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Field-based virtual screening: New trends to increase the chemical diversity of your leads

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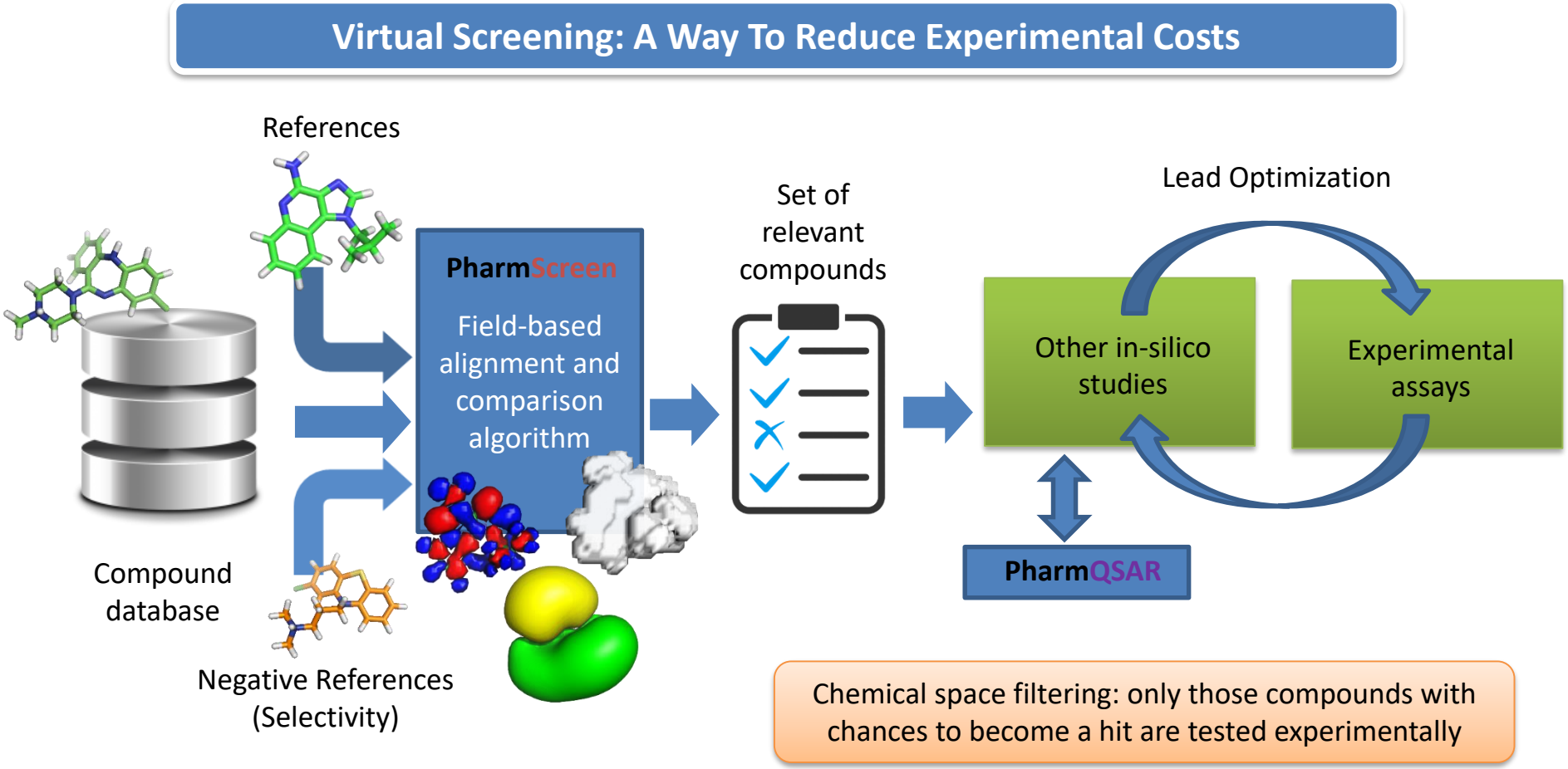
Field-based virtual screening: New trends to increase the chemical diversity of your leads

Graphical abstract:



Abstract:

Computational chemistry methods can significantly reduce experimental costs in early stages of a drug development project by filtering out unsuitable candidates and discovering new chemical matter. Molecular alignment is a key pre-requisite for 3D similarity evaluation between compounds and pharmacophore elucidation. Relying on the hypothesis that the variation in maximal achievable binding affinity for an optimized drug-like molecule is largely due to desolvation, we explore herein a novel small molecule 3D alignment strategy that exploits the partitioning of molecular hydrophobicity into atomic contributions in conjunction with information about the distribution of hydrogen-bond donor/acceptor groups in each compound. A brief description of the method, as implemented in the software package PharmScreen, is presented. The computational procedure is calibrated by using a dataset of 402 molecules pertaining to 14 distinct targets taken from the literature and validated against the CCDC AstraZeneca test set of 121 experimentally derived molecular overlays. The results confirm the suitability of MST based-hydrophobic parameters for generating molecular overlays with correct predictions obtained for 100%, 93%, and 55% of the molecules classified into easy, moderate and hard sets, respectively. The potential of this tool in a drug discovery campaign is then evaluated in a retrospective study with the aim to evaluate the correlations between activities and similarity score of a series of sigma-1 receptor ligands. The results confirm the suitability of the tool for Drug Discovery purposes finding the 67% of the most active ligands (≤10 nM) in Q1 of the ranking and the most active compound in position five.

