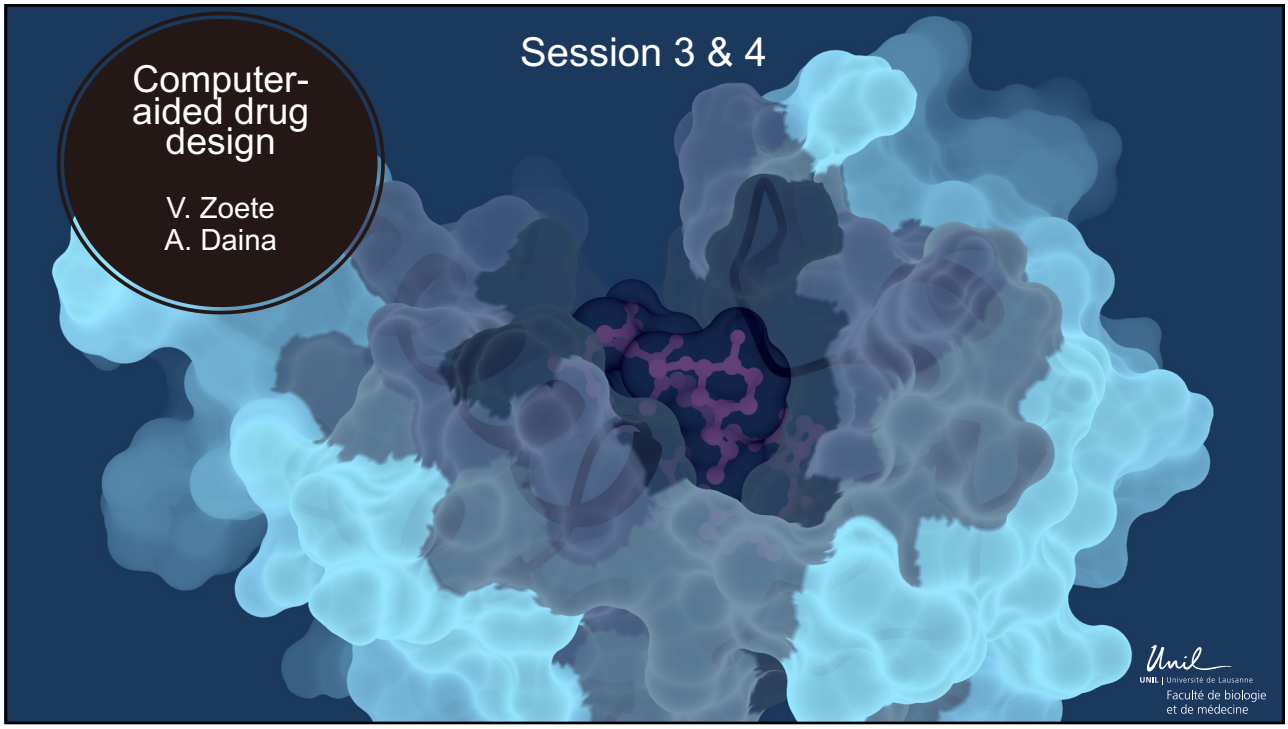


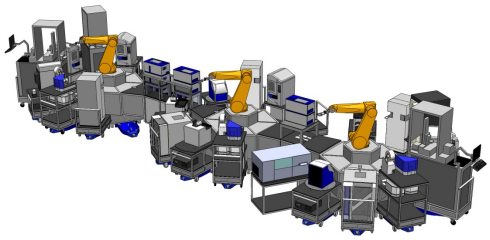
1

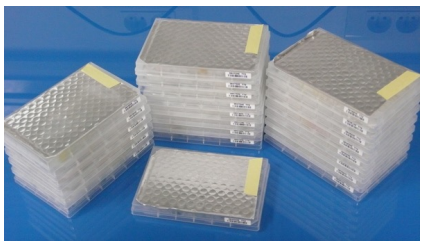
Lectures & Practices Agenda

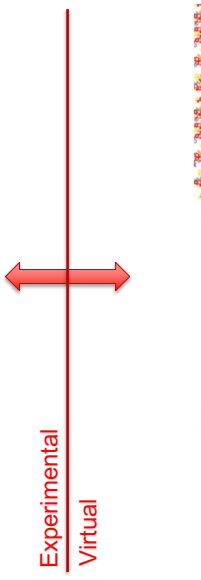
Session	Lecture	Practice
1	Prologue: molecular representation	
	Introduction to (computer-aided) drug design	
	Origin of 3D structures	
	Molecular recognition	Use of UCSF chimera to analyze protein-ligand complexes
2	Binding free energy estimation	
	Introduction to molecular docking	Ligand-protein docking with AutoDock Vina
3	Introduction to molecular (virtual) screening	Ligand-based virtual screening with **SwissSimilarity**
4	Short introduction on target prediction of small molecules	Use of **SwissTargetPrediction** to perform reverse screening.
5	Introduction to ADME, pharmacokinetics, druglikeness	Estimate physicochemical, pharmacokinetic, druglike and related properties with **SwissADME**
6	Short introduction to bioisosterism	Use of **SwissBioisostere** to perform bioisosteric design

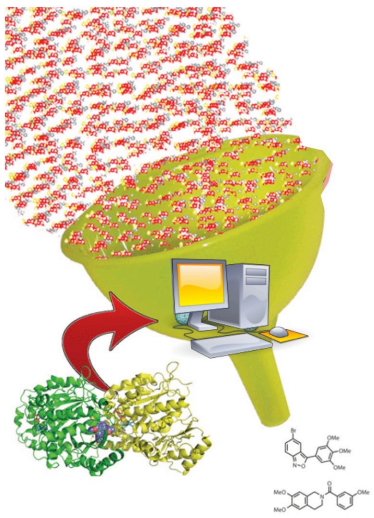
2

Introduction to Molecular (Virtual) Screening









Adapted from Chemical Biology & Drug Design
Volume 78, Issue 6, pages 913–922, December 2011

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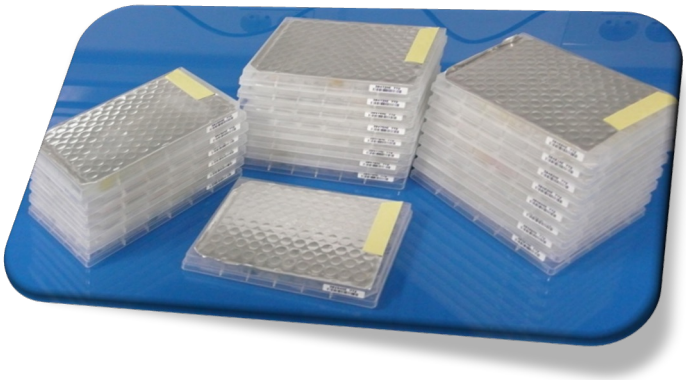
Introduction to Molecular (Virtual) Screening

1 Experimental screening	• Definition • Material and methods • Results and follow-up
2.1 Structure-based virtual screening	• Principle • Material and methods
2.2 Ligand-based virtual screening	• Principle • 2D molecular similarity • 3D molecular similarity
3 Oriented libraries	• Design of oriented libraries for experimental and virtual screening
4 Molecule filtering	• Filtering promiscuous compounds • Filtering toxic compounds

4

Introduction to Molecular (Virtual) Screening

Experimental Screening



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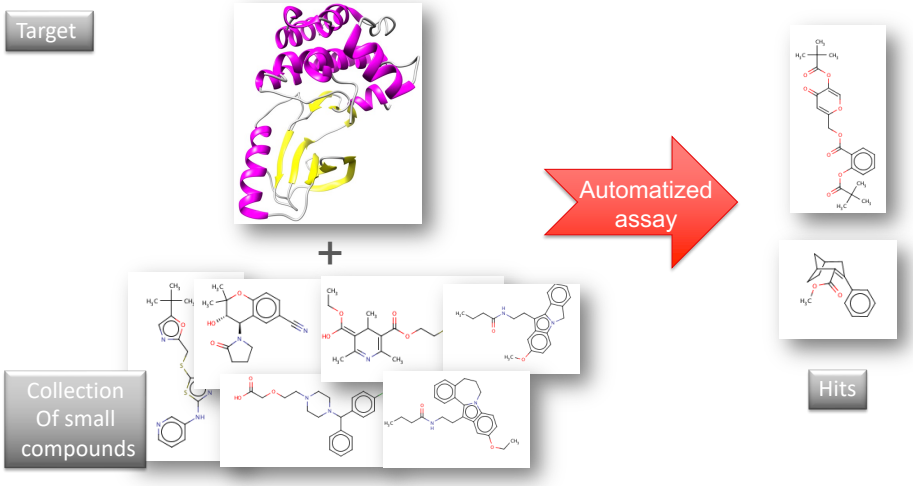
Experimental Screening – HTS

Experimental High Throughput Screening (HTS) consists in testing, using an automatized assay, a large collection of small molecules against a given target



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Experimental Screening – HTS

Example of commercially available "general" collections:

Vendor	Num. of compounds (Sep. 2018)
Asinex	533,412
Chembridge	1,508,897
ChemDiv	1,487,287
Enamine	2,152,818
LifeChemicals	379,184
Otava	258,919
Princeton	1,179,874
SPECS	212,184
TimTec	1,021,001
Vitas	1,406,461

For more, see http://zinc.docking.org

Cost:
- ~ 1 to 15 $ per molecule when buying entire large collection
- ~ 100 $ per molecule for cherry picking a few compounds among different collections

