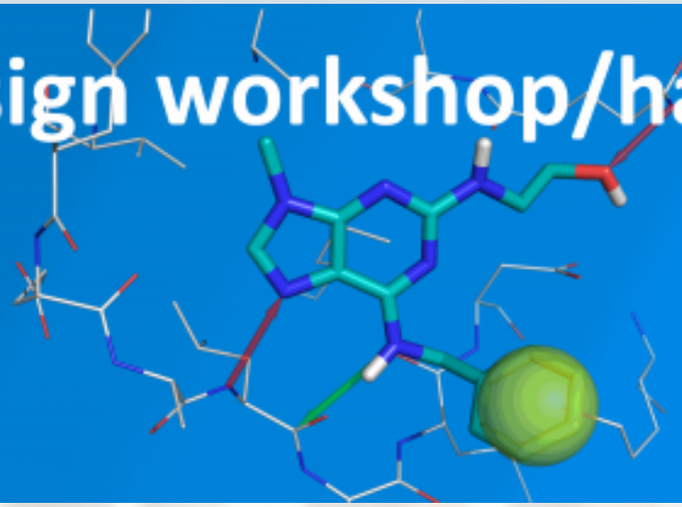
4th Advanced in silico Drug Design workshop/hackathon

21-25 January 2019
Olomouc, Czech Republic



Univerzita Palackého v Olomouci

Pharmacophore Modeling:
How to Enhance Virtual Screening Efficacy in Early Drug Discovery

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Thierry Langer

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Answer Important Questions

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Selection - Hit ID

- Which molecule(s) to chose for biological assessment ?

Optimize selectivity towards excluding false positives

Design - Lead Optimization

- How to modify molecules for optimizing properties ?

Optimize a structure towards multiple key parameters

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The Pharmacophore Concept

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

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

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Feature-based Pharmacophores

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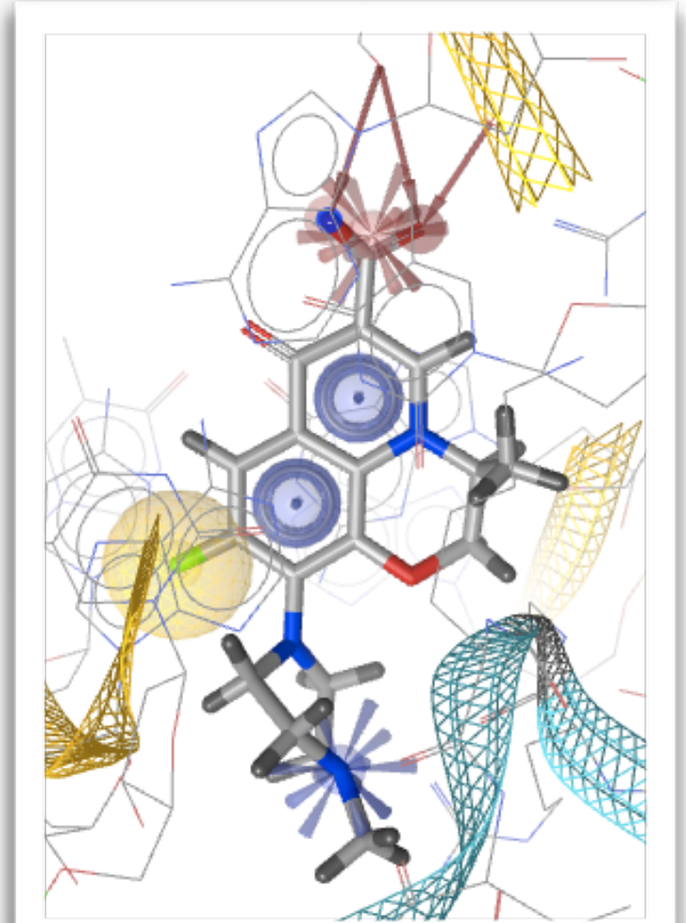
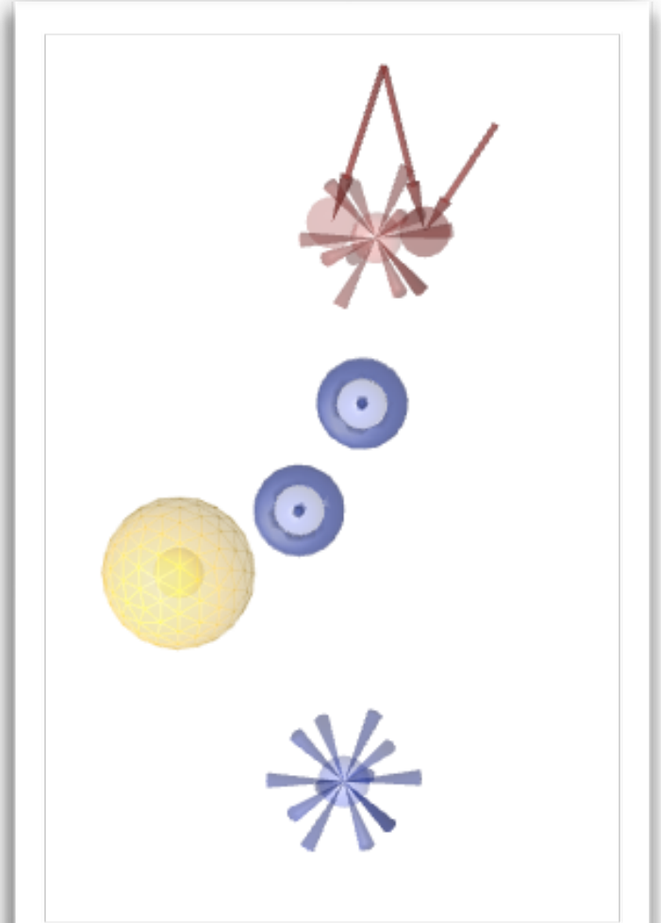
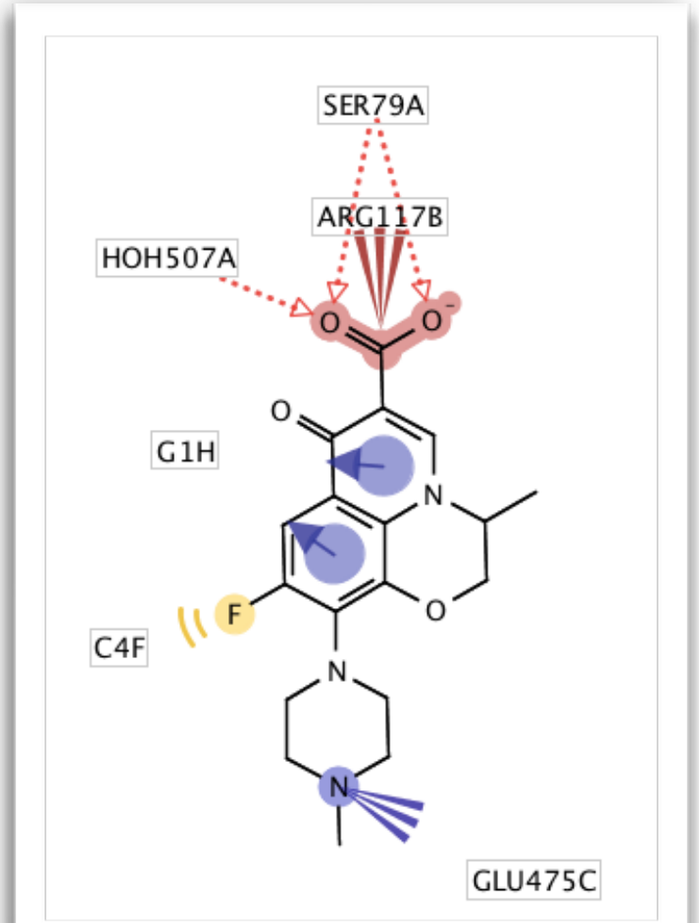
Totality of universal chemical features that represent a defined binding mode of a ligand to a bio-molecular target