Keywords: Drug Discovery; Virtual Screening; Molecular Alignment; Ligand-based; Hydrophobicity

Speech Goals

- Present the virtual screening techniques and how they can help finding better leads with high chemical diversity respect the reference structure.
  - Hydrophobicity in CADD
  - The value of considering multiple fields (electrostatic, steric and hydrophobic) when performing molecular alignment and virtual screening
  - The importance of finding chemical diversity using in-silico technologies
  - Case study

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Which Two Are More Similar ?

Strawberry

Orange

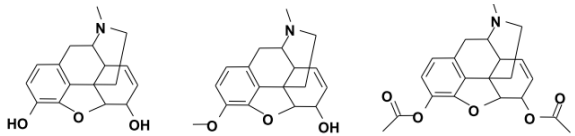
Basketball

There is no single measure of similarity:

“What is the essence of a molecule? What is it made of? What will it do?”

Molecular Similarity

Structurally similar molecules tend to have similar properties:



Morphine **Codeine** **Heroin**

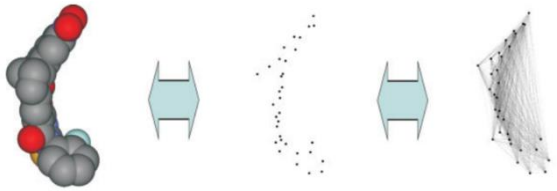
Problem: Subjective concept, with multiple ways of defining similarity

- 1D, 2D or 3D descriptors
- The weighting of these descriptors
- Mathematical expression of the similarity function.

3D-based similarity methods:

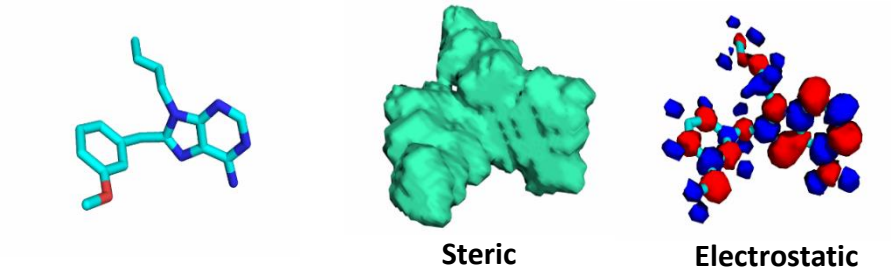
NONSUPERPOSITIONAL

The **analysis** of **atomic distances** to a set of reference positions



SUPERPOSITIONAL

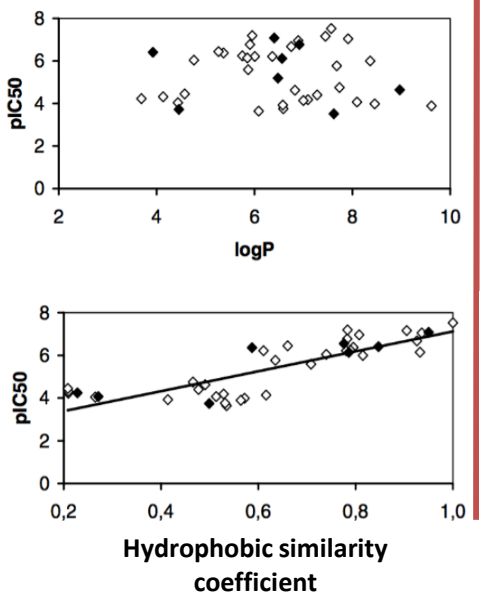
Correct alignment is critical



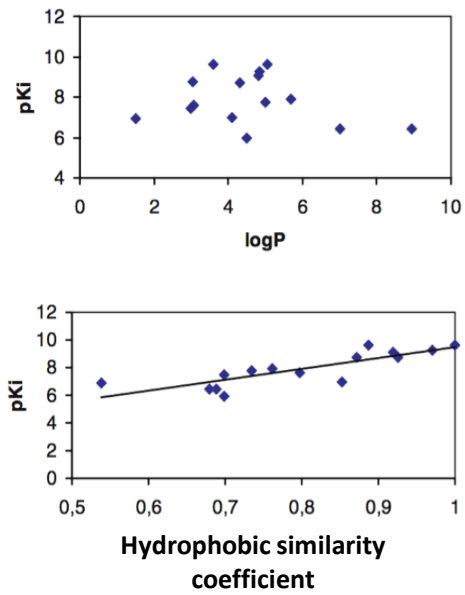
Steric **Electrostatic**

Hydrophobicity vs Binding Affinity And Activity

ACAT inhibitors



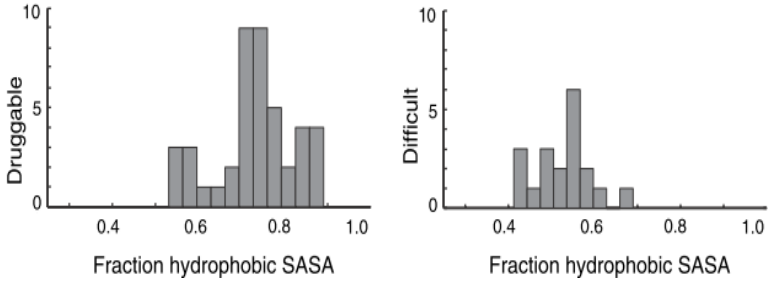
5-HT$_3$R



Structure-based maximal affinity model predicts small-molecule druggability

Alan C Cheng[1–3], Ryan G Coleman[1], Kathleen T Smyth[2], Qing Cao[1], Patricia Soulard[2], Daniel R Caffrey[1], Anna C Salzberg[1] & Enoch S Huang[1]

NATURE BIOTECHNOLOGY VOLUME 25 NUMBER 1 JANUARY 2007



A correlation emerges between the **pIC$_{50}$/ pK$_i$** and the global **hydrophobic similarity index**