Pharmaceutical companies have proprietary collections of up to 10 millions compounds

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Experimental Screening – HTS

Possibility of using smaller **oriented** libraries to increase the hit rate:

- Chemical scaffold: e.g., beta-lactam, 5-membered ring heterocycles, …
- Small libraries with maximal chemical diversity (limit redundancy)
- Origin: e.g., natural products, ...
- Classes of targets: e.g., Kinase, Nucleic acid, GPCR, or Ion-Channel targeted libraries
- Interaction type: e.g., protein-protein interaction inhibitors.
- Therapeutic activity: e.g., anti-inflammatory, anti-infective, …
- Body compartment: e.g., CNS-Set (BBB permeant ➔ access CNS)

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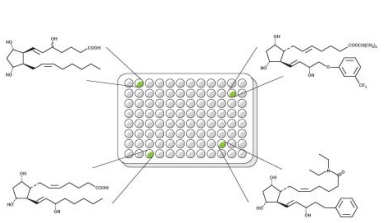
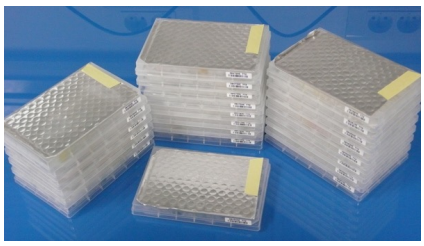
Experimental Screening – HTS

Format of the experimental collections:





University collection…

… pharmaceutical company collection.

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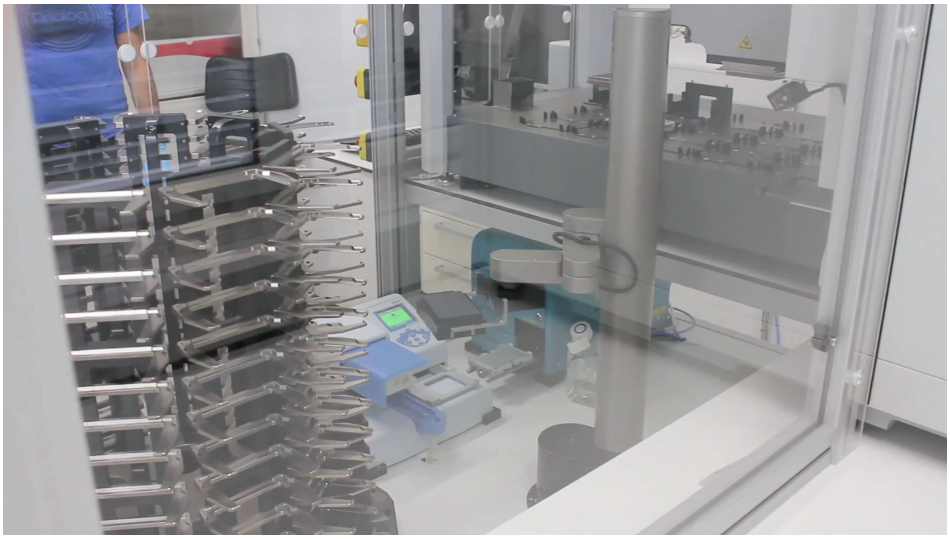
Experimental Screening – HTS

Assays are simplified, automated and performed using robots:



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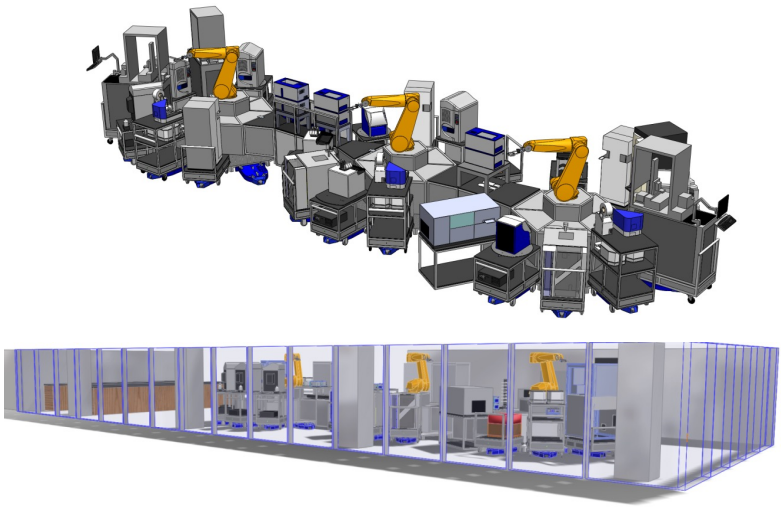
Experimental Screening – HTS

The industrial version :



Typical capacity: more than **100,000 compounds per day** in high-density 1536-well formats.

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Experimental Screening – HTS – Hit-to-Lead

Follow up:

1. Re-test the actives in the **primary assay to confirm** they are hits
2. Check whether the activity could be due to some **reactivity** (e.g. redox, alkylation,…) or some **physicochemical behavior** (absorbance, aggregation,…)
3. Perform a dose **response-curve** and determine IC_{50}
4. Check **the identity/purity** of the compound in the well (NMR, Mass spec.)
5. **Cluster actives** and see if (i) multiple members of the family are actives (ideal), (ii) only one member is active (problem?) or (iii) if all members are active (problem?)
6. Possibly synthesize (or buy) and test **some molecules similar** to the actives
7. Perform a **secondary assay** (different experimental conditions to verify that the activity is not assay-dependent)
8. Select, among the true, confirmed actives those that are the most **synthetically accessible**, with the best **ADME-tox profile**, etc…

↳ Lead compounds

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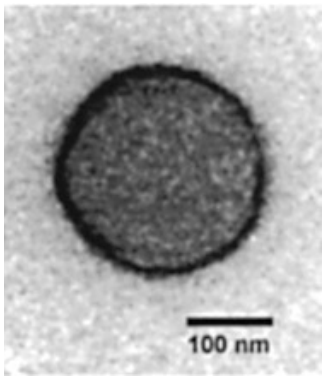
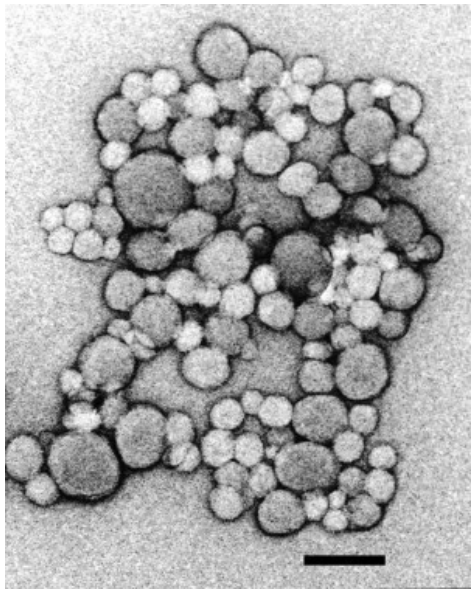
Experimental Screening – HTS – Hit-to-Lead

Aggregators:
Promiscuous inhibitors that form colloidal aggregates of 50-400 nm diameter that can adsorb proteins and block them

McGovern, S. L.; Caselli, E.; Grigorieff, N.; Shoichet, B. K. A Common Mechanism Underlying Promiscuous Inhibitors From Virtual and High-Throughput Screening. *J. Med. Chem.* **2002**, *45*, 1712–1722.

Ahil N Ganesh, Eric N Donders, Brian K Shoichet, Molly S Shoichet Colloidal aggregation: from screening nuisance to formulation nuance *Nano Today*, **2018:188-200**





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Experimental Screening – HTS – Success Rate

Success rate depends on the nature of the:

- **target**. Compound collections are full of molecules developed for intensively studied targets (e.g. GPCR). As a consequence, those targets lead to high success rate in HTS compared to new targets
- **interaction**. E.g. protein-protein interaction (PPI) inhibitors are hard to find
- **library**. E.g. kinase-focused libraries will provide higher success rate against kinases… but potentially less interesting discoveries

→
- Hits found in **half of the HTS campaigns**
- Number of hits corresponds to **1 to 3%** of the content of standard libraries against usual targets (0.1 to 1% for PPI).

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Experimental Screening – HTS – Cost

0.25 to 3 $ per molecule screened (excluding follow-up)

➡ Importance of **computational methods to:**
- to **decrease the number of molecules** to screen
- focus on the most probable **true hits possible to optimize**.

Experimental Screening – Help from in silico approaches

In silico approaches for molecular screening:

- Virtual screening
  - Structure-based: docking
  - Ligand-based: molecular similarity
- Creation of focused or targeted libraries
- Filtering of compounds
  - Finding most probable false positive molecules (promiscuous, dye, ...).
  - Finding ligands with potentially problematic fragments (toxic, unstable, ...)

