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de Concepción

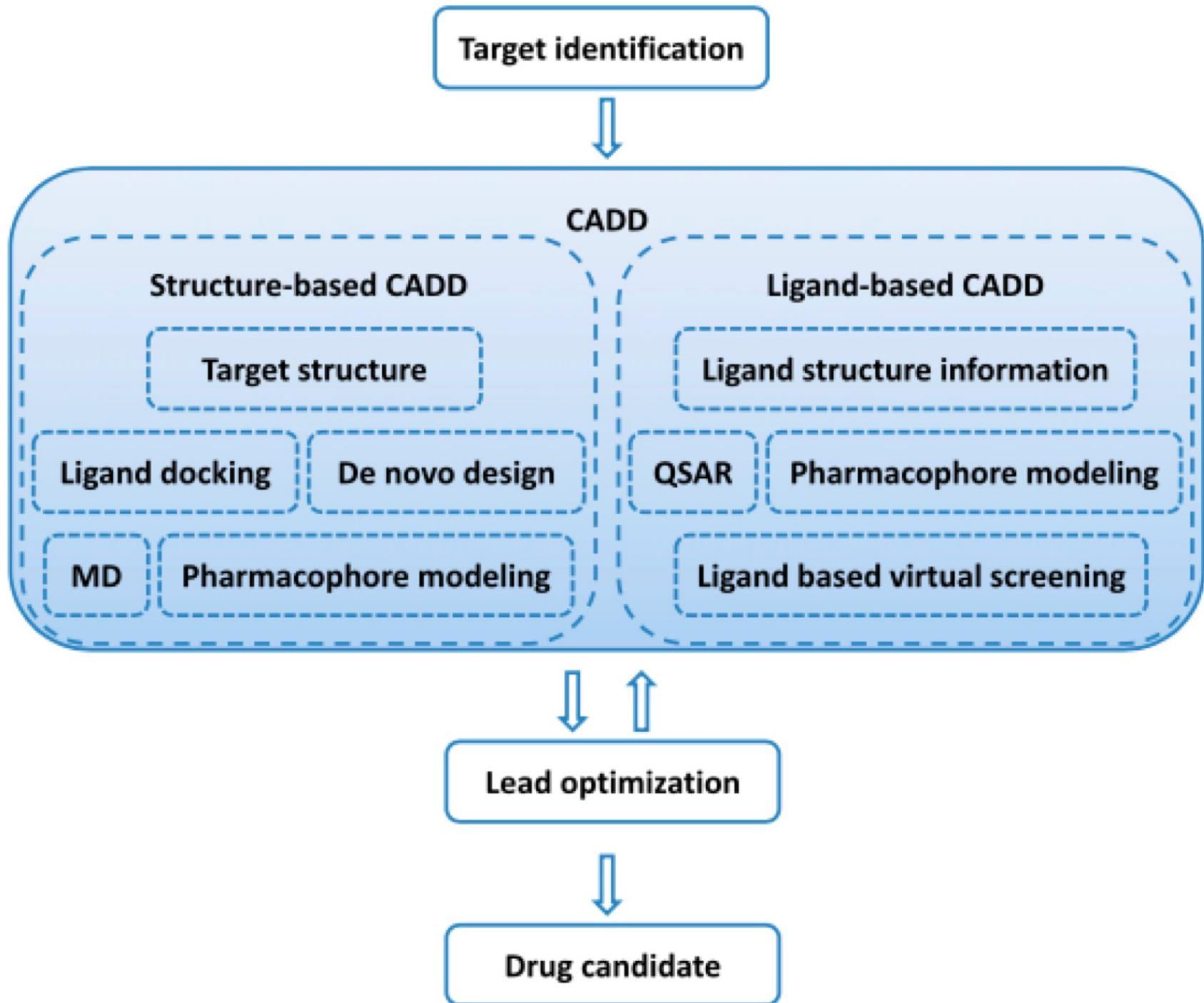


Diseño de Fármacos Basado en la Estructura

Dr. David Ramírez
dramirezs@udec.cl

Computer-aided drug design (CADD)

	Known ligand(s)	No known ligand
Known protein structure	Structure-based drug design (SBDD) Protein-ligand docking	<i>De novo</i> design
Unknown protein structure	Ligand-based drug design (LBDD) <i>1 or more ligands</i> <ul style="list-style-type: none">• Similarity searching <i>Several ligands</i> <ul style="list-style-type: none">• Pharmacophore searching <i>Many ligands (20+)</i> <ul style="list-style-type: none">• Quantitative Structure-Activity Relationships (QSAR)	CADD of no use Need experimental data of some sort



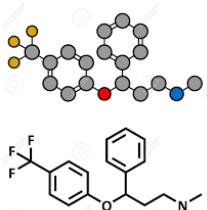
Conceptos Básicos:

Droga



Materia prima con más
De 1 principio activo

Fármaco



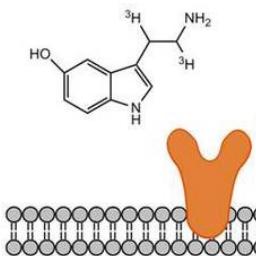
molécula bioactiva
Químicamente definida

Medicamento



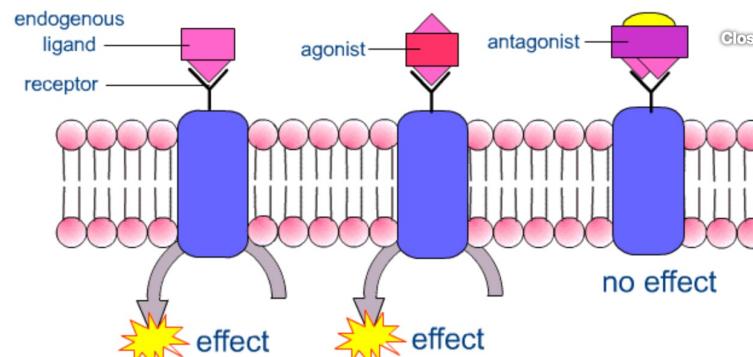
Forma farmacéutica
1 o más principios activos

Receptor



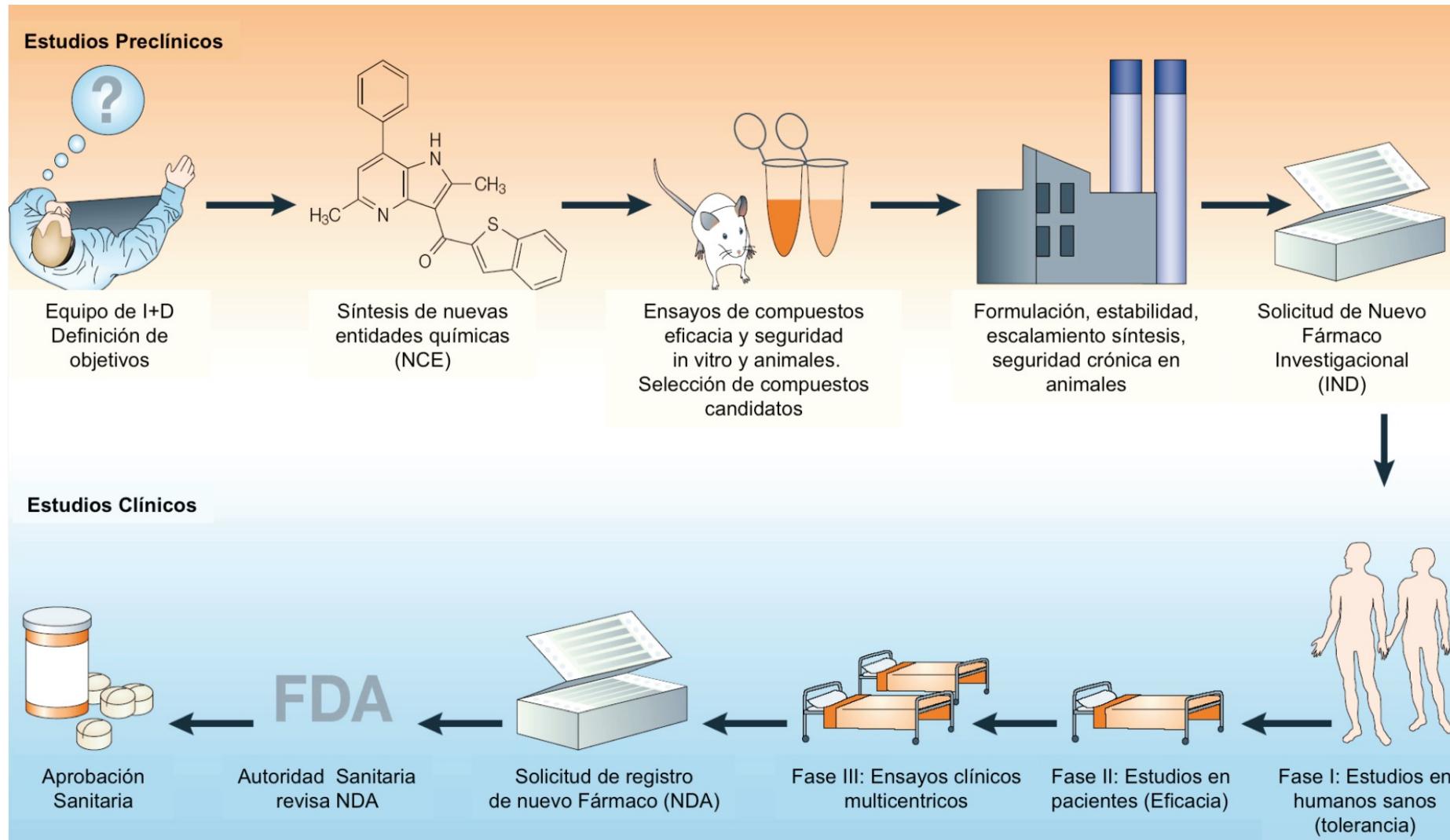
Donde se une una molécula
Respuesta fisiológica

Agonista



Antagonista

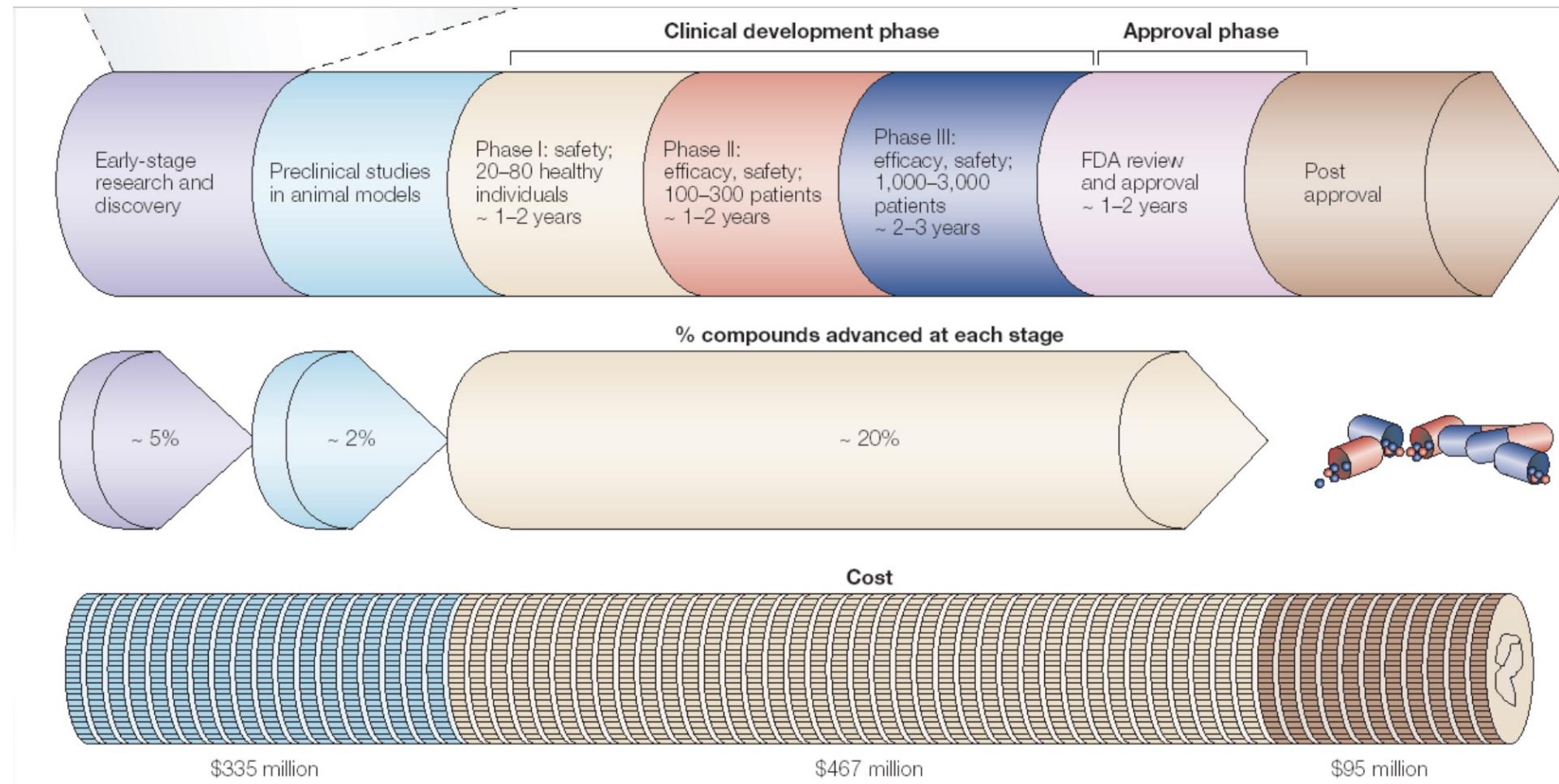
Investigación y desarrollo de nuevos medicamentos



Dos fases principales

Nat Rev Drug Discov 2004, 3, 360-4

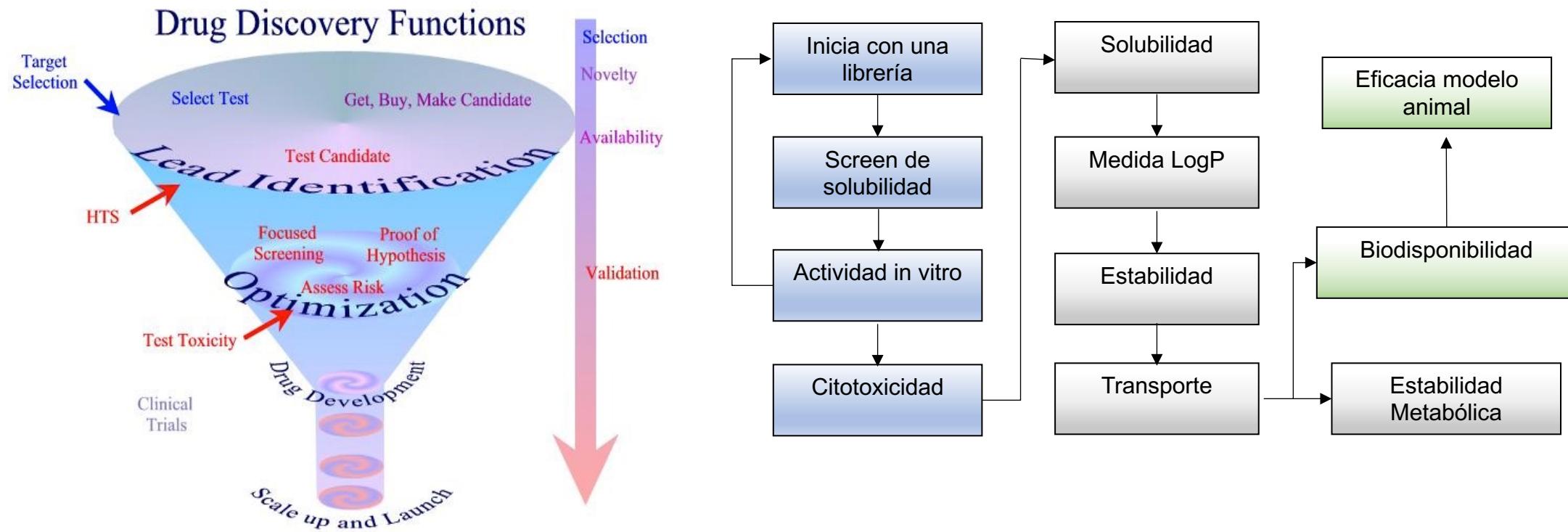
Costo para desarrollar un nuevo medicamento



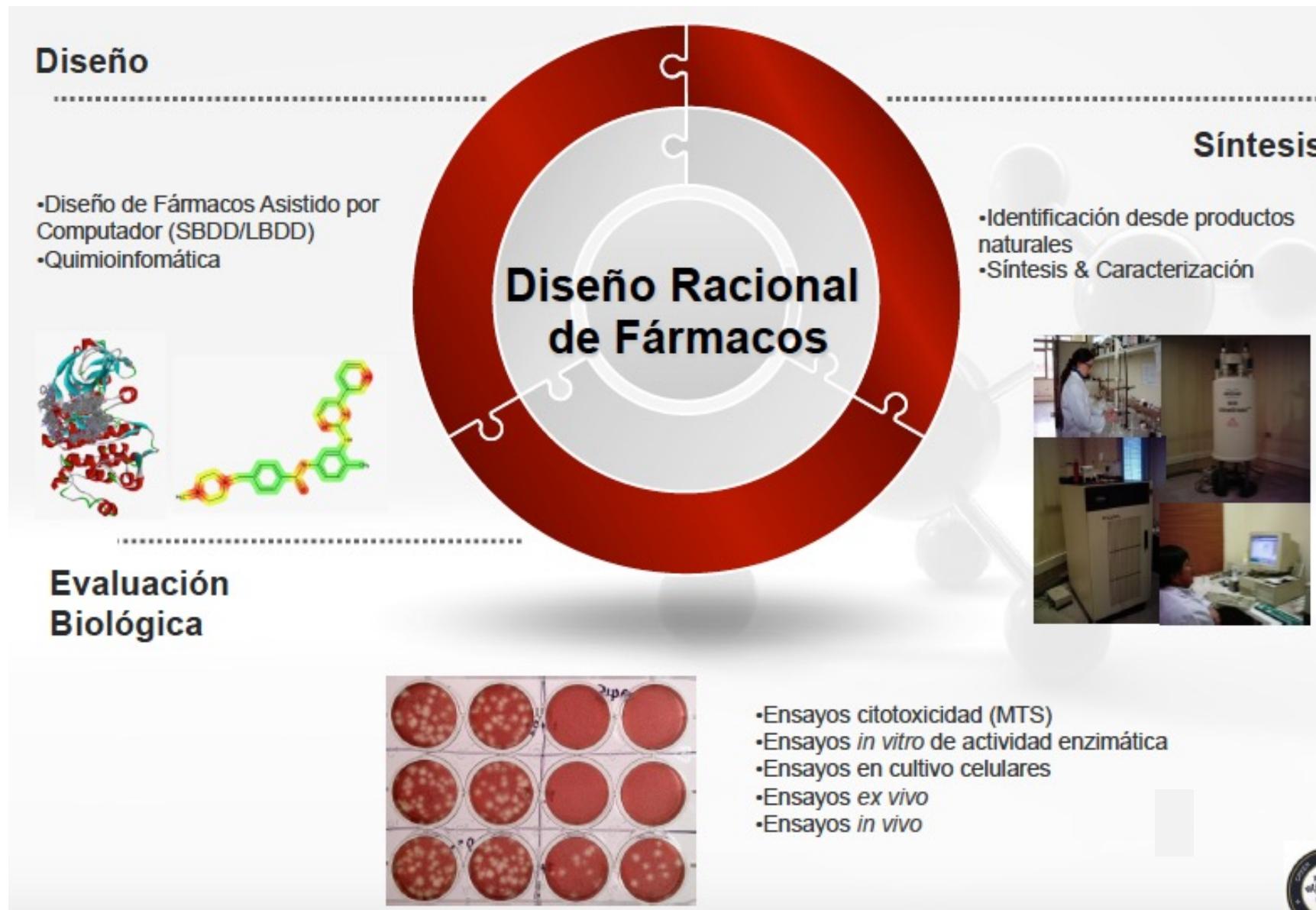
El costo aproximado de un programa de diseño de medicamentos es de US\$ 1000 millones por 8-15 años

Investigación preclínica

El descubrimiento de medicamentos es un proceso costoso y lento ... de 10000 compuestos obtenidos, solo uno llegará al mercado.



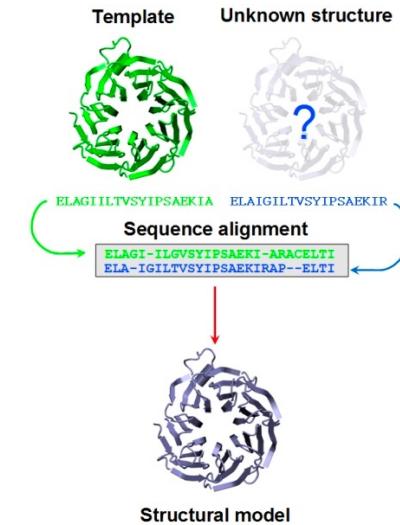
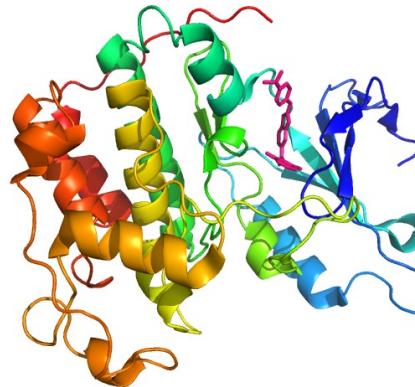
Ciclo de trabajo Diseño racional



Métodos de identificación asistidos por computadora

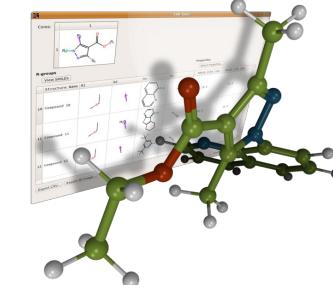
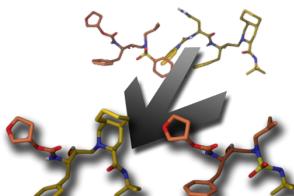
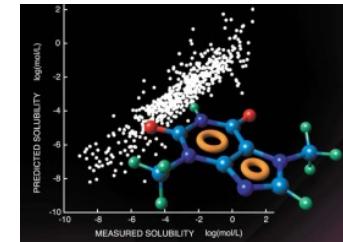
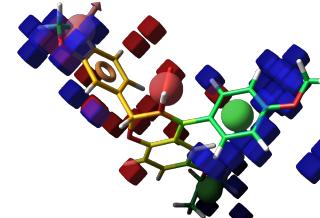
Métodos directos:

- Estructura 3D existente:
- SBDD
 - Rayos X o RMN
 - Modelo por homología



Métodos indirectos:

- Estructura 3D desconocida:
- LBDD
 - Diseño basado en análogos
 - QSAR
 - Farmacóforo
 - Similaridad



Bleicher, K. H.; Bohm, H. J.; Muller, K.; Alanine, A. I. Hit and lead generation: beyond high-throughput screening. *Nat Rev Drug Discov* 2003, 2, 369-78.

Sali, A.; Blundell, T. L. Comparative protein modelling by satisfaction of spatial restraints. *J Mol Biol* 1993, 234, 779-815.

Jorgensen, W. L. The many roles of computation in drug discovery. *Science* 2004, 303, 1813-8.

Ventajas y desventajas de SBDD y LBDD

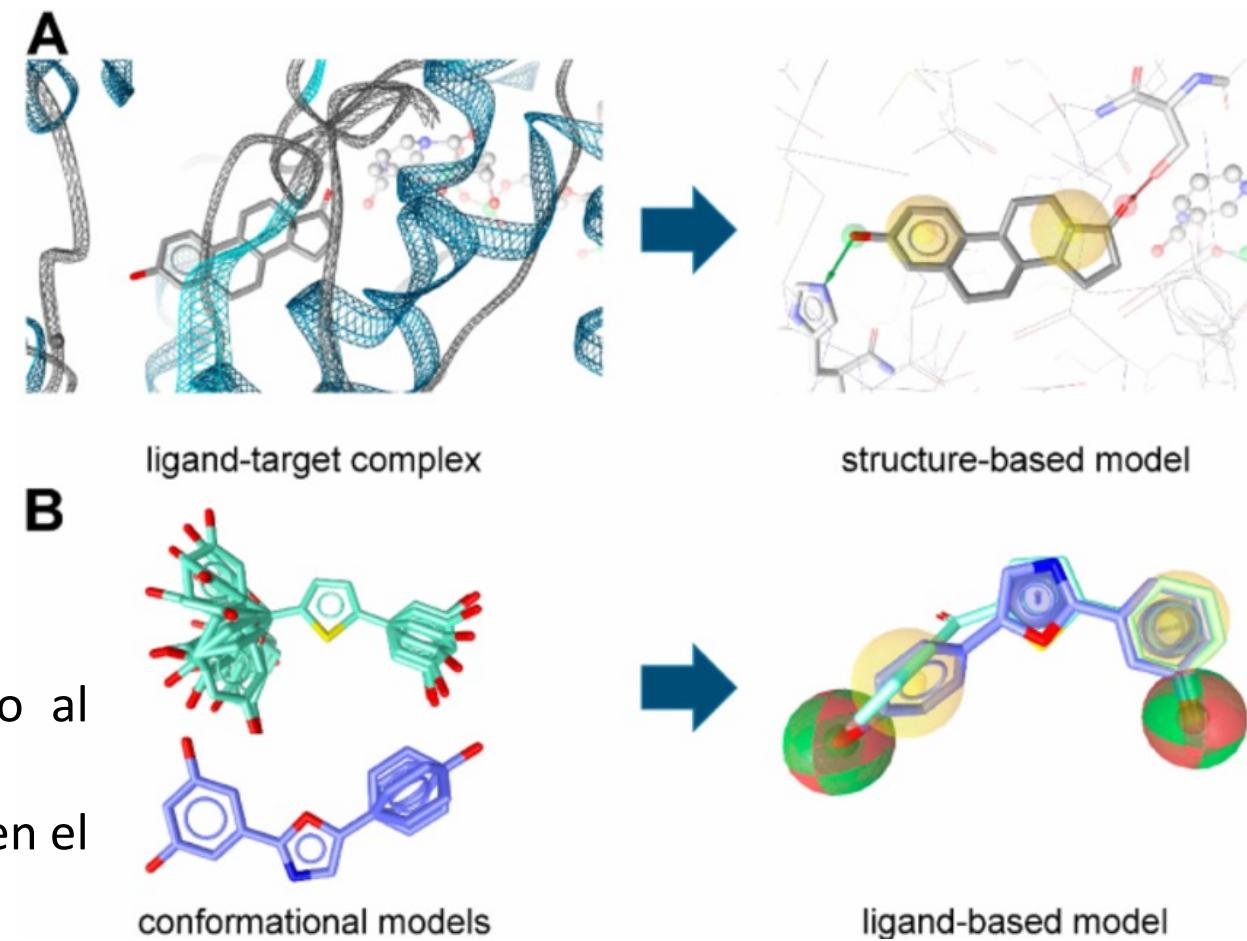
Métodos basados en estructura:

Ventaja: puede encontrar nuevos quimiotipos

Ventaja: no sesgado por ligandos conocidos

Pro: Calcula las contribuciones energéticas a de la unión

Con: los métodos precisos son relativamente lentos



Métodos basados en ligandos:

Pro: Rápido

Pro / Con: bueno para encontrar activos similares (o al menos perfiles de interacción similares)

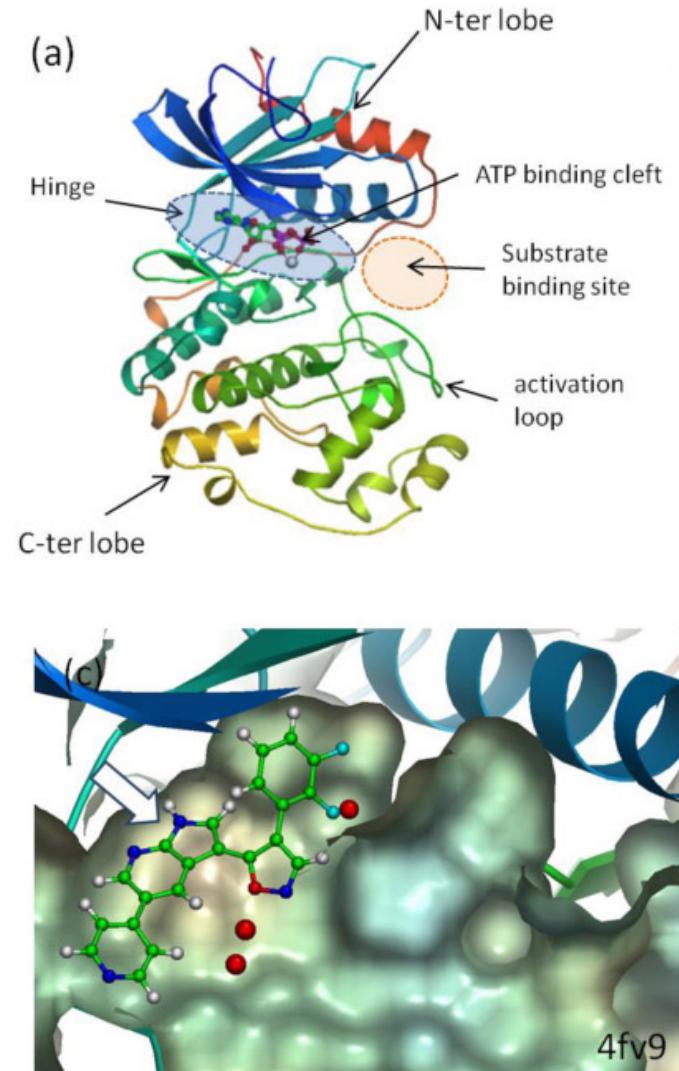
Pro / Con: a menudo más tolerante a cambios menores en el ligando

Con: a menudo se pierden los nuevos quimiotipos

Por que usar métodos in-silico en el descubrimiento desarrollo de fármacos

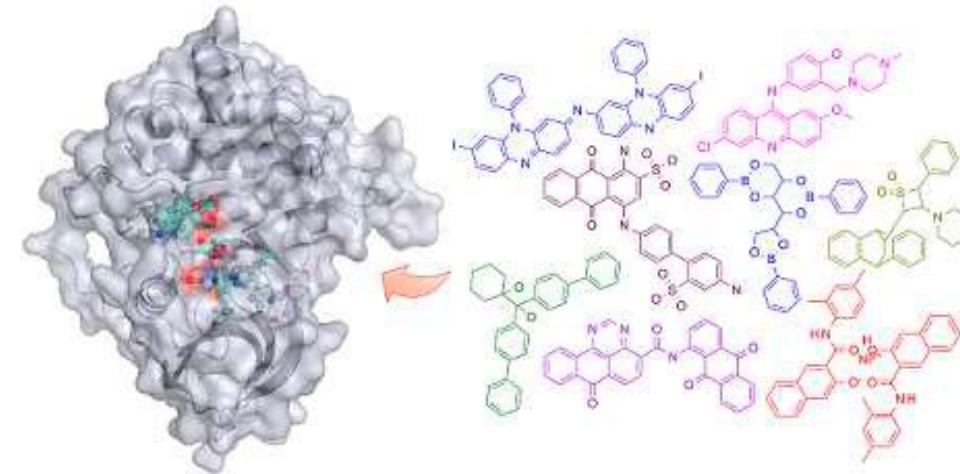
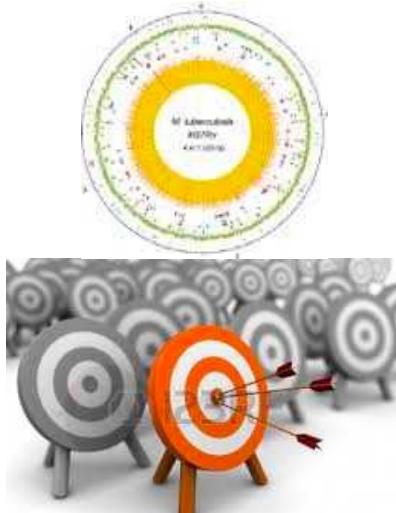
Herramientas “de uso corriente” en varias metodologías asociadas al proceso.

