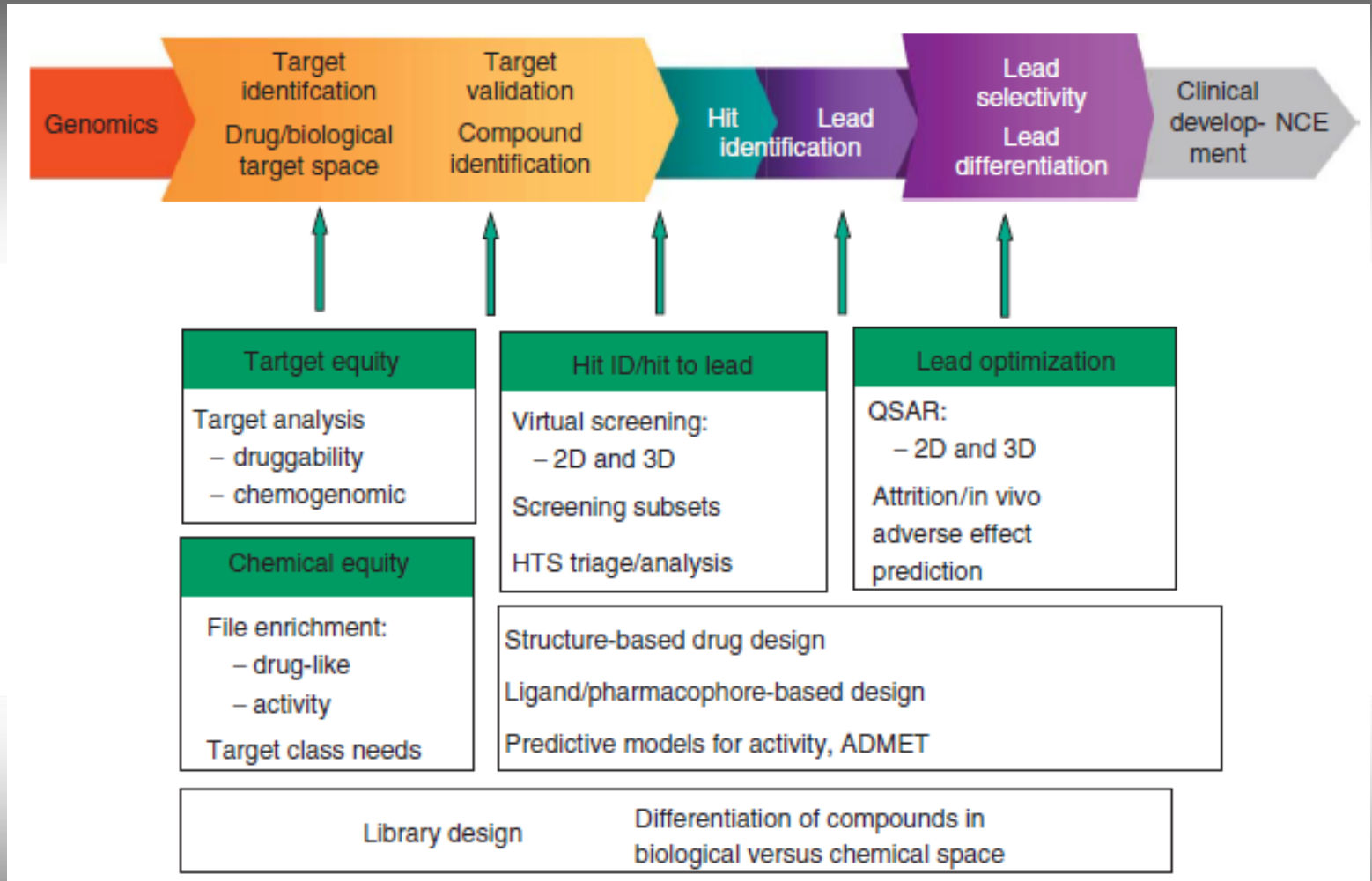
Introduction to Ligand-Based Drug Design