Features: Electrostatic interactions, H-bonding, aromatic interactions, hydrophobic regions, coordination to metal ions ...







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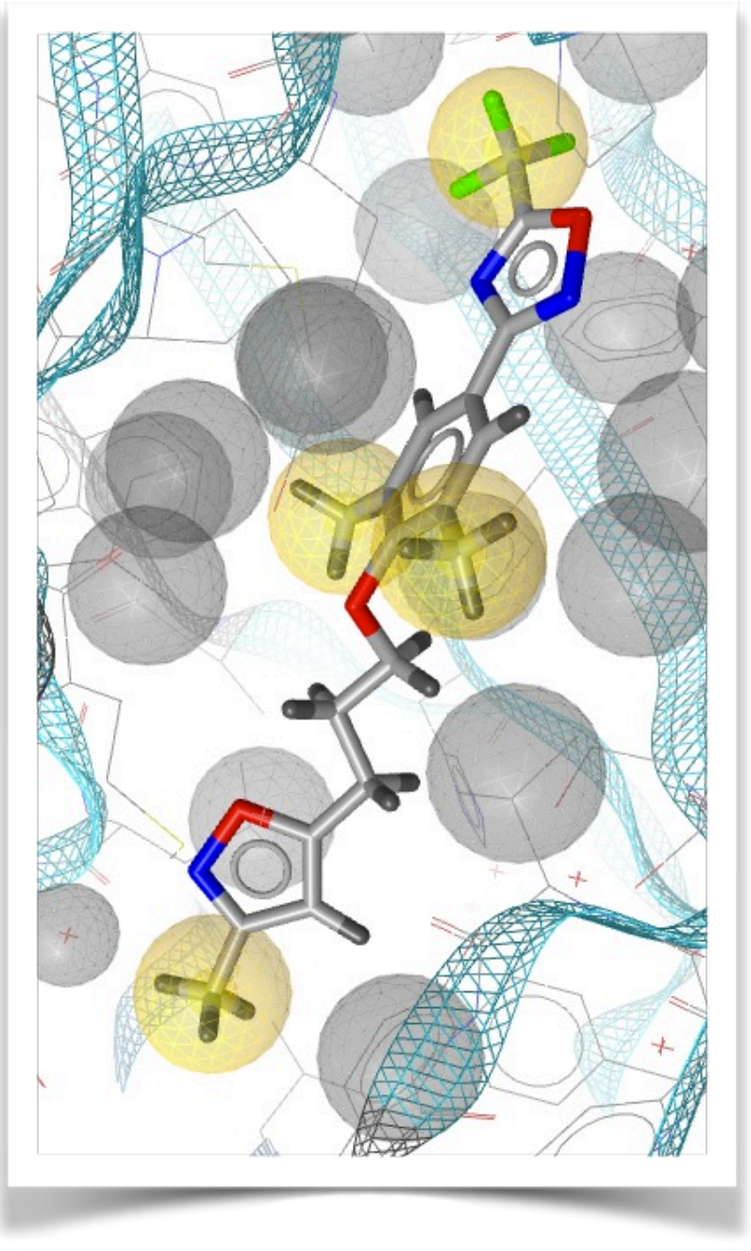
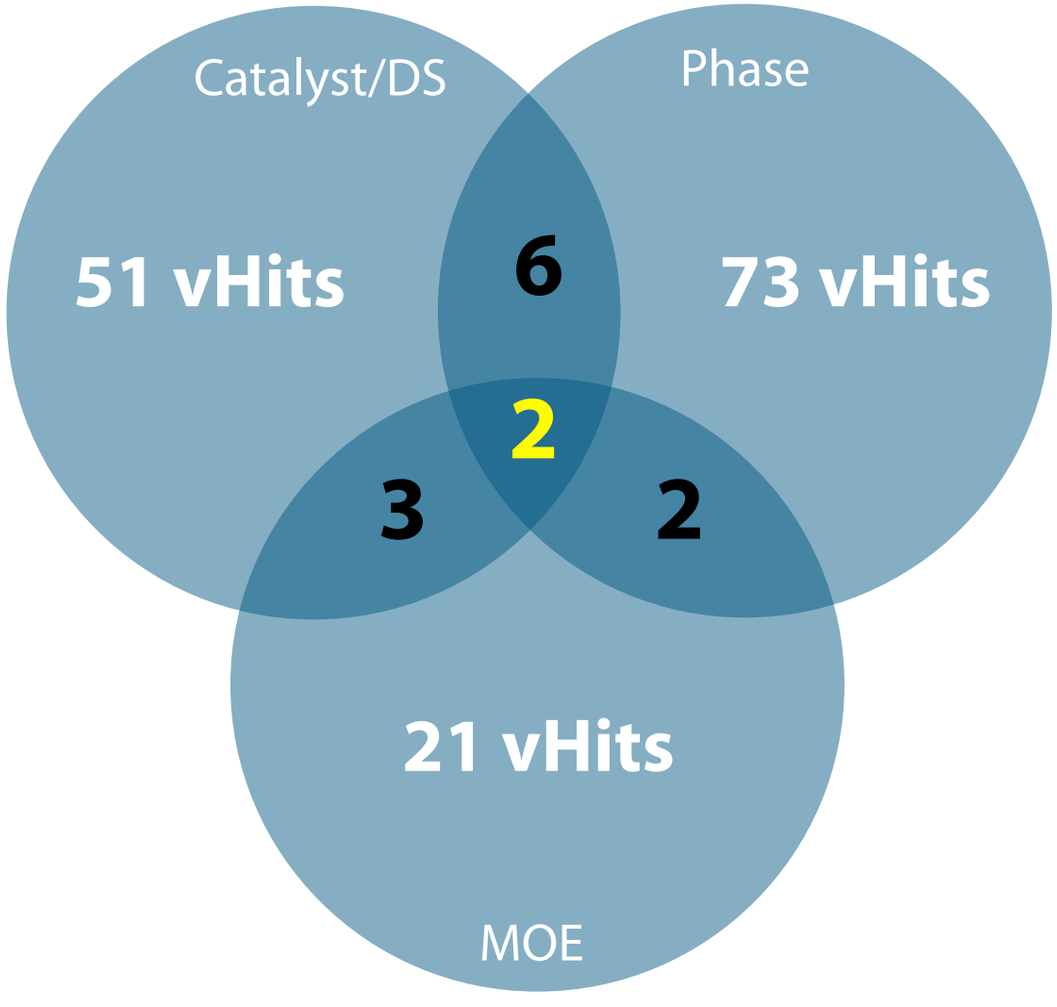
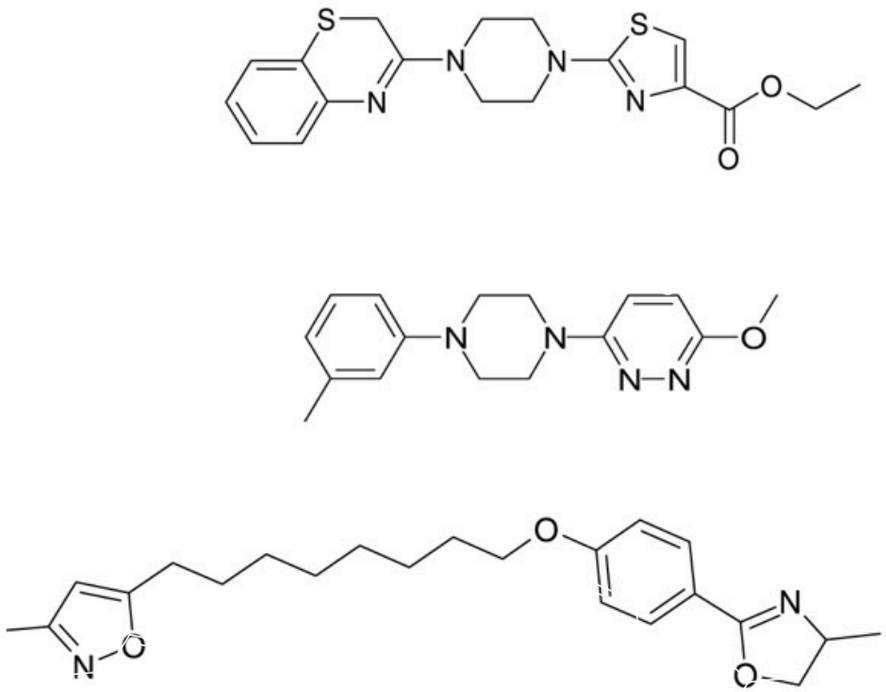
Pharmacophore Screening ...