- Reducir costos y reducir tiempos del proceso de desarrollo
- Descartar hipótesis con baja probabilidad de éxito
- Reducir el universo de ensayos a realizar
- Manejar e integrar grandes volúmenes de datos
- Genoma-transcriptoma-Metaboloma
- Bibliotecas de compuestos
- Comprender los mecanismos subyacentes de los procesos involucrados.
- Biología Estructural
- Química Teórica



Contribuciones de la Bioinformática Estructural al desarrollo de fármacos

1-Selección de Blancos



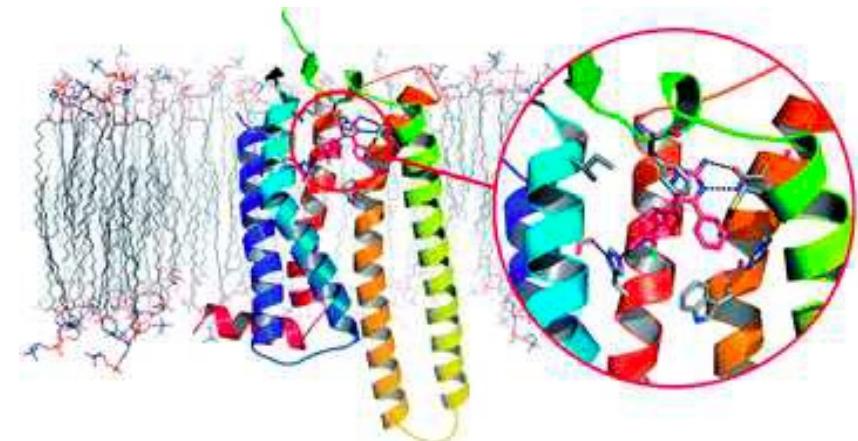
EGFR-TK, ball & stick
refers to binding residues

8 hits from NCI diversity database

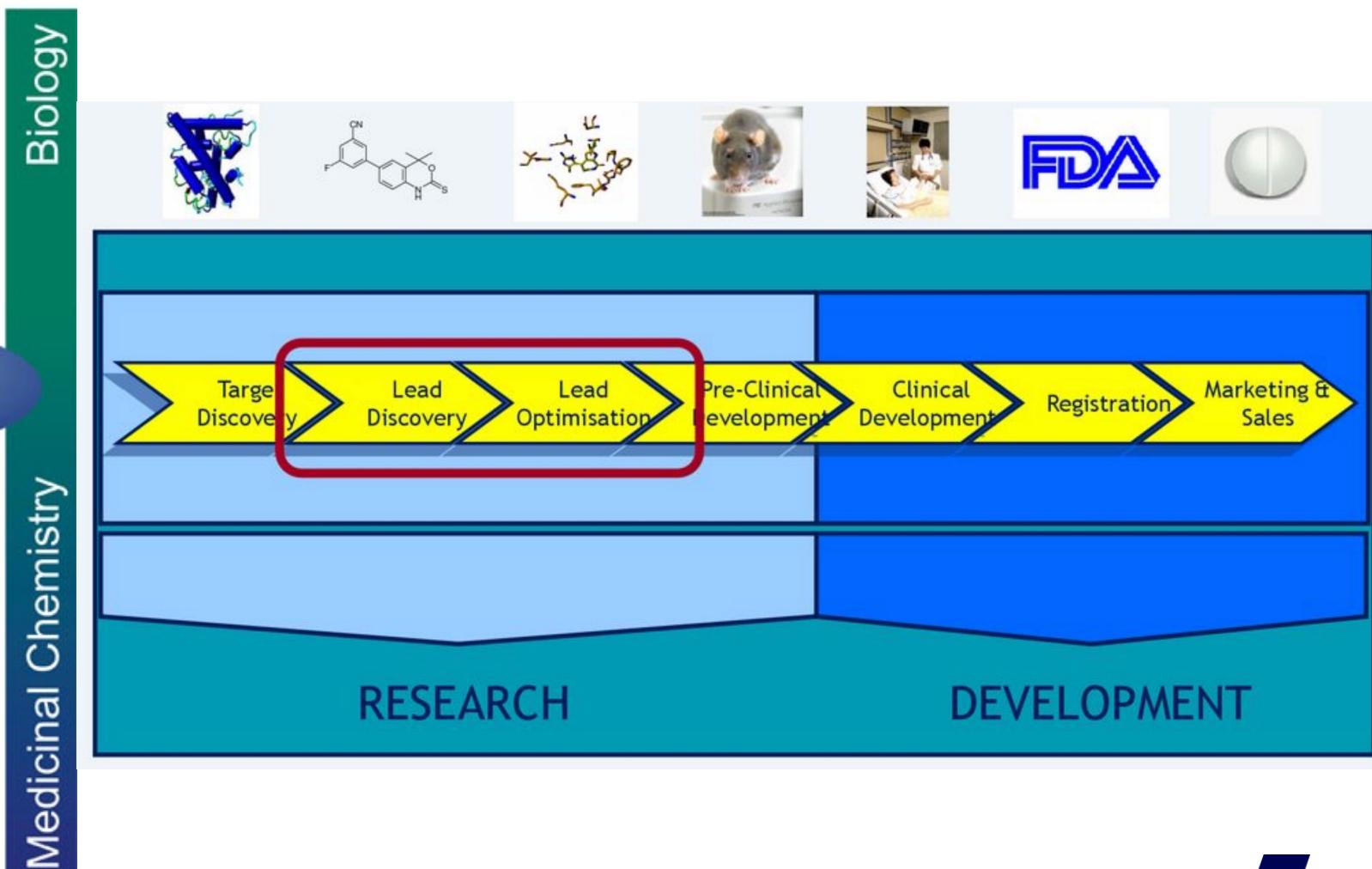
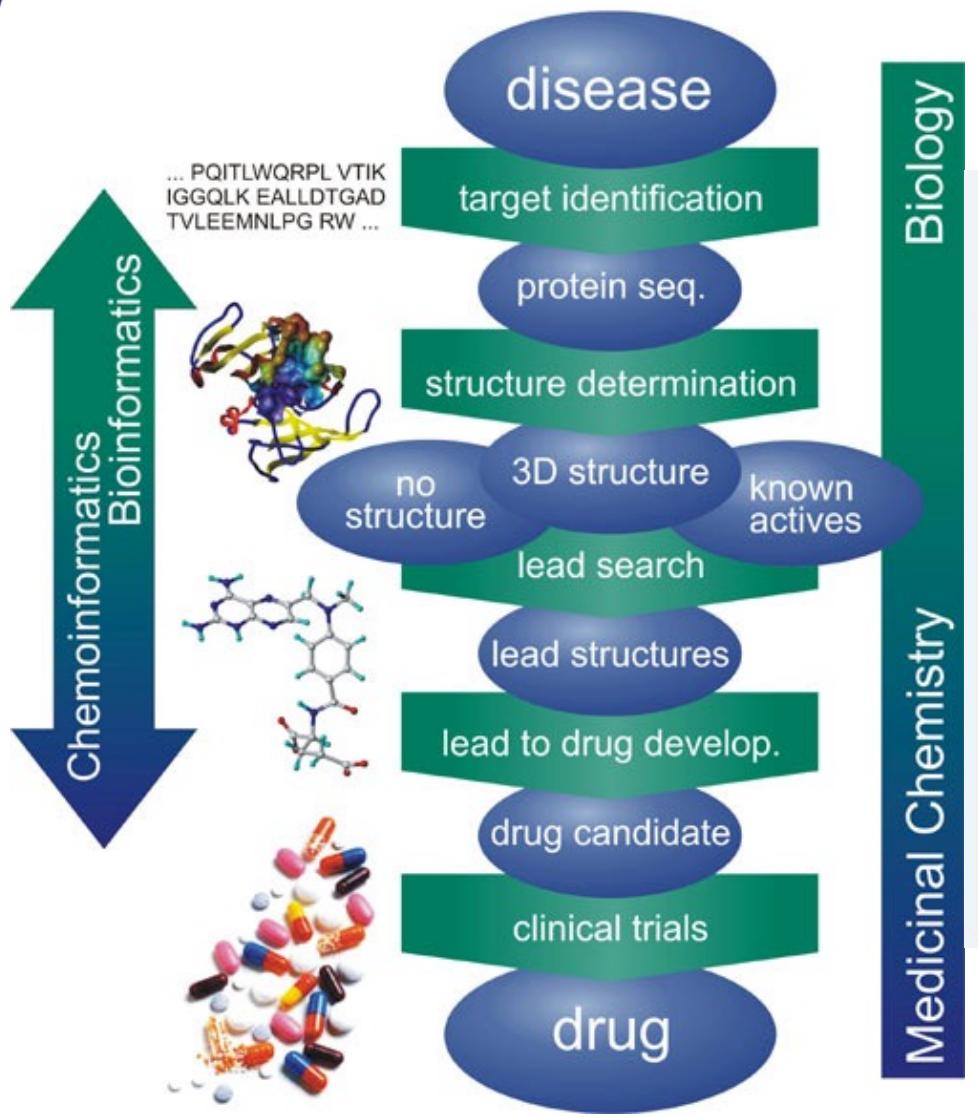
2-Selección de Compuestos candidatos

Absorción
Distribución
Metabolismo
Excreción

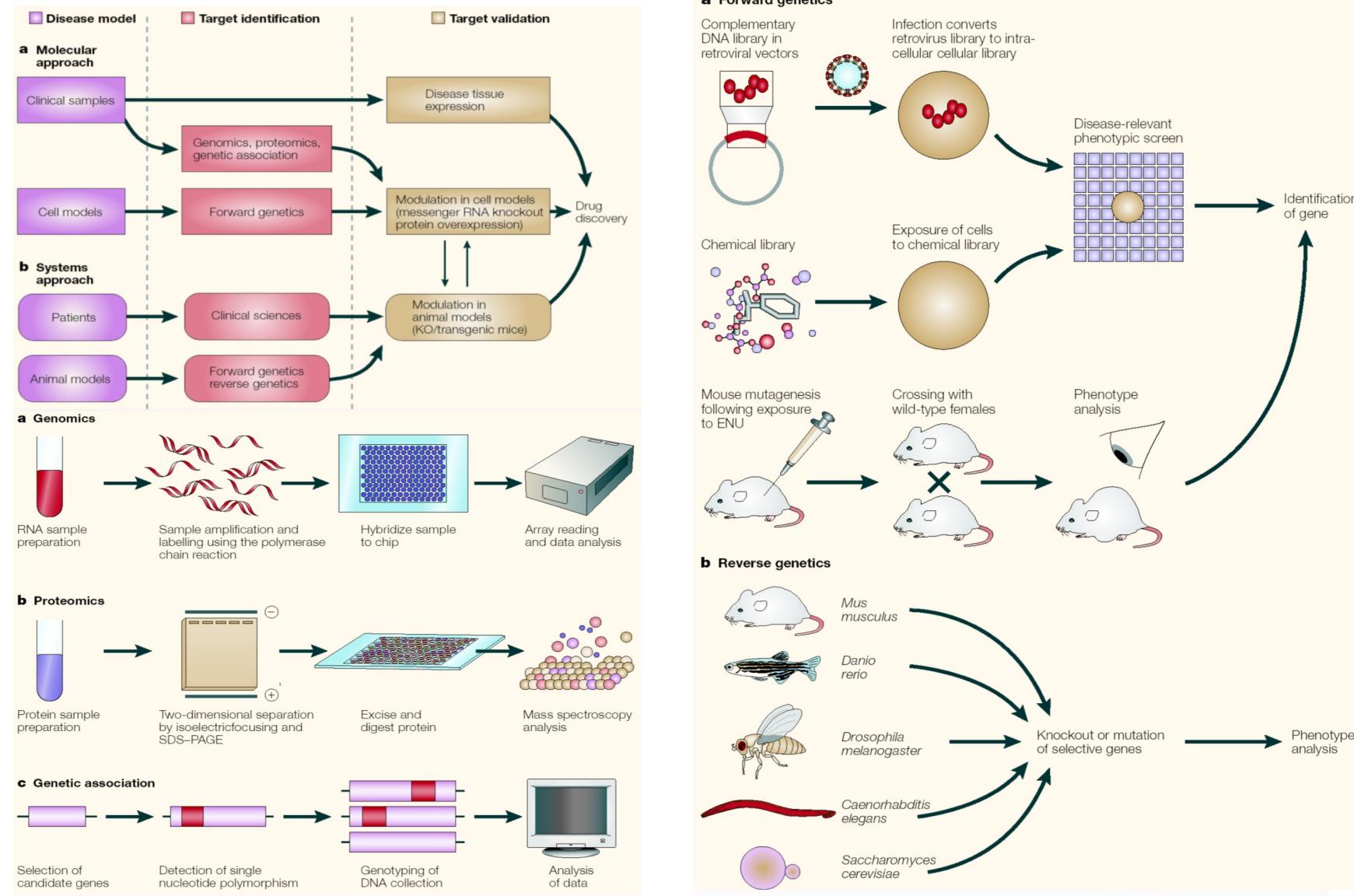
3-Diseño
racional basado
en estructura



Ciclo Diseño racional completo



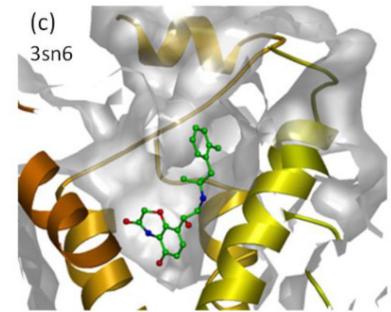
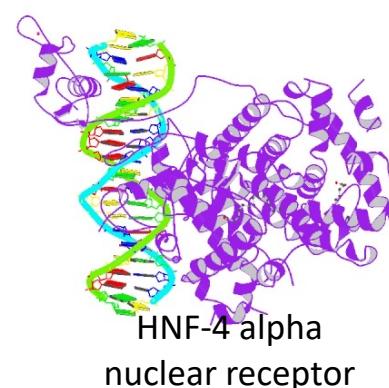
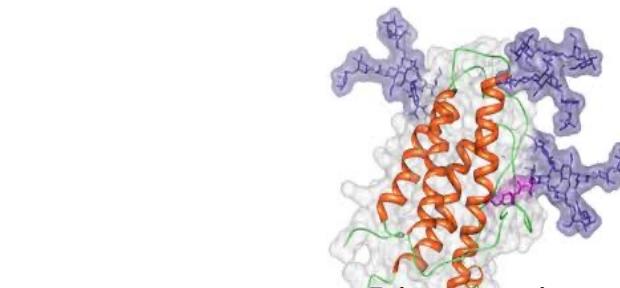
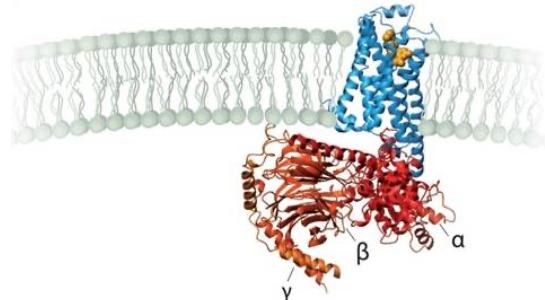
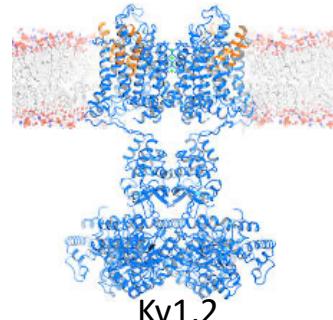
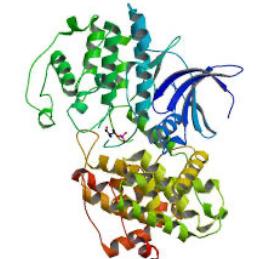
Identificación y validación de targets



Selección de target

Clases bioquímicas de targets:

- Receptores acoplados a proteínas-G
- Enzimas
- Hormonas y factores
- Canales iónicos
- Receptores nucleares



Concepto de Drogabilidad

Drogabilidad: Capacidad de una entidad molecular biológica (Proteína) de unir un compuesto tipo-droga capaz de modular su función y producir el efecto terapéutico deseado.

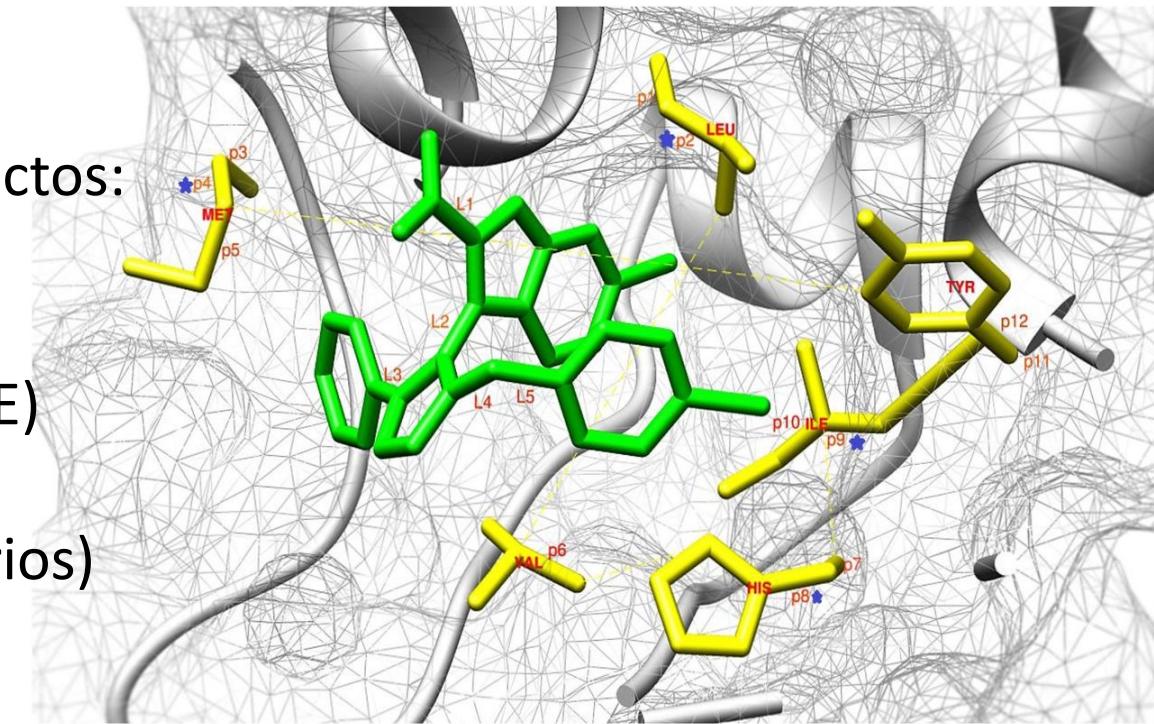
Podemos dividir el concepto en los siguientes aspectos:

Capacidad de unir compuestos “Bindability”

Capacidad de unir compuestos “tipo-droga” (ADME)

Modular su función (inhibir-activar)

Producir efecto deseado (y evitar efectos secundarios)

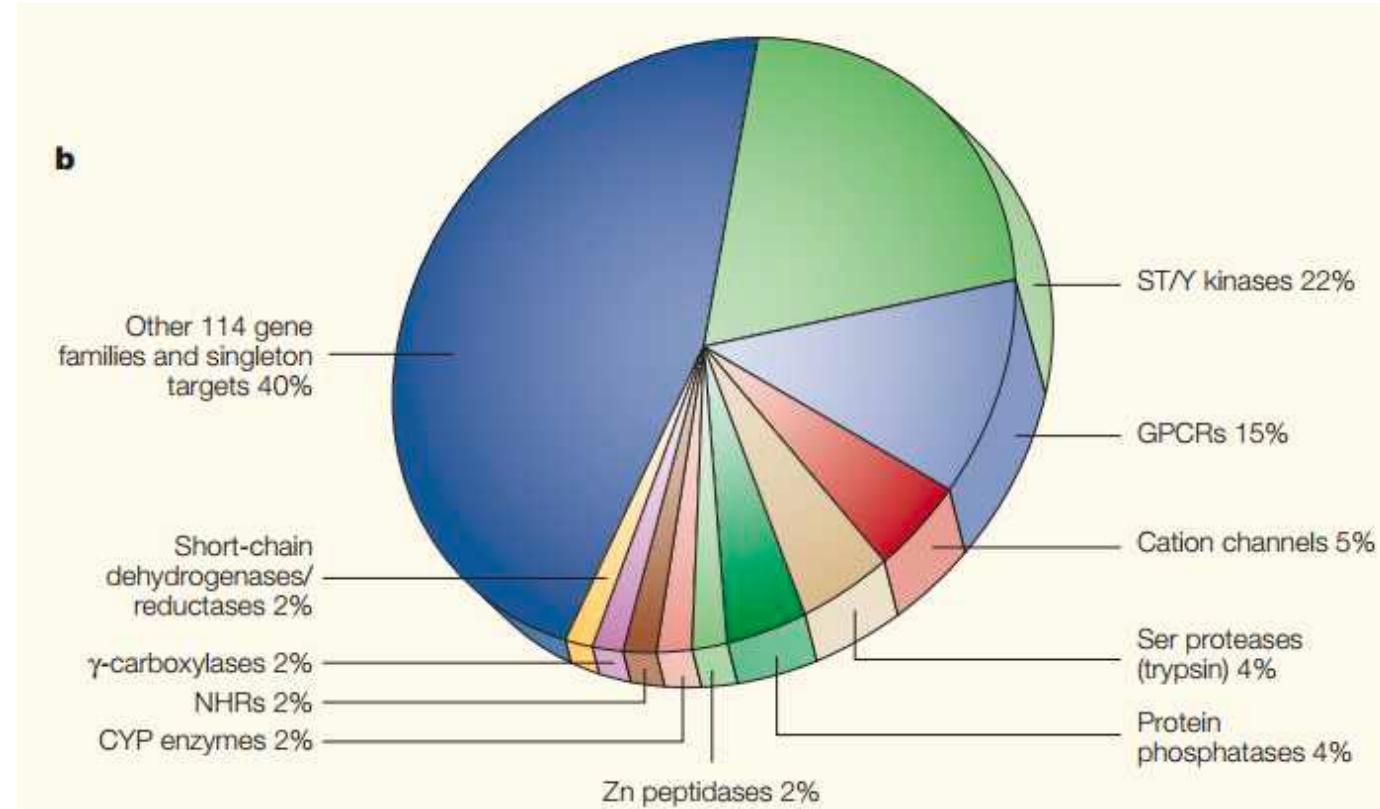


BindingDB, PubChem, SwissTargetPrediction, TargetHunter, Guide to pharmacology, National Center for Biotechnology Information (NCBI), and Protein data bank.

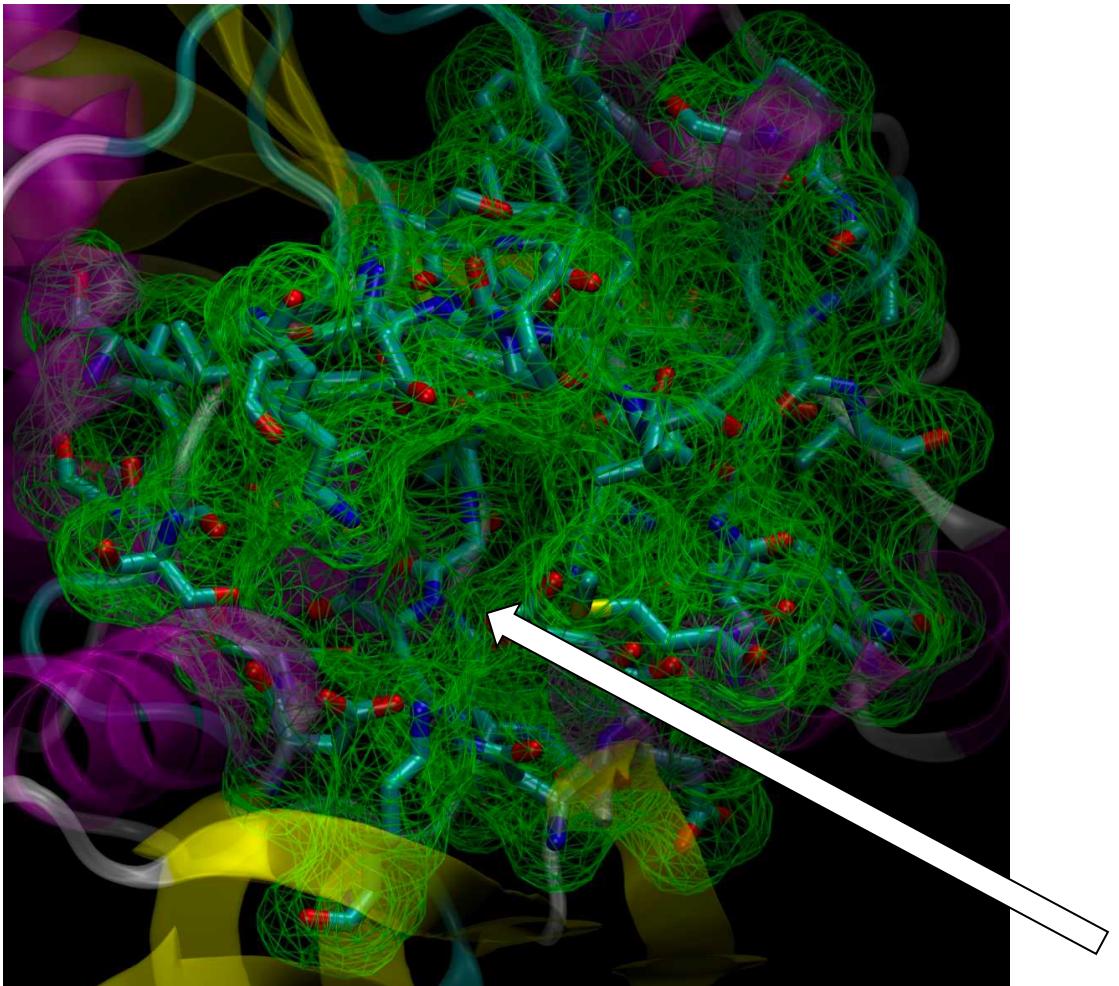
Que parte de un genoma es drogable?

Que proteínas (enzimas) son posibles de ser inhibidas?

Que información necesito para predecir esta capacidad?



Concepto de “bindability”



Determinar la capacidad de una proteína (un bolsillo) de unir un compuesto tipo-droga

Como determinarlo?

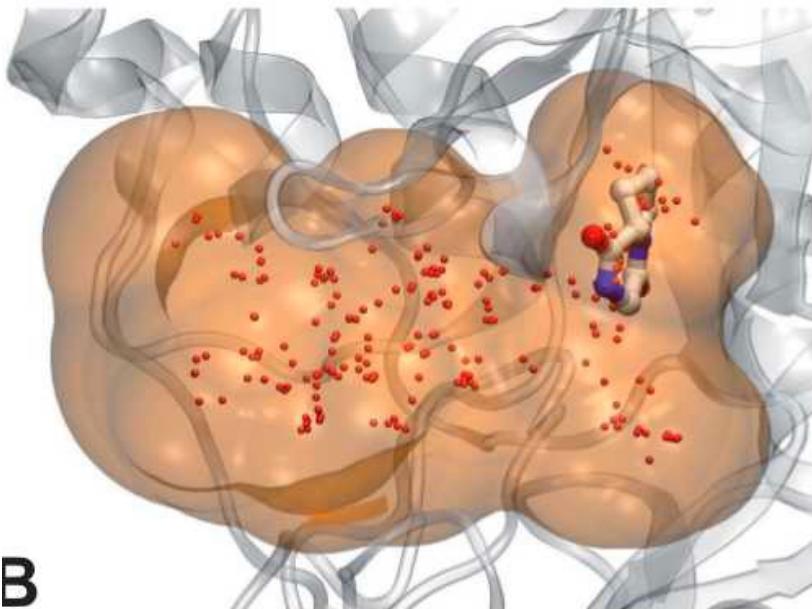
- 1) Determinar los bolsillos
- 2) Determinar sus Propiedades

Entra una droga aquí?

¿Qué características posee un bolsillo drogable?

Definición y caracterización de bolsillos con fpocket. Metapocket and DeepSite.
pockets predictors.

Bolsillo se define a través de “esferas alfa” y sus características.

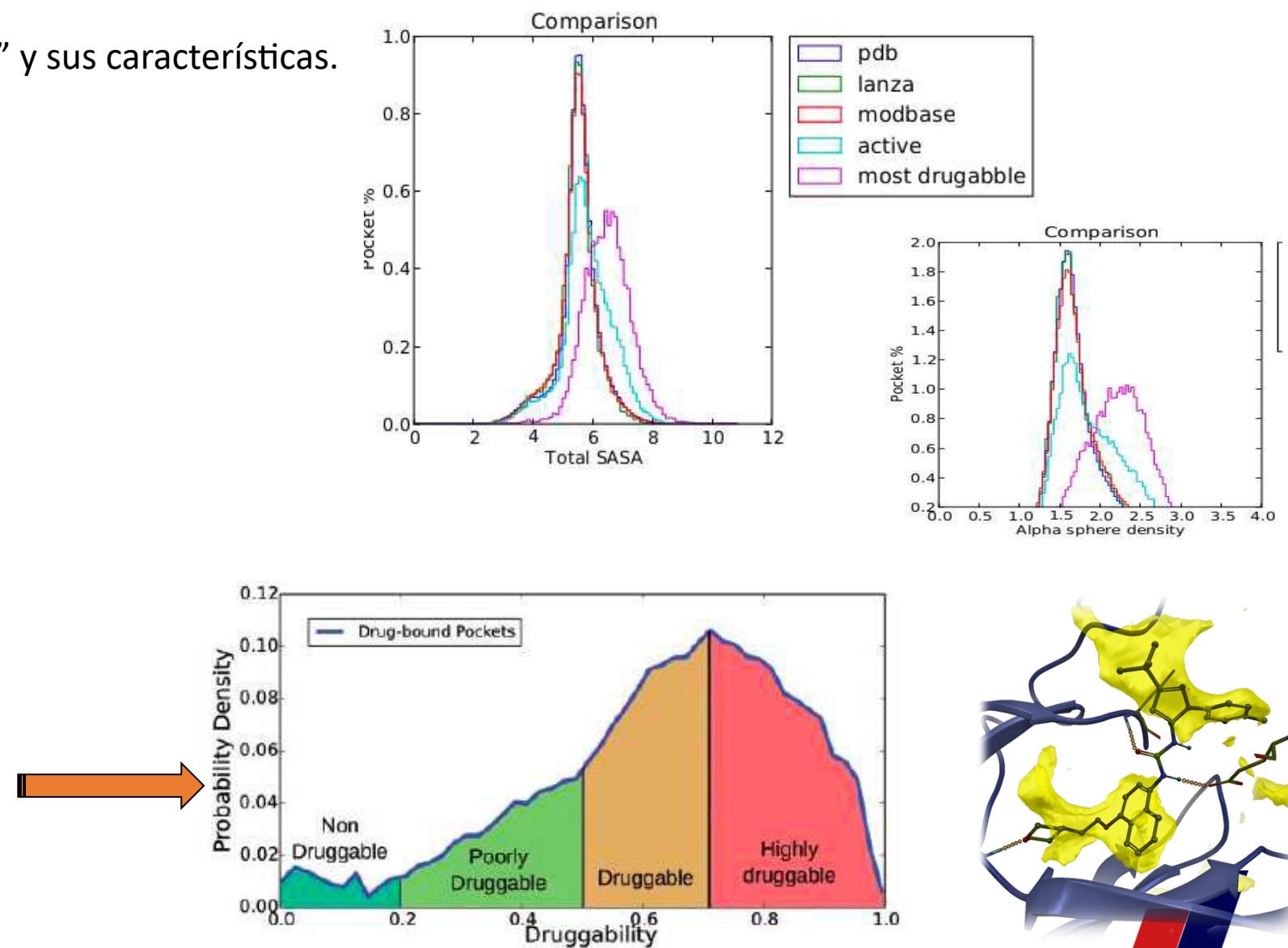


B

Puntaje de “Drogabilidad” 0 a 1



19



¿Qué otra información adicional (a la estructura) es importante?