J. Muñoz-Muriedas et al., *J. Comput. Aid. Mol. Des.*, **2005**, *23*

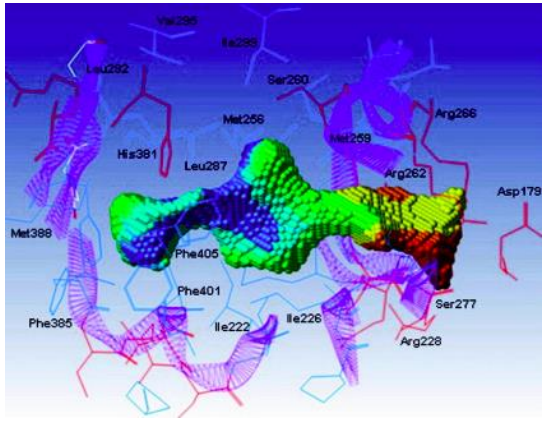
The defined draggability model assumes that favorable drug binding is **largely driven by the hydrophobic effect**

Can We Adopt Only Hydrophobic Descriptors?

Previous implementation based on empirical hydrophobic descriptors

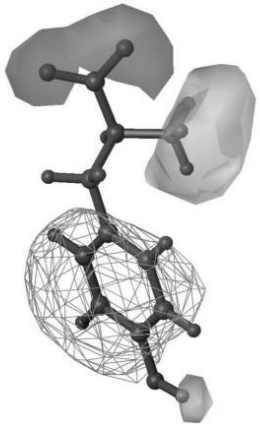
- Molecular Lipophilicity Potential **(MLP)**

Combines empirical fragmental contribution to lipophilicity with a distance-dependent function.



- Hydropathic INTeractions **(HINT) scoring function**

Rank compounds according to hydrophobic complementarity



G.E. Kellogg et al. J. Comput. Aided. Mol. Des. 1991; 5(6):545–552
P. Gaillard et al. J. Comput. Aided Mol. Des. 1994; 8(2):83-96
R. D. Cramer et al. J. Am. Chem. Soc. 1988,110, 5959.

Our Strategy: Atomic-Level Contributions To Hydrophobicity

MST Model

Derived from the Quantum Mechanical IEF/PCM-MST Solvation Models

Partitioning of the solvation free energy in the MST continuum models.

$$\Delta G_{sol} = \Delta G_{ele} + \Delta G_{cav} + \Delta G_{vW}$$

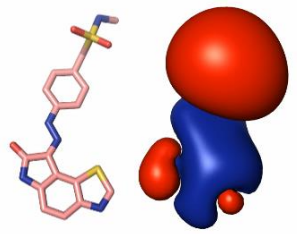
$$\Delta G_{sol} = \sum_{i=1}^{N} \Delta G_{sol,i} = \sum_{i=1}^{N} (\Delta G_{ele,i} + \Delta G_{cav,i} + \Delta G_{vW,i})$$

Atomic Contribution to Log P

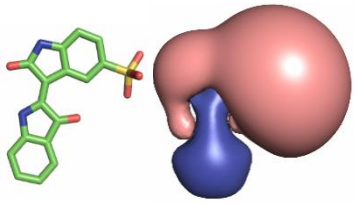
$$\log P_X = \sum_{i=1}^{N} \log P_{X,i} = \sum_{i=1}^{N} -\frac{\Delta G_{X,i}^{o/w}}{2.303RT} \quad (X: \text{ ele, cav, vW})$$

$$\text{Log } P_{i,total} = \text{LogP}_{i,ele} + \text{Log } P_{i,cav} + \text{Log } P_{i,vW}$$

Electrostatic contributions

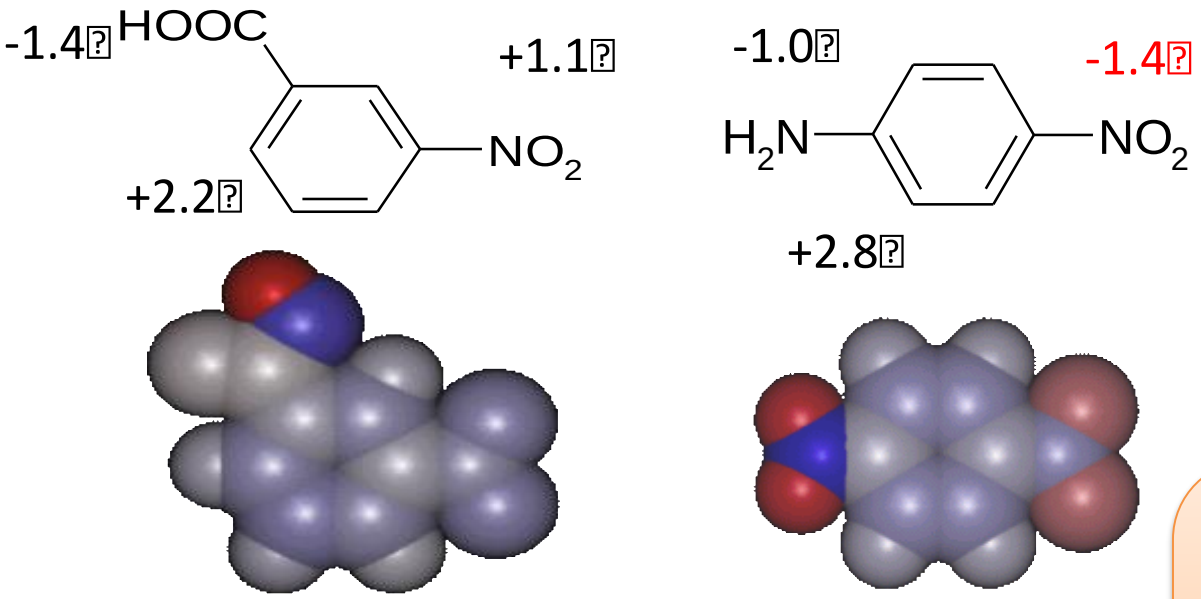


Non electrostatic contributions



F.J. Luque, M. J .Comput Aided Mol Des (1999) 13: 139.
Miertus, S., Scrocco, E. and Tomasi, J., Chem. Phys., 55(1981) 117.
Miertus, S. and Tomasi, J., Chem. Phys., 65 (1982) 239.