Introduction to Molecular (Virtual) Screening

Virtual Screening

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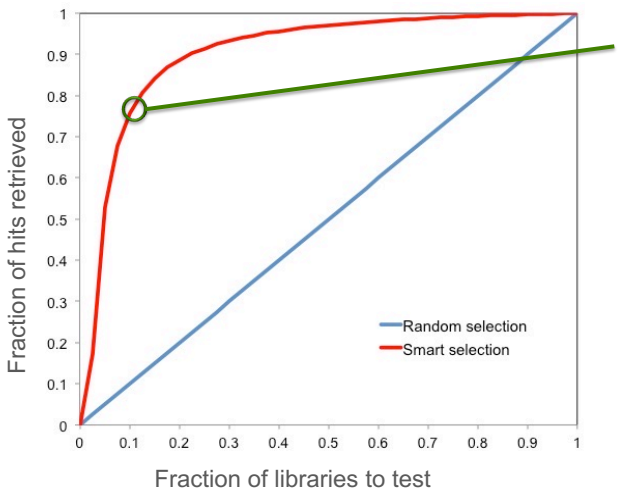
Virtual Screening – General objective

Virtual screening: Use of CADD algorithms to decrease the number of molecules to test experimentally. i.e. Create a short list of molecules to test in priority



Only need to screen 10% of the library to retrieve 75% of the hits

Enrichment procedure

- Will not find all actives
- Will not find only actives

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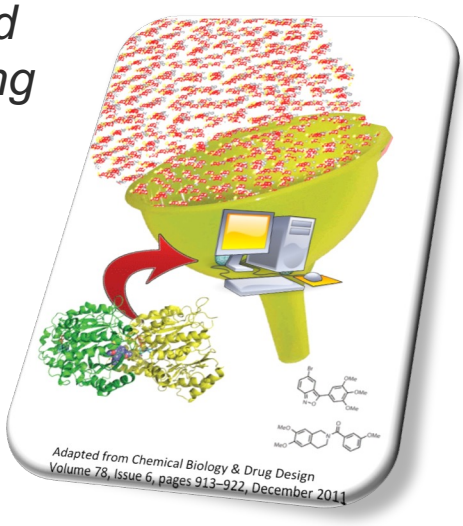
Introduction to Molecular (Virtual) Screening

Structure-Based Virtual Screening



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Structure-Based Virtual Screening - Definition

Structure-based virtual screening: Use of a docking software to systematically assess the binding mode of the entire collection of compounds and rank the putative ligands.

The docking software needs to be fast. Between 10 to 60 seconds per docking.

60 seconds x 1 million molecules ≈ 700 days

→ Compromise between precision and speed.
Impossible to get a precise binding mode for each molecule.

↳ Enrichment procedure

The scoring function needs to be able to rank ligands on the target of interest.
Possibly use of consensus score.

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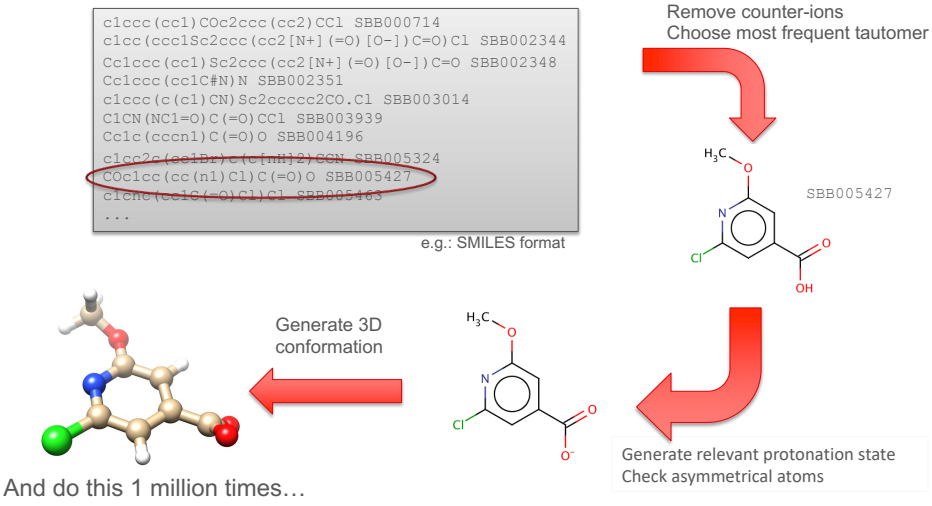
Structure-Based Virtual Screening – Typical Procedure

1. Prepare library of small molecule



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Structure-Based Virtual Screening – Typical Procedure

1. Prepare library of small molecule

Tools to perform those activities:

- Free and open source:
  - OpenBabel
  - CDK
  - RDKit
  - …
- Free for academic but not for commercial usage:
  - ChemAxon
  - BioVia (previously Accelrys)
  - OpenEye
  - Omega
  - CACTVS
  - Corina
  - …

See **click2drug.org** for a more complete list

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Structure-Based Virtual Screening – Typical Procedure

2. Prepare the target structure

As for docking:

- Add missing side-chains and residues
- Remove unwanted molecules (ligand, water molecules, ions)
- Check Protonation states (Asp, Glu, Lys, Arg, His)
- Add hydrogens

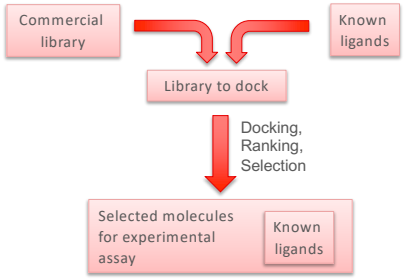
3. Choose the most appropriate docking software

a. Find **known ligands** of the target, possibly with known experimental binding modes
b. Dock them with several docking programs
c. Score the best binding modes with several scoring functions
d. Check which combination of docking program(s) and score(s) allows to predict best the binding modes and the ligand ranking

Structure-Based Virtual Screening – Typical Procedure

4. Add known ligands in the compound library

Useful to check the final results: **known ligands should be found in the top-ranked ligands** at the end of the process



5. Perform the dockings

6. Potentially re-rank the molecules/binding modes (consensus score)

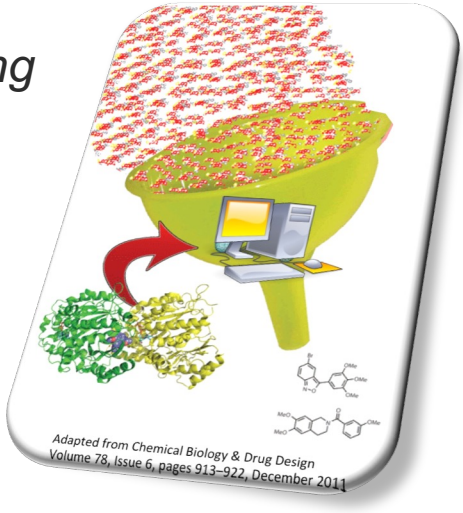
7. Visualize the calculated binding mode of the top-ranked molecules and eliminate unrealistic results

8. Check whether known ligands are in the top-ranked molecules

9. Select the molecules to be tested in priority (typically 10% of the entire library)

Introduction to Molecular (Virtual) Screening

Ligand-Based Virtual Screening



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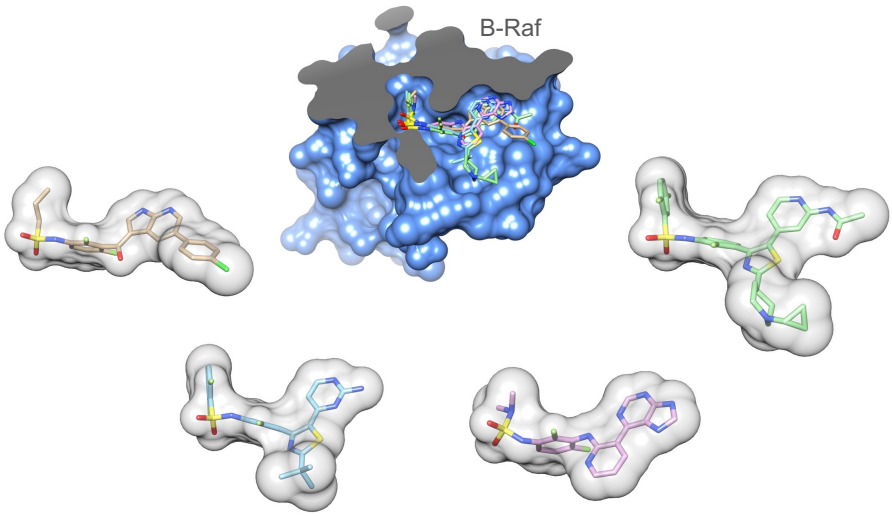
From Structure-Based to Ligand-Based Drug Design



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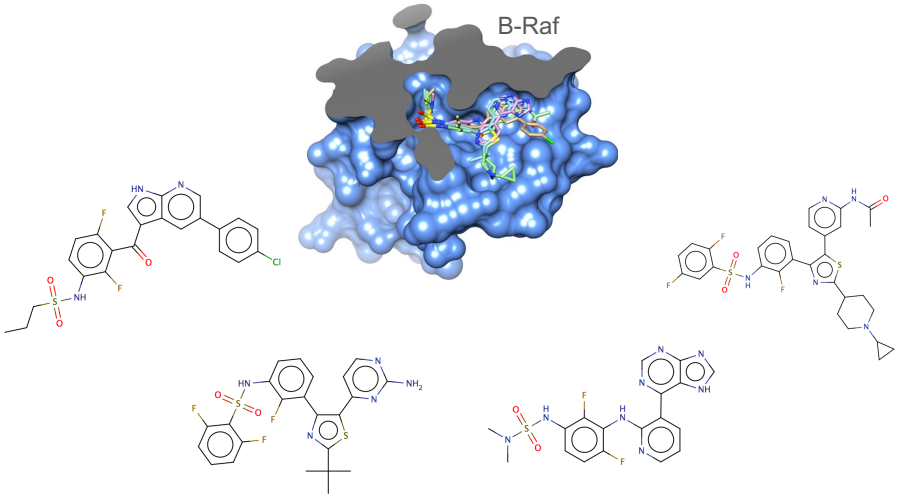
From Structure-Based to Ligand-Based Drug Design