SAPIENZA
UNIVERSITÀ DI ROMA

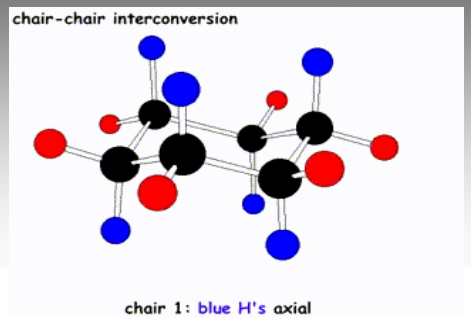
Summary

1. **Overview on LBDD**
   A. Definition and Methods
   B. Pharmacophore Approach
   C. QSAR
   D. 3-D QSAR
2. **Application (and demonstration) of 3-D QSAR to medicinal chemistry**

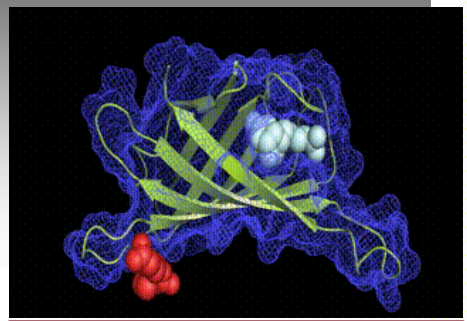
Drug Discovery Process



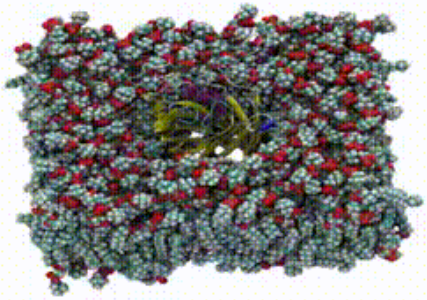
Computational Techniques in Medicinal Chemistry