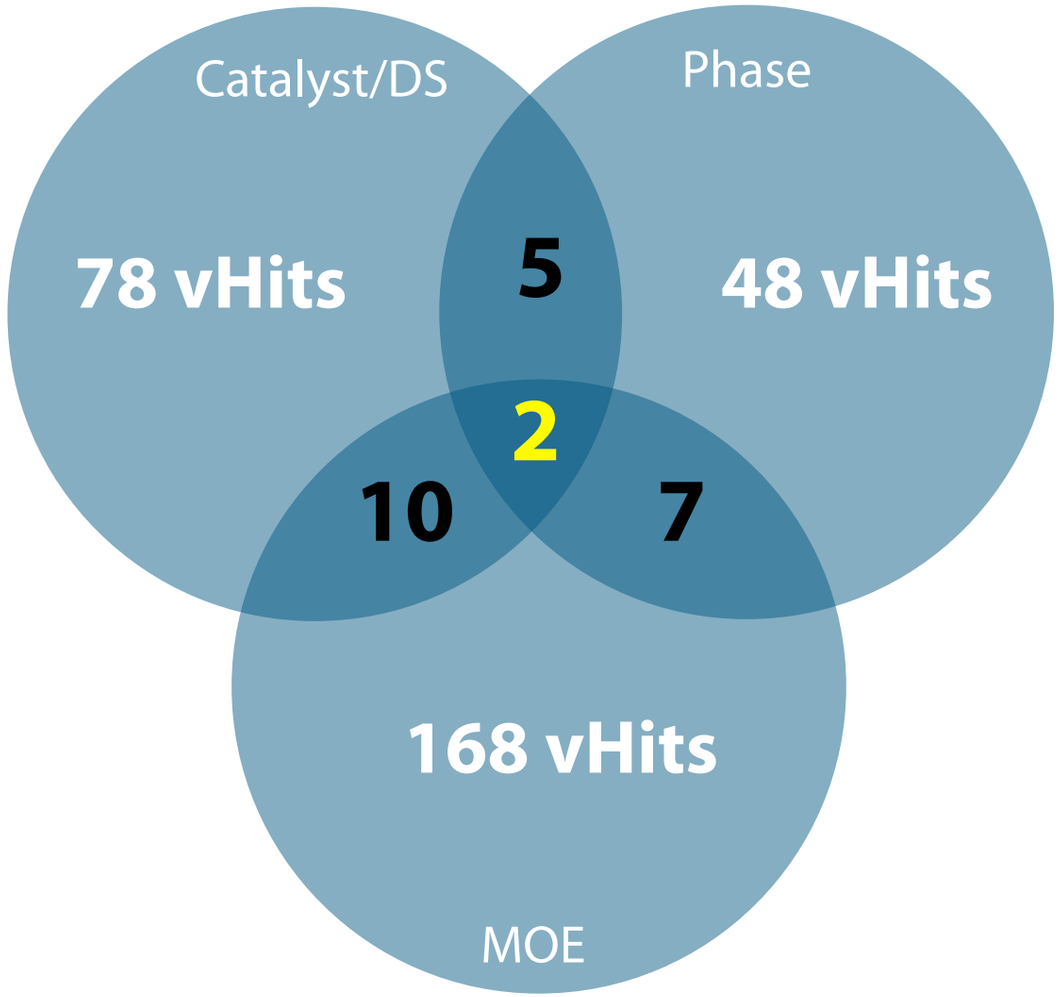




[Mangold 2006] Martina Mangold. *Human Rhinovirus Coat Protein Inhibitors - A Pharmacophore Modeling Approach.* Master's thesis at the University of Innsbruck (2006)

Pharmacophore Screening ...





[Mangold 2006] Martina Mangold. *Human Rhinovirus Coat Protein Inhibitors - A Pharmacophore Modeling Approach.* Master's thesis at the University of Innsbruck (2006)

There Is A Problem ...

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- "Old" 3D pharmacophore methods suffer from severe limitations
  - different tools return inconsistent results
  - alignment by graph matching ----> slow
  - low number of features ----> inaccurate

What is the solution ?

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Pattern Recognition

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… Breaking the Code

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- Why Yuor Barin Can Raed Tihs

http://www.livescience.com/18392-reading-jumbled-words.html

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… Breaking the Code

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- It deson’t mttaer in waht oredr the ltteers in a wrod aepapr, the olny iprmoatnt tihng is taht the frist and lsat ltteer are in the rghit pcale. The rset can be a toatl mses and you can sitll raed it wouthit pobelrm.

http://www.livescience.com/18392-reading-jumbled-words.html

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… Breaking the Code

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- S1M1L4RLY, YoUR M1ND 15 R34D1NG 7H15 4U70M471C4LLY W17HoU7 3V3N 7H1NK1NG 4BoU7 17

http://www.livescience.com/18392-reading-jumbled-words.html

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Distance Characteristics

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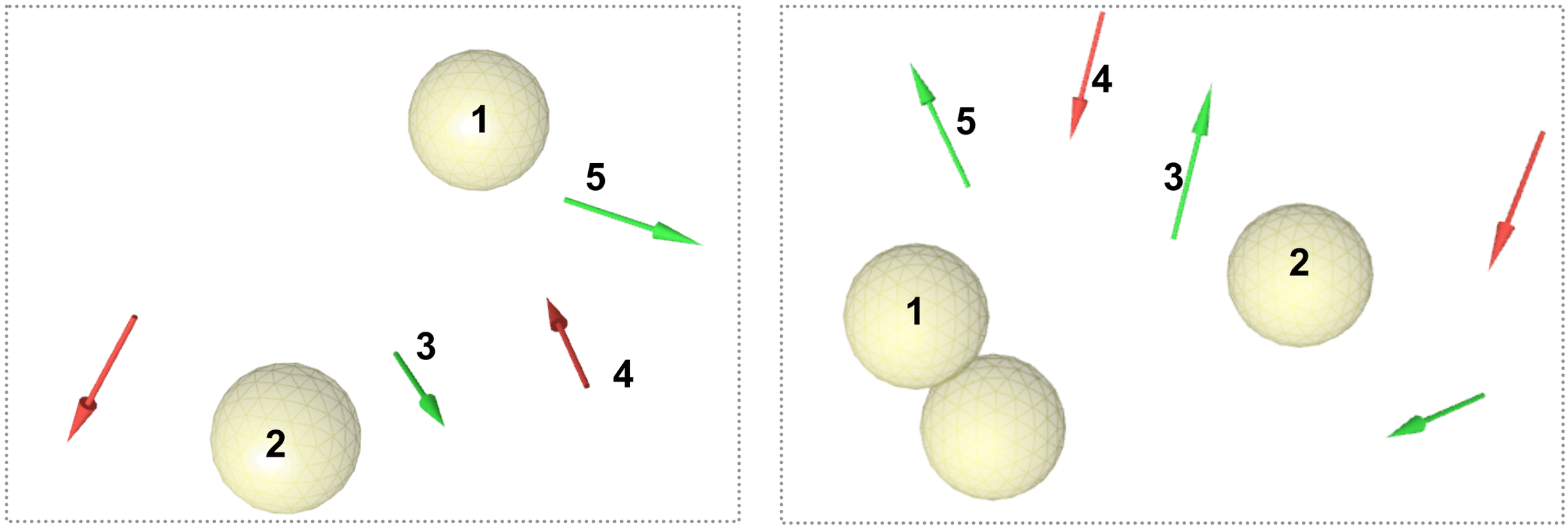
Result: Best matching pairs for each feature