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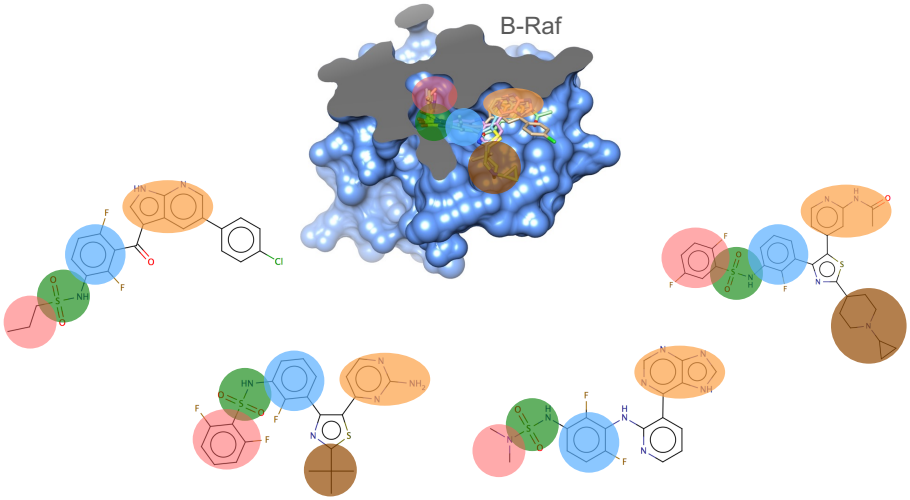
From Structure-Based to Ligand-Based Drug Design



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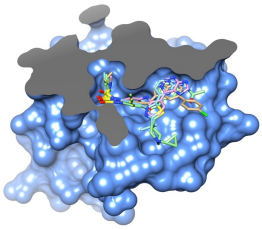
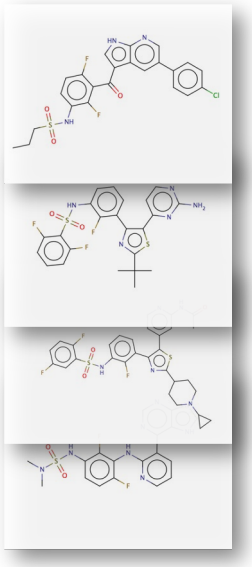
From Structure-Based to Ligand-Based Drug Design





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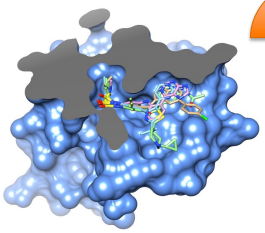
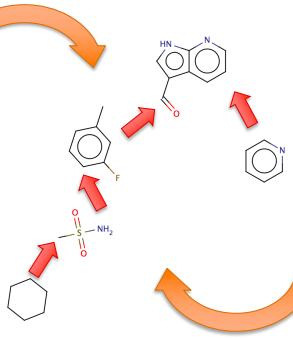
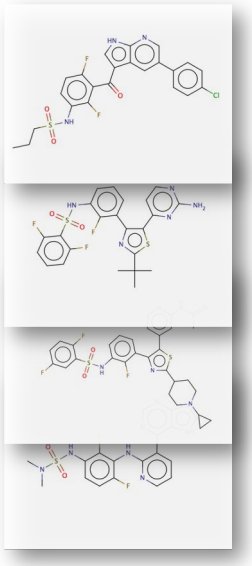
From Structure-Based to Ligand-Based Drug Design



Structure-based design
Docking
MD simulations
…



Ligand-based design
Molecular similarity
Machine Learning



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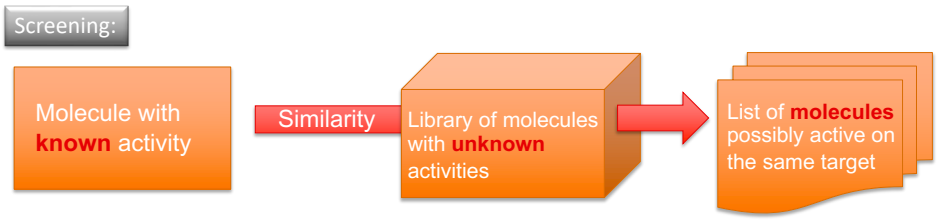
Ligand-Based Virtual Screening – General Approach

Assumption (similarity principle): **if two molecules are very similar, they are prone to be active on the same target**



We need at least one molecule active on the target of interest

This molecule does not need to be a drug. It can be:
- a substrate
- a natural product
- a molecule from a competitor (patent)

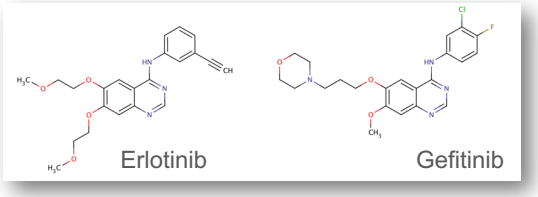
If several molecules are available, several screenings can be done.

→ Consensus screening

Ligand-Based Virtual Screening – Definition of Molecular Similarity

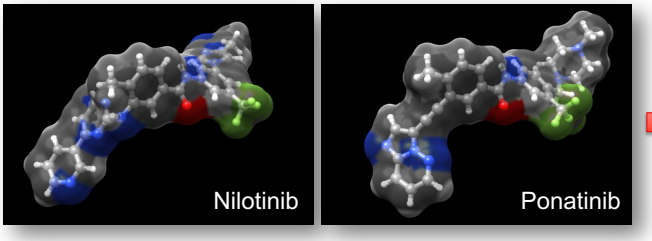
Assumption (similarity principle): **if two molecules are very similar, they are prone to be active on the same target**

- 2D: Similar by chemical structure (Fingerprints)



→ Very fast, but quite limited to similar scaffolds

- 3D: Similar by shape (electrostatics and lipophilicity)

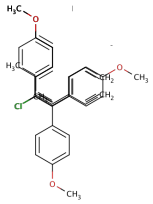


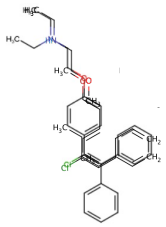
→ Slower, but allows various scaffolds

Ligand-Based Virtual Screening – Definition of Molecular Similarity

Chemical similarity (2D fingerprints)

Identify molecular features





A=(0, 1 , 0, 1 , 0, 0, 1 , 0, 0, …)

B=(0, 1 , 0, 1 , 0, 0, 1 , 0, **1** , …)

Ligand-Based Virtual Screening – Definition of Molecular Similarity

Chemical similarity (2D fingerprints)

The similarity value between molecules A and B is given by the **Tanimoto coefficient** T:

$$T = \frac{c}{a+b+c}$$, where

a is the count of bits at 1 in molecule A **but not** in molecule B
b is the count of bits at 1 in molecule B **but not** in molecule A
c is the count of bits at 1 in both molecules A **and** B

A=(0, 1, 0, 1, 0, 0, 1, 0, 0, …)

T ranges from 0 for totally different molecules to 1 for identical molecules

Speed: 1,000,000 comparisons per second

B=(0, 1, 0, 1, 0, 0, 1, 0, **1**, …)

Ligand-Based Virtual Screening – Definition of Molecular Similarity

Shape similarity (3D similarity)

Two main methods to calculate 3D shape similarity:

- **Superpose** molecules and calculate similarity based on **volume match**

  Ex: ROCS (OpenEye), Align-IT (Silicos-IT), …

- Transform 3D conformers of molecules into vectors of **real numbers**, and **compare vectors** (e.g. with Tanimoto, Manhattan distance, …)

  Ex: Electroshape, Spectrophores, …

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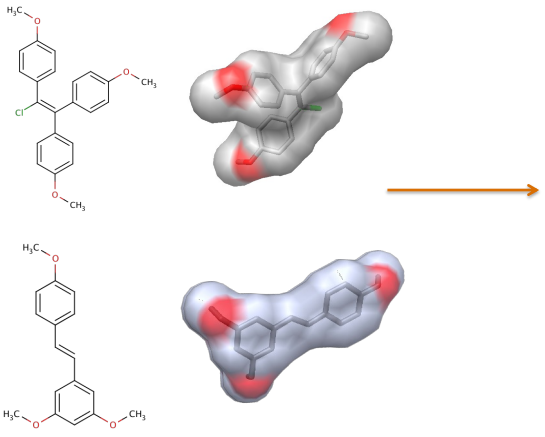
Ligand-Based Virtual Screening – Definition of Molecular Similarity

Shape similarity (3D similarity) – Superimposition (ROCS)

Grant, J.A., Gallardo, M.A., Pickup, B., *J. Comp. Chem.*, **1996**, *17*, 1653.

Molecules have similar shape if their volumes overlay well and any volume mismatch is a measure of dissimilarity.

ROCS uses a smooth Gaussian function to represent the molecular volume, so it is possible to rapidly minimize to the best global match.