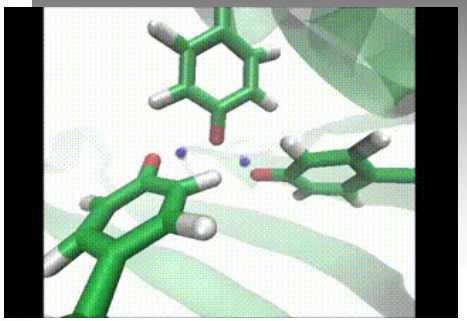
Conformational Search



Molecular Docking

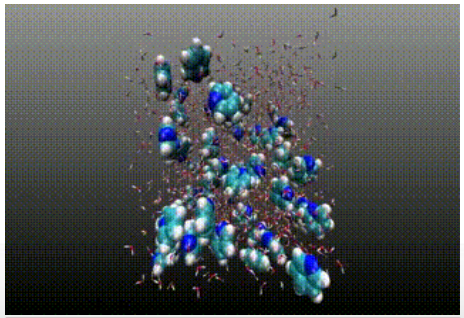


Simulate Annealing

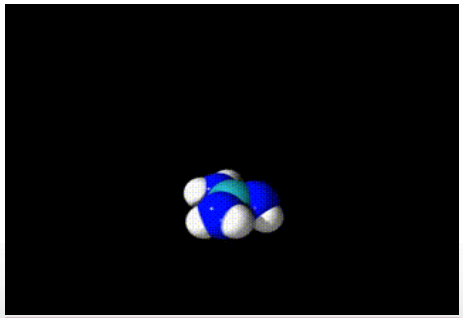


Ab Initio QM

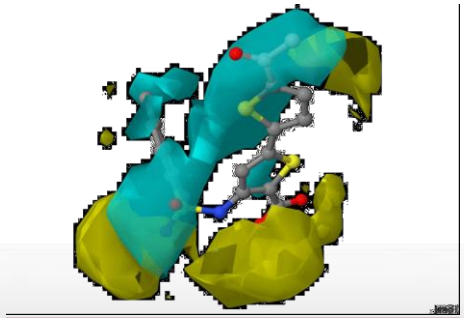
QSAR



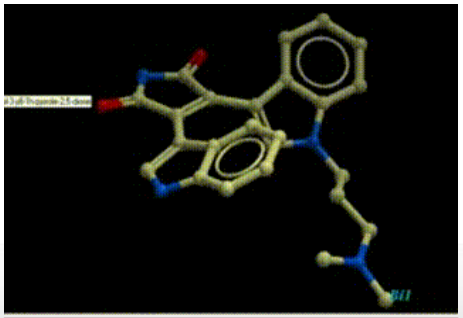
Molecular Dynamics



Graphical Visualization



3-D QSAR



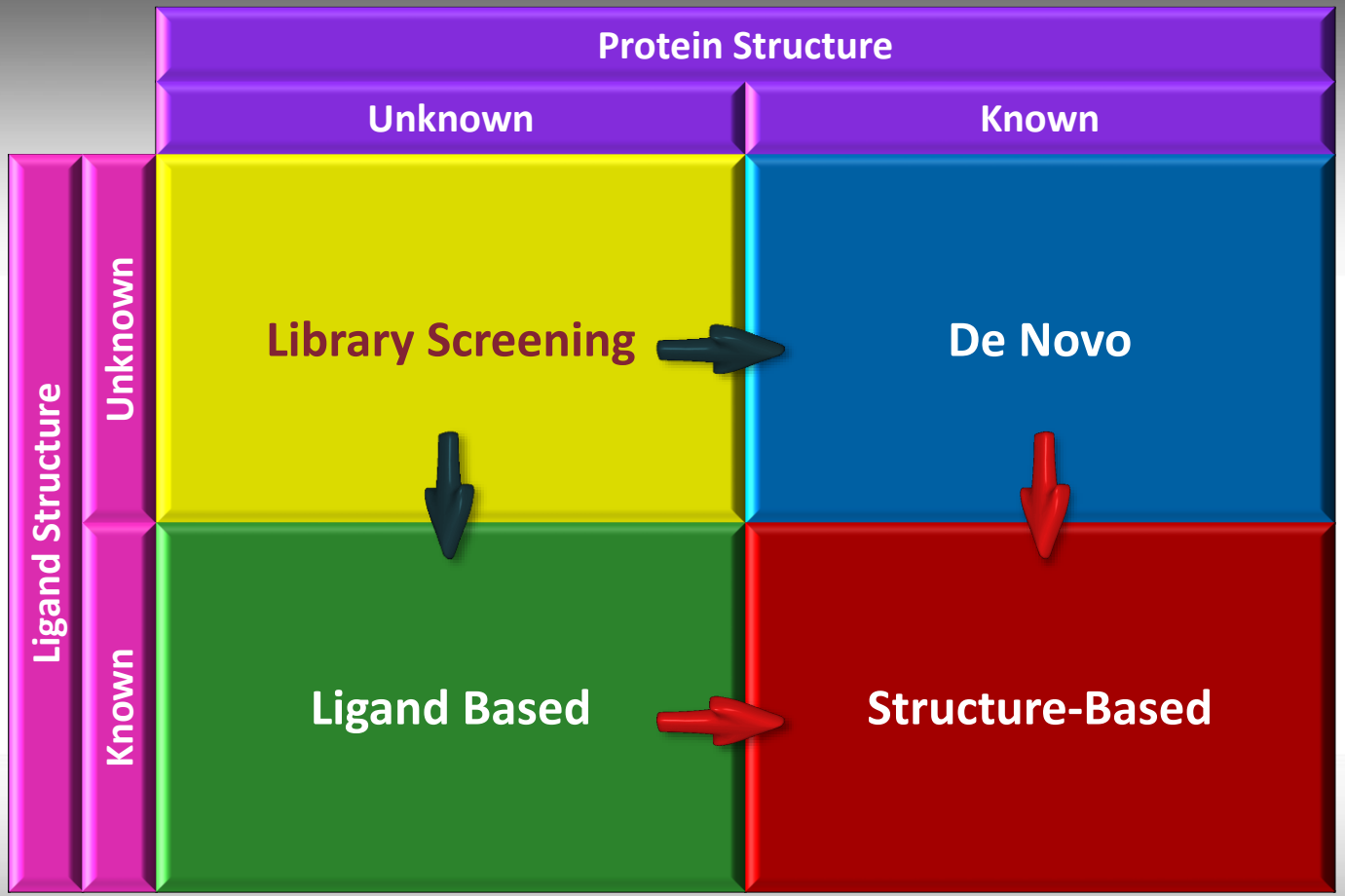
Pharmacophore

QSAR, COMBINE, Scoring Functions, Homology Modeling,…..