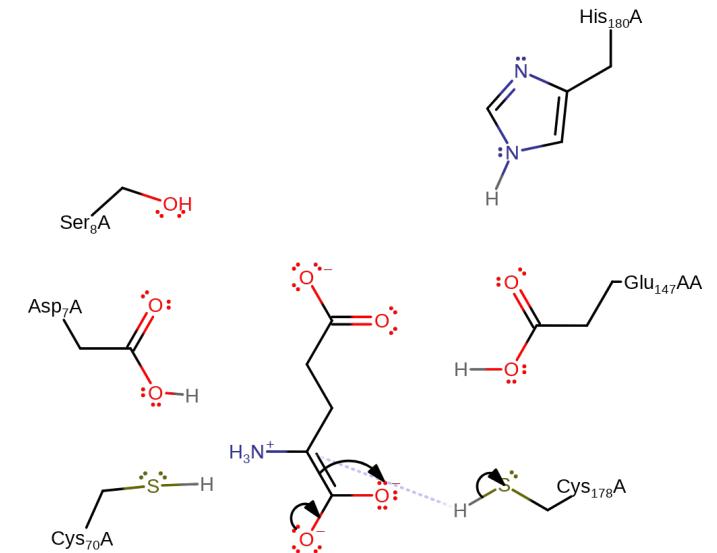
El bolsillo esta formado por los residuos catalíticamente relevantes:

Utilización de información de CSA-Catalytic Site Atlas



Utilización de información de participación de residuos en procesos biológicos (derivado de UniprotKB)

El bolsillo esta formado por los residuos conservados:
Determinación de conservación en la familia (PFAM)



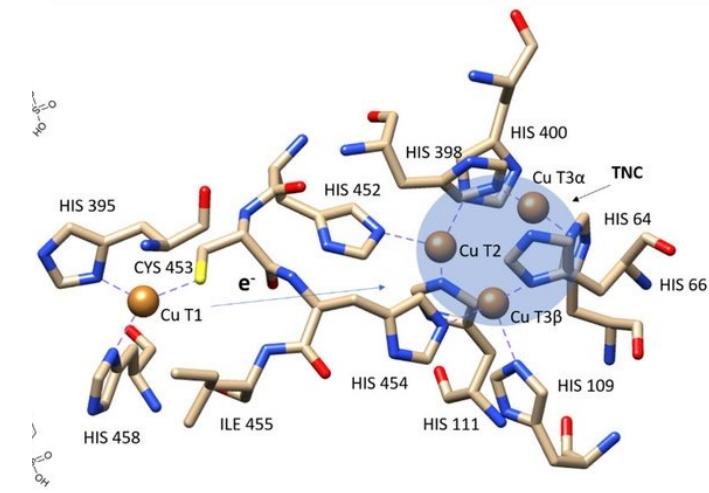
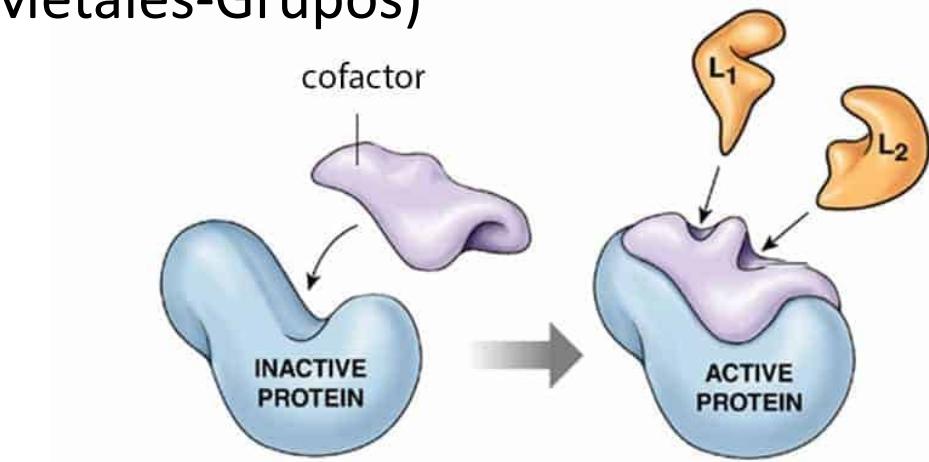
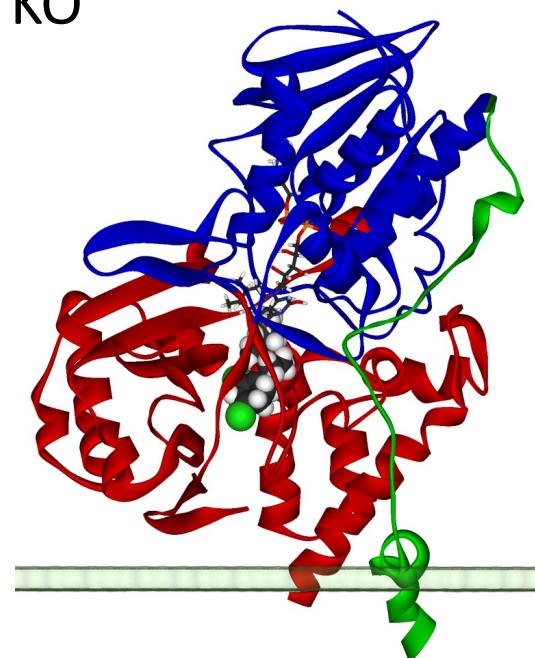
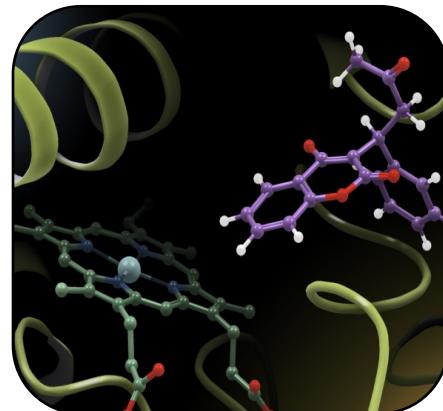
¿Qué otra información adicional (a la estructura) es importante?

El bolsillo es adyacente a la presencia de Cofactores (Metales-Grupos)

Información adicional de la proteína

Perfil/sitio/condición de expresión

Efecto biológico de mutantes KO



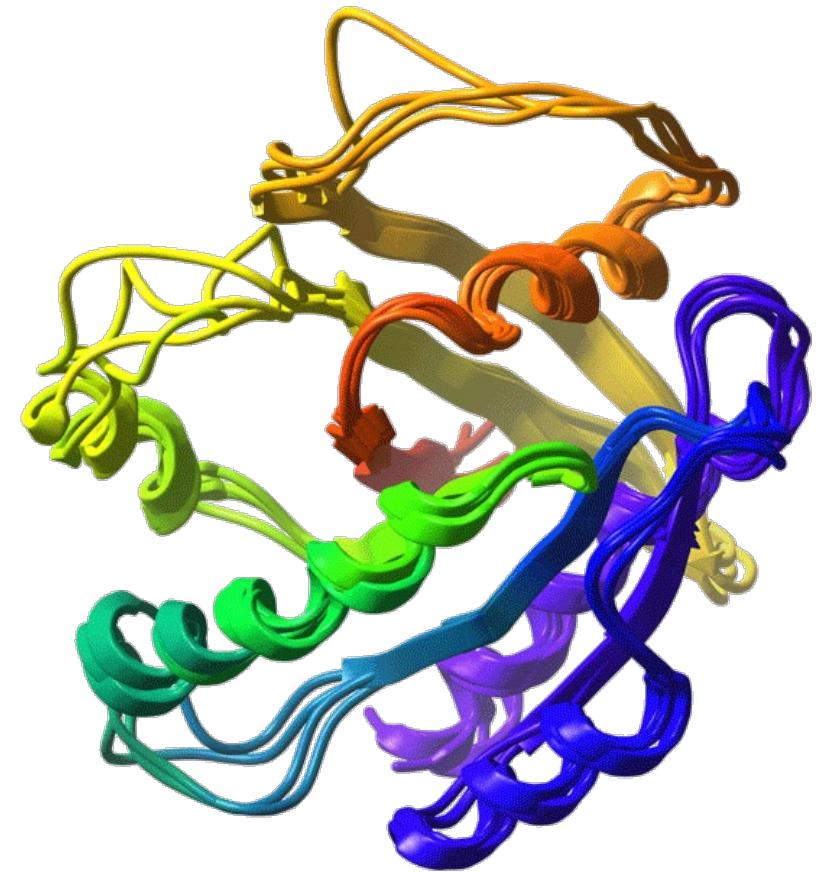
Modelos

Doble reconocimiento.

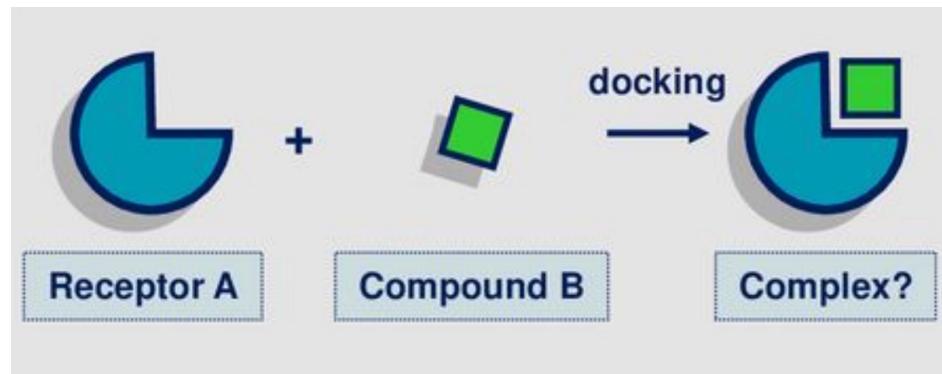
La búsqueda de homología remota se implementó usando iteraciones de PSI BLAST contra una gran base de datos de secuencias agrupadas (BigDB), guardando un perfil de búsqueda y reiniciando la búsqueda de PSI BLAST contra una biblioteca de plantillas (TempIDB) usando el perfil.

Modelado

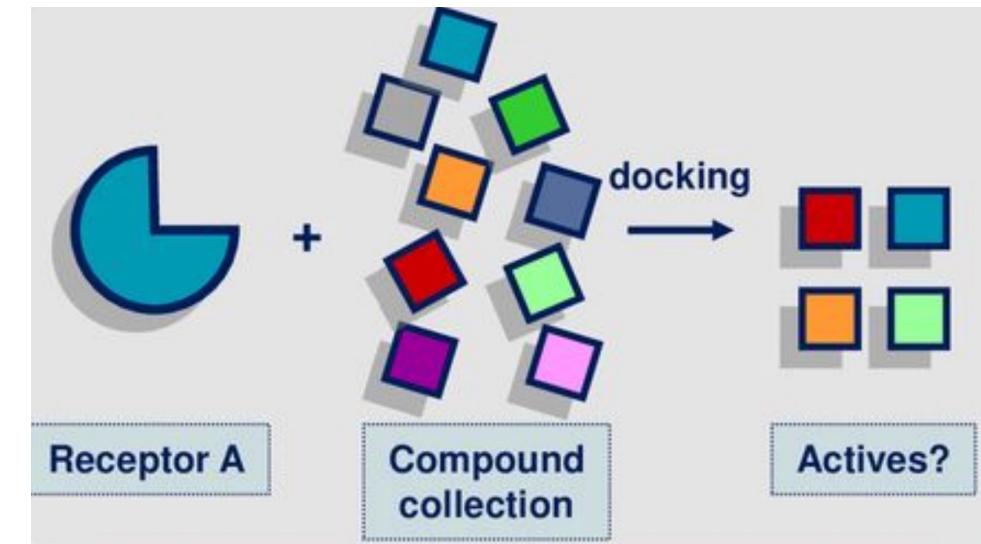
Se utiliza MODELLER en coordenadas de plantilla y alineación local a partir de la búsqueda de homología remota, lo que produce un número fijo de modelos para cada objetivo.



Docking Molecular



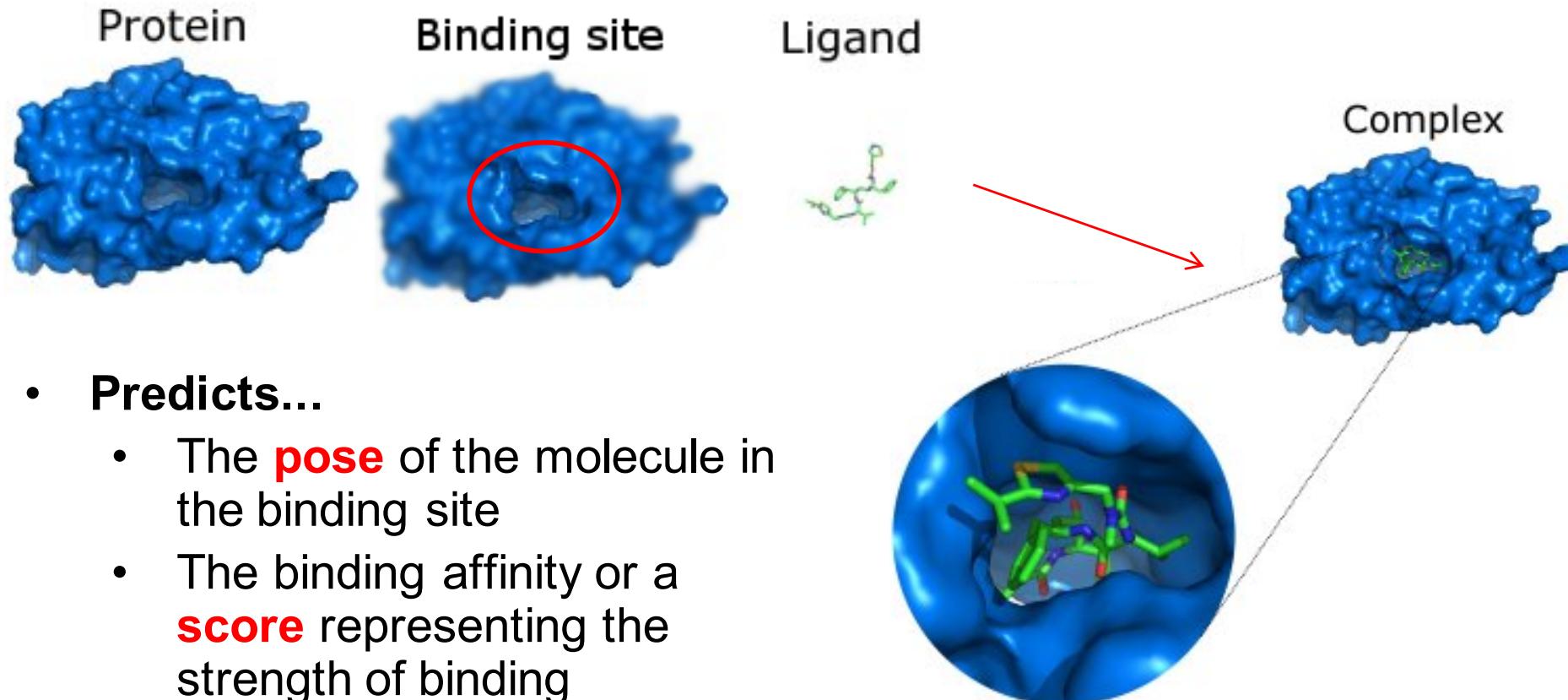
Cómo luce el complejo



Cuáles compuestos en una colección podrían ser activos

Protein-ligand docking

- A Structure-Based Drug Design (SBDD) method
 - “structure” means “using protein structure”
- Computational method that mimics the binding of a ligand to a protein
- **Given...**



The Structure Based Workflow

Docking



Scoring



Filtering

What possible poses can my ligand adopt in the binding site?

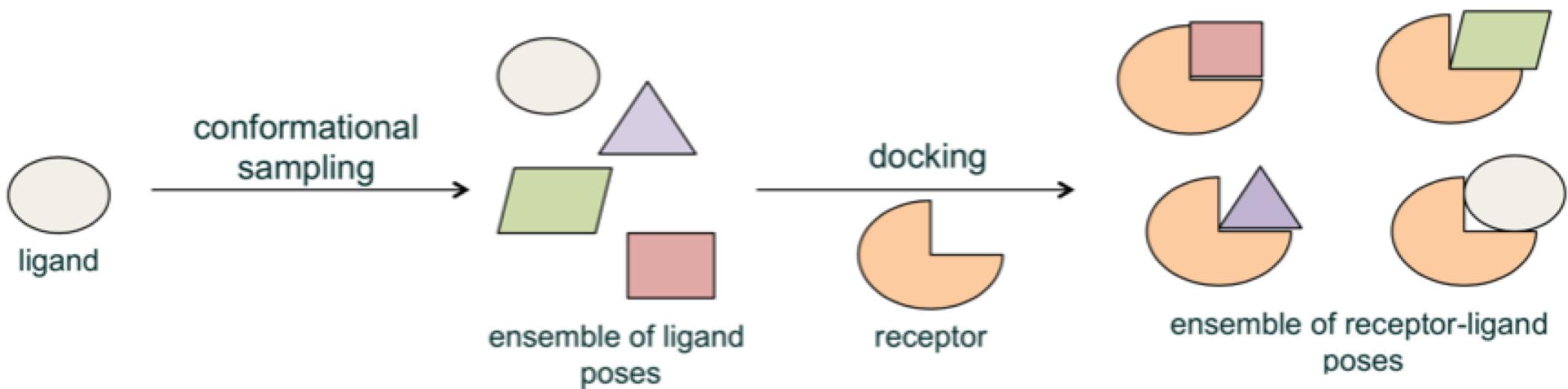
Which of those poses makes the best interactions with the receptor?

Which of those make the contacts I care about?

Docking

Docking

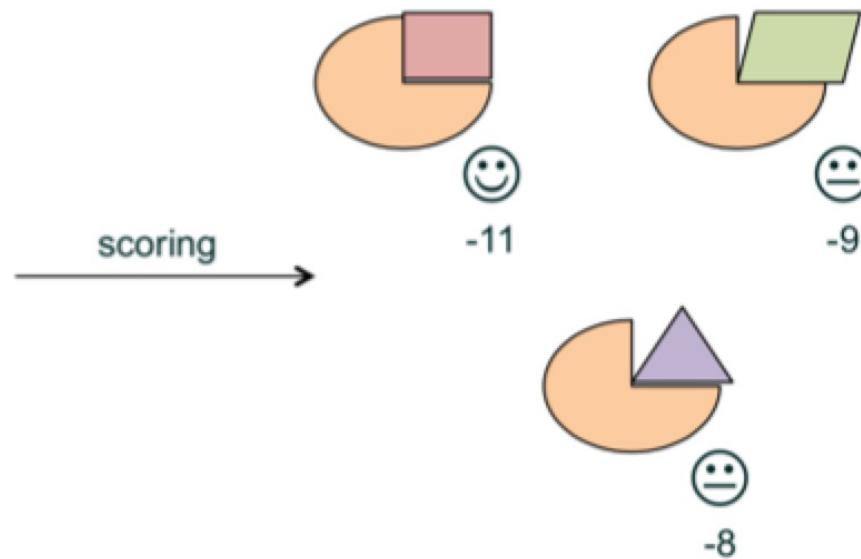
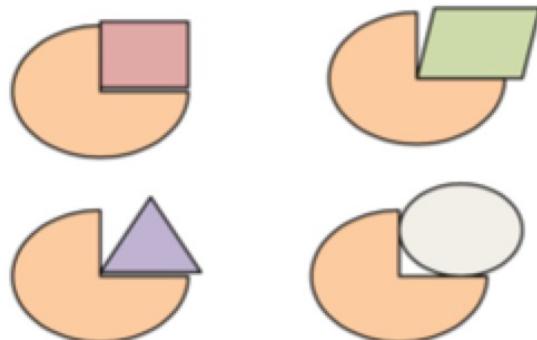
- Assume receptor is rigid
- Assume ligand is flexible



Scoring



How “good” is a given pose?



SCHRÖDINGER.



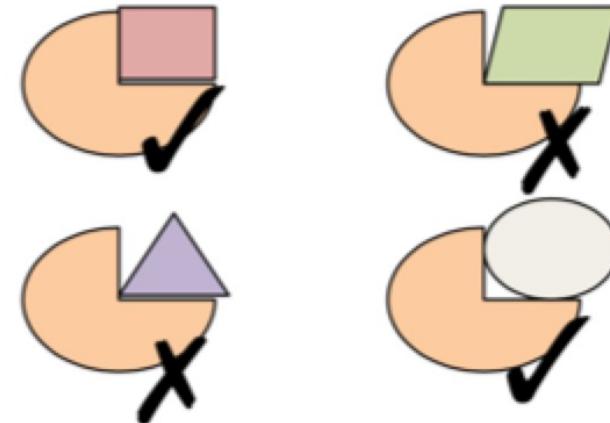
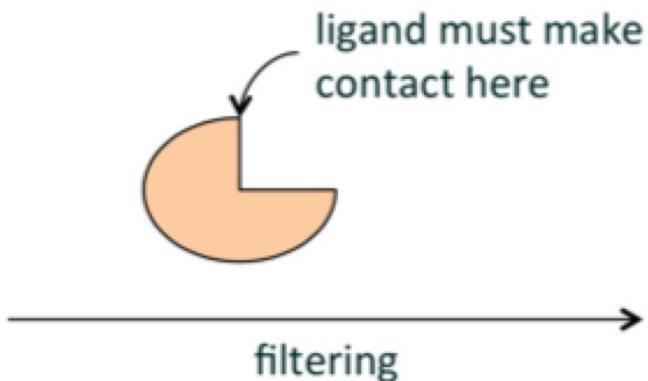
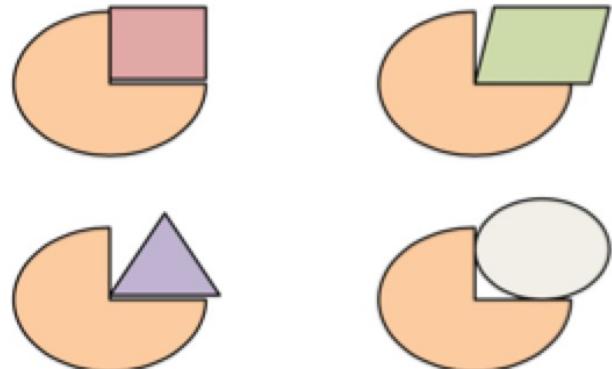
Filtering

Docking

Scoring

Filtering

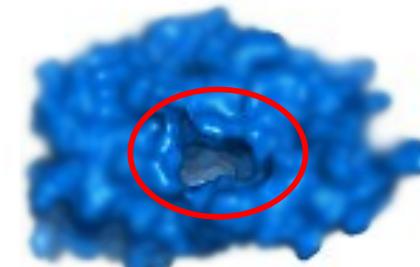
Keep only the poses that make the contacts you want



Pose vs. binding site

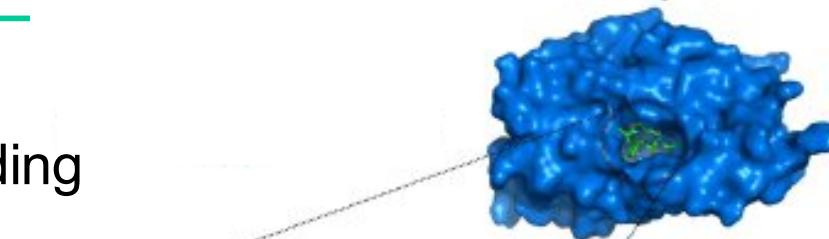
- **Binding site** (or “active site”)
 - the part of the protein where the ligand binds
 - generally a cavity on the protein surface
 - can be identified by looking at the crystal structure of the protein bound with a known inhibitor

Binding site

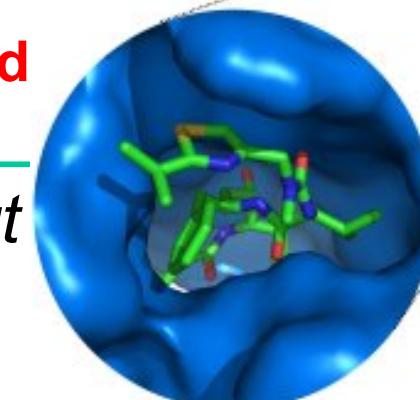


- **Pose** (or “binding mode”)
 - The *geometry* of the ligand in the binding site
 - Geometry = **location, orientation and conformation**

Complex

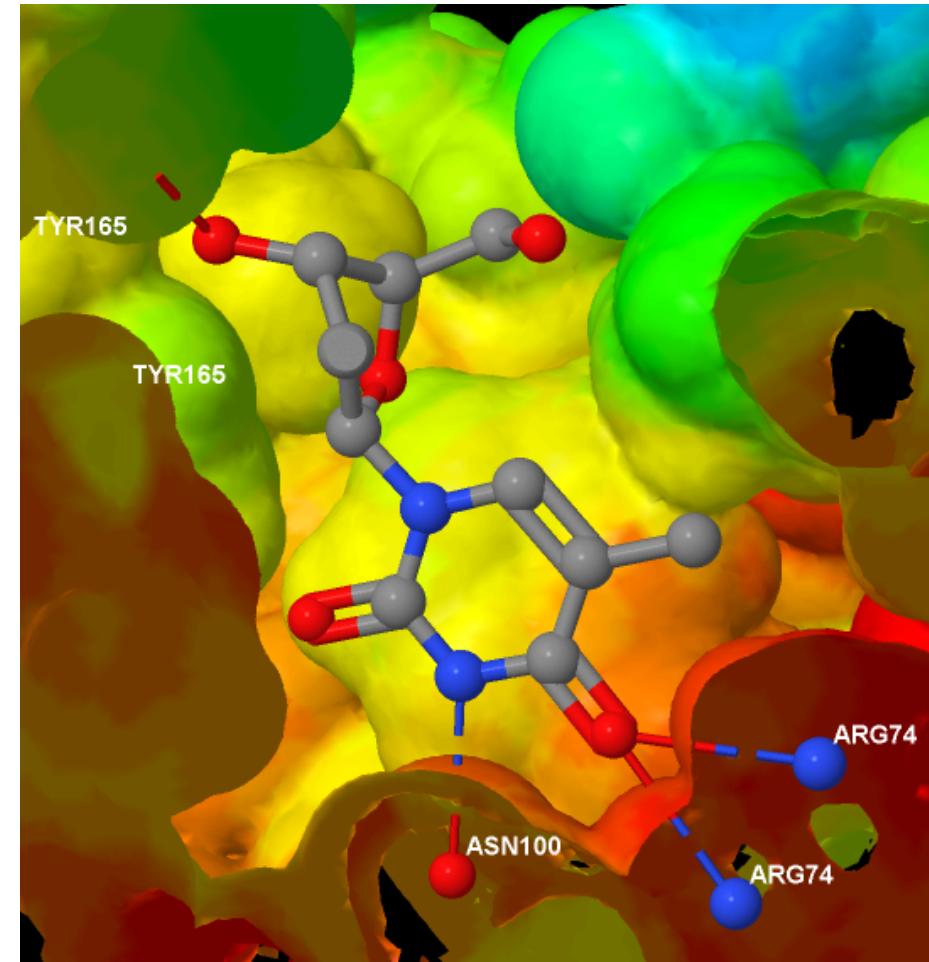


- *Protein-ligand docking is **not** about identifying the binding site*



Uses of docking

- The main uses of protein-ligand docking are for
 - Virtual screening, to identify potential lead compounds from a large dataset (see next slide)
 - Pose prediction
- **Pose prediction**
- If we know exactly where and how a known ligand binds...
 - We can see which parts are important for binding
 - We can suggest changes to improve affinity
 - Avoid changes that will ‘clash’ with the protein

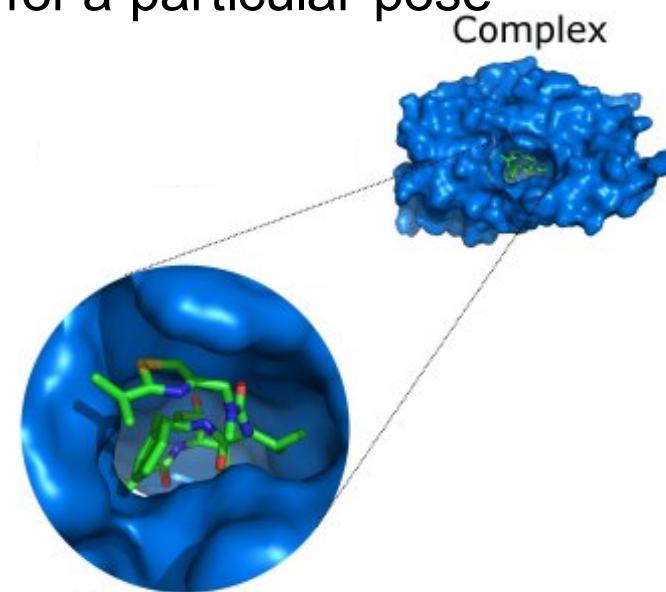


Virtual screening

- Virtual screening is the computational or *in silico* analogue of biological screening
- The aim is to **score**, **rank** or **filter** a set of chemical structures using one or more computational procedures
 - Docking is just one way to do this
- It can be used
 - to help decide which compounds to screen (experimentally)
 - which libraries to synthesise
 - which compounds to purchase from an external company
 - to analyse the results of an experiment, such as a HTS run

Components of docking software

- Typically, protein-ligand docking software consist of two main components which work together:
 - **1. Search algorithm**
 - Generates a large number of poses of a molecule in the binding site
 - **2. Scoring function**
 - Calculates a score or binding affinity for a particular pose
- **To give:**
 - The **pose** of the molecule in the binding site
 - The binding affinity or a **score** representing the strength of binding