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Distance Characteristics

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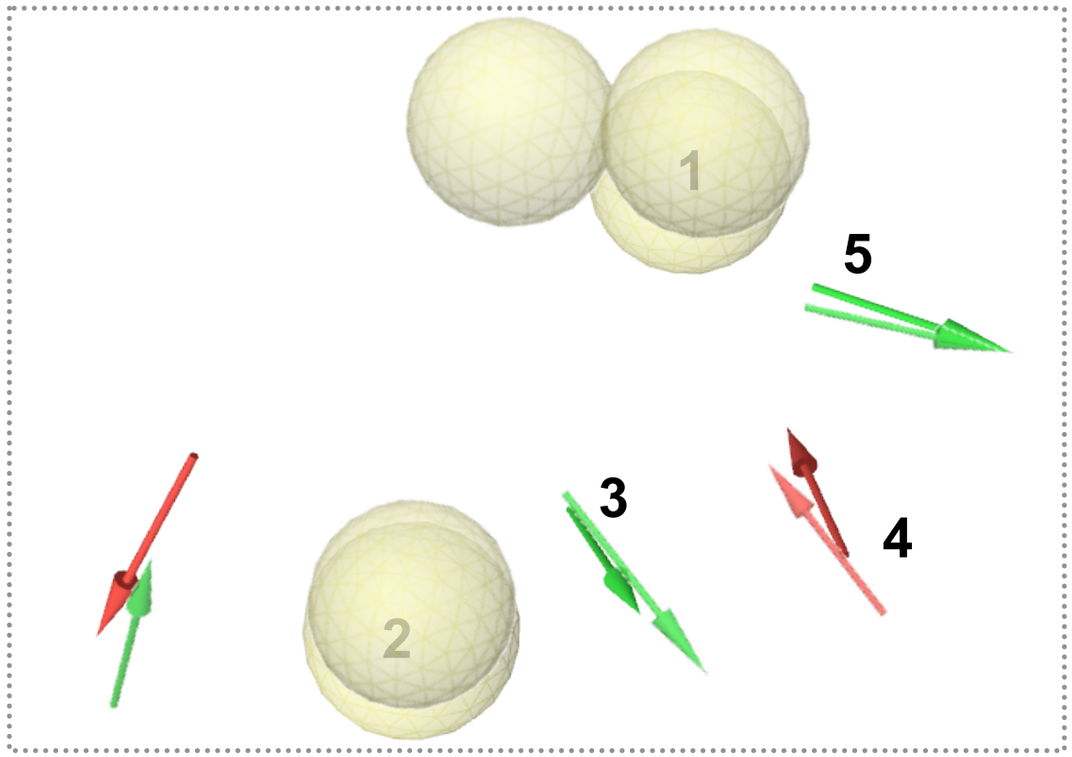

Final step: 3D rotation using Kabsch algorithm

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LigandScout Prototype 2003

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High Throughput Pharmacophore Model Generation from Ligand-Target Complexes as a Basis for Activity Profiling