Why Use QM-Based Methods ?



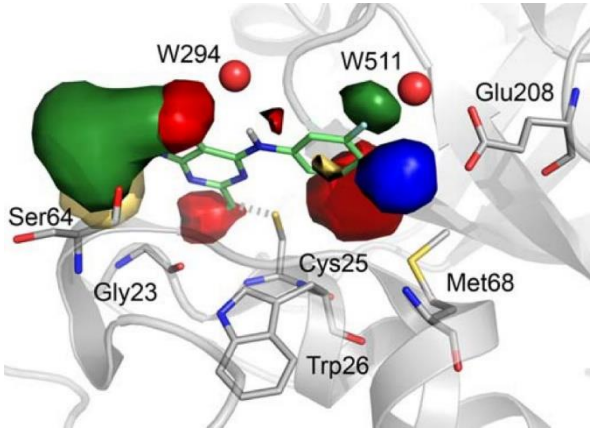
The atomic contribution is influenced by the whole molecule

- Take into account **conformation impact**
- **Model new chemical groups** not present in empirical databases

J. Muñoz-Muriedas et al., *J. Comput. Aided Mol. Des.*, **2005**, *23*

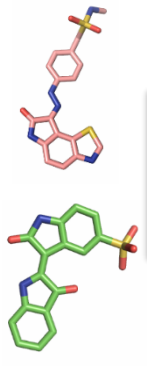
Hydrophobic Descriptors Validated for QSAR

- T. Ginex[1], J. Muñoz-Muriedas[2], E. Herrero[3], E. Gibert[3], P. Cozzini[4], F. J. Luque[1], "*Development and validation of hydrophobic molecular fields from the quantum mechanical IEF/PCM-MST solvation models in 3D-QSAR*", Journal of Computational Chemistry (JCC), January 2016
  - Hydrophobic fields usage in QSAR studies
- T. Ginex[1], J. Muñoz-Muriedas[2], E. Herrero[3], E. Gibert[3], P. Cozzini[4], F. J. Luque[1], "*Application of the Quantum Mechanical IEF/PCM-MST Hydrophobic Descriptors to Selectivity in Ligand Binding*", Journal of Molecular Modelling (JMM), June 2016
  - Hydrophobic fields usage in selectivity evaluation



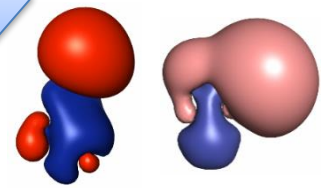
(1) Universitat de Barcelona (2) GlaxoSmithKline (3) Pharmacelera (4) Università di Parma

PharmScreen: MST-based Alignment



Parameter calculation

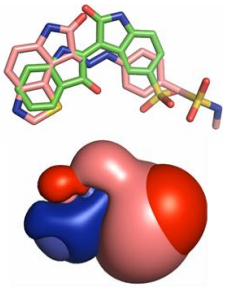
Expansion center and tensors calculation



Alignment pool

Similarity Function

Tanimoto
Tversky



Final Alignment

LogP$_{ele}$ *Quadrupolar tensor*

$$\boldsymbol{Q} = \sum_{i=1}^{N} \log P_{o/w,i} \left(3\vec{r}_i\vec{r}_i - \left|\vec{r}_i\right|^2 \mathbf{1} \right)$$

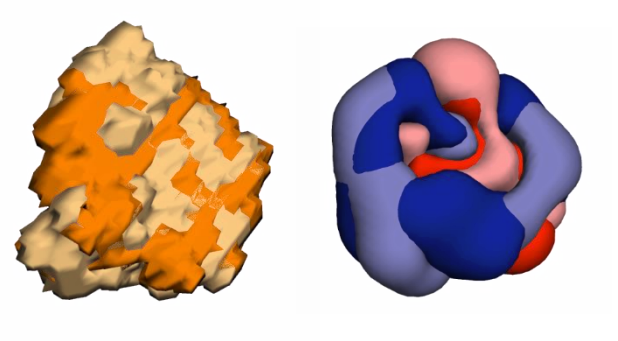
LogP$_{cav}$ *Inertial tensor*

$$\boldsymbol{I} = \sum_{i=1}^{N} \log P^{cav}_{o/w,i} \left(\left|\vec{r}_i\right|^2 \mathbf{1} - \vec{r}_i\vec{r}_i \right)$$

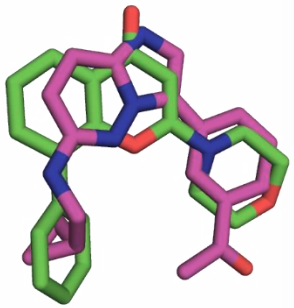
Molecular Fields are agnostic to chemotypes

Better Ligand-Receptor Interaction Model

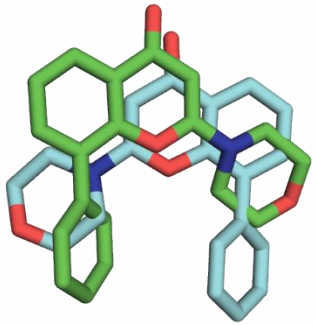
Traditional fields (Shape – Electro)