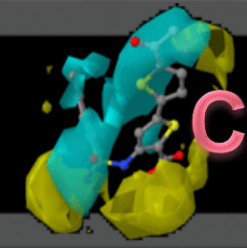
Drug Design = Computational & Synthesis Tandem

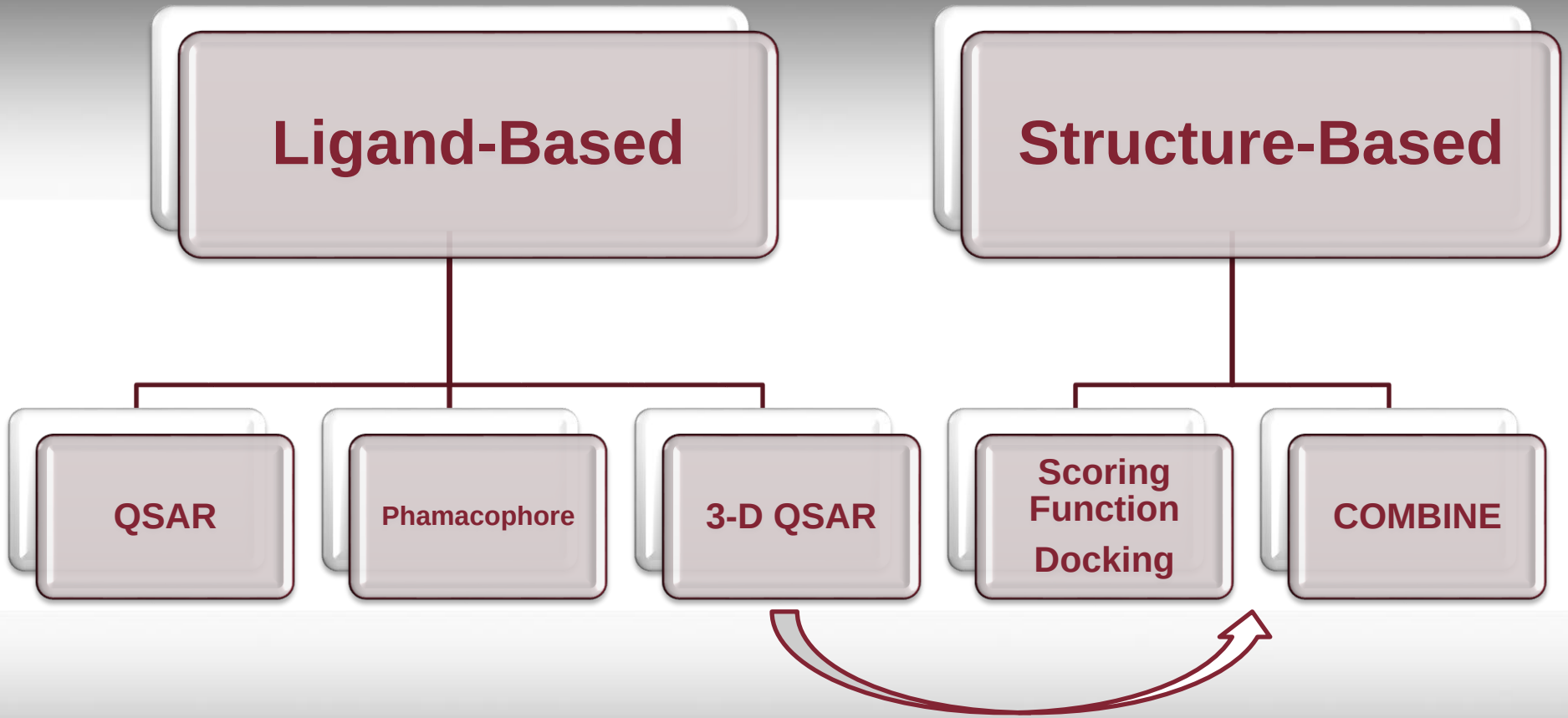
Basic Research → Target Ident → Target Valid → Hit Ident → Hit to Lead → Lead Opt → Preclin → Clinical Trial → Prod → Diagnos