20 to 40 overlays per second

Similar 3D shape

Courtesy of Prof. David Gfeller

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Ligand-Based Virtual Screening – Definition of Molecular Similarity

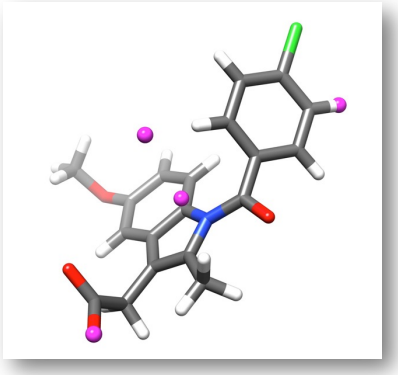
Shape similarity (3D similarity) – Electroshape

M. S. Armstrong et al., *J. Comput.-aided Mol. Des.*, **2010**, 24, 789-801

Idea: transform a 3D conformation into a 1D vector
5D (Charge, Lipophilicity)

1. Place important points (centroids) around the molecule:
- C1, baricenter of all atoms
- C2, furthest atom from C1
- C3, furthest atom from C2
- C4, C5 and C6 are defined by vector cross products

2. Calculate 3 values for each centroid:
- Average of the distance to each atom
- Standard deviation of the distance
- Third moment of the distance



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Ligand-Based Virtual Screening – Definition of Molecular Similarity

Shape similarity (3D similarity) – Electroshape

M. S. Armstrong et al., *J. Comput.-aided Mol. Des.*, **2010**, 24, 789-801

20 conformers, and thus 20 vectors, are calculated for each molecule

Vectors of both compounds are compared using Manhattan distance score

$$\text{Score} = \left(1 + \frac{1}{n}\sum_{1 \le i \le n} \left| x_i^{molA} - x_i^{molB} \right| \right)^{-1}$$

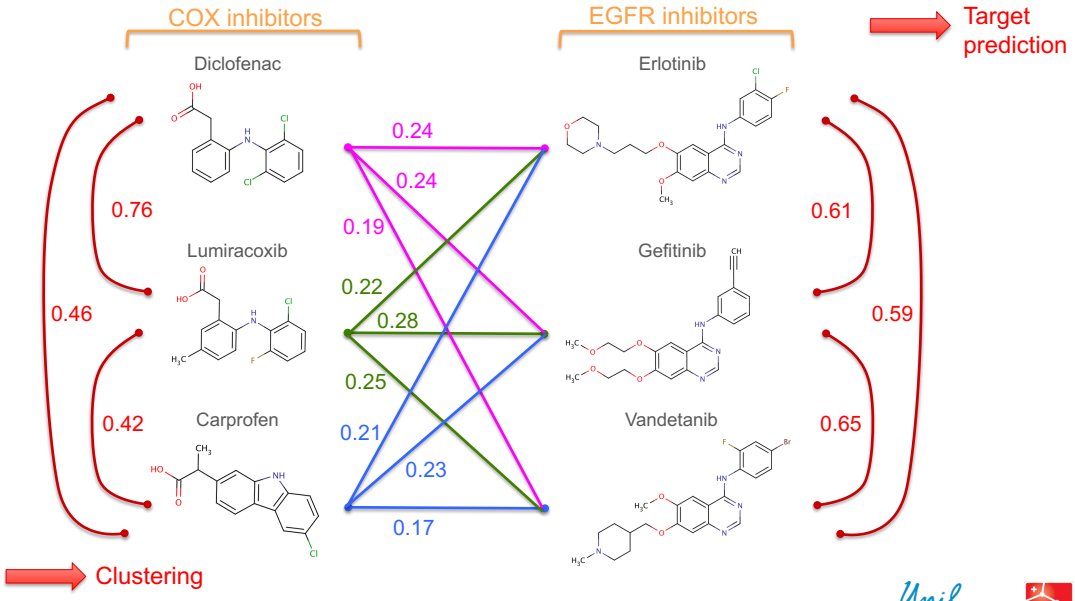
Score ranges from 0 (totally different shapes) to 1 (perfect match)

Advantages:
- independent of molecular orientation
- does not need molecular superposition

Speed: 10,000 comparisons per second
(20 conformers of the first compound against 20 conformers of second compound)

Ligand-Based Virtual Screening – Definition of Molecular Similarity

Using 2D fingerprints molecular similarity



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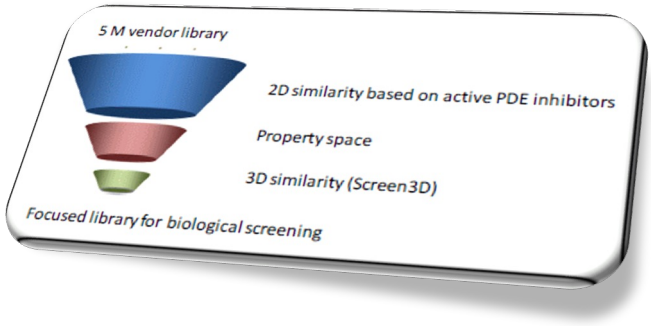
Introduction to Molecular (Virtual) Screening

Oriented Libraries



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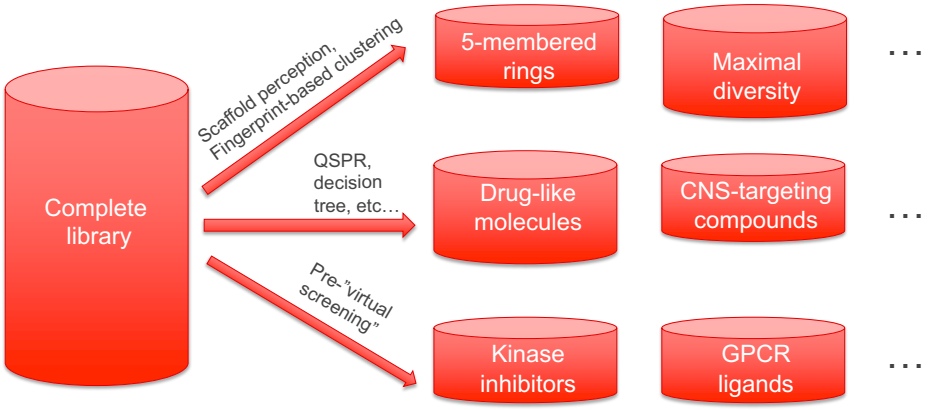
Molecular Screening – Design of oriented libraries for screening

Objective: to create small(er) libraries to perform more efficient experimental or virtual screenings

Method: Use computer-aided tools to filter compounds from an existing library



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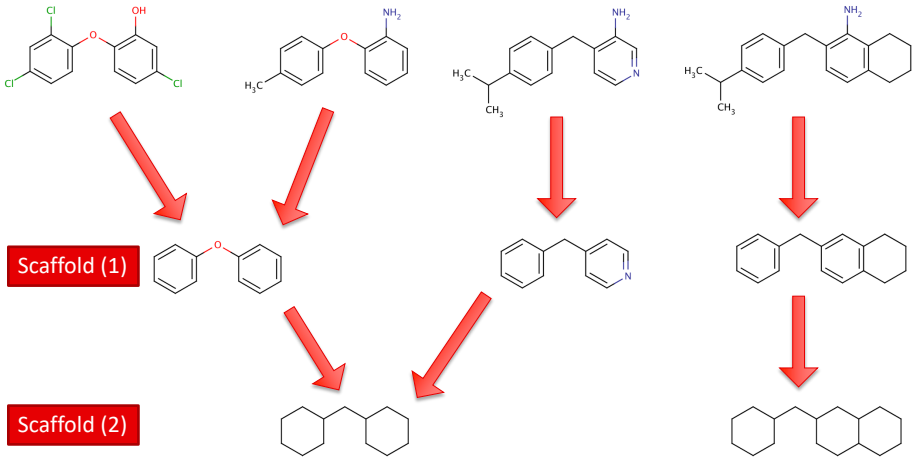
Molecular Screening – Design of oriented libraries for screening

Example: maximal diversity in a limited number of compounds (limit redundancy), using scaffold perception

Scaffold perception using Strip-IT from Silicos-IT. Several definitions of scaffolds.



(1) Rings with linkers (no side chain)
(2) Definition of Murcko (rings with linkers, no side chain, no info regarding heteroatoms and connectivity)

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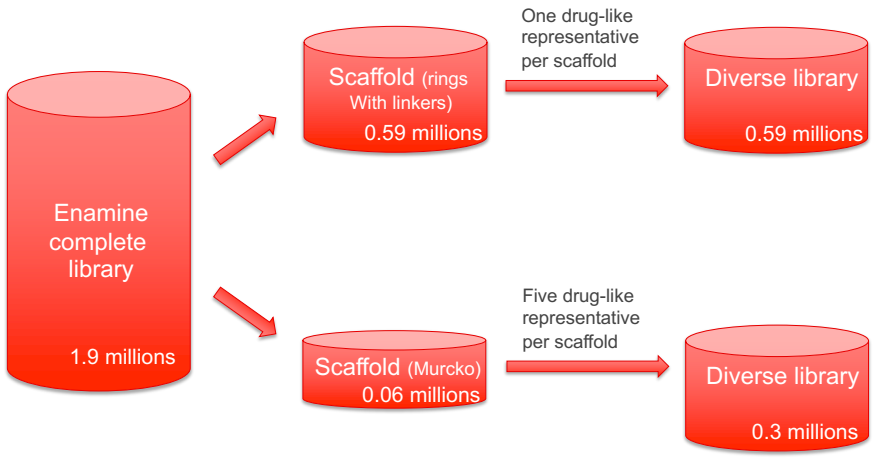
Molecular Screening – Design of oriented libraries for screening