Content list available at: www.benthamopen.com/TOMCJ/

DOI: 10.2174/1874104501610010007



Computational Methods Applied to Rational Drug Design

David Ramírez*

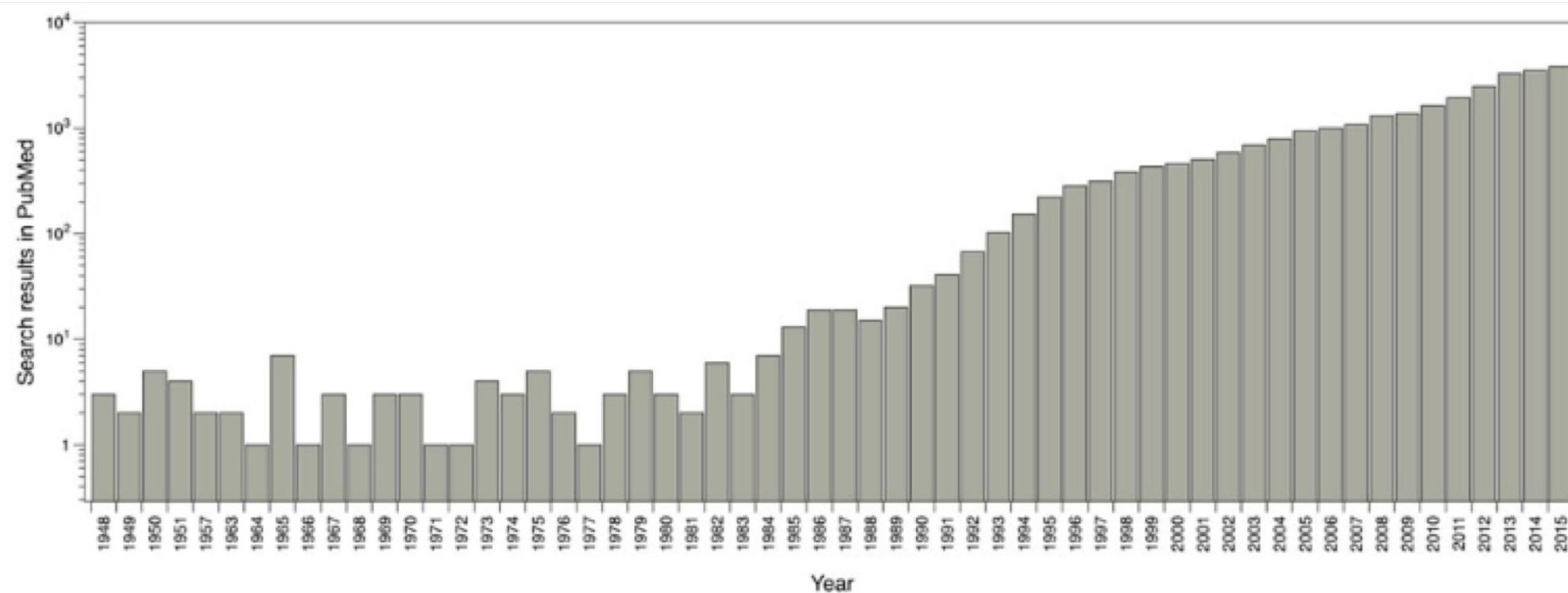
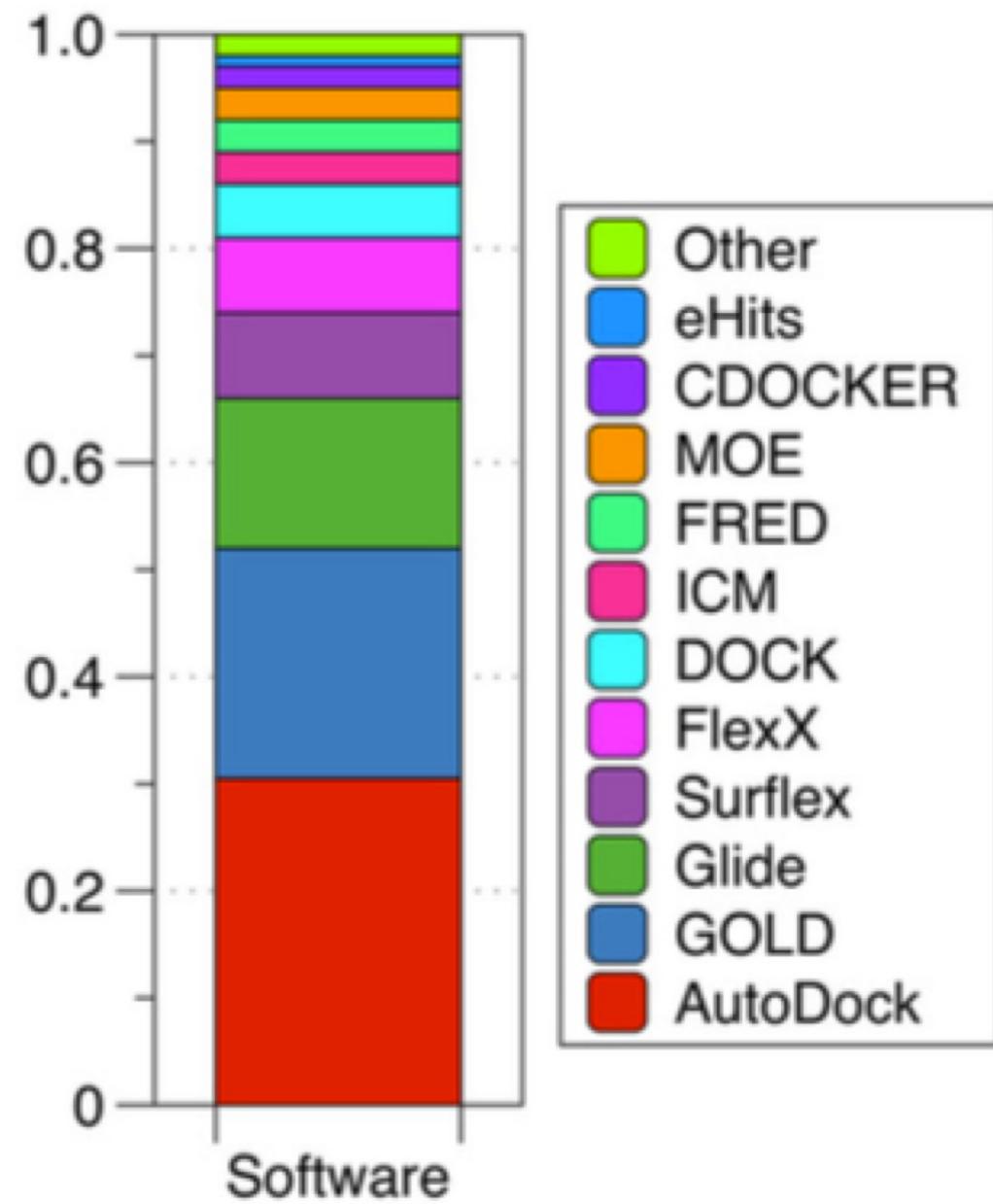
Centro de Bioinformática y Simulación Molecular, Universidad de Talca, 2 Norte 685, Casilla, Talca, Chile

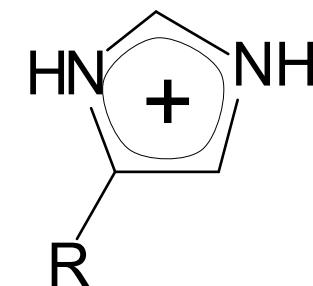
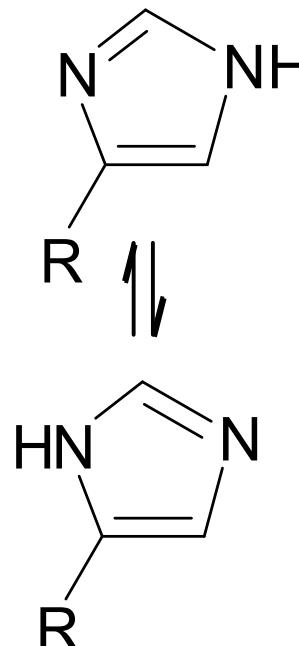
Fig. (1). Reported publications number where molecular docking was used. Results from PubMed using the word 'docking' as search criteria.



Preparing the protein structure

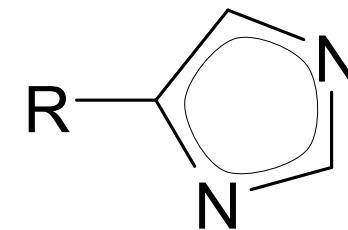
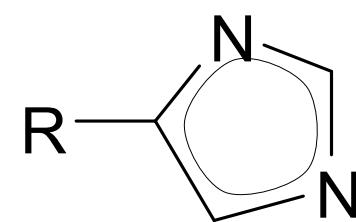
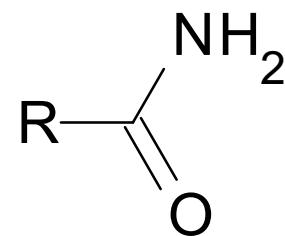
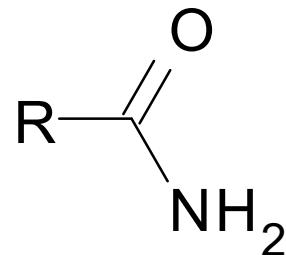
- PDB structures often contain water molecules
 - In general, **all water molecules are removed** except where it is known that they play an important role in coordinating to the ligand
- PDB structures are missing all **hydrogen atoms**
 - Many docking programs require the protein to have explicit hydrogens. In general these can be added unambiguously, except in the case of acidic/basic side chains

- An incorrect assignment of **protonation states** in the active site will give poor results
- Glutamate, Aspartate have COO- or COOH
 - OH is hydrogen bond donor, O- is not
- Histidine is a base and its neutral form has two tautomers



Preparing the protein structure

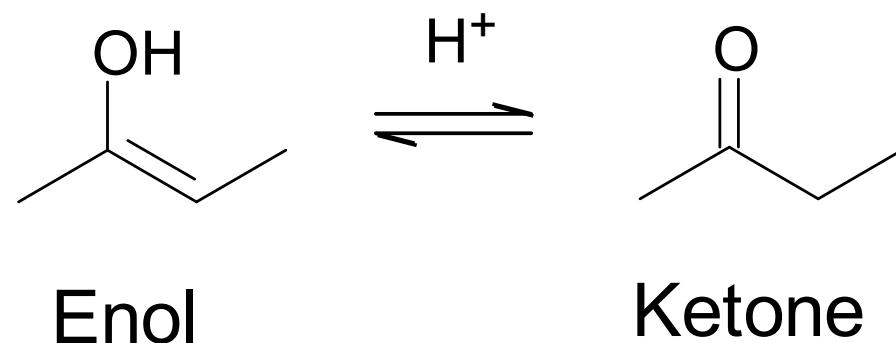
- For particular protein side chains, the PDB structure can be incorrect
- Crystallography gives electron density, not molecular structure
 - In poorly resolved crystal structures of proteins, **isoelectronic groups** can give make it difficult to deduce the correct structure



- Affects asparagine, glutamine, histidine
- Important? Affects hydrogen bonding pattern
- May need to **flip amide or imidazole**
 - How to decide? Look at hydrogen bonding pattern in crystal structures containing ligands

Ligand Preparation

- A **reasonable 3D structure** is required as starting point
 - During docking, the bond lengths and angles in ligands are held fixed; only the torsion angles are changed
 - The **protonation state** and **tautomeric form** of a particular ligand could influence its hydrogen bonding ability
 - Either protonate as expected for physiological pH and use a single tautomer
 - Or generate and dock all possible protonation states and tautomers, and retain the one with the highest score

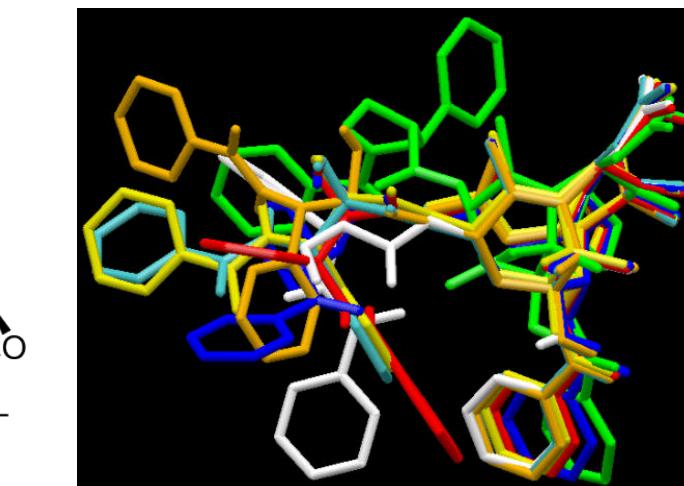
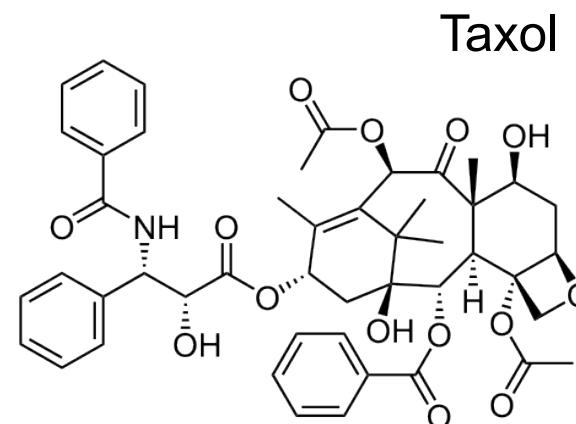
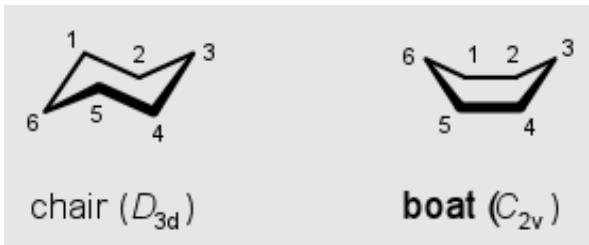


The search space

- The difficulty with protein–ligand docking is in part due to the fact that it involves **many degrees of freedom**
 - The translation and rotation of one molecule relative to another involves six degrees of freedom
 - There are in addition the conformational degrees of freedom of both the ligand and the protein
 - The solvent may also play a significant role in determining the protein–ligand geometry (often ignored though)
- The search algorithm generates poses, orientations of particular conformations of the molecule in the binding site
 - Tries to cover the search space, if not exhaustively, then as extensively as possible
 - There is a tradeoff between time and search space coverage

Ligand conformations

- Conformations are different three-dimensional structures of molecules that result from rotation about single bonds
 - That is, they have the same bond lengths and angles but different torsion angles
- For a molecule with N rotatable bonds, if each torsion angle is rotated in increments of θ degrees, number of conformations is $(360^\circ / \theta)^N$
 - If the torsion angles are incremented in steps of 30° , this means that a molecule with 5 rotatable bonds will have $12^5 \approx 250K$ conformations
- Having too many rotatable bonds results in “combinatorial explosion”
- Also ring conformations



Search Algorithms

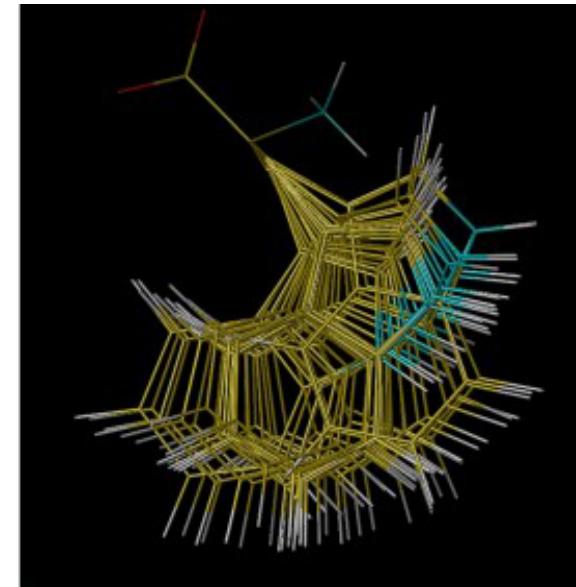
- We can classify the various search algorithms according to the degrees of freedom that they consider
- **Rigid docking or flexible docking**
 - With respect to the ligand structure
- **Rigid docking**
- The ligand is treated as a rigid structure during the docking
 - Only the translational and rotational degrees of freedom are considered
- To deal with the problem of ligand conformations, a large number of conformations of each ligand are generated in advance and each is docked separately
- Examples: FRED (Fast Rigid Exhaustive Docking) from OpenEye, and one of the earliest docking programs, DOCK

Flexible docking

- **Flexible docking** is the most common form of docking today
 - Conformations of each molecule are generated on-the-fly by the search algorithm during the docking process
 - The algorithm can avoid considering conformations that do not fit
- Exhaustive (systematic) searching computationally too expensive as the search space is very large
- One common approach is to use **stochastic search** methods
 - These don't guarantee optimum solution, but good solution within reasonable length of time
 - Stochastic means that they incorporate a degree of randomness
 - Such algorithms include **genetic algorithms** (GOLD), **simulated annealing** (AutoDock)
- An alternative is to use **incremental construction** methods
 - These construct conformations of the ligand within the binding site in a series of stages
 - First one or more “base fragments” are identified which are docked into the binding site
 - The orientations of the base fragment then act as anchors for a systematic conformational analysis of the remainder of the ligand
 - Example: FlexX

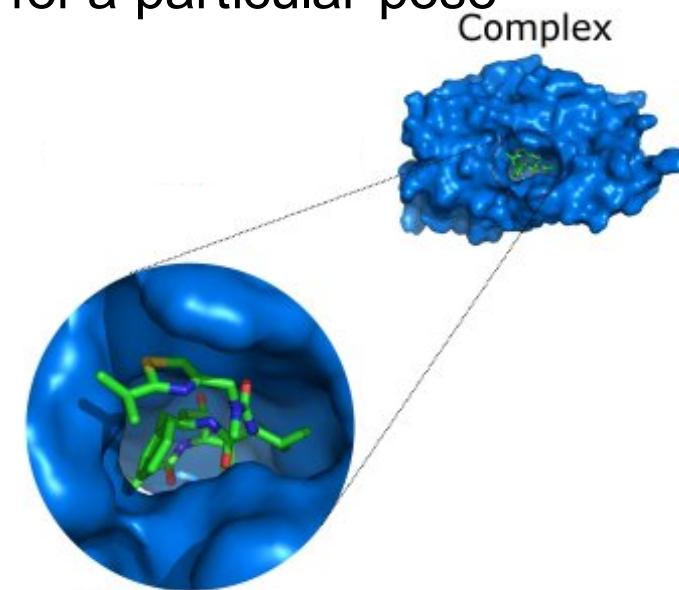
Handling protein conformations

- Most docking software treats the protein as rigid
 - Rigid Receptor Approximation
- This approximation may be invalid for a particular protein-ligand complex as...
 - the protein may deform slightly to accommodate different ligands (ligand-induced fit)
 - protein side chains in the active site may adopt different conformations
- Some docking programs allow protein side-chain flexibility
 - For example, selected side chains are allowed to undergo torsional rotation around acyclic bonds
 - Increases the search space
- Larger protein movements can only be handled by separate dockings to different protein conformations
 - Ensemble docking (e.g. GOLD 5.0)



Components of docking software

- Typically, protein-ligand docking software consist of two main components which work together:
 - **1. Search algorithm**
 - Generates a large number of poses of a molecule in the binding site
 - **2. Scoring function**
 - Calculates a score or binding affinity for a particular pose
- **To give:**
 - The **pose** of the molecule in the binding site
 - The binding affinity or a **score** representing the strength of binding



The perfect scoring function will...

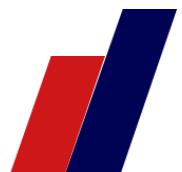
- Accurately calculate the **binding affinity**
 - Will allow actives to be identified in a virtual screen
 - Be able to rank actives in terms of affinity
- Score the poses of an active higher than poses of an inactive
 - Will rank actives higher than inactives in a virtual screen
- Score the **correct pose** of the active higher than an incorrect pose of the active
 - Will allow the correct pose of the active to be identified
- “actives” = molecules with biological activity

Pose prediction accuracy

- Given a set of actives with known crystal poses, can they be docked accurately?
- Accuracy measured by **RMSD** (root mean squared deviation) compared to known crystal structures
 - RMSD = square root of the average of (the difference between a particular coordinate in the crystal and that coordinate in the pose)²
 - Within 2.0Å RMSD considered cut-off for accuracy
 - More sophisticated measures have been proposed, but are not widely adopted
- In general, the best docking software predicts the correct pose about **70%** of the time
- Note: it's always easier to find the correct pose when docking back into the active's own crystal structure
 - More difficult to **cross-dock**

Final thoughts

- Protein-ligand docking is an essential tool for computational drug design
 - Widely used in pharmaceutical companies
 - Many success stories (see Kolb et al. *Curr. Opin. Biotech.*, 2009, 20, 429)
- But it's not a golden bullet
 - The perfect scoring function has yet to be found
 - The performance varies from target to target, and scoring function to scoring function
 - See for example, Plewczynski et al, "Can we trust docking results? Evaluation of seven commonly used programs on PDBbind database", *J. Comp. Chem.*, Online 1 Sep 2010.
- Care needs to be taken when preparing both the protein and the ligands
- The more information you have (and use!), the better your chances
 - Targeted library, docking constraints, filtering poses, seeding with known actives, comparing with known crystal poses



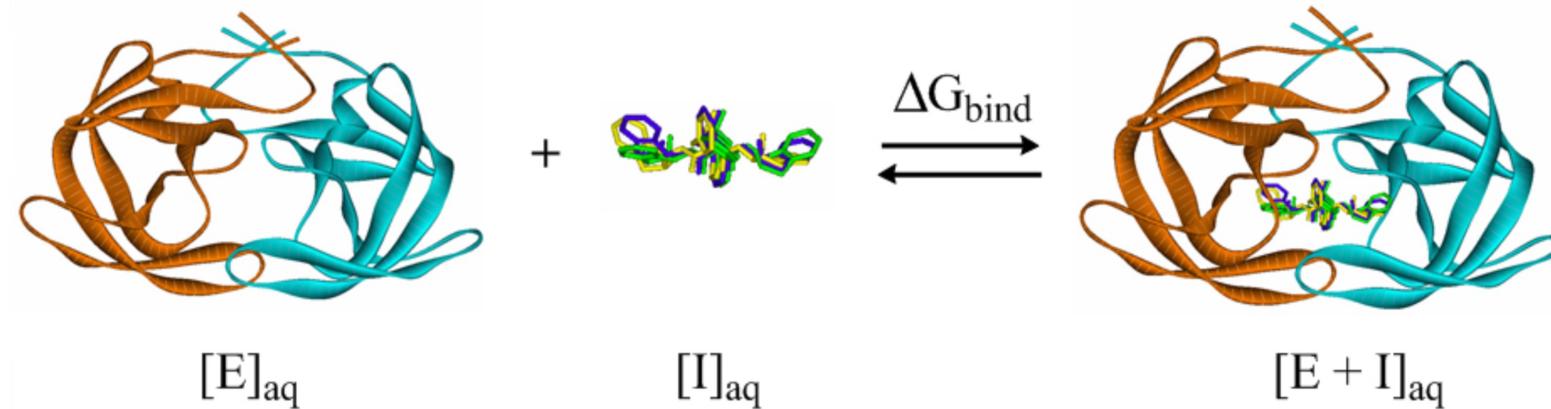
Acoplamiento molecular

Realiza una búsqueda basada en energía en un sitio de unión en un target de las posibles conformaciones proteína-ligando, a partir de las cuales se estima la afinidad mediante una función de puntaje que calcula la suma de las interacciones moleculares.



$$K_A = K_i^{-1} = \frac{[EI]}{[E][I]}$$

$$\Delta G = -RT \ln K_A$$



Acoplamiento molecular

Docking involucra muchos grados de libertad

Translacional

Rotacional

Configuracional

Pasos:

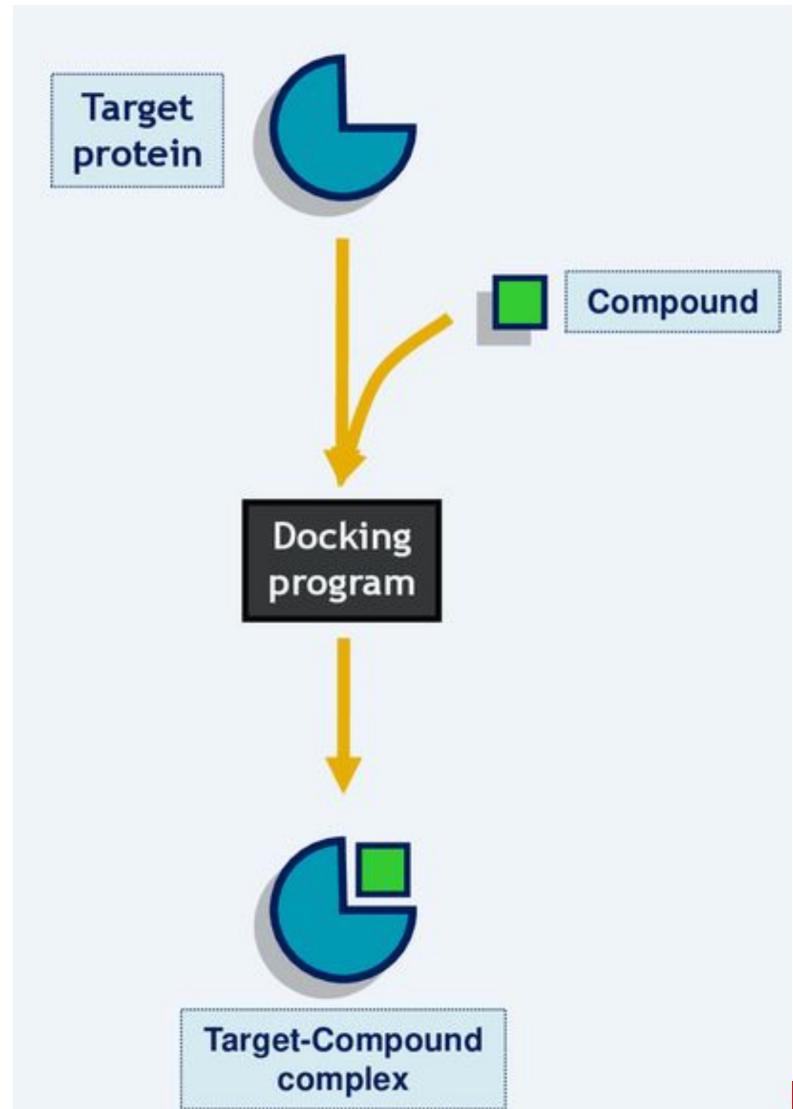
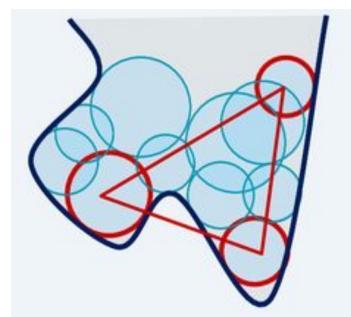
Exploración del espacio conformacional y configuracional

Evaluación de la fuerza de interacción receptor-ligando.

Puntuación.

Muestreo: Caracterización del sitio de unión

Orientación del ligando.



A tener en cuenta:

- ¿Es la estructura de alta o baja resolución?
- ¿Es aceptable el valor R-libre (base útil para ponderar adecuadamente la estereoquímica y los factores estructurales durante un proceso de refinamiento)?
- Faltan cadenas laterales o bucles?
- ¿Corresponde el mapa de densidad electrónica a la estructura real?

3KFN

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◀ Biological Assembly ?

More Images...

View in Jmol SimpleViewer Other Viewers ▾ Protein Workshop

Biological assembly assigned by authors and generated by PISA (software)

Deposition Summary Hide
Authors: Stout, C.D.
Deposition: 2009-10-27
Release: 2010-02-23

Experimental Details Hide
Method: X-RAY DIFFRACTION
Experimental Data: [EDS]
Resolution[Å]: 1.77
R-Value: 0.217 (obs.)
R-Free: 0.274
Space Group: P 21 21 2
Unit Cells:

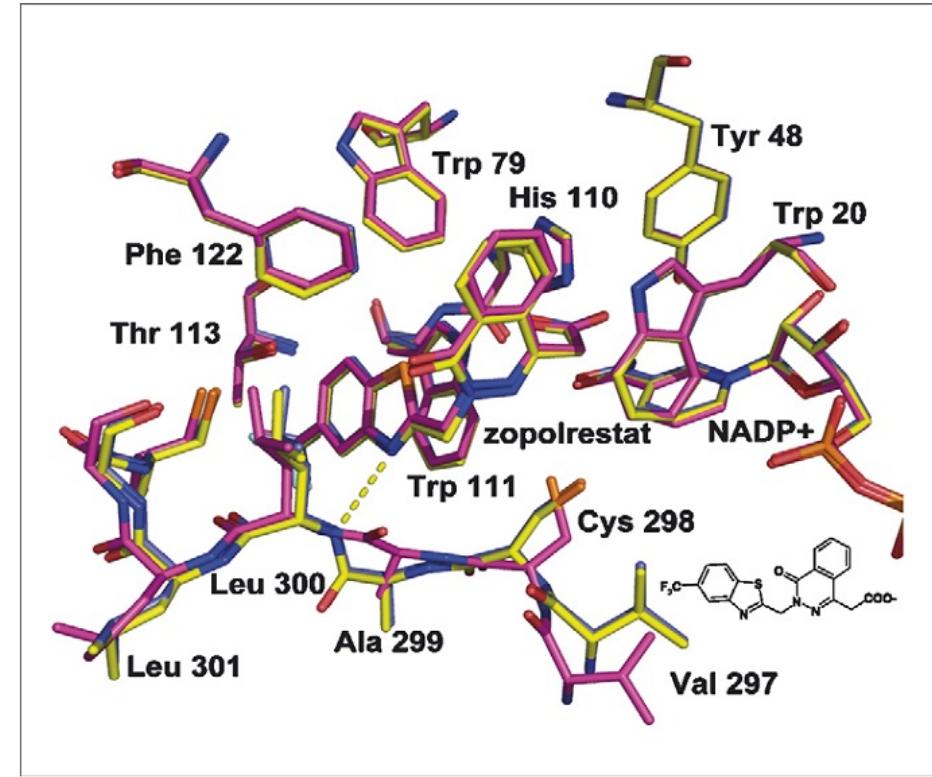


FIGURE 1

Binding mode differs with soaking and co-crystallization conditions.