Computational Medicinal Chemistry



CADD methods in Drug Design





LBDD

In the absence of three-dimensional (3-D) structures of potential drug targets, ligand-based drug design is one of the popular approaches for drug discovery and lead optimization. **3-D structure activity relationships (3-D QSAR) and pharmacophore modeling are the most important and widely used tools in ligand-based drug design** that can provide crucial insights into the nature of the interactions between drug target and ligand molecule and provide predictive models suitable for lead compound optimization.

Pharmacophore Definition

"A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response."

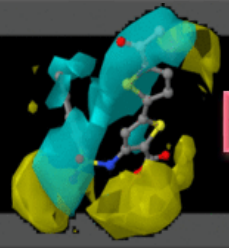
C.-G. Wermuth et al., *Pure Appl. Chem.* 1998, 70: 1129-1143

Definition by IUPAC

A **pharmacophore** is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response.

A **pharmacophore** does not represent a real molecule or a real association of functional groups, but a purely abstract concept that accounts for the common molecular interaction capacities of a group of compounds towards their target structure.

The **pharmacophore** can be considered as the largest common denominator shared by a set of active molecules. This definition discards a misuse often found in the **medicinal chemistry** literature which consists of naming as **pharmacophores** simple chemical functionalities such as guanidines, sulfonamides or dihydroimidazoles (formerly imidazolines), or typical structural skeletons such as flavones, phenothiazines, prostaglandins or steroids.



Pharmacophoric Descriptors

Interaction sites used to define a **pharmacophore**,

- H-bonding,
- hydrophobic
- Electrostatic

Defined by atoms, ring centers and virtual points.

The First Paper on Pharmacophoric Approach

The Conformational Parameter in Drug Design: The Active Analog Approach

GARLAND R. MARSHALL, C. DAVID BARRY, HEINZ E. BOSSHARD, RICHARD A. DAMMKOEHLER, and DEBORAH A. DUNN

Departments of Physiology and Biophysics, of Pharmacology and of Computer Science and the Computer Systems Laboratory, Washington University, St. Louis, MO 63110