Example: maximal diversity in a limited number of compounds (limit redundancy), using scaffold perception

Using Enamine Library:



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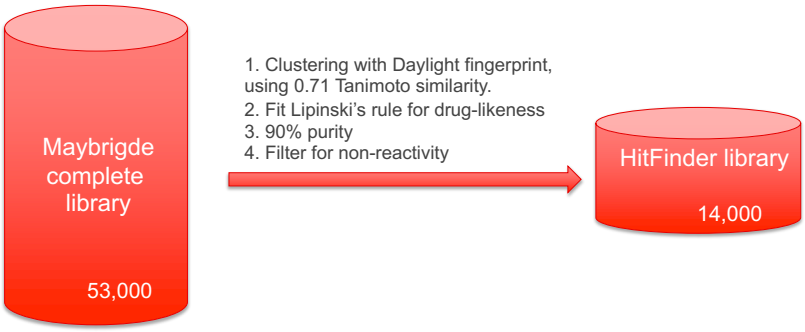
Molecular Screening – Design of oriented libraries for screening

Example: maximal diversity, using fingerprint-based clustering



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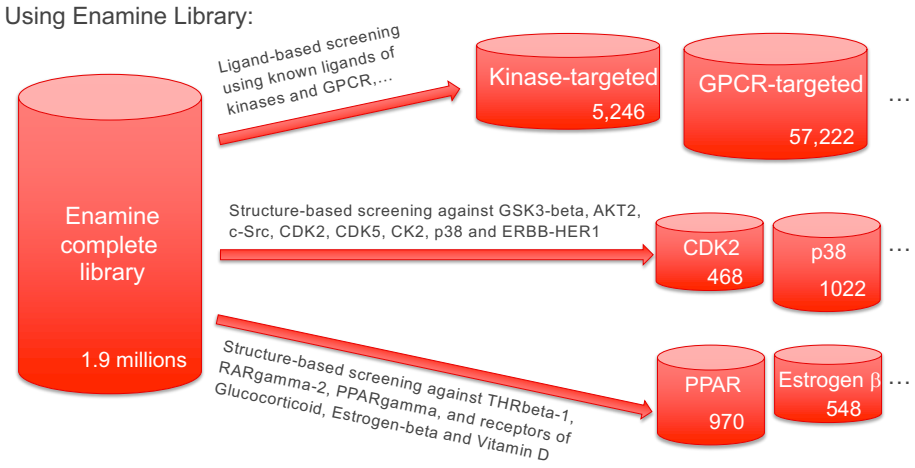
Molecular Screening – Design of oriented libraries for screening

Example: targeted (or focused) libraries, using ligand-based or structure-based screening



Molecular Screening – Molecule Filtering

Filtering can be done to:

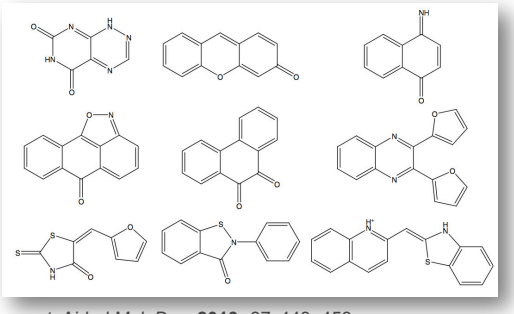
- Concentrate the search on **drug-like** molecules (Lipinski's rule of 5, …) or **given physchem properties** (log *P*, MW, …)
- Remove **promiscuous** or **dye** compounds
- Remove compounds with **toxic** moieties (stability, reactivity, ...)

Molecular Screening – Molecule Filtering – Promiscuous compounds

Promiscuous compounds are molecules found actives on multiple targets from different families.

Possible reasons:
- unspecific chemical reactivity (acyl halides, Michael addition, alkylating agents…),
- redox reactions,
- instability (acetals, …),
- interference with assay measurement (fluorescence, absorbance, chelators…),
- aggregators
- …

Examples of some of the most promiscuous scaffolds



Jane Tseng, Y. et al. *J. Comput. Aided Mol. Des.* **2013**, *27*, 443–453.

Molecular Screening – Molecule Filtering – Promiscuous compounds

Methods to predict promiscuous molecules were developed by:

1. Compiling sets of known promiscuous and non-promiscuous compounds
2. Analysis of frequent scaffolds, fragments or molecular features in promiscuous molecules
3. Creation of rules/filters to identify promiscuous compounds
4. Test predictive ability on sets established in 1.

Ex.:
- **Lilly MedChem.** Bruns, R. F.; et al. *J. Med. Chem.* **2012**, *55*, 9763–9772.
- **PAINS**. Baell, J. B.; et al. *J. Med. Chem.* **2010**, *53*, 2719–2740.
- **Pfizer LINT**. Blake, J. F. et al. *Med Chem* **2005**, *1*, 649–655.
- **Abott ALARM NMR**. Huth, J. R.; et al. *J. Am. Chem. Soc.* **2005**, *127*, 217–224.
- **Structural alert.** Brenk, R.; et al. *ChemMedChem* **2008**, *3*, 435–444.

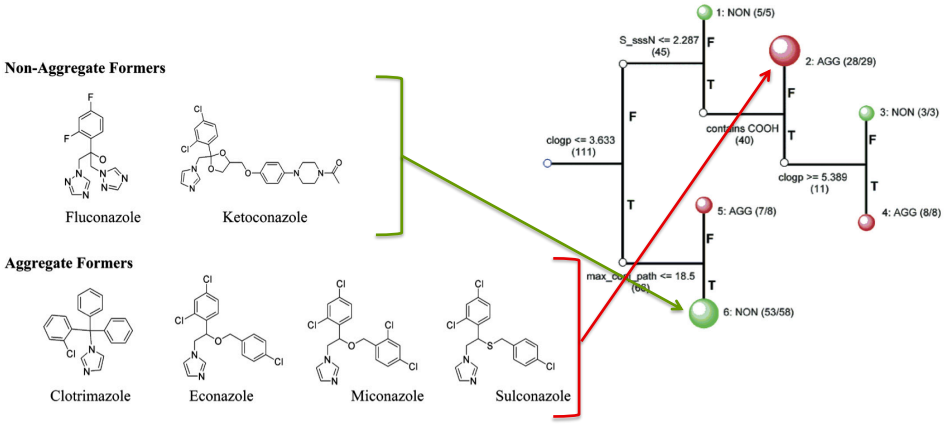
Molecular Screening – Molecule Filtering – Promiscuous compounds

Particular case of aggregators.

Seidler, J.; et al. *J. Med. Chem.* **2003**, *46*, 4477–4486.

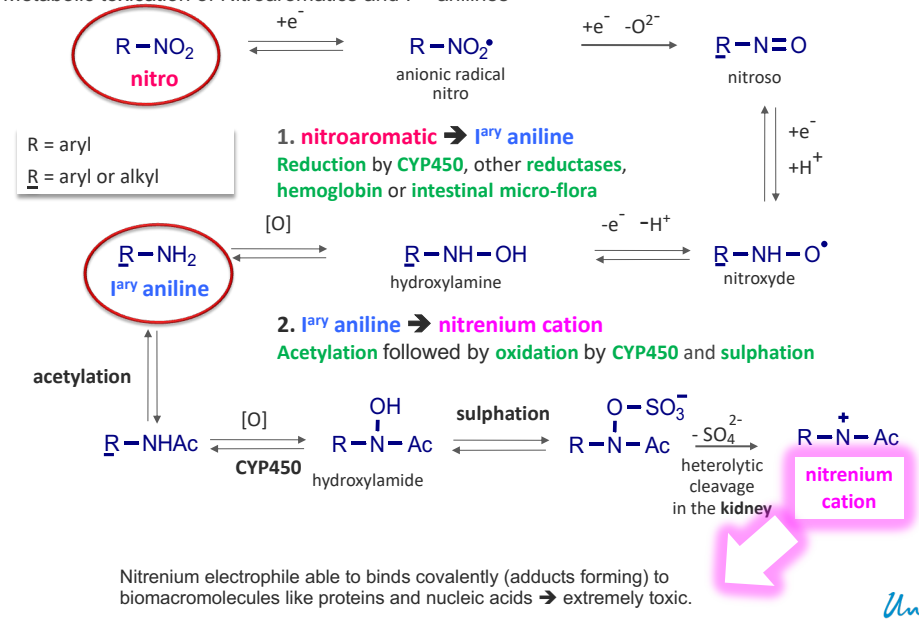
Model developed from 47 aggregators and 64 non-aggregators.

Aggregators have high log *P* and low water solubility



Molecular Screening – Molecule Filtering – Toxic compounds

Metabolic toxication of Nitroaromatics and I^{ary} anilines



Nitrenium electrophile able to binds covalently (adducts forming) to biomacromolecules like proteins and nucleic acids ➔ extremely toxic.