Receptor

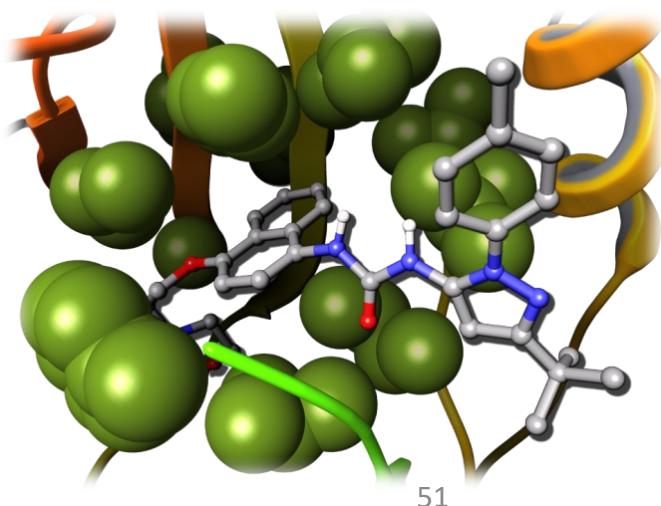
Refinamiento de la estructura cristalina de proteínas

Ubicación del ligando

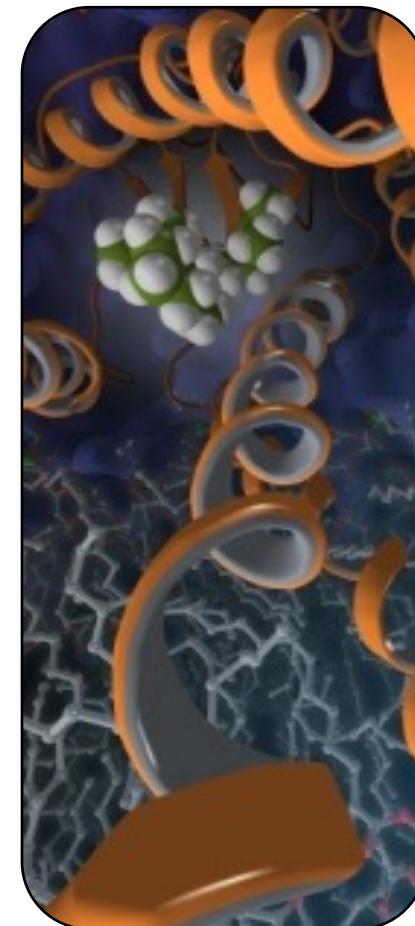
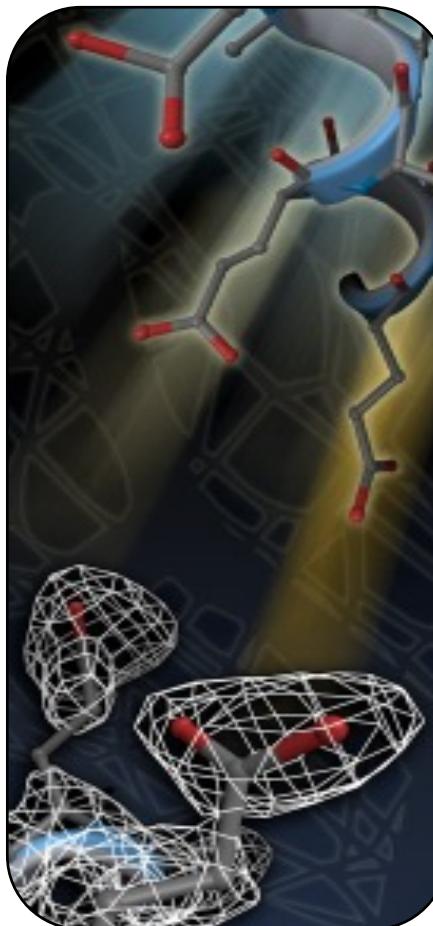
Refinamiento de bucle

MD, recocido simulado

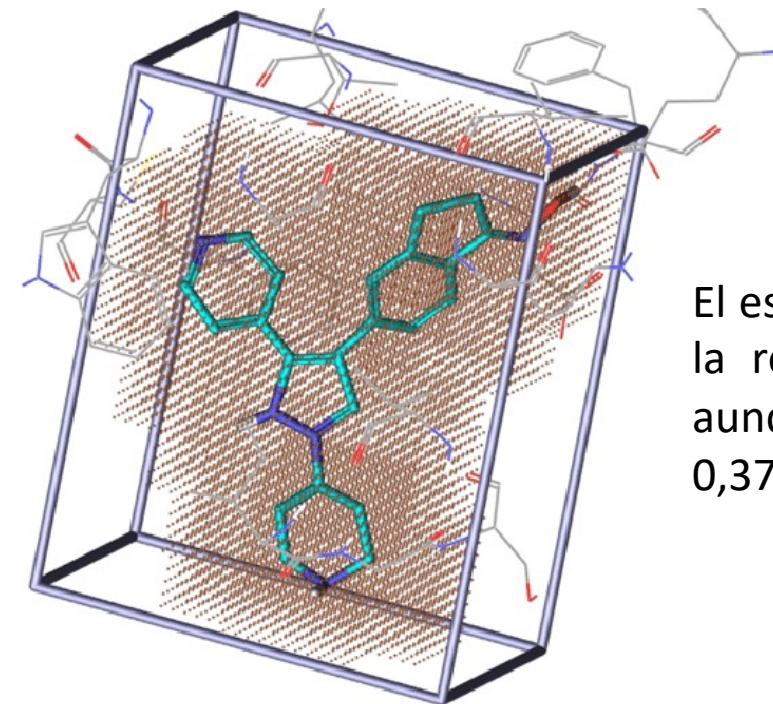
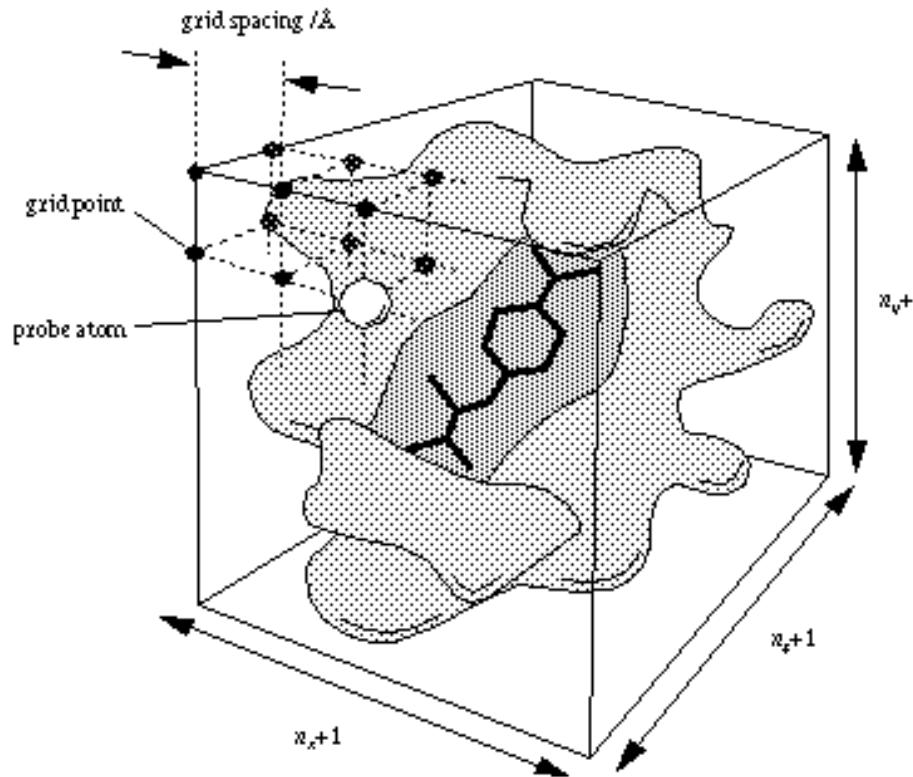
Agregar hidrógenos



51



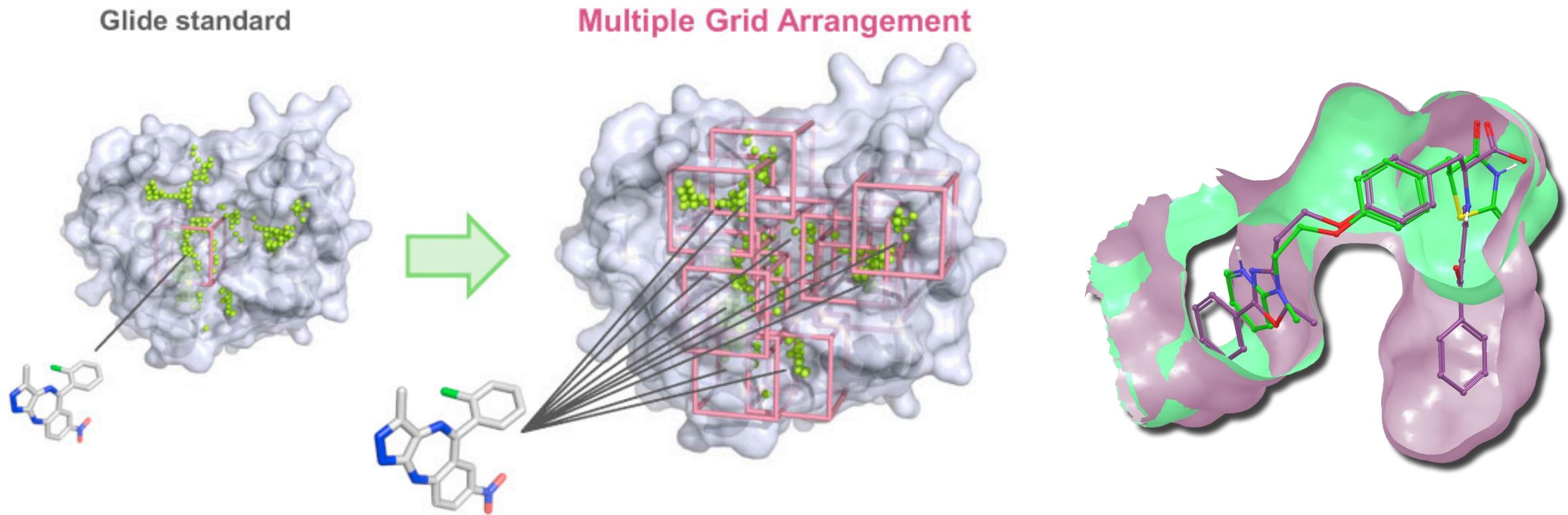
Generación de grilla



El espaciado típico de los puntos de la rejilla varía de 0,2 Å a 1,0 Å, aunque el valor predeterminado es 0,375 Å.

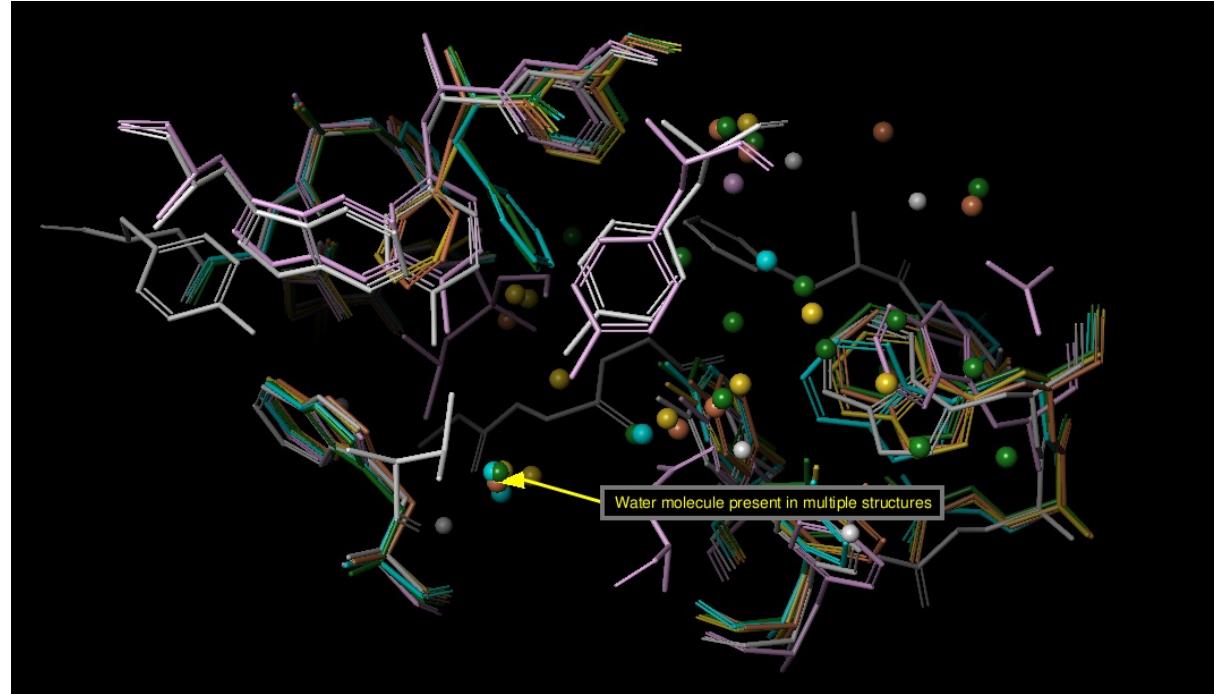
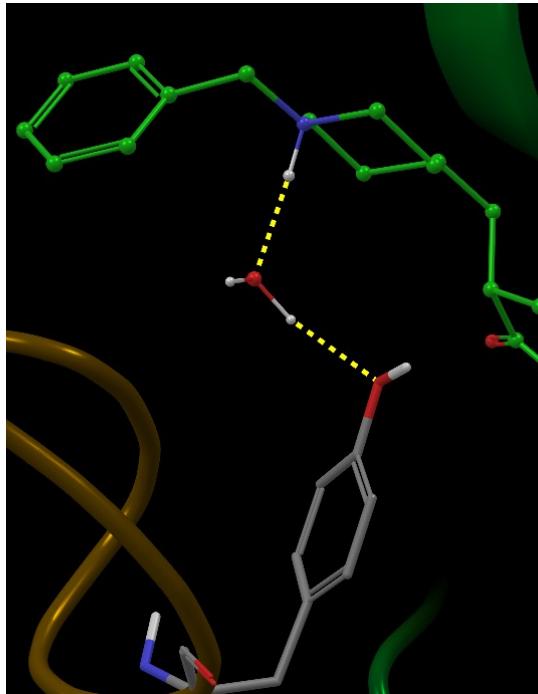
Un mapa de cuadrícula consiste en una red tridimensional de puntos regularmente espaciados, que rodean (total o parcialmente) y se centran en alguna región de interés de la macromolécula en estudio. La precisión del acoplamiento depende del tamaño de la rejilla del receptor.

Generación de grilla



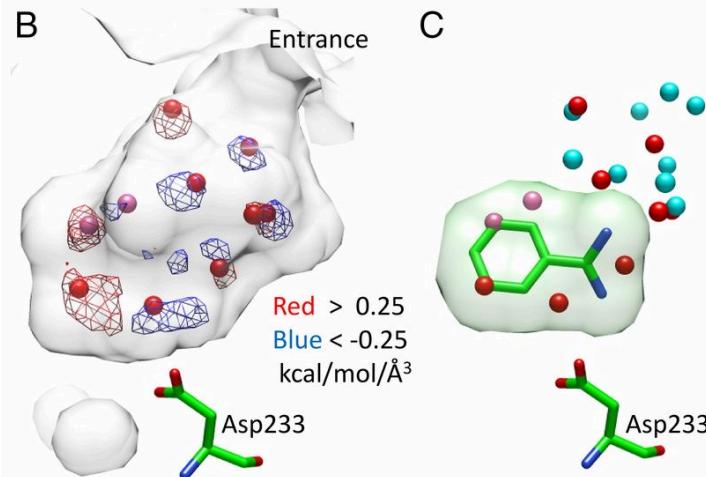
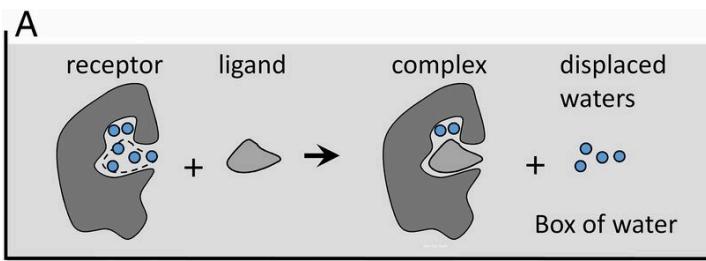
El acoplamiento de ligandos permite la visualización de un complejo óptimo que puede predecirse a partir de una estructura de proteína diana y un compuesto farmacológico candidato.

Tratar con moléculas de agua en el sitio activo.

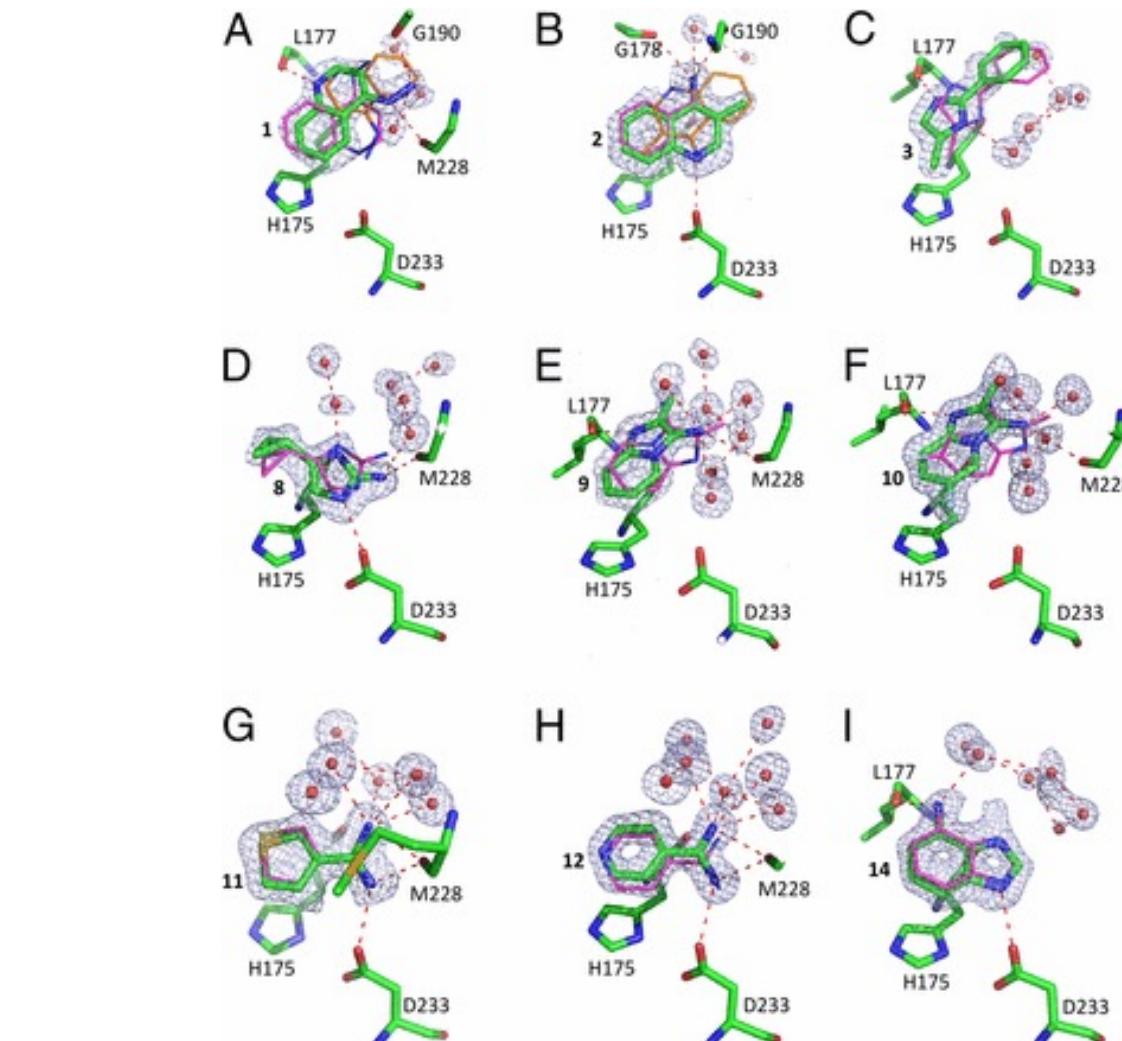
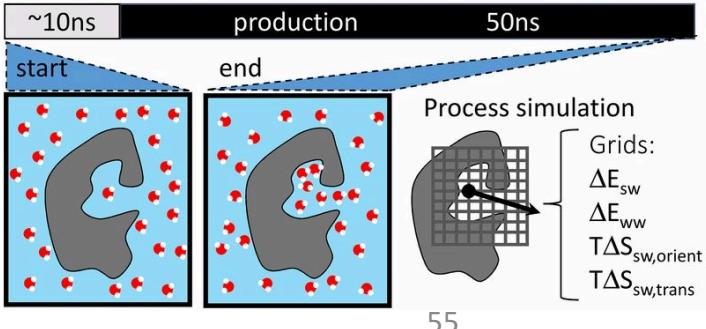


- “Aguas estructurales” que median en la unión del receptor-ligando pueden mantenerse.
- Estas moléculas de agua pueden eliminarse si los ligandos son capaces de desplazarlas

Rol de las moléculas de agua

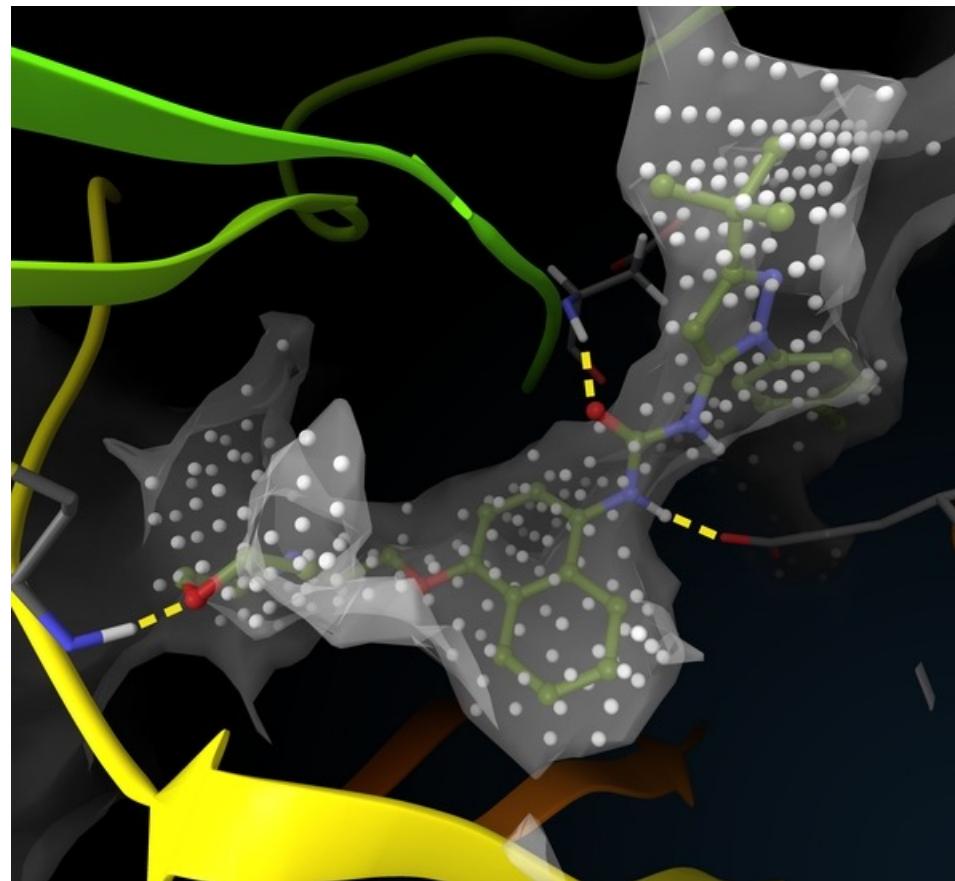


D Molecular Dynamics → GIST grid generation equilibration



Visualización de los resultados

BIRB 796 in p38 MAP kinasa

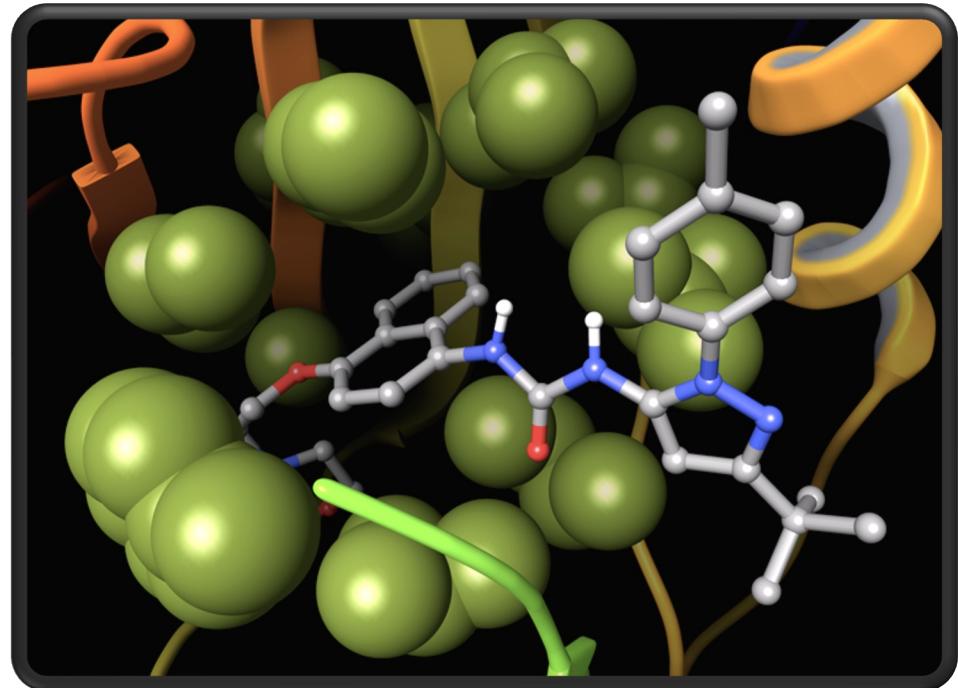


Ligando acceptor
de HB

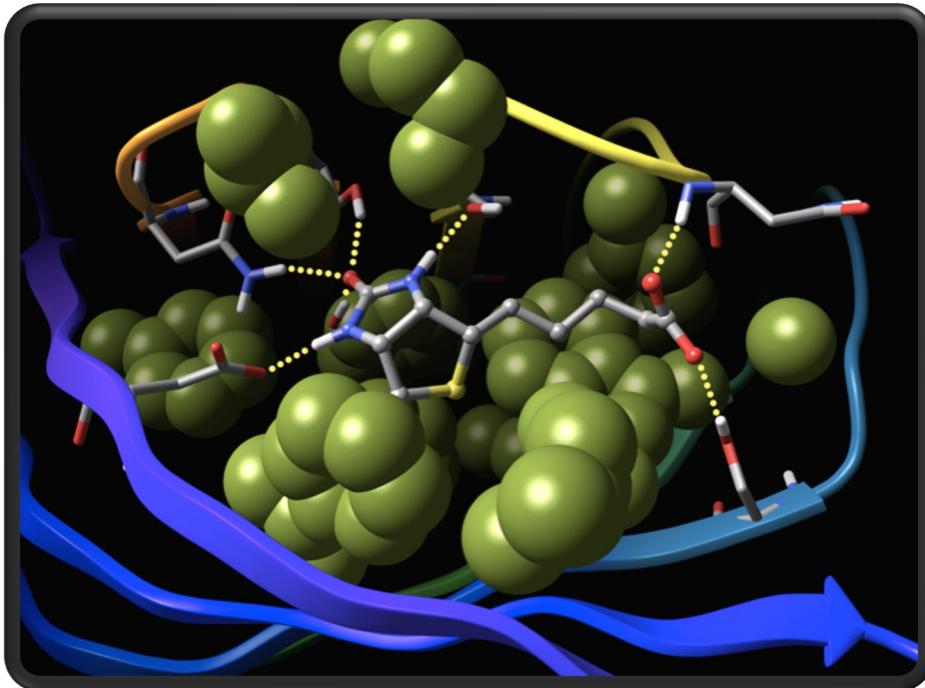
Región
hidrofóbica

Ligando HB donor

Hydrophobic Enclosure



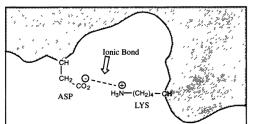
Pair Correlated Hydrogen-Bonds



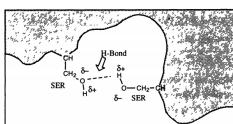
Biotina unida a estreptavidina. Triplete de enlaces de hidrógeno correlacionados en una región encerrada hidrofóbicamente.

Fuerzas intermoleculares

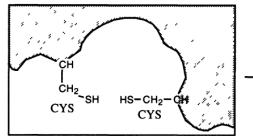
Ion-Ion



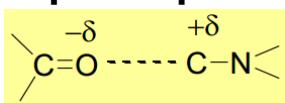
Enlace de hidrógeno



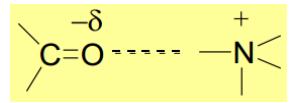
Van der Waals



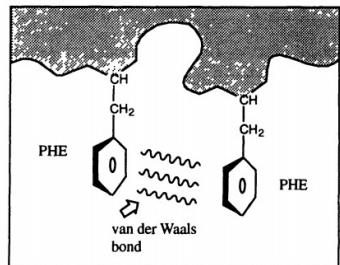
Dipolo-dipolo



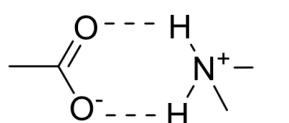
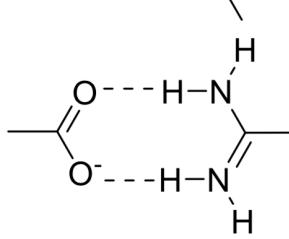
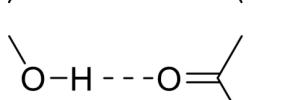
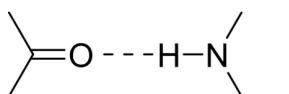
Ion-dipolo



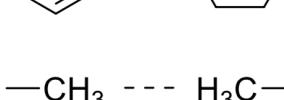
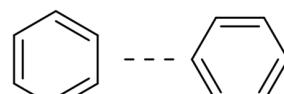
Enlace covalente



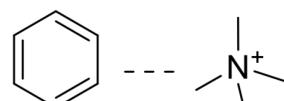
proteína ligando



puentes de hidrógeno



interacciones hidrofóbicas



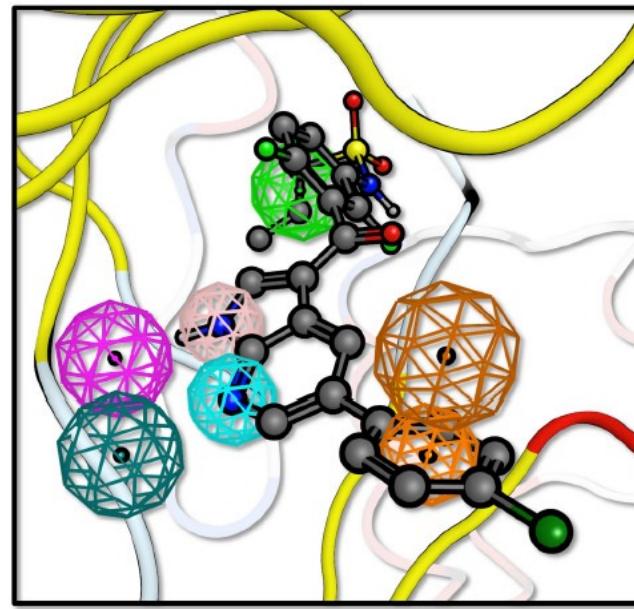
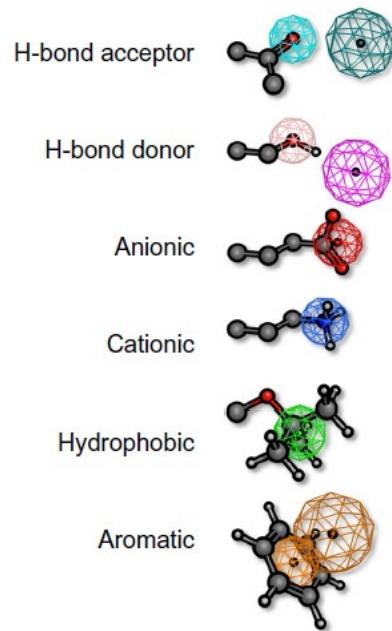
interacciones $\text{p}-$ catiónicas



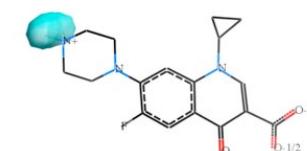
complejación de metales

interacciones electrostáticas

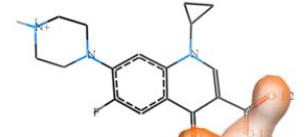
Características a tener en cuenta:



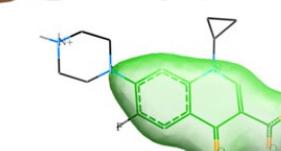
1. Hydrogen bond donors



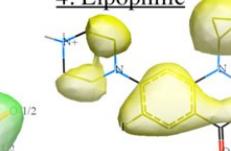
2. Hydrogen bond acceptors



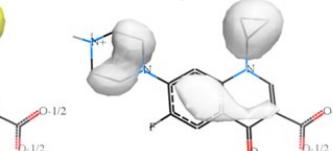
3. Sp² hybridized



4. Lipophilic



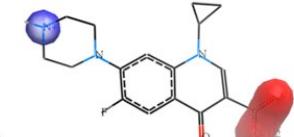
5. Size (large)



7. Electropositive/negative

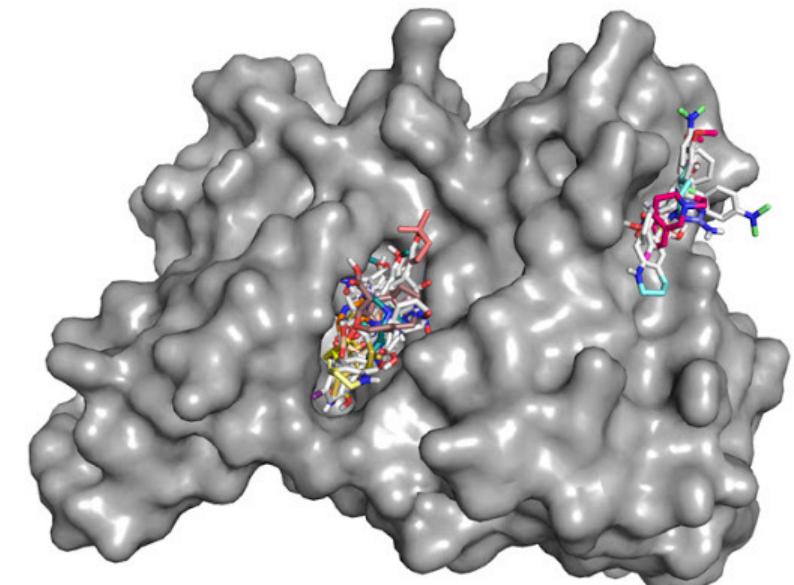
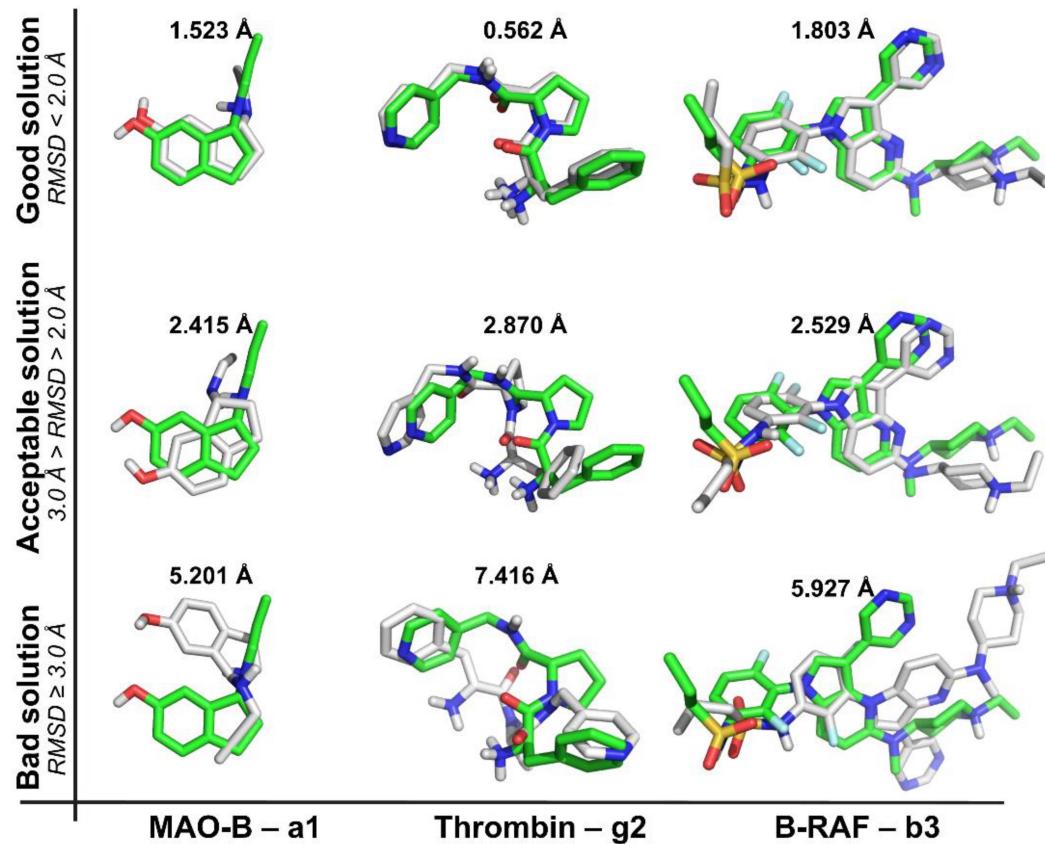


6. Charge: positive/negative



RMSD

la desviación de la raíz cuadrada media (RMSD) para el ligando entre el complejo determinado experimentalmente y el complejo predicho debe ser <2,0 Å cuando se superponen las estructuras de proteínas.