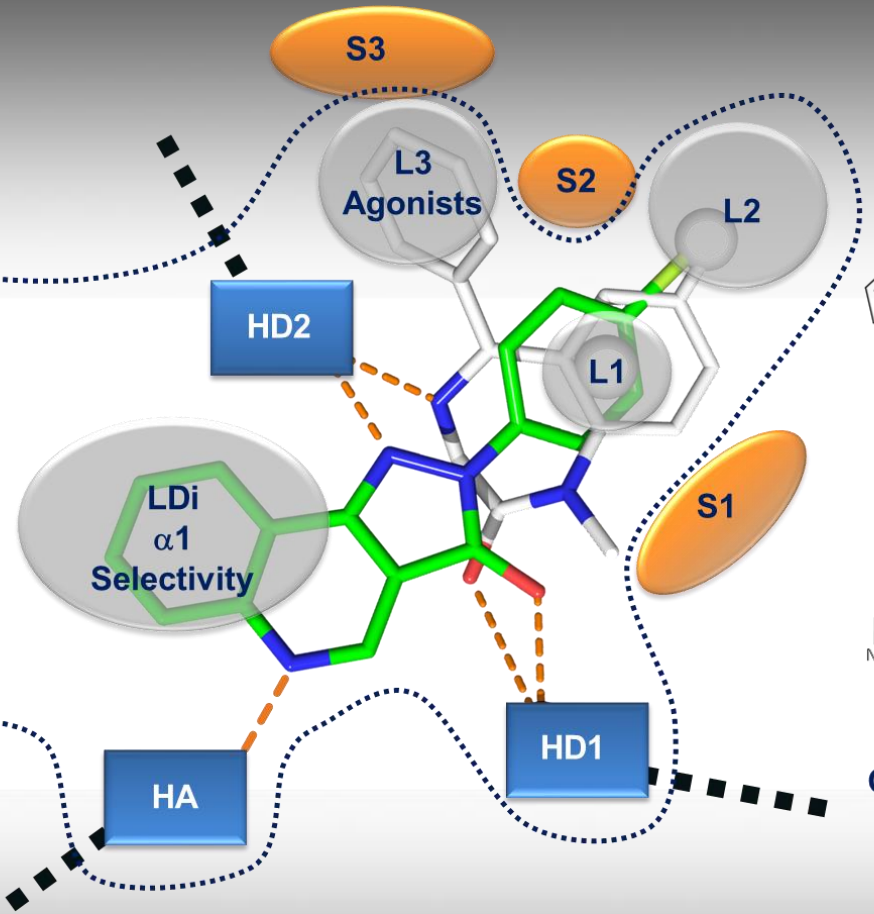
BDZ Cook Model

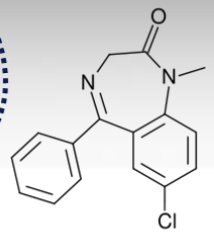
HD: H Donator
HA: H Acceptors
L: Lipophyolic
S: Steric Repulsion

Agonists
HD1, HD2, HA, L2 (L3)