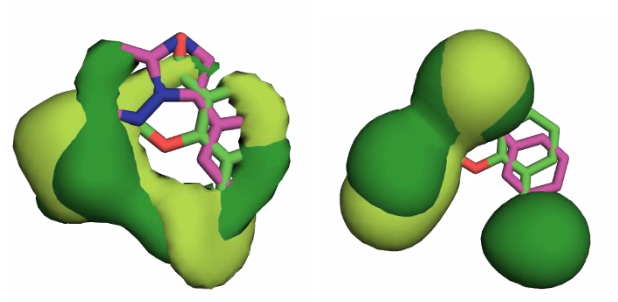
Ref overlay

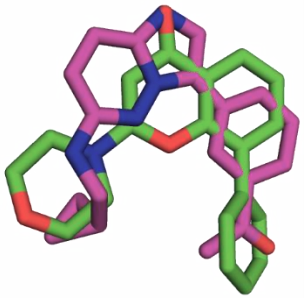


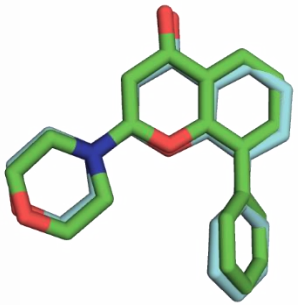
Crystal overlay



PharmScreen interaction fields







PIM-1 INHIBITORS ALIGNMENT

PharmScreen fields better represent ligand-protein interactions vs traditional fields

PharmScreen Provides Superior Alignment

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING
Article
Cite This: J. Chem. Inf. Model. 2018, 58, 1596−1609
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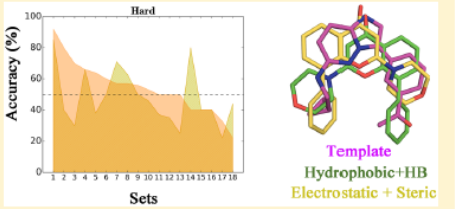
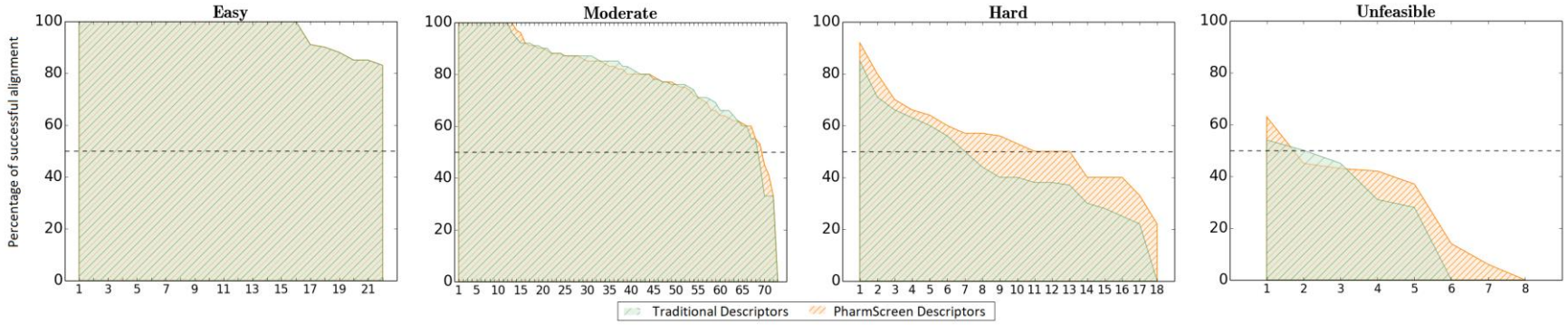
Development and Validation of Molecular Overlays Derived from Three-Dimensional Hydrophobic Similarity with PharmScreen

Javier Vázquez,[†,‡] Alessandro Deplano,[†] Albert Herrero,[†] Tiziana Ginex,[‡] Enric Gibert,[†] Obdulia Rabal,[§] Julen Oyarzabal,[§] Enric Herrero,[†] and F. Javier Luque*[,‡]

ABSTRACT: Molecular alignment is a standard procedure for three-dimensional (3D) similarity measurements and pharmacophore elucidation. This process is influenced by several factors, such as the physicochemical descriptors utilized to account for the molecular determinants of biological activity and the reference templates. Relying on the hypothesis that the maximal achievable binding affinity for a drug-like molecule is largely due to desolvation, we explore a novel strategy for 3D molecular overlays that exploits the partitioning of molecular hydrophobicity into atomic contributions in conjunction with information about the distribution of hydrogen-bond (HB) donor/acceptor groups. A brief description of the method, as implemented in the software package PharmScreen, including the derivation of the fractional hydrophobic contributions within the quantum mechanical