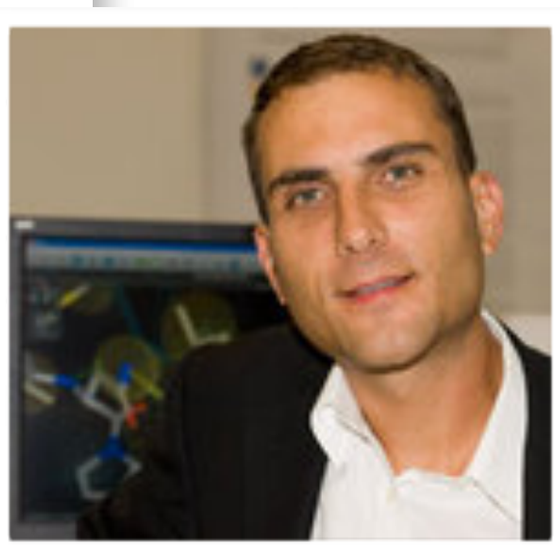
euro QSAR 2004 istanbul turkey

Thierry Langer[1)] and Gerhard Wolbe

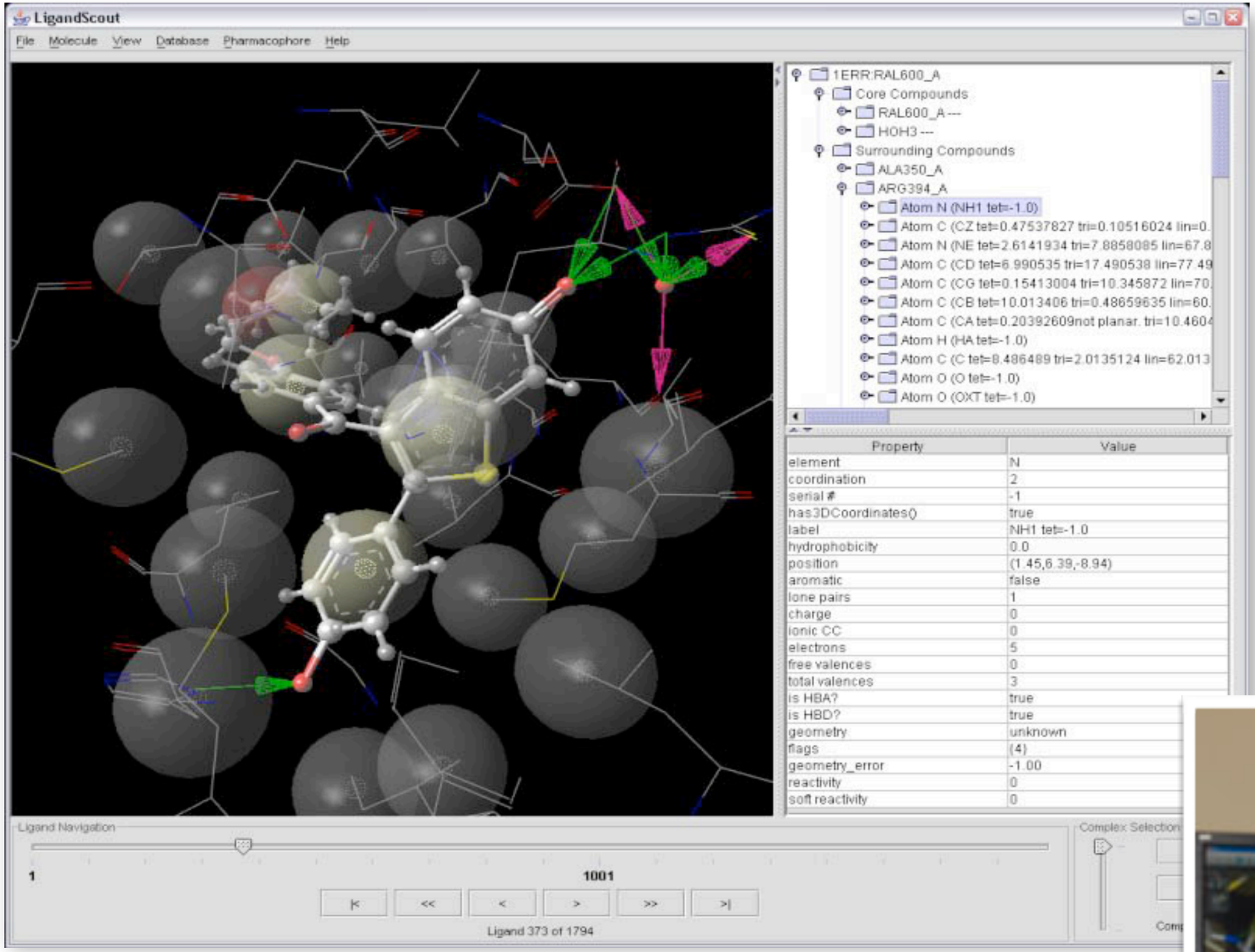
[1)] University of Innsbruck, Innsbruck, Aust
[2)] Inte:Ligand GmbH, Vienna, Aust

Gerhard Wolber

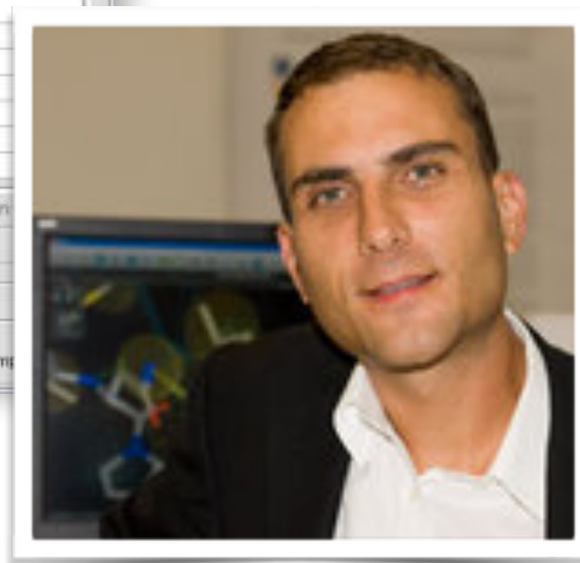
University of Innsbruck



LigandScout Prototype 2003



Gerhard Wolber
University of Innsbruck



T. Langer, 2019-01-23

LigandScout Evolution

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- Automated structure-based pharmacophores
- Alignment algorithm development
- Ligand-based pharmacophore generation & clustering
- Virtual screening
- Software code refactoring
- Implementation of dynamic relational databases
- Including docking algorithms & rescoring technology
- Creation of Inte:Ligand KNIME Extension Nodes
- Pharmacophore-based analysis of MD trajectories

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LigandScout 4.4 Expert

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Your partner for in-silico drug discovery.