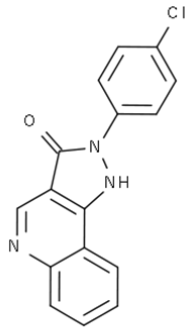
Inverse Agonists
HD1, HA e L1

Antagonists
HD1, HD2 e HA



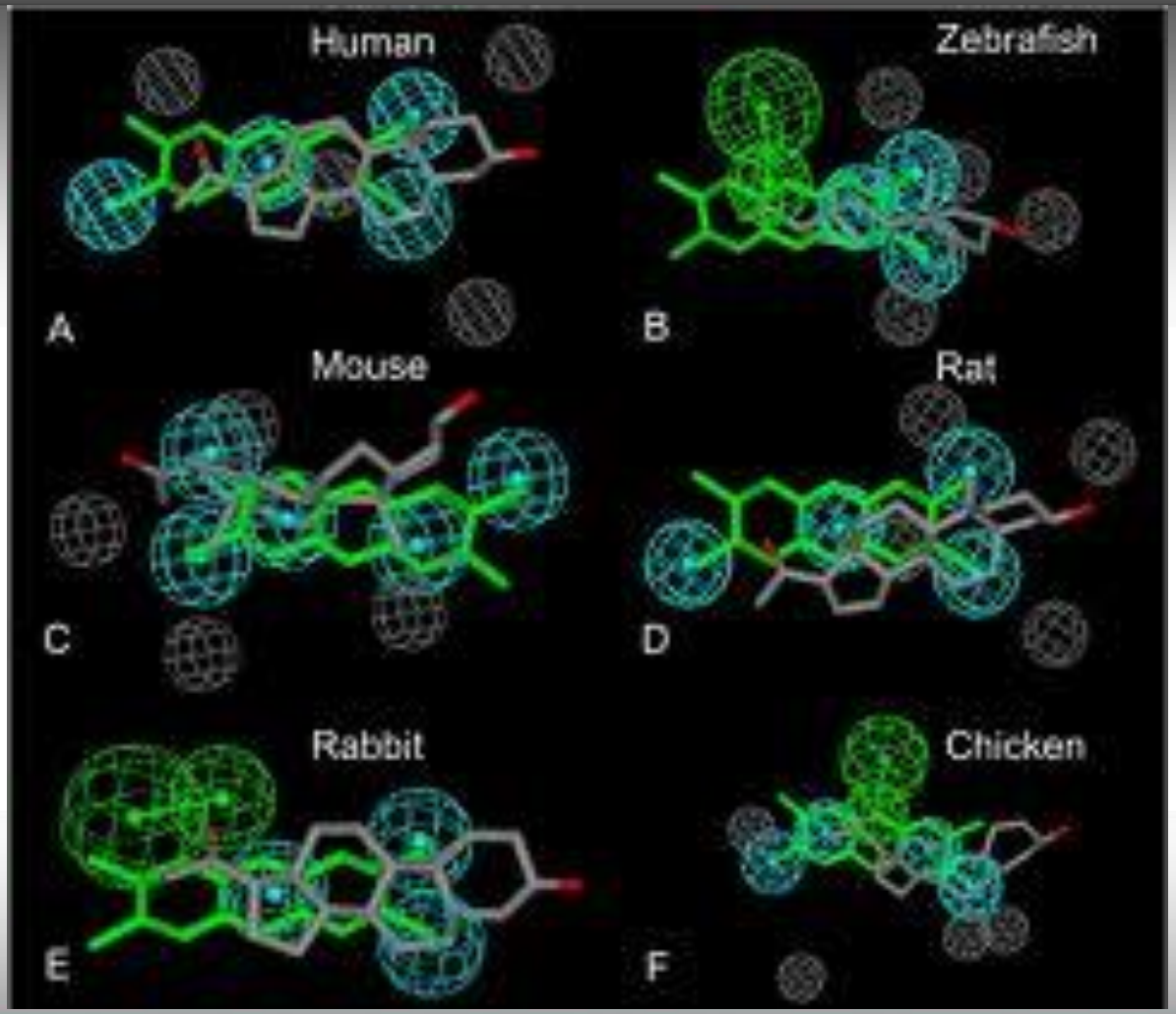


Diazepam



CGS9896

Modern Pharmacophore Model



The Beginning of QSAR

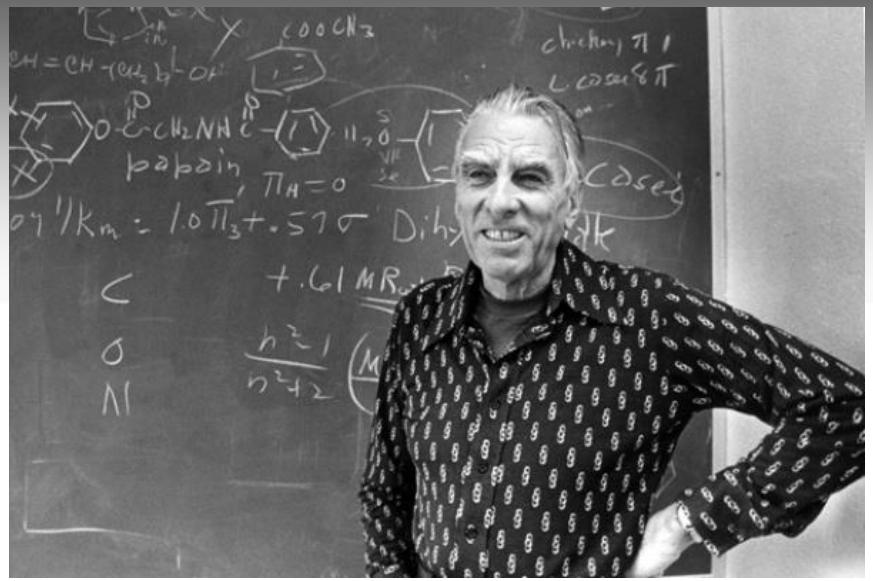
QSAR date back to the 19th century

In 1863, A.F.A. Cros at the University of Strasbourg observed that toxicity of alcohols to mammals increased as the water solubility of the alcohols decreased

In the 1890's, Hans Horst Meyer of the University of Marburg and Charles Ernest Overton of the University of Zurich, working independently, noted that the toxicity of organic compounds depended on their lipophilicity.