AZ / CCDC Dataset:
1456 crystal structures from 121 receptors



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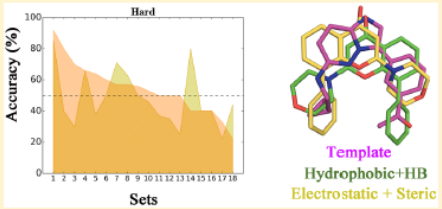
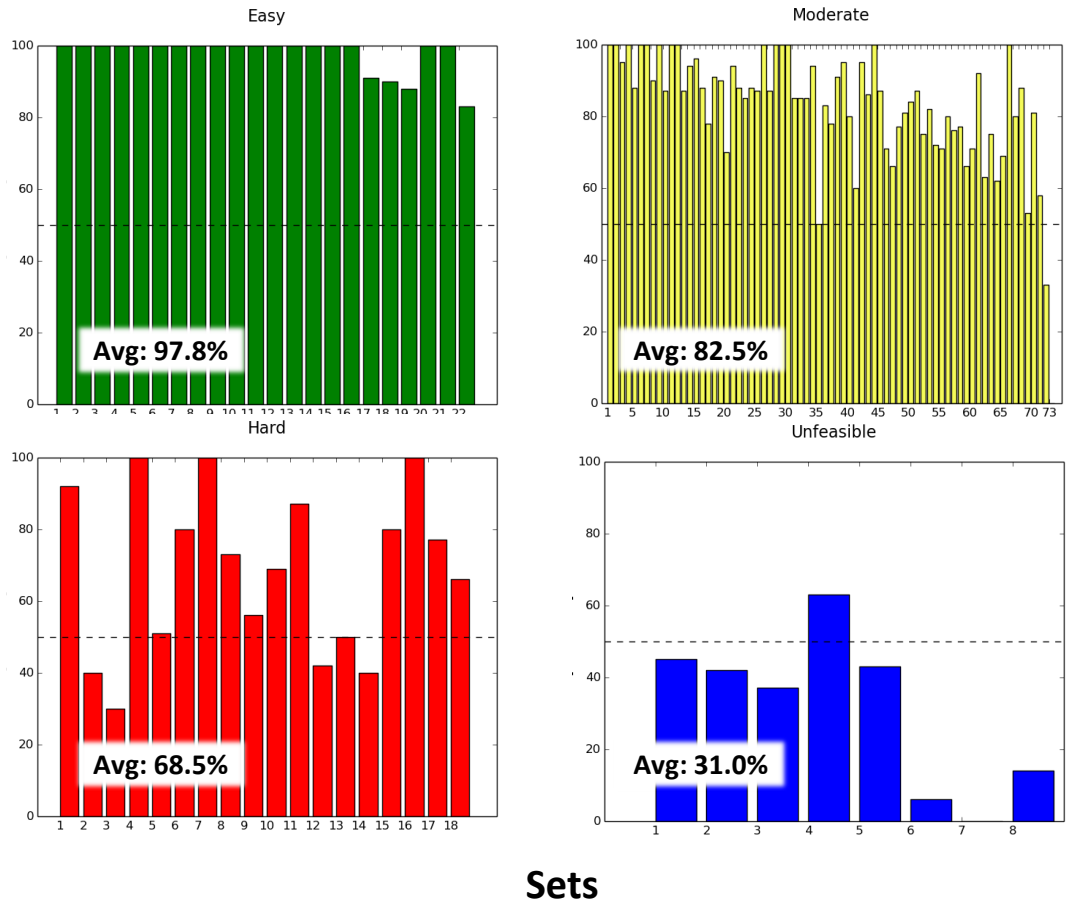


AZ / CCDC Dataset:
1456 crystal structures from 121 receptors

	Easy	Moderate	Hard	Unfeasible
AstraZeneca	95%	73%	39%	0%
MolAlign	100%	76%	54%	0%
PharmScreen	**100%**	**96%**	**72%**	**12.5%**

Do These Descriptors Provide The Same Overlays?



Percentage of equal overlays between hydrophobic/HB and steric/electrostatic fields

Generated overlays differ significantly for complex cases highlighting the complementarity of both approaches

ESTEVE Study

Project goal: Virtual screening quality evaluation.

Explore correlations between activities and molecular similarity.

Data:

- 174 sigma-1 receptor ligands from existing publications analyzed
- Public external references from RCSB Protein Data Bank: 5HK1 and 5HK2[1,2,3]

Workflow:

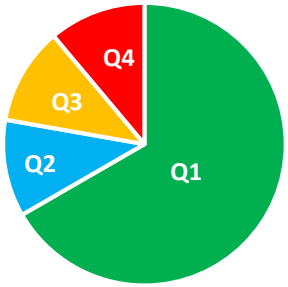
- Library preparation
  - Generation 3D structure, isomers, tautomers and conformers of the molecules (~20.000 total molecules).
- As reference was used a ligand from a crystal structure external to the papers.
- Virtual screening with PharmScreen using hydrophobic and hydrogen bonds fields.

1. **Crystal structure of the human σ1 receptor Hayden.** H. R. Schmidt, S. Zheng, E. Gurpinar, A. Koehl, A. Manglik, A. C. Kruse, Nature, 2016, *532* (7600), 527-530
2. **The Pharmacology of the Novel and Selective Sigma Ligand, PD 144418.** H. C. Akunne, S. Z. Whetzel, J. N. Wiley, A. E. Corbin, F. W. Ninteman, H. tecle, Y Pei, T. A. Pugsley, T. G. Heffner, Neuropharmacology, 1997, 36, 51-62
3. **Synthesis and Characterization of [^{125}I]-N-(N-Benzylpiperidin-4-yl)-4-iodobenzamide, a New σ Receptor Radiopharmaceutical: High-Affinity Binding to MCF-7 Breast Tumor Cells.** C. S. Jhon, B. J. Vilner, W. D. Bowen, J. Med. Chem. 1994, 37, 1737-1739