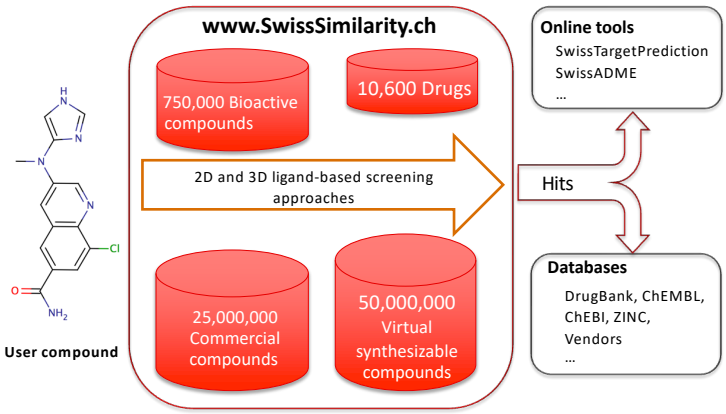
Molecular Screening – Molecule Filtering – Toxic compounds

Objective: Identify compounds really active for the good reasons, but potentially toxic, to
- remove them early in the drug design process if a large number of other compounds are available for the follow-up
- keep them if only few other interesting molecules are available, knowing that the fragment responsible for toxicity is to be replaced (optimization).

Methods: use a list of toxic fragments to filter hits (e.g. SMARTS format)

Molecular Screening – SwissSimilarity.ch

A web tool to perform ligand-based virtual screening

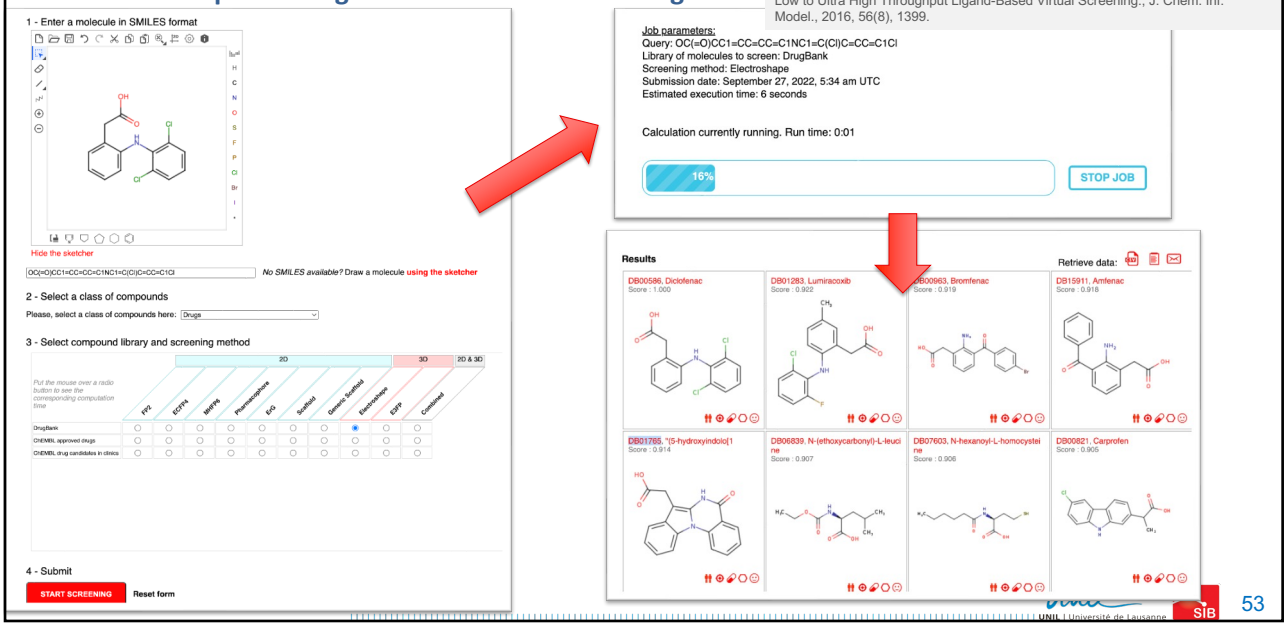


Molecular Screening – SwissSimilarity.ch

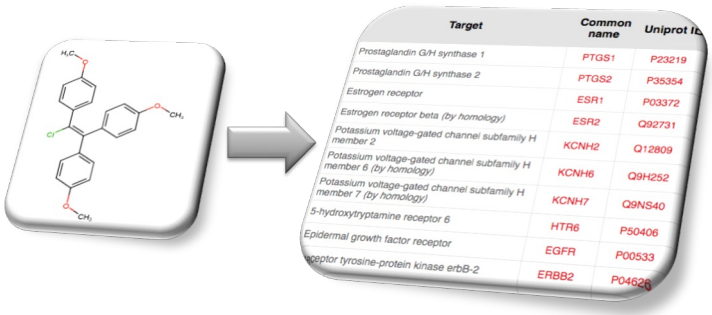
A web tool to perform ligand-based virtual screening

Bragina, ME., Daina, A., Perez, MAS., Michielin, O. & Zoete, V. SwissSimilarity 2021 Web Tool: Novel Chemical Libraries and Additional Methods for an Enhanced Ligand-Based Virtual Screening Experience., Int. J. Mol. Sci, 2022, 23(2), 811.

Zoete, V., Daina, A., Bovigny, C., & Michielin, O. SwissSimilarity: A Web Tool for Low to Ultra High Throughput Ligand-Based Virtual Screening., J. Chem. Inf. Model., 2016, 56(8), 1399.

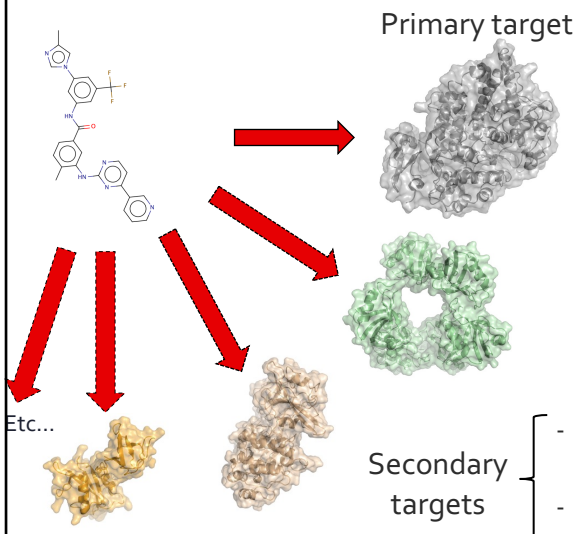


Reverse Screening and Target Prediction



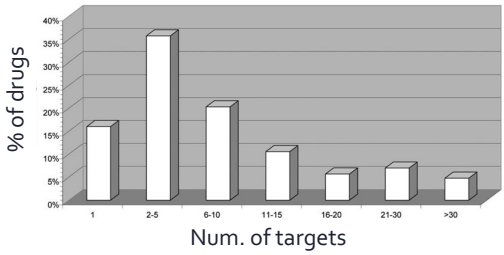
Reverse Screening and Target Prediction – General Objective

Usual vision: "The effect of a drug is explained by its interaction with one well-identified protein target". But…



- Side-effects, Toxicity (negative)
- Drug repurposing, polypharmacology (positive)

- 15% of drugs have only one known target
- ~17% of bioactive small molecules and 10% of FDA approved drugs without any known target (ChEMBL, DrugBank)



Courtesy of Prof. David Gfeller

Reverse Screening and Target Prediction – General Objective

Methods:

1. Molecular similarity

   Calculate molecular similarities between query molecule and ligands of known targets (e.g. SEA, SwissTargetPrediction, …)

2. Protein structure-based

   Systematically dock the query molecules to all possible protein targets with available 3D structure (e.g. TarFisDock, idTarget, …)

3. Data mining and machine learning methods

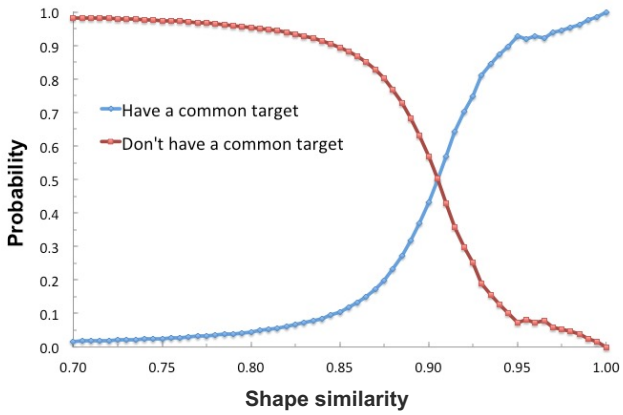
   Use machine learning to associate molecular substructures and target names (e.g. A. Bender, et al., ChemMedChem, 2007, 861–873)

4. Analysis of bioactivity spectra

   Experimental readouts (e.g. expression profiles) of small molecules are used as molecular descriptor to compare molecules and suggest new drug applications (e.g. Mantra, …)

Reverse Screening and Target Prediction – SwissTargetPrediction

Target prediction by molecular similarity
Quantifying the similarity principle



Probability, for a pair of bioactive molecules showing a given similarity, to be active on a common target

Calculated on 350,000 small molecules having an activity lower than 10 μM on one of the 1654 human targets listed by ChEMBL.

Gfeller, D.; Michielin, O.; Zoete, V. Shaping the Interaction Landscape of Bioactive Molecules. *Bioinformatics* 2013, 29, 3073–3079.