LigandScout Scientific Articles

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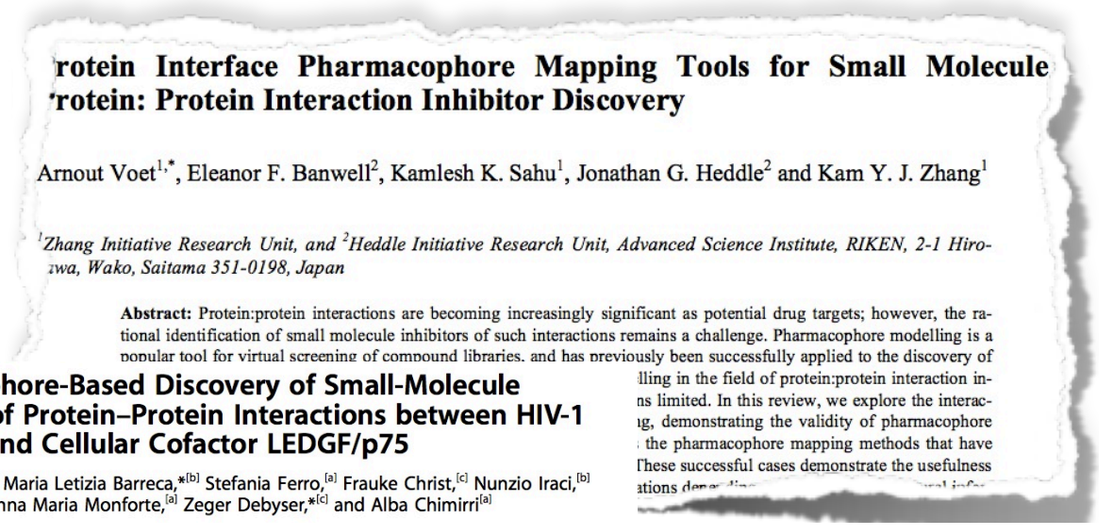
- More than 1700 papers*
  - structure-based modeling
  - ligand-based modeling
  - virtual screening
- Hit identification
- Fragment-based design
- Lead structure optimization
- Protein-Protein Interactions
- Drug repurposing
- Profiling (side-effects)



rotein Interface Pharmacophore Mapping Tools for Small Molecule rotein: Protein Interaction Inhibitor Discovery

Arnout Voet[1,*], Eleanor F. Banwell[2], Kamlesh K. Sahu[1], Jonathan G. Heddle[2] and Kam Y. J. Zhang[1]

[1]Zhang Initiative Research Unit, and [2]Heddle Initiative Research Unit, Advanced Science Institute, RIKEN, 2-1 Hiro-wa, Wako, Saitama 351-0198, Japan

Abstract: Protein:protein interactions are becoming increasingly significant as potential drug targets; however, the rational identification of small molecule inhibitors of such interactions remains a challenge. Pharmacophore modelling is a popular tool for virtual screening of compound libraries, and has previously been successfully applied to the discovery of lling in the field of protein:protein interaction in- ns limited. In this review, we explore the interac- g, demonstrating the validity of pharmacophore the pharmacophore mapping methods that have These successful cases demonstrate the usefulness ations dep

Pharmacophore-Based Discovery of Small-Molecule Inhibitors of Protein–Protein Interactions between HIV-1 Integrase and Cellular Cofactor LEDGF/p75

Laura De Luca,*[a] Maria Letizia Barreca,*[b] Stefania Ferro,[a] Frauke Christ,[c] Nunzio Iraci,[b] Rosaria Gitto,[a] Anna Maria Monforte,[a] Zeger Debyser,*[c] and Alba Chimirri[a]

The cellular protein lens epithelium transcriptional coactivator p75 (LED in HIV integration. The protein–pro tween HIV-1 integrase (IN) and its may therefore serve as targets for anti-HIV drugs. In this work, a struc model for potential small-molecu LEDGF/p75 interaction was develop software. The 3D model obtained ing of our in-house chemical datab identification of compound CHIBA for further optimization. The rationa

Identification of the first non-peptidic small molecule inhibitor of the c-Abl/14-3-3 protein–protein interactions able to drive sensitive and Imatinib-resistant leukemia cells to apoptosis

Valentina Corradi[a,†], Manuela Mancini[b], Fabrizio Manetti[a], Sara Petta[b], Maria Alessandra Santucci[b], Maurizio Botta[a,*]

[a] Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, Via Aldo Moro 2, I-53100 Siena, Italy
[b] Dipartimento di Ematologia e Scienze Oncologiche "Lorenzo e Ariosto Seràgnoli", Università di Bologna, Via Massarenti 9, I-40138 Bologna, Italy

ARTICL

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Revised 3 Augus
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Available online

Molecular Cancer Therapeutics

Therapeutic Discovery

New Use for an Old Drug: Inhibiting ABCG2 with Sorafenib

Yinxiang Wei[1,3], Yuanfang Ma[3], Qing Zhao[1,4], Zhiguang Ren[1,3], Yan Li[1], Tingjun Hou[2], and Hui Peng[1]

Abstract

Human ABCG2, a member of the ATP-binding cassette transporter superfamily, represents a promising target for sensitizing MDR in cancer chemotherapy. Although lots of ABCG2 inhibitors were identified, none of them has been tested clinically, maybe because of several problems such as toxicity or safety and pharmacokinetic uncertainty of compounds with novel chemical structures. One efficient solution is to rediscover new uses for existing drugs with known pharmacokinetics and safety profiles. Here, we found the new use for

* scholar.google.com, Jan 2019

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A Few Recent Success Stories (1)