Docking de ligandos

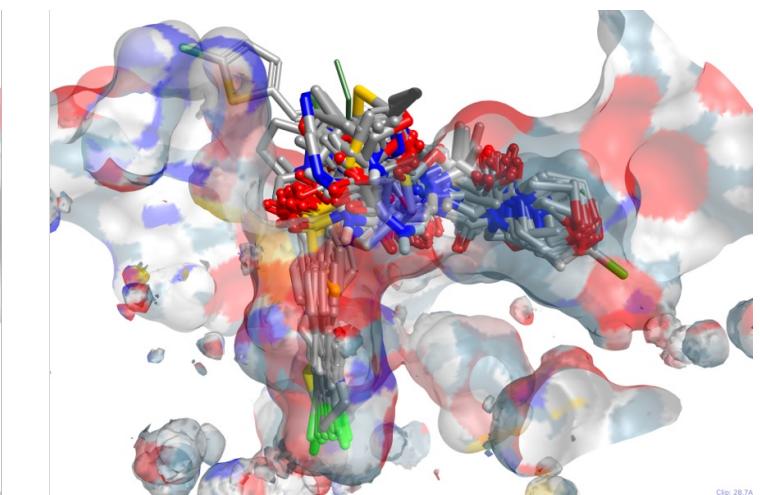
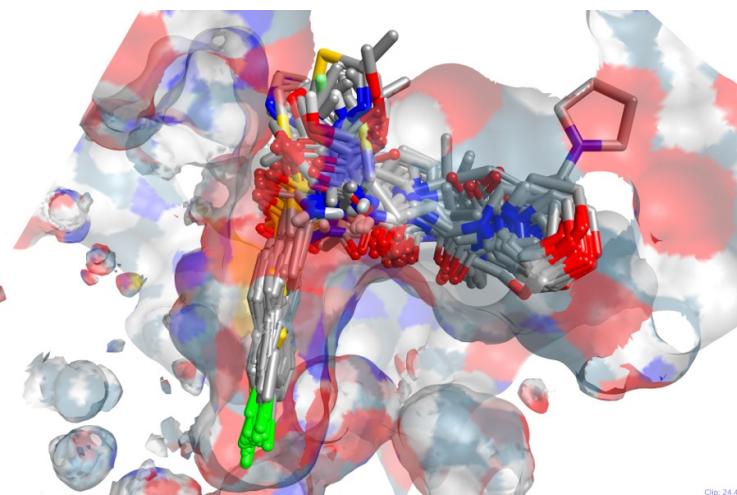
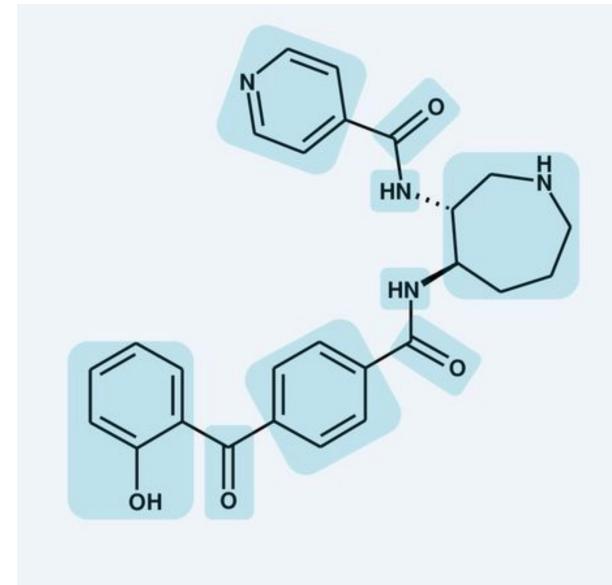
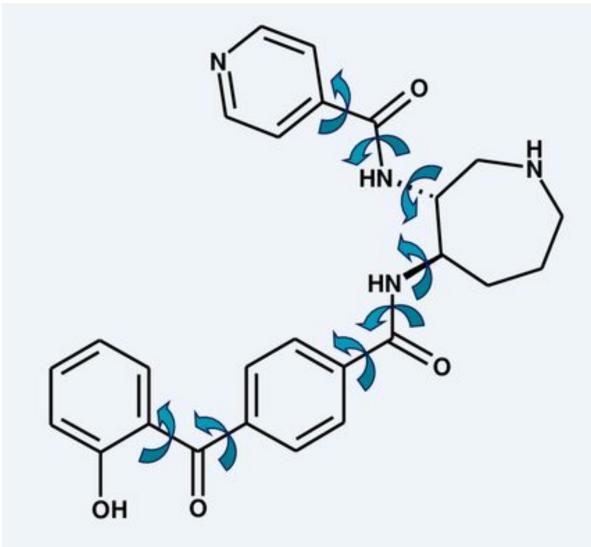
Flexibilidad de moléculas químicas: 70% tienen entre 2 y 8 enlaces rotables.

Los enfoques de fragmentación en los ligandos se usan para reconstruir ligandos en el sitio de unión

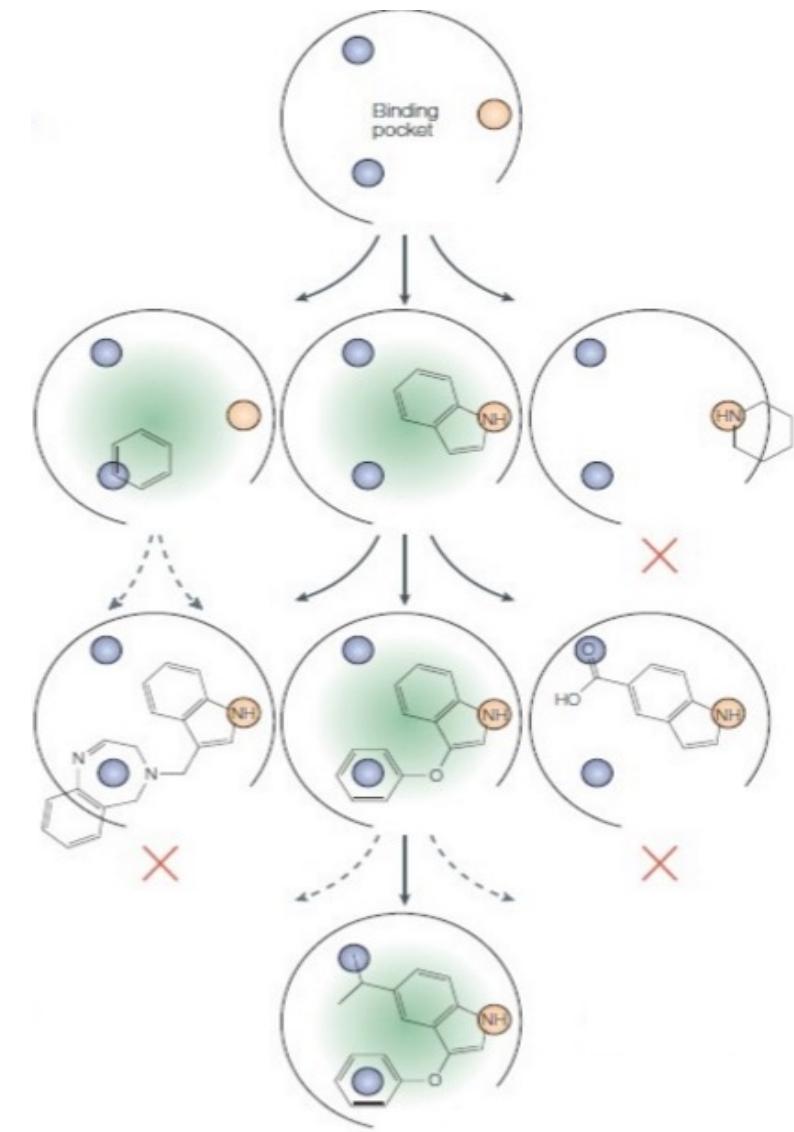
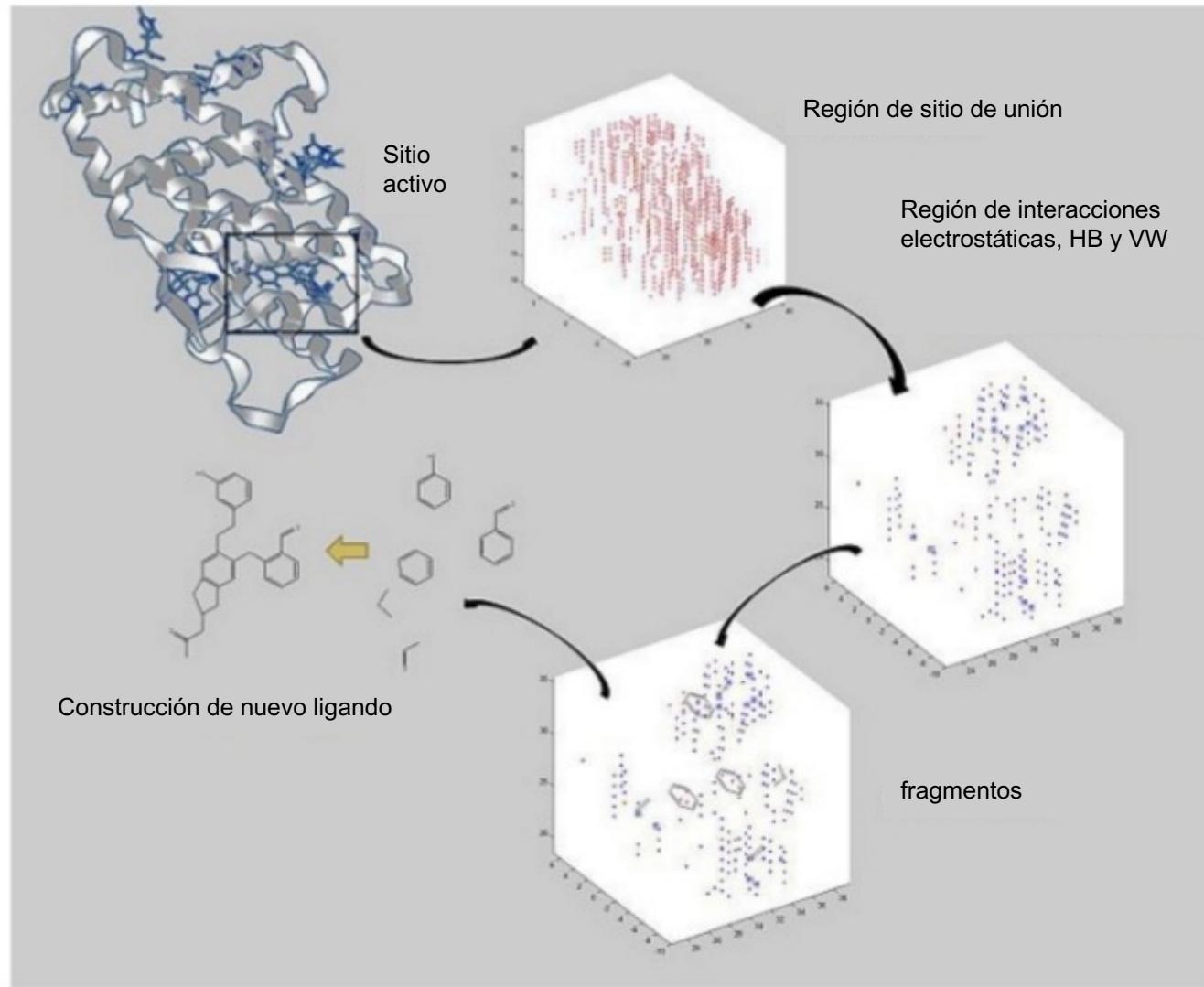
Bloques de fragmentos pequeños y rígidos.

Dockear los fragmentos independientes en el sitio de unión.

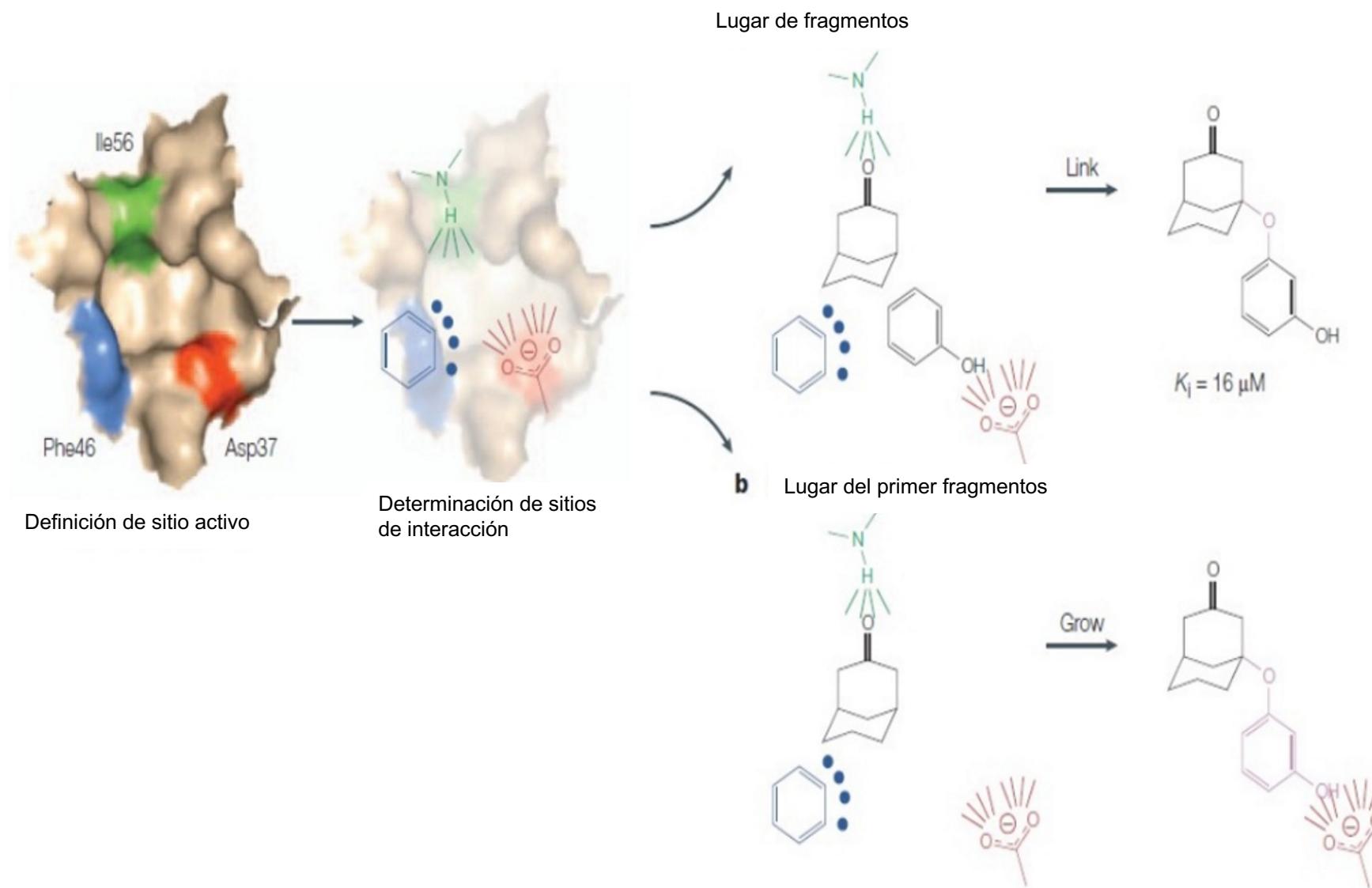
Debilidad: no todos los fragmentos son localizados en la posición de mínima energía.



Diseño de drogas basado en estructura



Diseño de drogas basado en estructura



Puntuación o scoring

Docking genera un gran número de diferentes poses.

Necesitan ser rankeados con base en la afinidad por el receptor

Funciones de puntuación.

Campos de fuerza en MM que contiene términos intra-M

Longitudes de enlace

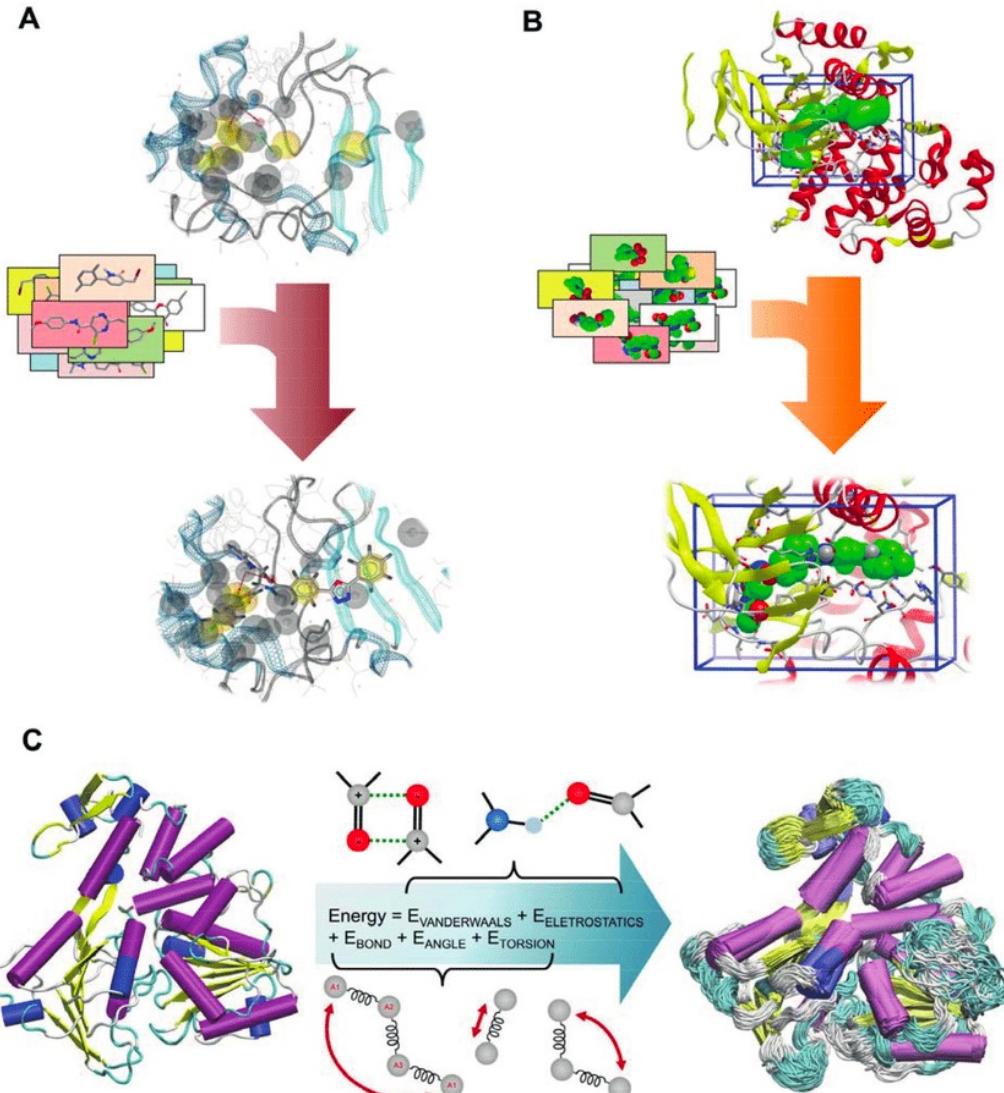
Ángulos de enlace

Dihedros

Términos intermoleculares:

VdW (no polares)

Interacciones electrostáticas (Polares)



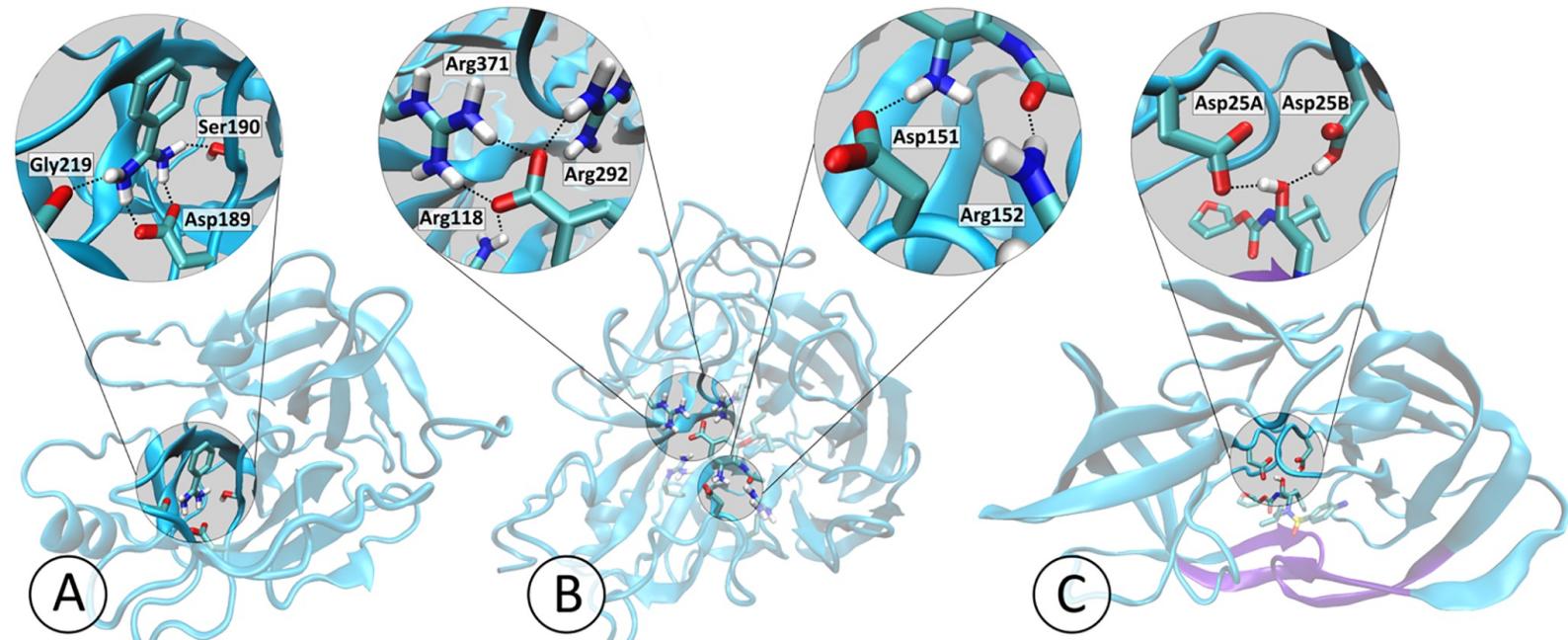
$$E_{\text{bind}} = E_{\text{intra}} + E_{\text{nonpolar}} + E_{\text{polar}}$$

Flexibilidad del receptor

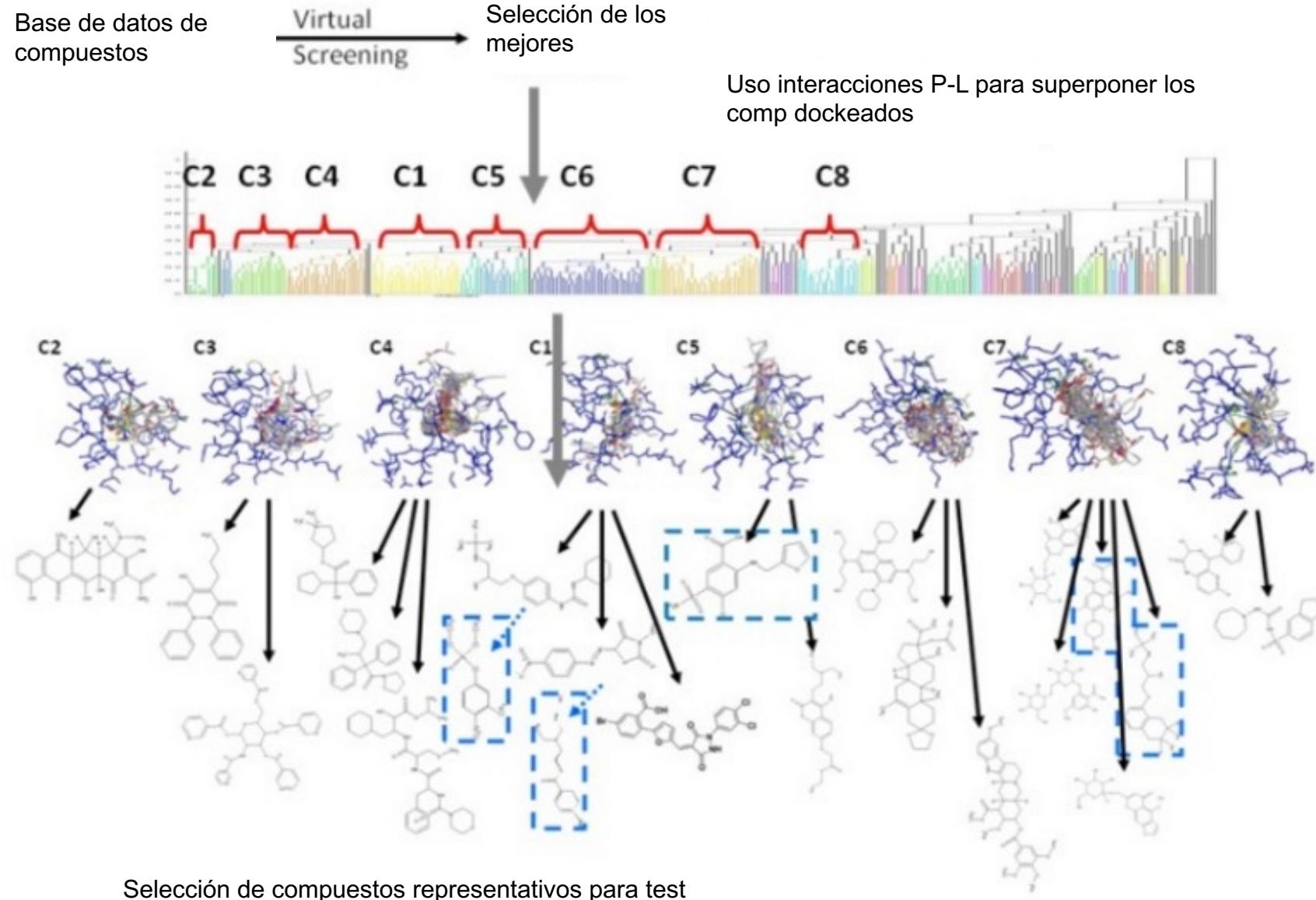
Para docking el receptor normalmente es rígido.

Para incluir flexibilidad al receptor se realizan simulaciones de dinámica molecular en agua.