High Correlation PharmScreen Ranking And Active Hits

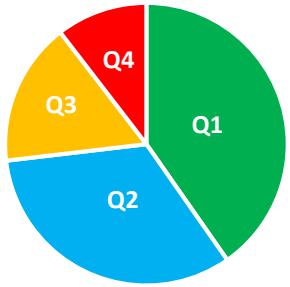
- Ligands with higher activity found in the initial results
  - Molecule with highest activity in position 5 of the VS ranking
- Molecule from the existing patent in position 15 of the VS ranking

a≤10nM

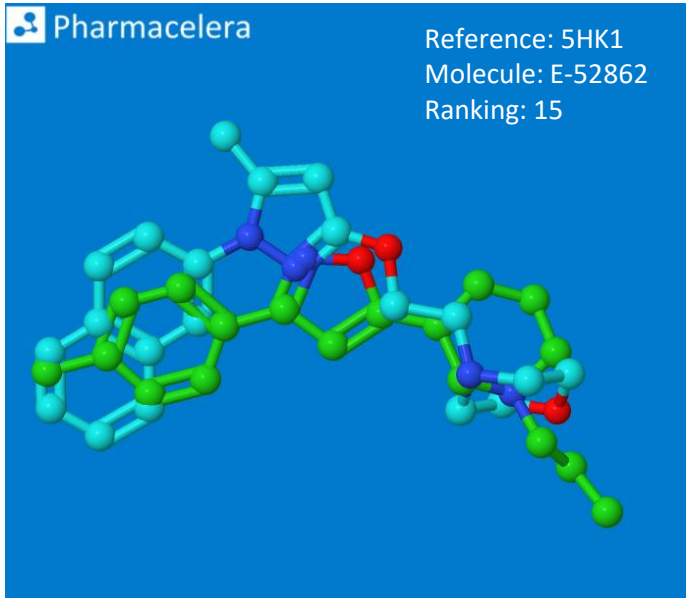


67% of the active ligands (activity≤10 nM) are in Q1

10nM<a<100nM



42% of the molecules with an activity between 10 nM and 100 nM are in Q1



DUD Study

Project goal: Virtual screening quality evaluation.

Explore how much chemical diversity can be retrieved

Data:

- 11 sets from Directory of Useful Decoys[1,2]

  Available in http://dud.docking.org/

Workflow:

- Use the reference structure provided in the dataset
- Virtual screening with PharmScreen using hydrophobic and hydrogen bonds fields.
- Compute weighted ROC curves and ROC enrichment[3]

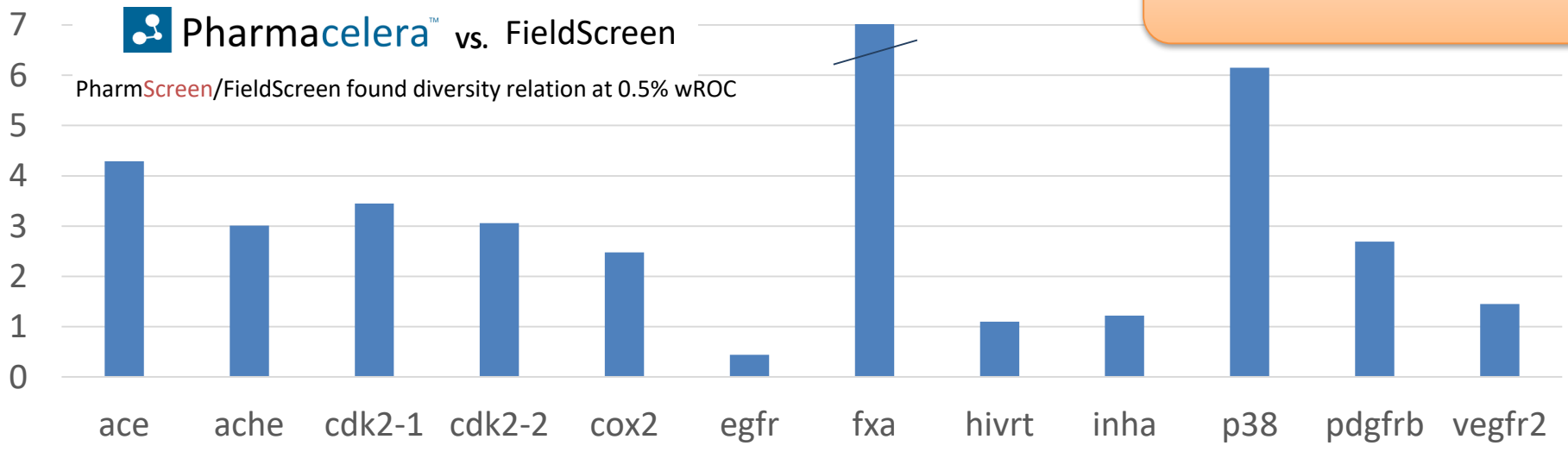
Set	Actives	Decoys
ACE	46	1796
AChE	99	3859
CDK2	47	2070
COX-2	212	12606
EGFr	365	15560
Fxa	64	2092
HIVRT	34	1494
InhA	57	2707
P38	137	6779
PDGFrb	124	5603
VEGFr2	74	2647

[1] Huang, Shoichet and Irwin, *J. Med. Chem.*, 2006, 49(23), 6789-6801.
[2] Good AC, Oprea TI; "Optimization of CAMD Techniques 3. Virtual Screening Enrichment Studies: a Help or Hindrance in Tool Selection?", J.Comput.-Aided Mol. Des.2008,22(3–4):169–178.
[3] Robert D. Clark and Daniel J. Webster-Clark. Managing bias in ROC curves. Journal of Computer-Aided Molecular Design, 2008, 22(3-4):141–146.

