HCT-15 Estimado
Log 1/IC50HCT-15 Experimental
0.0
-0.3
-0.6
-0.9
-1.2
-1.5
-1.8
-2.1
-2.1
-1.8
-1.5
-1.2
-0.9
-0.6
-0.3
0.0

Conclusiones

- Las ecuaciones modelan adecuadamente la actividad de los complejos.
- Validez en el uso de descriptores únicamente teóricos.
- El tercer anillo aromático es necesario para incrementar la actividad del complejo.
- Citotoxicidad esta directamente relacionada con la toxicidad *in vivo*
- El centro metálico esta involucrado en el mecanismo de acción.
- Sustituyentes electrodonadores desplazan el $E_{1/2}$ hacia potenciales más negativos e incrementan la actividad antiproliferativa.
- La hidrofobicidad de los ligantes podría facilitar el transporte no regulado de cobre.

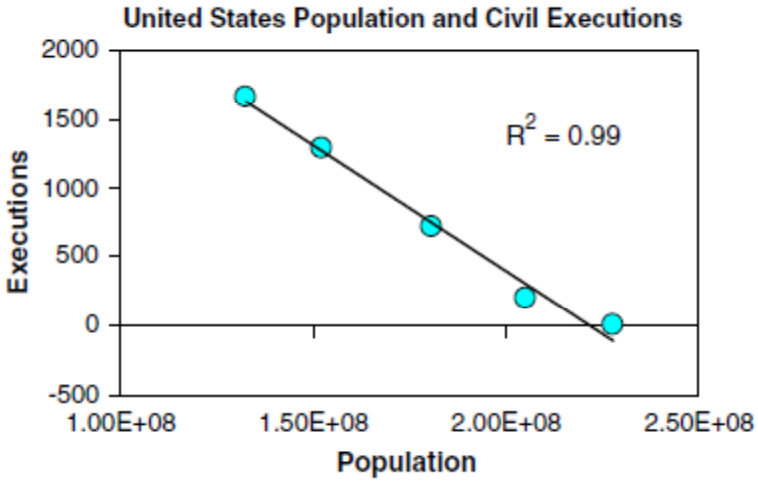
The basic questions that must be addressed when design and develop metal based drugs is:

Which parts of the active compound are essential for activity (Pharmacophore):

- Is the metal essential for activity?
- Is the intact complex responsible for activity?
- Is the metal itself?
- Is the metal plus some of the released ligands?
- Is only the ligands?

Clasification according to metal role

- The metal has a functional role
- The metal has a structural role
- The metal is a carrier for active ligands that are delivered *in vivo*
- The metal compound behaves as a catalyst *in vivo* (ROS) that cause cell damage
- The metal compound is photoactive and behaves as a photo-sensitizer.



QSAR is inherently a valuable tool based on sound statistical principles which can, at the very least, retrospectively explain SAR and, at the most, provide synthetic guidance leading to experimentally testable hypotheses.

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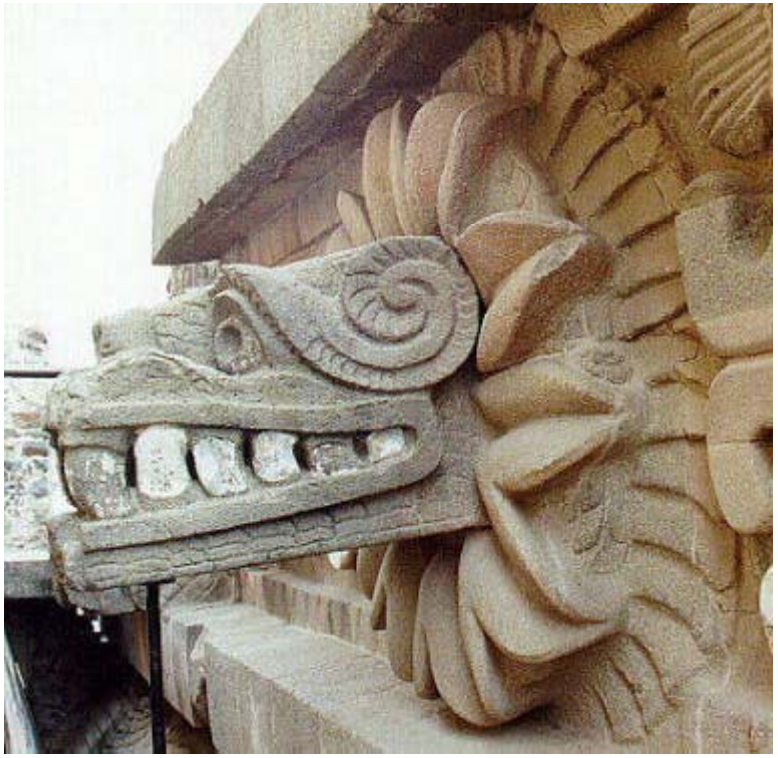

THANK YOU!!!!!