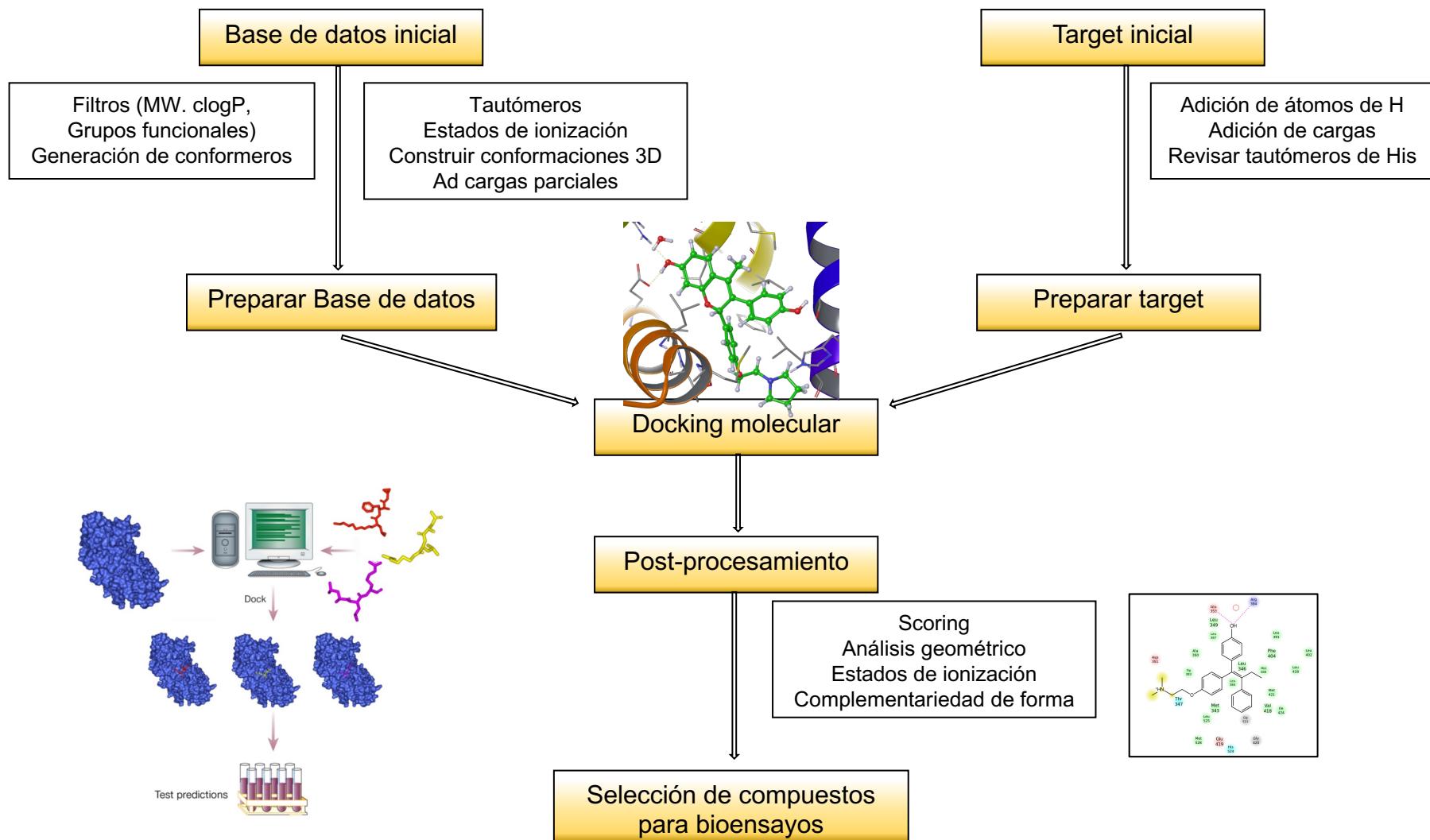
O considerar la flexibilidad de receptor en docking molecular.



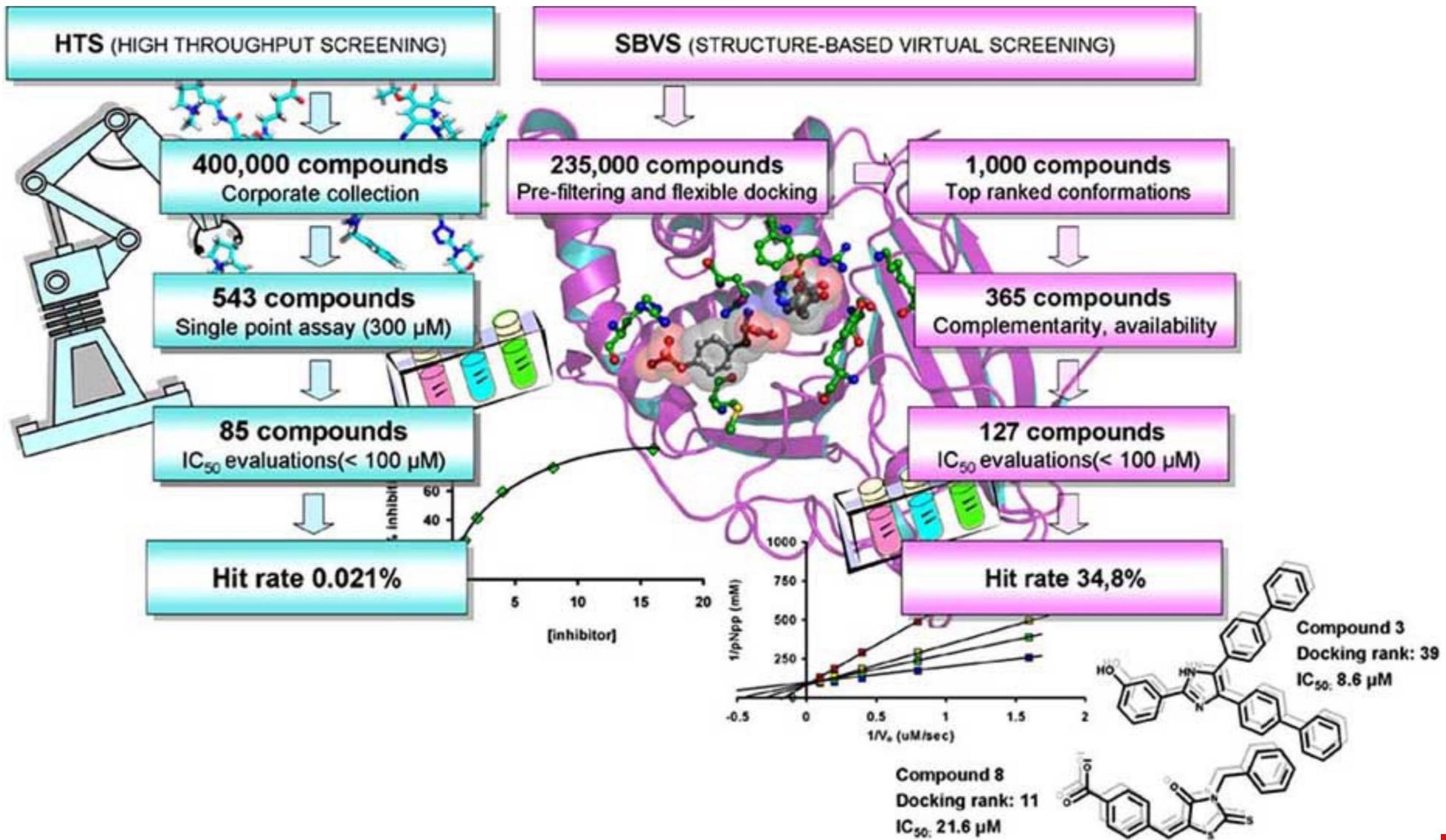
Diseño de drogas basado en estructura: Virtual screening



Flujo de Virtual screening



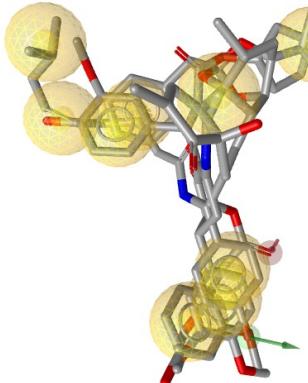
HTS v/s Virtual Screening



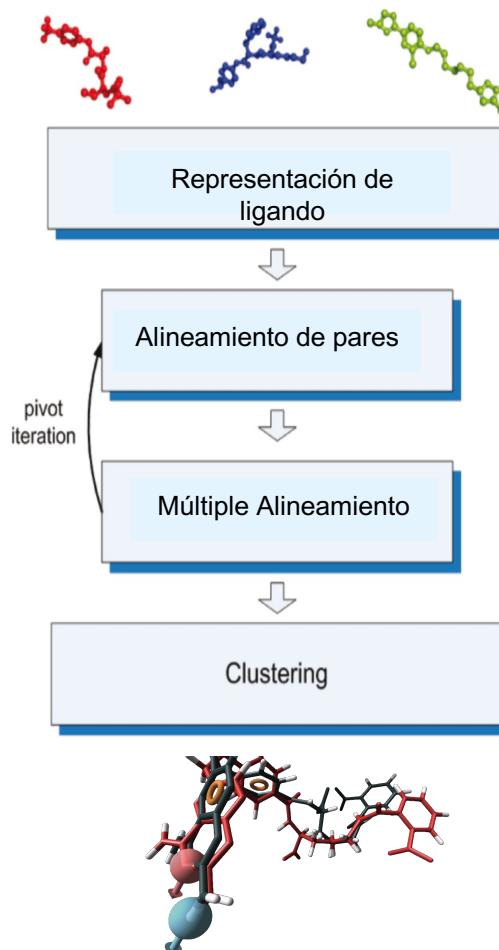
Farmacóforo

El farmacóforo es el arreglo espacial de las características moleculares que le permiten a una molécula interactuar en un modo de unión específico a su blanco terapéutico.

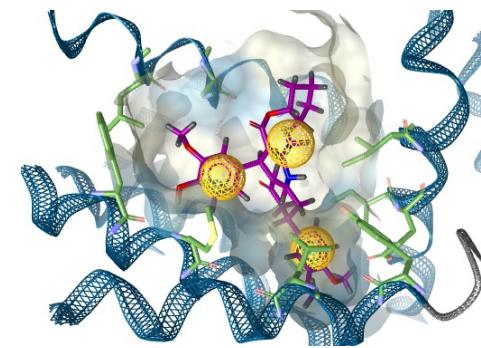
Una vez identificado puede servir para racionalmente diseñar compuestos con la misma actividad biológica.



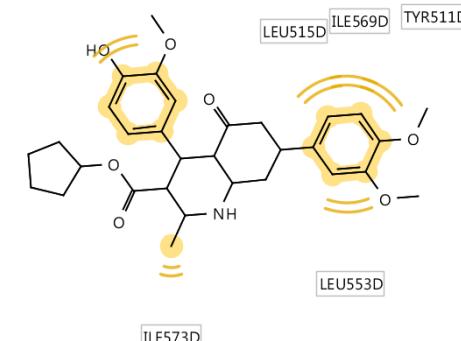
Farmacóforo basado en ligando



Farmacóforo basado en estructura



MET547D



Hypothesis

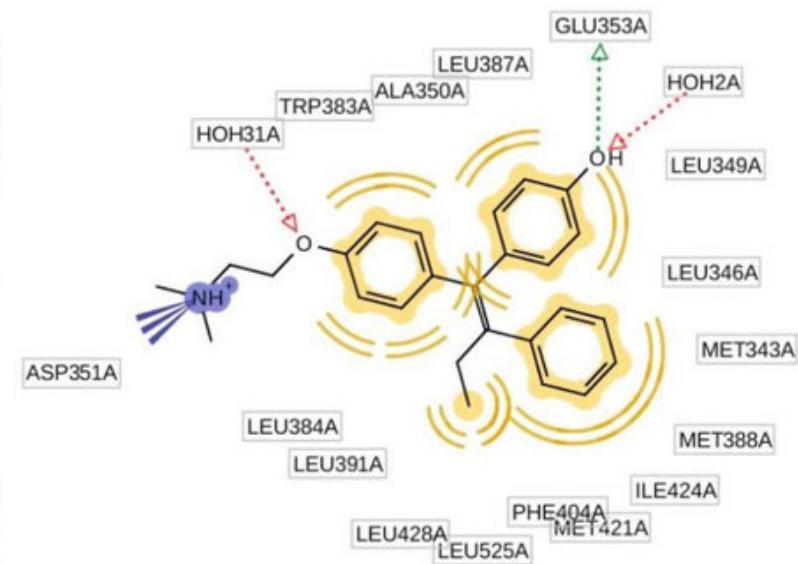
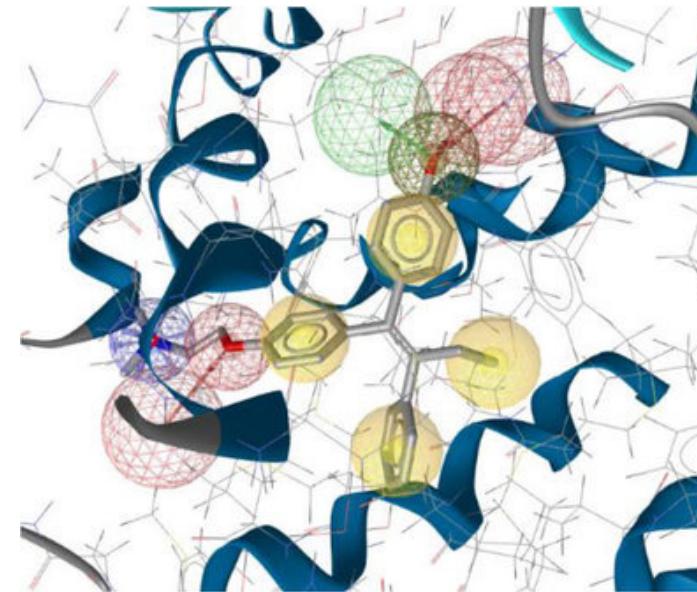
Se puede desarrollar un farmacóforo basado en la estructura a partir de una pose de ligando unido único que contenga información suficiente para recuperar una gran cantidad de compuestos activos de una base de datos.

La información basada en la estructura debería producir una mejor hipótesis que un método de solo ligando.

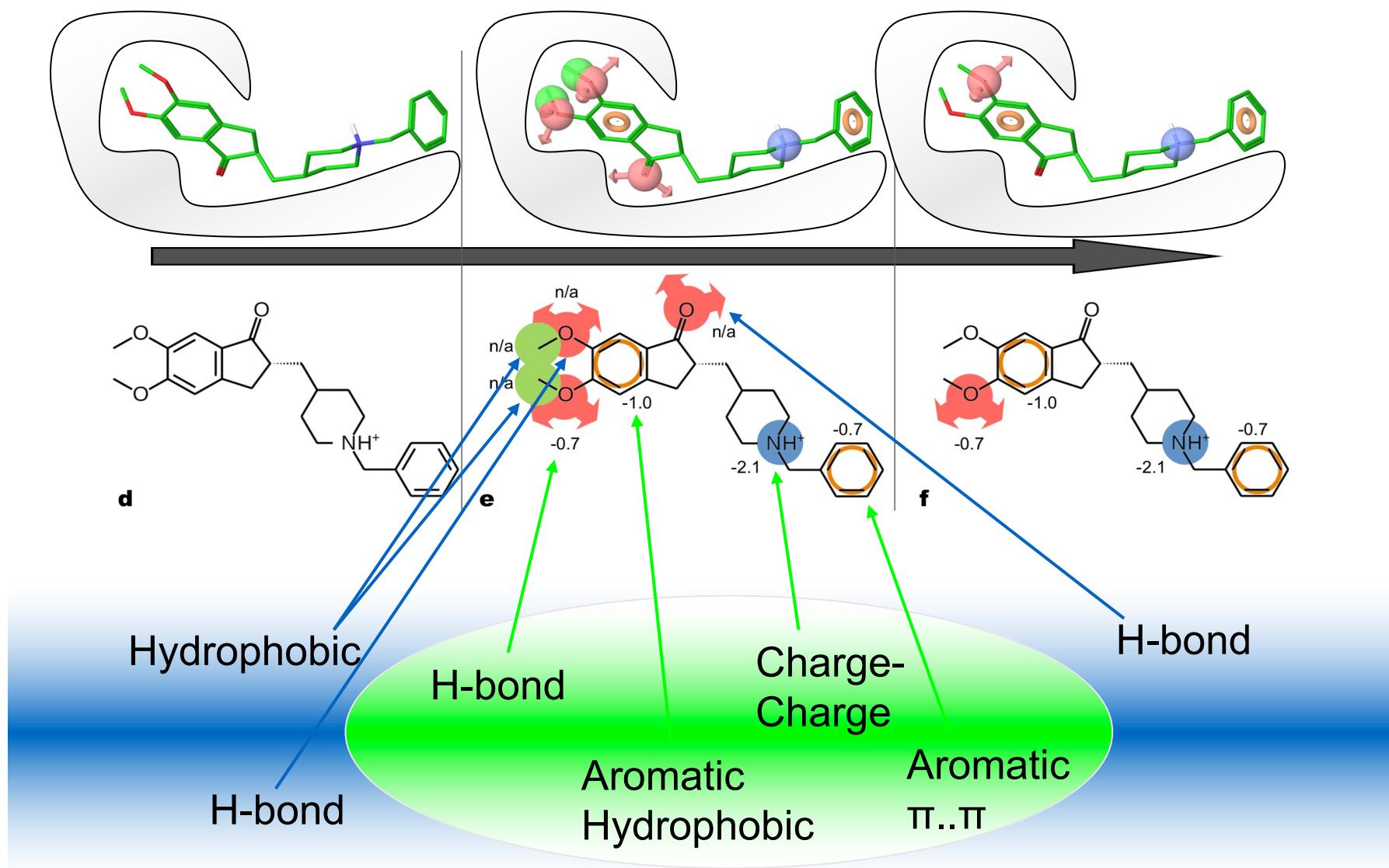
El uso de información energética precisa para desarrollar la hipótesis mejorará los resultados.

Precisión y diversidad de estructuras

Velocidad y tolerancia de ligando basado



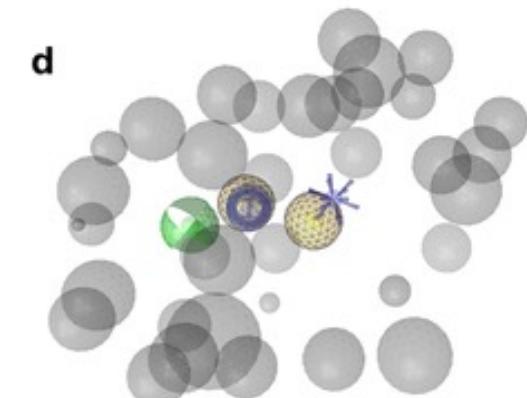
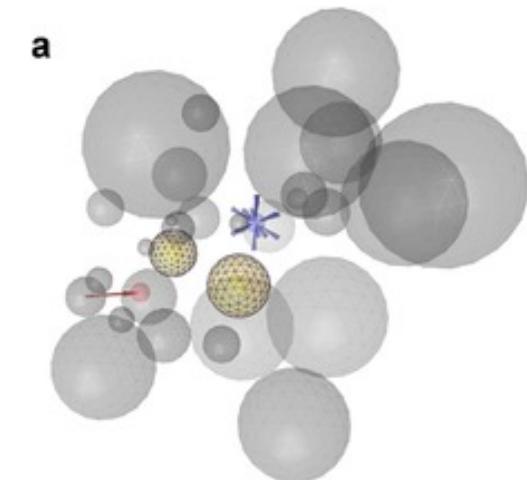
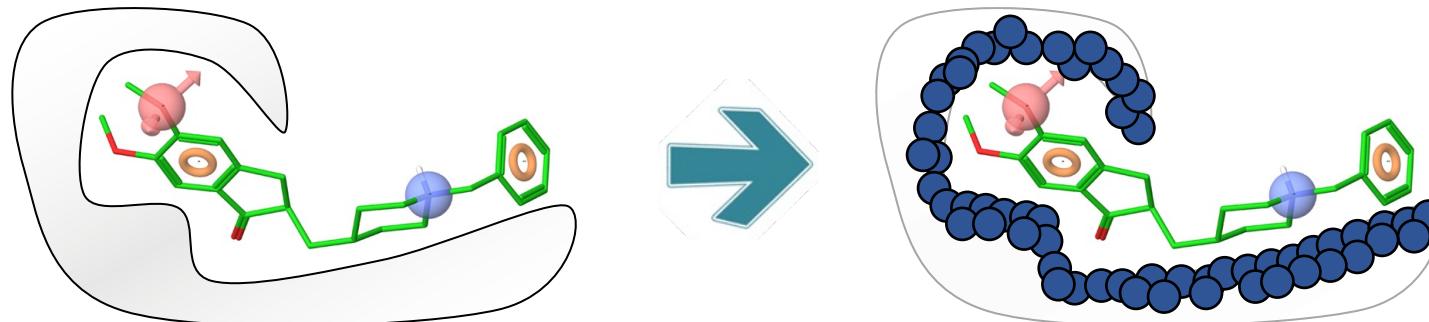
Farmacóforo basado en estructura



Volúmenes de exclusión

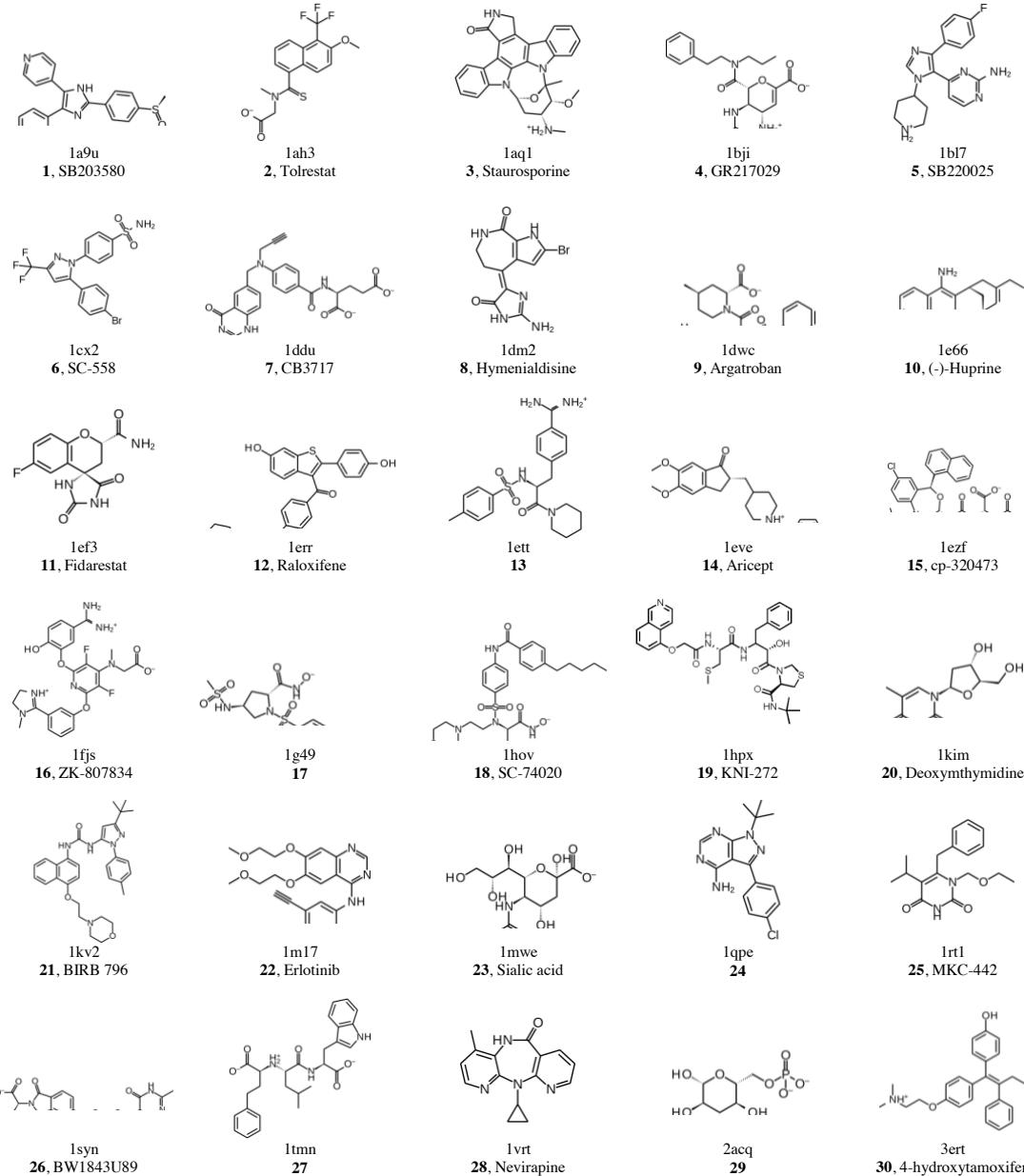
El objetivo es tener en cuenta la forma del receptor sin hacer que la puntuación sea demasiado difícil.

Usar todos los átomos receptores con una distancia [Sum (vdW) +1.5] a [Sum (vdW) +5.0] y escalar en un 50%

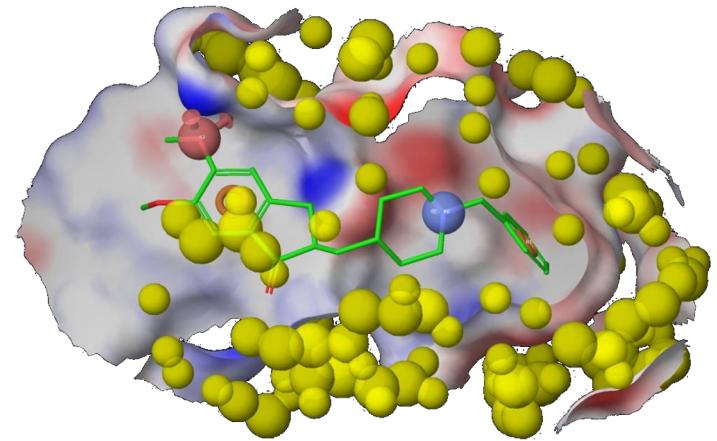
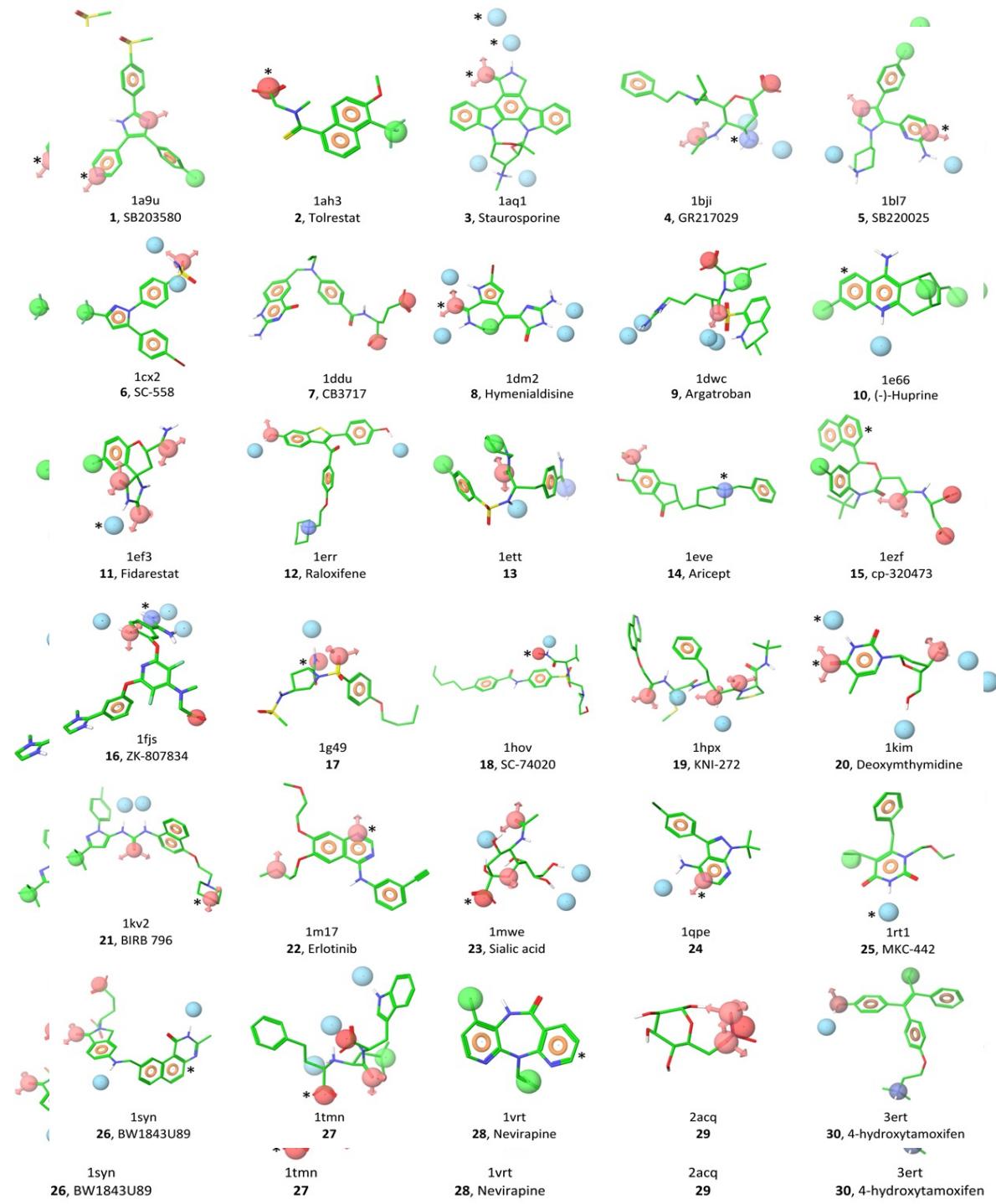


Test Dataset

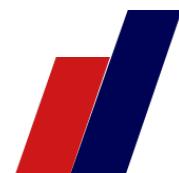
- 30 target de la suite de pruebas Glide
- Diversas dianas y grupos funcionales de ligandos
- 1000 compuestos set señuelo Glide
- 7-36 activos por objetivo
- La agrupación de 20 activos se realizó en casos con más de 36 activos para evitar la saturación y obtener un subconjunto diverso.
- Actividades mejores que 10 μM para todos los ligandos excepto los inhibidores de neuraminidasa