Louis Hammett (1938) Electronic Parameters (Sigma-Rho)
Robert W. Taft (1952) Steric Parameters (Es)
Corvin Hansch (1964) Hydrophobic Parameter (LogP - π)

The Hansch Equation



The Hansch Equation

$$\delta_X \log k_i = \delta_X \Delta G_{hydrophobic} + \delta_X \Delta G_{electronic} + \delta_X \Delta G_{steric}$$

The first QSAR equations were based on the observation that partition coefficients, as expressed by log *P* values, are to some extent, correlated to certain biological endpoints.

$$\log(1/C) = k1 \log P + k2\sigma + k3$$

Conc. of compound required to produce a standard response in a given t

Logarithm of the molecule's partition coefficient (1-octanol/water)

Hammet Parameter (molecule's electronic characteristics)

'60: QSAR Golden Age

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

$\rho-\sigma-\pi$ Analysis. A Method for the Correlation of Biological Activity and Chemical Structure

BY CORWIN HANSCH AND TOSHIO FUJITA[1]

RECEIVED AUGUST 19, 1963

Using the substituent constant, σ, and a substituent constant, π, defined as $\pi = \log P_X - \log P_H$ (P_H is the partition coefficient of a parent compound and P_X that of a derivative), regression analyses have been made of the effect of substituents on the biological activity of benzoic acids on mosquito larvae, phenols on gram-positive and gram-negative bacteria, phenyl ethyl phosphate insecticides on houseflies, thyroxine derivatives on rodents, diethylaminoethyl benzoates on guinea pigs, and carcinogenic compounds on mice.

Journal of Medicinal Chemistry

VOLUME 7, NUMBER 4 JULY 6, 1964

A Mathematical Contribution to Structure–Activity Studies

SPENCER M. FREE, JR., AND JAMES W. WILSON

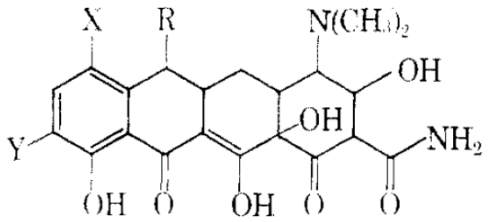
Free-Wilson

Journal of Medicinal Chemistry

VOLUME 7, NUMBER 4 JULY 6, 1964

A Mathematical Contribution to Structure–Activity Studies

SPENCER M. FREE, JR., AND JAMES W. WILSON



where R was H or CH_3; X was Br, Cl, or NO_2; and Y was NO_2, NH_2, or CH_3CONH.

BIOLOGICAL ACTIVITY OF TEN TETRACYCLINES

Compound	Compound identification: R: H	R: CH_3	X: NO_2	X: Cl	X: Br	Y: NO_2	Y: NH_2	Y: CH_3CONH	Biological activity
III	1		1			1			60
IV	1			1		1			21
V	1				1	1			15
VI	1			1			1		525
VII	1				1		1		320
VIII	1		1				1		275
IX		1	1				1		160
X		1	1					1	15
XI		1			1		1		140
XII		1			1			1	75

CONTRIBUTION OF STRUCTURAL CHANGES[a]

Side chain positions: R		X		Y	
a[H]	75	b[Cl]	84	c[NH_2]	123
a[CH_3)	−112	b[Br]	−16	c[CH_3CONH—]	18
		b[NO_2]	−26	c[NO_2]	−218

Mixed Hansch/Free-Wilson

Full Papers

A Combined Hansch/Free-Wilson Approach as Predictive Tool in QSAR Studies on Propafenone-Type Modulators of Multidrug Resistance[1]

Claudia Tmej[a], Peter Chiba[b], Mario Huber[a], Elisabeth Richter[b], Manuela Hitzler[b], Klaus-Jürgen Schaper[c], and Gerhard Ecker[a]*

Arch. Pharm. Pharm. Med. Chem. 0365-6233/98/0708/0233 $17.50 +.50/0