PharmScreen Finds More Chemical Diversity

- **Virtual Screening** for 11 DUD sets (active hits clustered in families)

PharmScreen finds 2.7x more chemical diversity

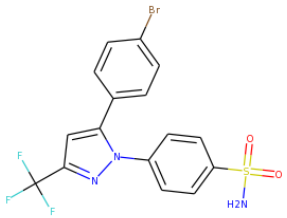


[1] Cheeseright et al. "FieldScreen: Virtual Screening Using Molecular Fields. Application to the DUD Data Set", J. Chem. Inf. Model. 2008, 48, 2108-2117

PharmScreen Finds More Chemical Diversity

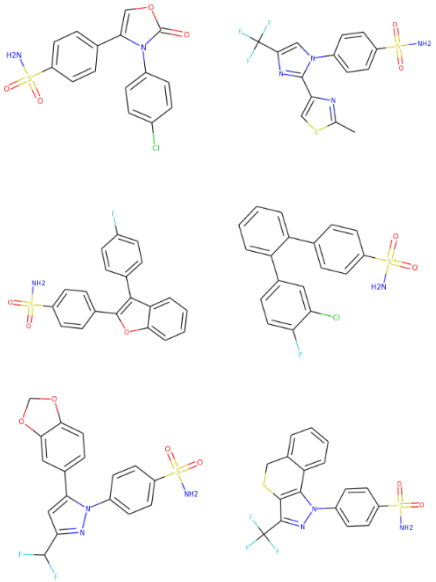
- COX-2 (PDB: 1cx2), Cyclooxygenase-2 (prostaglandin synthase-2) study
  - 12818 compounds – 212 actives in 44 families

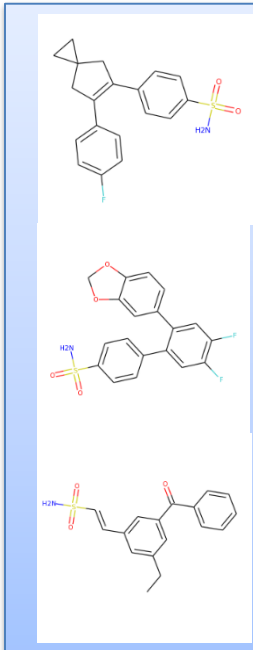
Reference structure



Families found	
PharmScreen	**9**
FieldScreen	5
FieldScreen+P	6
2SHA	3
DOCK	2
OAAP	6
OAK	3
OAK_Flex	3
MACCS	4

Families found among first 50 structures



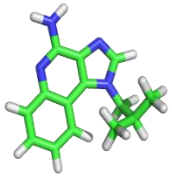


Active Structures found only by PharmScreen

3 more families found

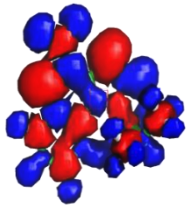
Summary

- Virtual Screening:
  - Reduces the search space in initial drug discovery stages
  - Can provide **significant savings** in a drug discovery project
- Pharmacelera's field-based virtual screening technology:
  - **Full 3D representation of all relevant fields of interaction (shape, electrostatic and hydrophobic)** for molecular alignment AND similarity
  - Atomic-level LogP partitioning with semi-empirical quantum mechanical solvation models

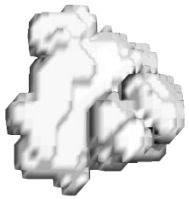


Molecular structure

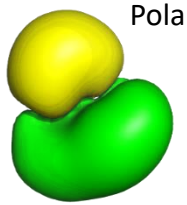
Electrostatic Field



Steric Field



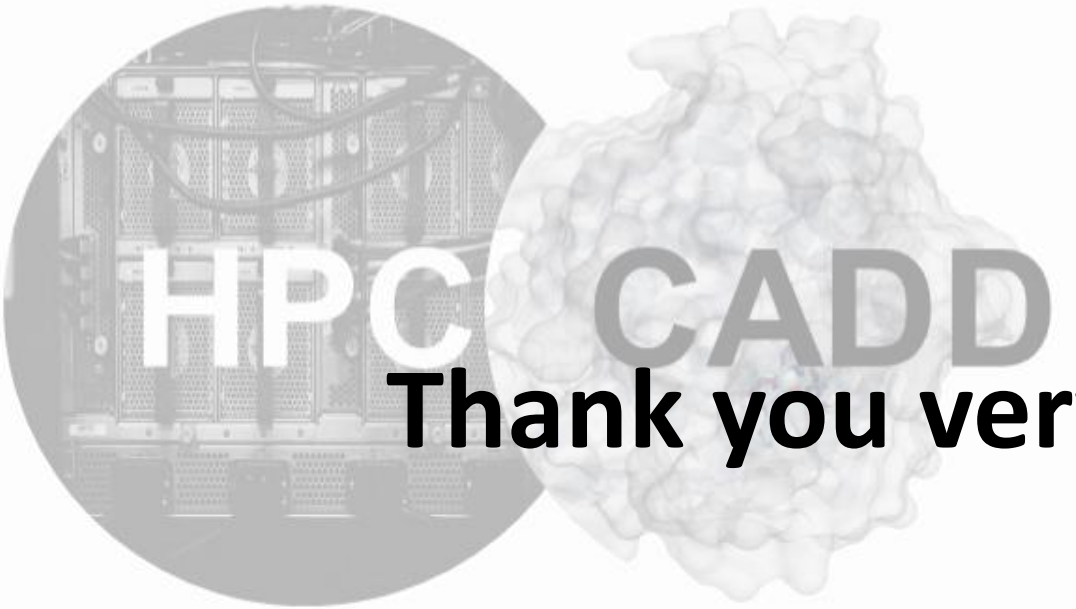
Hydrophobic field



Polar Region

Apolar Region

Interaction fields are chemotype agnostic → more chemical diversity found



Thank you very much!

Pharmacelera™

NEXT GENERATION DRUG DISCOVERY SOLUTIONS