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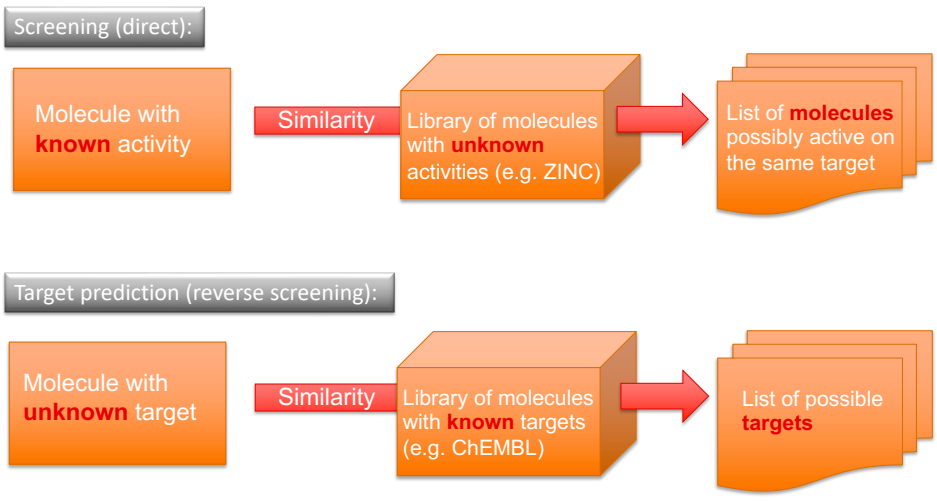
Reverse Screening and Target Prediction – SwissTargetPrediction

Target prediction by molecular similarity



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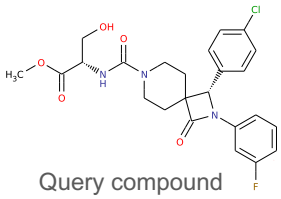
Reverse Screening and Target Prediction – SwissTargetPrediction

Use of 2D and 3D similarity



Query compound

Voltage-gated T-type calcium channel alpha-1H subunit

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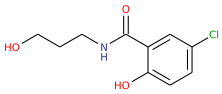
Reverse Screening and Target Prediction – SwissTargetPrediction

Use of 2D and 3D similarity



Query compound

Cyclin-dependent kinase 1

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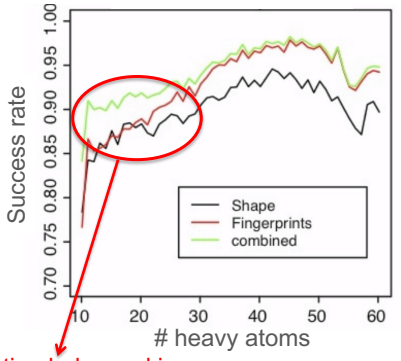
Reverse Screening and Target Prediction – SwissTargetPrediction

Use of 2D and 3D similarity

- Gfeller, D.; Michielin, O.; Zoete, V. Shaping the Interaction Landscape of Bioactive Molecules. *Bioinformatics.* **2013**, *29*, 3073–3079.
- Gfeller, D.; Grosdidier, A.; Wirth, M.; Daina, A.; Michielin, O.; Zoete, V. SwissTargetPrediction: a Web Server for Target Prediction of Bioactive Small Molecules. *Nucleic Acids Res.* **2014**, *42(Web Server issue)*, W32-8.
- Gfeller D., Zoete V. Protein homology reveals new targets for bioactive small molecules. *Bioinformatics*. **2015**, *31*, 2721-7.
- Daina A., Michielin O., Zoete, V. SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. *Nucleic Acids Res.*, **2019**, *47 (Web Server issue)*, W357–W364

Predictions based on comparisons
excluding similar molecules

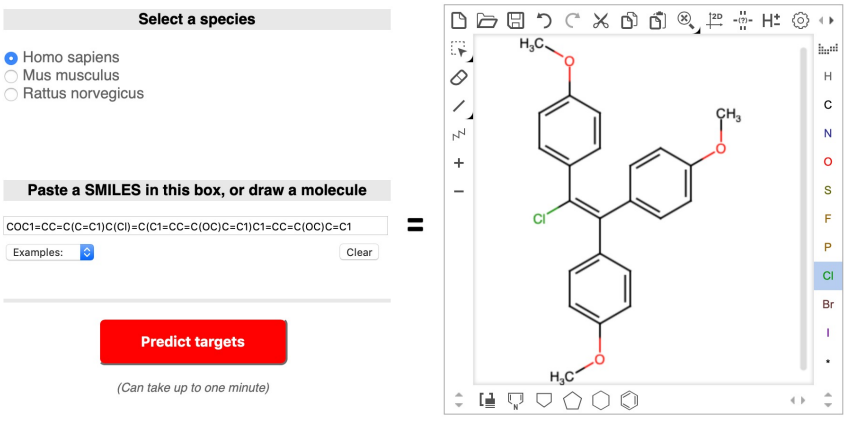


Dual scoring function helps making
predictions for drug-like first-in-class compounds

Reverse Screening and Target Prediction – SwissTargetPrediction.ch

SwissTargetPrediction: a web tool to predict to which protein target a bioactive small molecule could bind.

Note that SwissTargePrediction does not predict that a small molecule is bioactive, i.e. that it will bind a protein
SwissTargetprediction answers the question “If a small molecule is able to bind at least one protein, to which proteins is it likely to bind?”

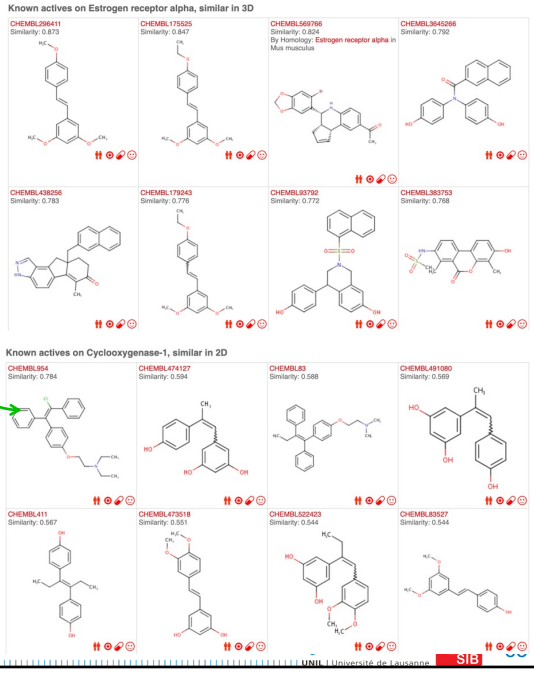


Reverse Screening and Target Prediction – SwissTargetPrediction.ch

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Receptor protein-tyrosine kinase erbB-2	ERBB2	P04626	CHEMBL1824	Kinase		76 / 2
Epidermal growth factor receptor erbB1	EGFR	P00533	CHEMBL203	Kinase		277 / 5
Estrogen receptor alpha	ESR1	P03372	CHEMBL206	Nuclear receptor		28 / 81
Muscarinic acetylcholine receptor M4	CHRM4	P08173	CHEMBL1821	Family A G protein-coupled receptor		19 / 2
Serotonin 6 (5-HT6) receptor	HTR6	P50406	CHEMBL3371	Family A G protein-coupled receptor		76 / 5
HERG	KCNH2	Q12809	CHEMBL240	Voltage-gated ion channel		94 / 3
Cyclooxygenase-1	PTGS1	P23219	CHEMBL221	Oxidoreductase		27 / 20
Serotonin transporter	SLC6A4	P31645	CHEMBL228	Electrochemical transporter		60 / 5
Beta-3 adrenergic receptor	ADRB3	P13945	CHEMBL246	Family A G protein-coupled receptor		0 / 2
Anti-estrogen binding site (AEBS)	EBP	Q15125	CHEMBL4931	Enzyme		0 / 4
Sigma opioid receptor	SIGMAR1	Q99720	CHEMBL287	Membrane receptor		27 / 7
Dopamine D3 receptor	DRD3	P35462	CHEMBL234	Family A G protein-coupled receptor		82 / 3
Adenosine A3 receptor	ADORA3	P0DMS8	CHEMBL256	Family A G protein-coupled receptor		58 / 3
Cytochrome P450 19A1	CYP19A1	P11511	CHEMBL1978	Cytochrome P450		280 / 30
Serotonin 2a (5-HT2a) receptor	HTR2A	P28223	CHEMBL224	Family A G protein-coupled receptor		137 / 6

Showing 1 to 15 of 100 entries

Previous 1 2 3 4 5 6 7 Next



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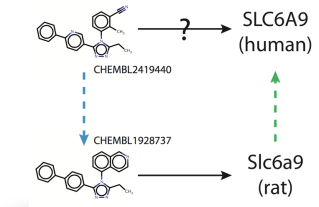
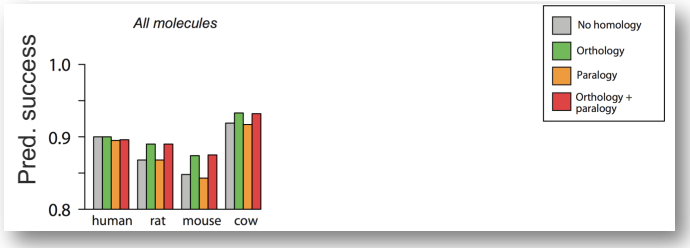
Reverse Screening and Target Prediction – SwissTargetPrediction.ch

Prediction by homology

Use of **protein homology** relationships to predict the targets of small molecules across different species:

- exploiting target homology **improves the predictions**, especially for molecules experimentally tested in other species,
- mapping small molecule interactions among orthologs improves prediction accuracy,
- including paralogs does not.





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(Virtual) Screening and Reverse Screening

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