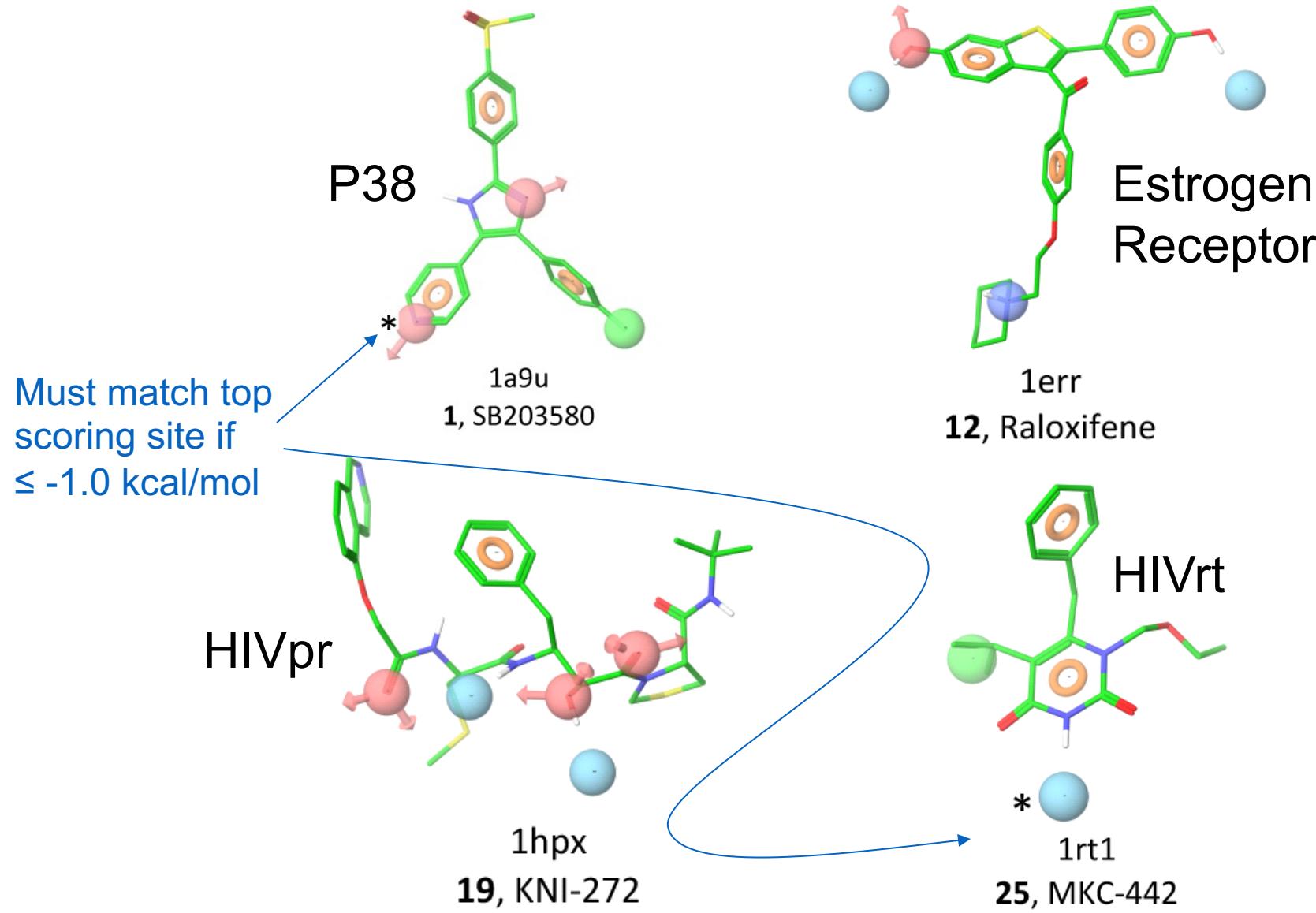
E-Pharmacophores



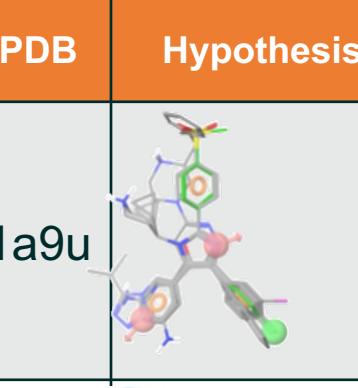
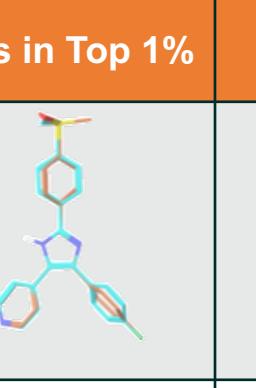
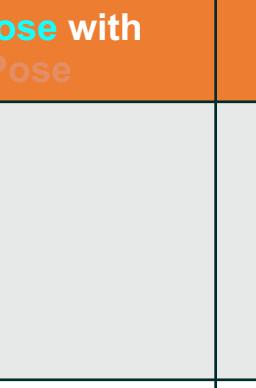
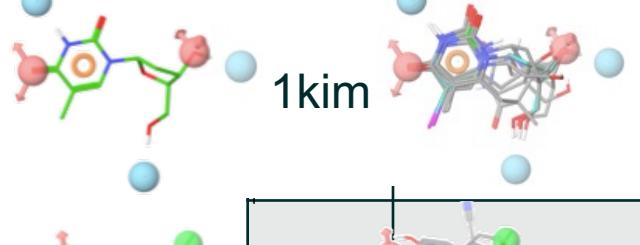
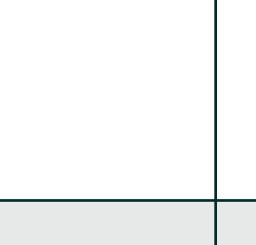
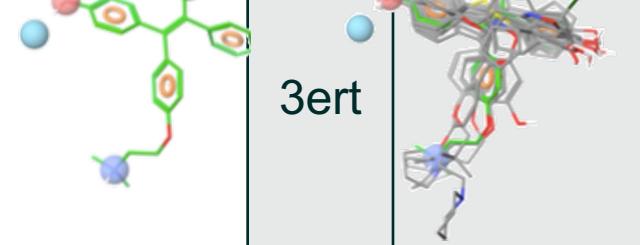
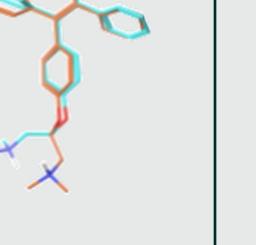
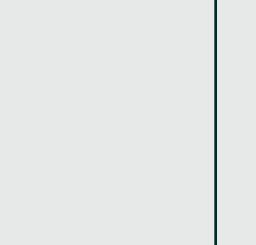
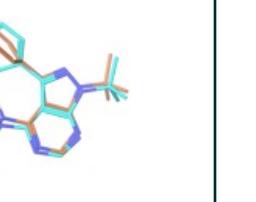
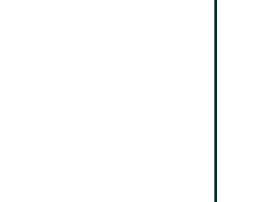
Receptor excluded volumes
used for each hypothesis



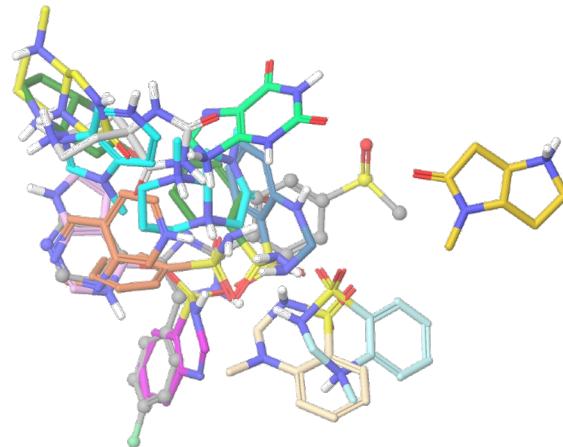
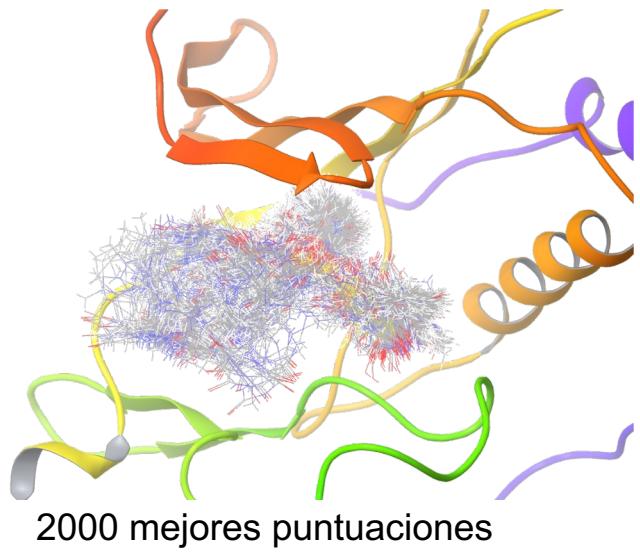
Example e-Pharmacophores



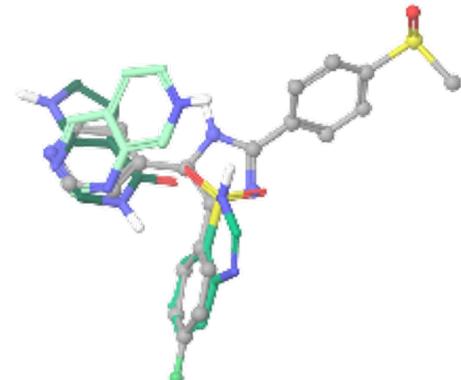
Pose Accuracy

PDB	Hypothesis	Active Hits in Top 1%	Alignment Pose with Crystal Pose	RMSD (Å)
1a9u				0.85
1kim				0.69
3ert				1.39
1qpe				0.67

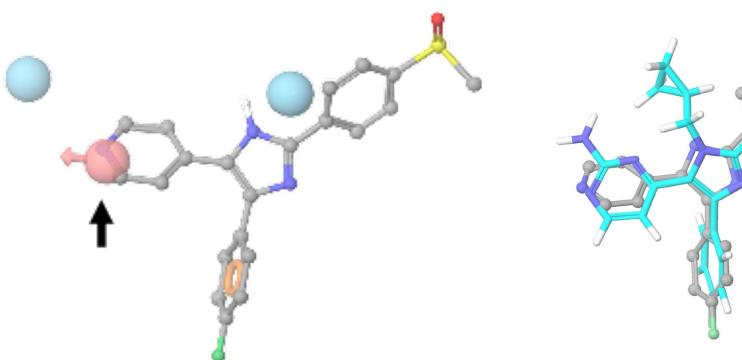
Búsqueda de moléculas



15 top-scoring fragmentos post volumen



Mejores fragmentos + ligando

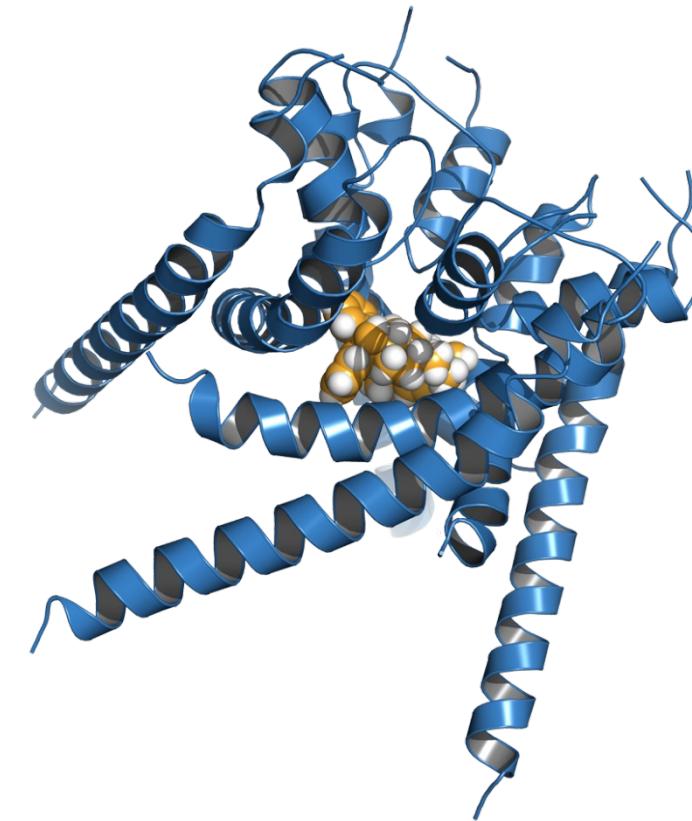
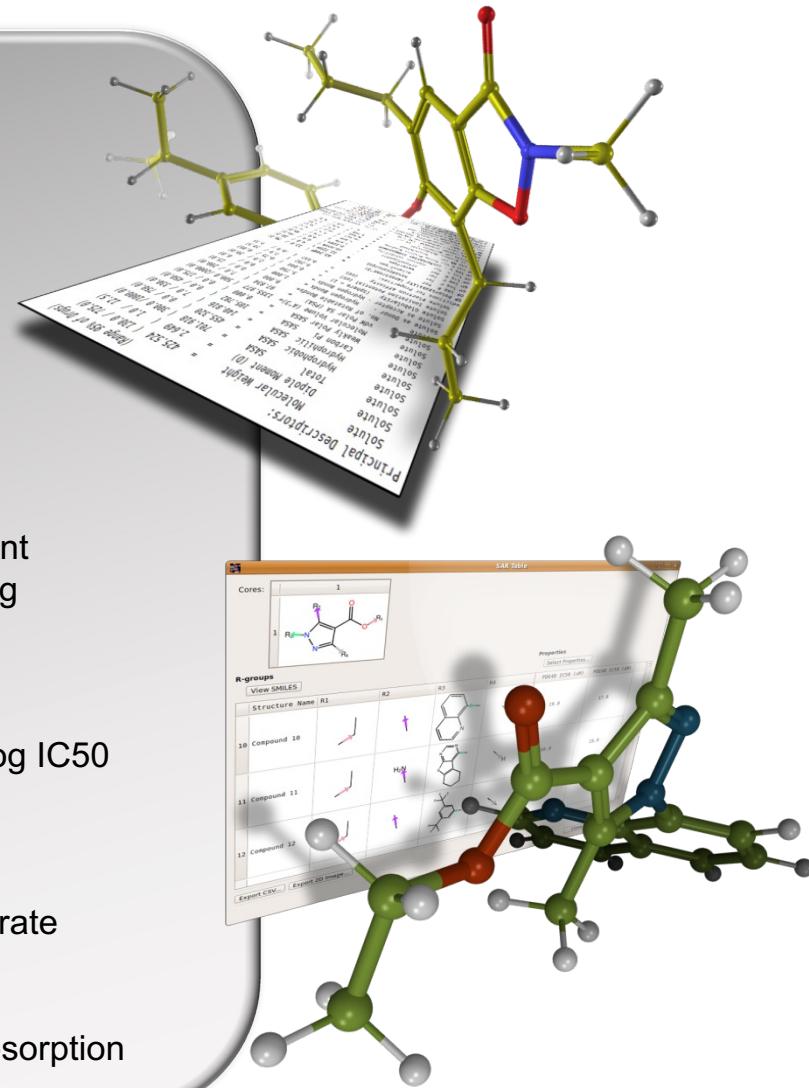


Hipótesis final + ligando

Propiedades fisicoquímicas

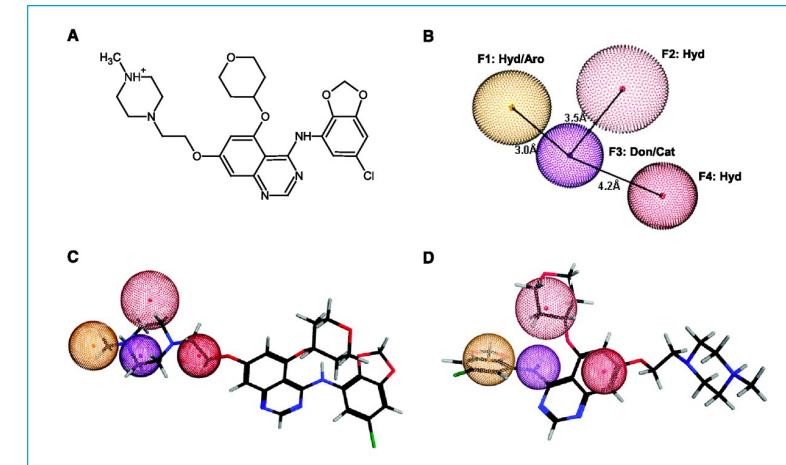
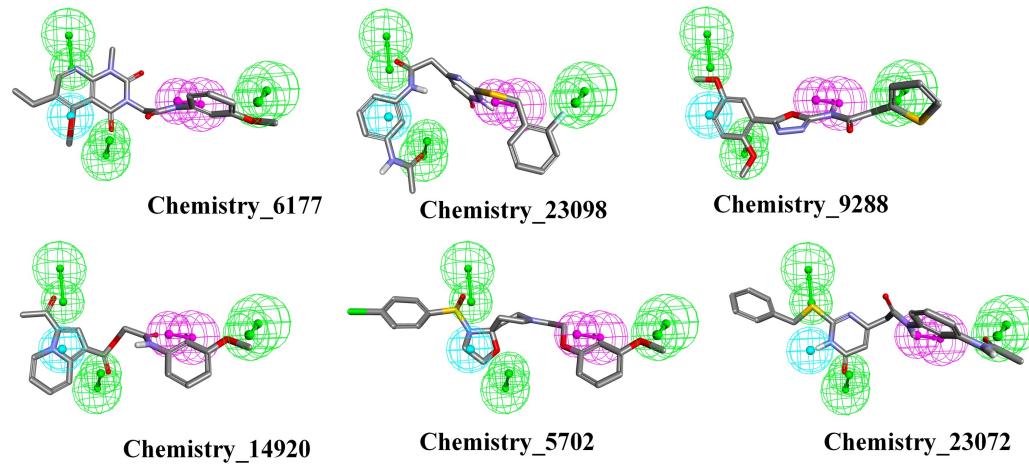
ADME Property Prediction

- Polarizability
- log P for hexadecane/gas
- log P for octanol/gas
- Log P for water/gas
- log P for octanol/water
- log S for aqueous solubility
- log S - conformation independent
- log K hsa Serum Protein Binding
- log BB for brain/blood
- No. of Primary Metabolites
- Predicted CNS Activity
- HERG K⁺ Channel Blockage: log IC50
- Apparent Caco-2 Permeability
- Apparent MDCK Permeability
- log K_p for skin permeability
- J_m, max transdermal transport rate
- Lipinski Rule of 5 Violations
- % Human Oral Absorption in GI
- Qual. Model for Human Oral Absorption



Diseño de drogas basado en ligando

- Examina las características de ligandos activos e inactivos.
- Genera una hipótesis acerca de grupos químicos necesarios para la función biológica.
- Da nuevos ligandos con grupos qcos en localización 3D similar.

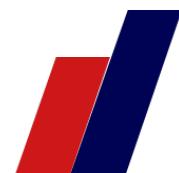


Ventaja: No necesitan conocer estructura de receptor

Colección de datos



Ejemplos





Article

Is It Reliable to Use Common Molecular Docking Methods for Comparing the Binding Affinities of Enantiomer Pairs for Their Protein Target?

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Academic Editors: Humberto González-Díaz, Roberto Todeschini and Alejandro Pazos Sierra

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Table 1. Percentages of match and mismatch for the categories E , D^R , or D^S in the comparison between C^A and C^P for enantiomer pairs.

Target	Results	Glide HTVS	Glide SP	Glide XP	Autodock Vina
ChE	Match %	28.70	8.11	24.32	2.78
	Mismatch %	71.30	91.89	75.68	97.22
	Error	3.21	4.68	3.82	0.00
	Total pairs	36	36	37	36
MAO	Match %	22.86	18.92	31.08	5.41
	Mismatch %	77.14	81.08	68.92	94.59
	Error	2.86	2.70	1.91	0.00
	Total pairs	35	37	37	37
ACE	Match %	25.29	37.14	28.57	24.76
	Mismatch %	74.71	62.86	71.43	75.24
	Error	3.98	5.71	8.08	6.60
	Total pairs	29	35	35	35
NEP	Match %	21.57	7.84	20.59	31.37
	Mismatch %	78.43	92.16	79.41	68.63
	Error	6.79	3.40	12.48	13.58
	Total pairs	17	17	17	17
ECE	Match %	26.19	44.44	23.33	15.56
	Mismatch %	73.81	55.56	76.67	84.44
	Error	4.12	10.18	14.14	7.70
	Total pairs	14	15	15	15
Total	Match %	25.19	22.14	25.53	13.81
	Mismatch %	74.81	77.86	74.47	86.19
	Error	0.00	3.78	3.75	2.18
	Total pairs	131	140	141	140

HTVS: High-throughput virtual screening, SP: standard precision, XP: extra precision, ChE: cholinesterase, MAO: monoamine oxidase, ACE: angiotensin I converting enzyme, NEP: neutral endopeptidase, ECE: endothelin converting enzyme I.



Novel *N*-allyl/propargyl tetrahydroquinolines: Synthesis via Three-component Cationic Imino Diels–Alder Reaction, Binding Prediction, and Evaluation as Cholinesterase Inhibitors

Yeray A. Rodríguez¹, Margarita Gutiérrez^{1,*}, David Ramírez², Jans Alzate-Morales², Cristian C. Bernal³, Fausto M. Güiza³ and Arnold R. Romero Bohórquez^{3,*}

Alzheimer's disease (AD) is the most complex and common form of dementia in elderly people.

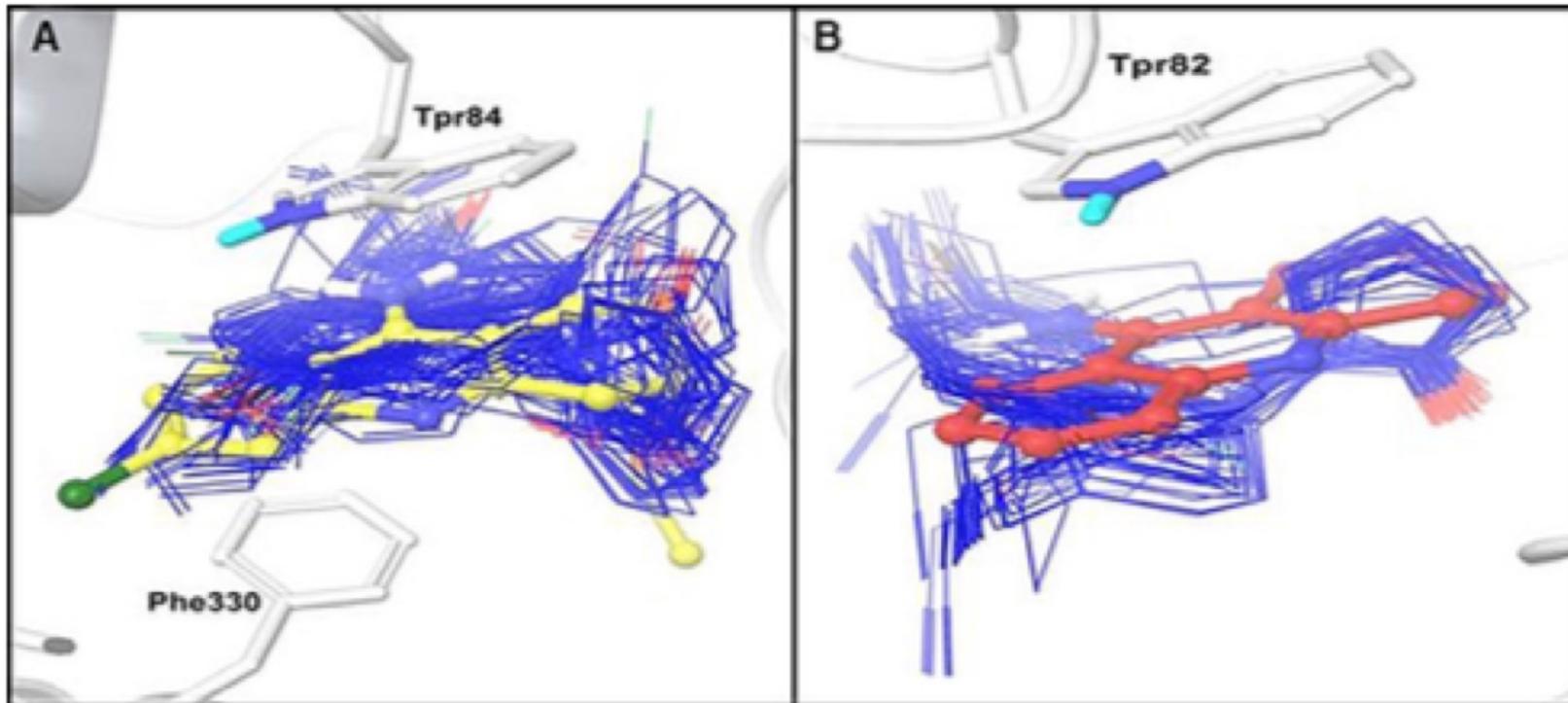
It is a neurodegenerative disease that causes progressive damage to the central nervous system and is manifested

Comp.	R	N-alkyl	AChE (μM) ^a	BChE (μM) ^a	SI ^b
4aa	H	$\text{CH}_2=\text{CHCH}_2$	211.72 ± 0.02	456.95 ± 0.03	2.16
4ab	CH_3	$\text{CH}_2=\text{CHCH}_2$	75.17 ± 0.01	31.66 ± 0.01	0.42
4ac	OCH_3	$\text{CH}_2=\text{CHCH}_2$	75.10 ± 0.01	62.23 ± 0.02	0.83
4ad	Cl	$\text{CH}_2=\text{CHCH}_2$	293.52 ± 0.02	62.26 ± 0.08	0.21
4ae	CH_2CH_3	$\text{CH}_2=\text{CHCH}_2$	173.96 ± 0.02	25.58 ± 0.02	0.15
4af	F	$\text{CH}_2=\text{CHCH}_2$	72.91 ± 0.01	135.29 ± 0.02	1.86
4ag	Br	$\text{CH}_2=\text{CHCH}_2$	168.03 ± 0.06	29.08 ± 0.03	0.17
4ba	H	$\text{HC}\equiv\text{CCH}_2$	421.30 ± 0.03	896.70 ± 0.03	2.13
4bb	CH_3	$\text{HC}\equiv\text{CCH}_2$	259.63 ± 0.01	455.59 ± 0.01	1.75
4bc	OCH_3	$\text{HC}\equiv\text{CCH}_2$	412.69 ± 0.01	1206.84 ± 0.01	2.92
4bd	Cl	$\text{HC}\equiv\text{CCH}_2$	392.91 ± 0.04	1327.55 ± 0.17	3.38
4be	CH_2CH_3	$\text{HC}\equiv\text{CCH}_2$	443.66 ± 0.01	1976.73 ± 0.09	4.46
4bf	F	$\text{HC}\equiv\text{CCH}_2$	375.61 ± 0.03	894.37 ± 0.03	2.38
4bg	Br	$\text{HC}\equiv\text{CCH}_2$	661.38 ± 0.09	894.77 ± 0.06	1.35
Galantamine	-	-	0.54 ± 0.7	8.80 ± 0.5	16.29

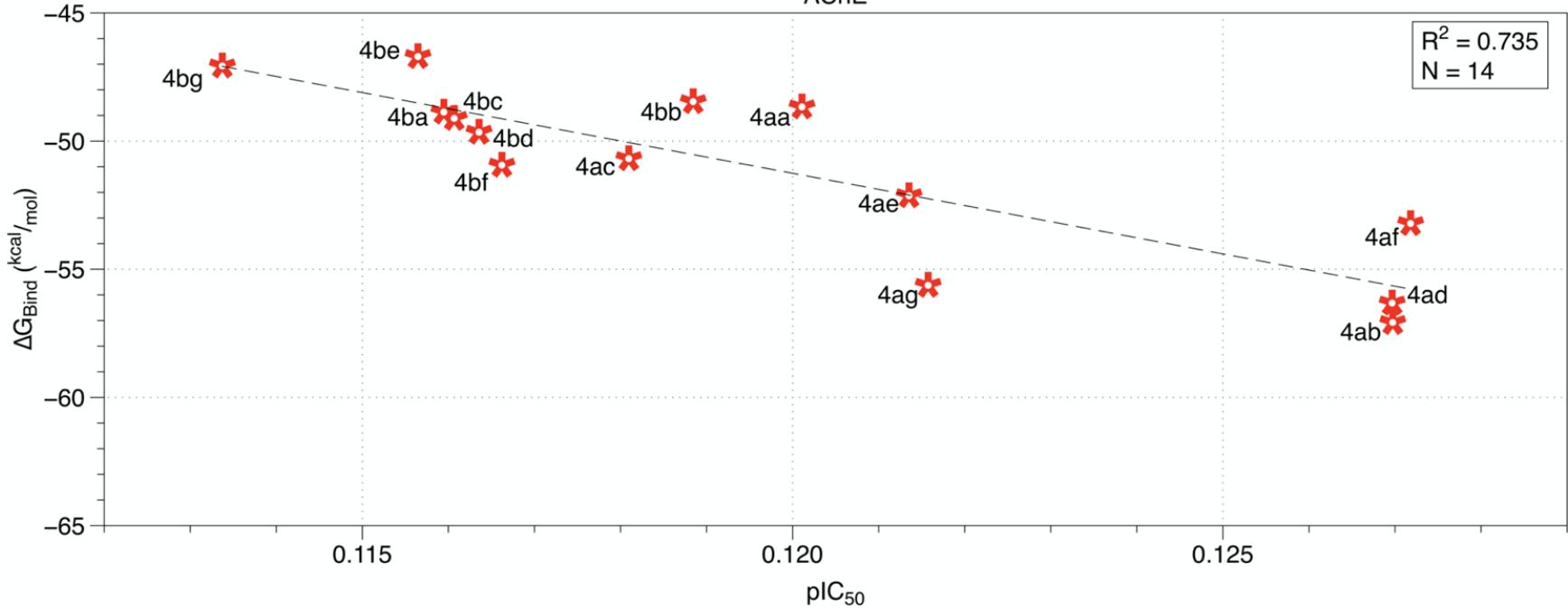
^aValues are the average from three independent experiments.

^bSelectivity for AChE is defined as $\text{IC}_{50}(\text{BChE})/\text{IC}_{50}(\text{AChE})$.

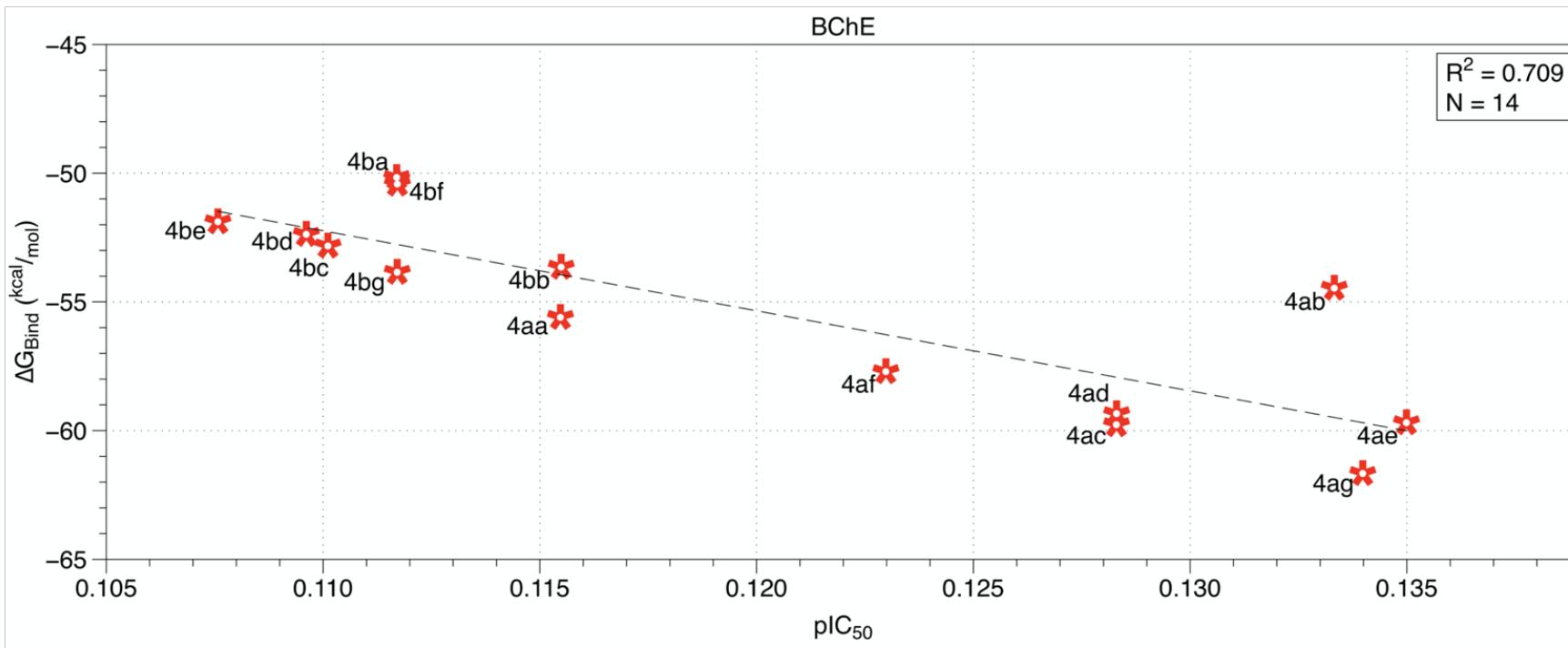
Figure 2: Predicted binding conformations of new ligands. The most populated clusters are showed in stick representation (blue). Reference ligands, huprine (yellow) and tacrine (red) are shown in ball & stick representation. The binding site residues are shown in stick representation (white). (A) acetylcholinesterase and (B) butyrylcholinesterase.



AChE



BChE





Article

Structural Insights into the Substrate Transport Mechanisms in GTR Transporters through Ensemble Docking

Carlos Peña-Varas ¹, Christa Kanstrup ², Ariela Vergara-Jaque ³, Mariela González-Avendaño ³,
Christoph Crocoll ², Osman Mirza ⁴, Ingo Dreyer ³, Hussam Nour-Eldin ² and David Ramírez ^{1,5,*}

TDP-43 Modulation by Tau-Tubulin Kinase 1 Inhibitors: A New Avenue for Future Amyotrophic Lateral Sclerosis Therapy

Vanesa Nozal, Loreto Martínez-González, Marta Gomez-Almeria, Claudia Gonzalo-Consuegra, Paula Santana, Apirat Chaikuad, Eva Pérez-Cuevas, Stefan Knapp, Daniel Lietha, David Ramírez, Sabrina Petralla, Barbara Monti, Carmen Gil, Angeles Martín-Requero, Valle Palomo, Eva de Lago, and Ana Martinez*



Cite This: <https://doi.org/10.1021/acs.jmedchem.1c01942>



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