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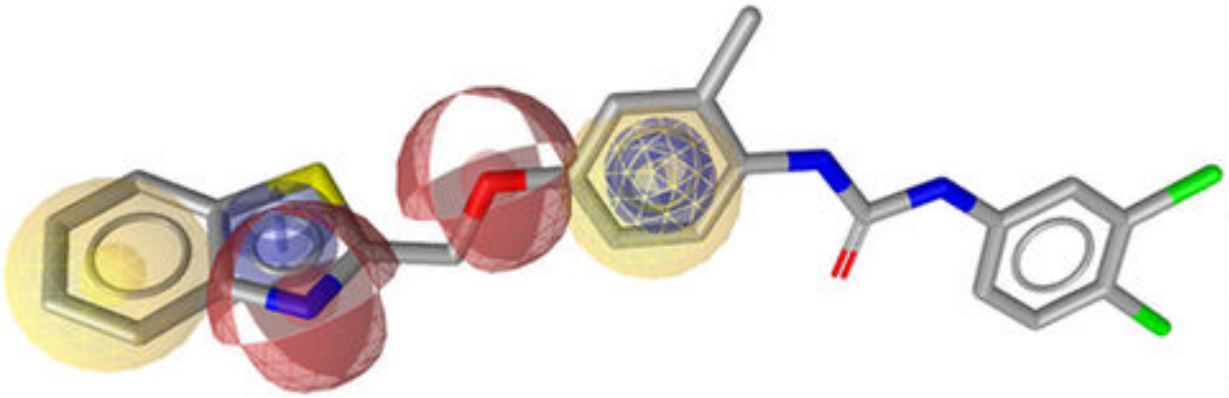
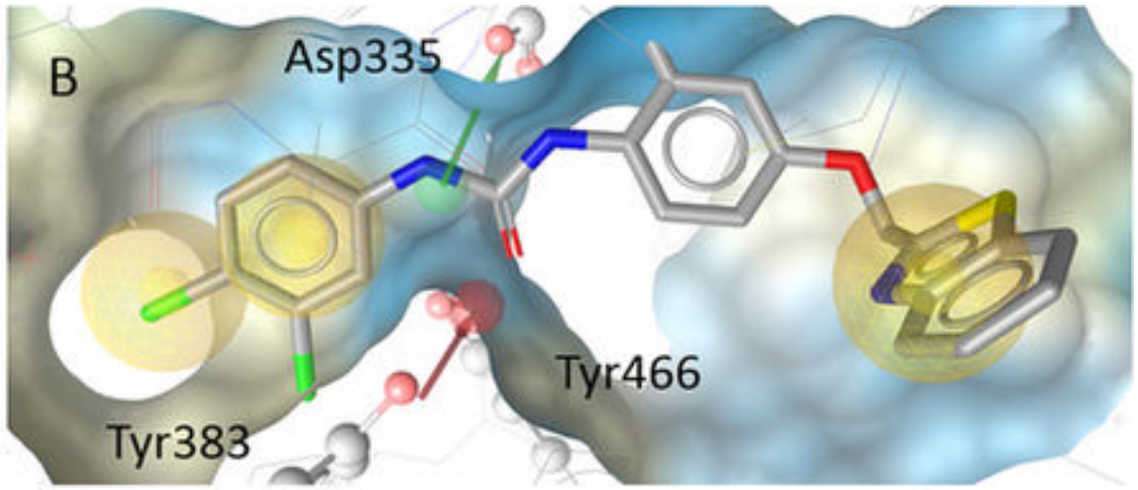
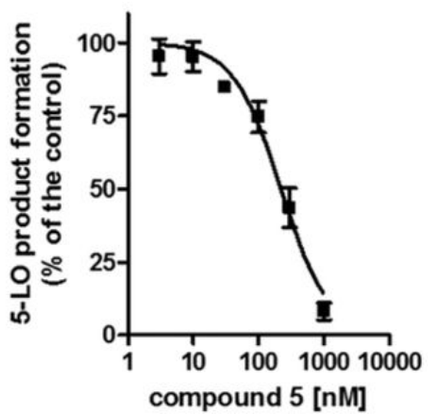
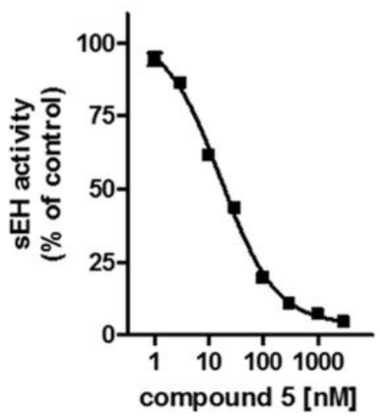
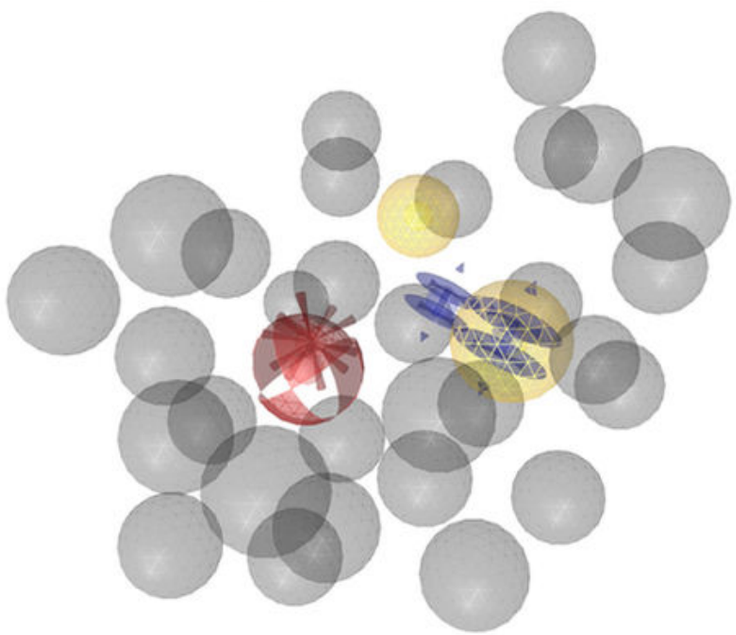
- First dual inhibitor of the 5-lipoxygenase-activating protein and soluble epoxide hydrolase by pharmacophore-based VS











FLAP (IC_{50} = 200 nM)

sEH (IC_{50} = 20 nM)

Temml, V. et al., Nature Sci. Rep., 7, 42751; doi: 10.1038/srep42751 (2017)

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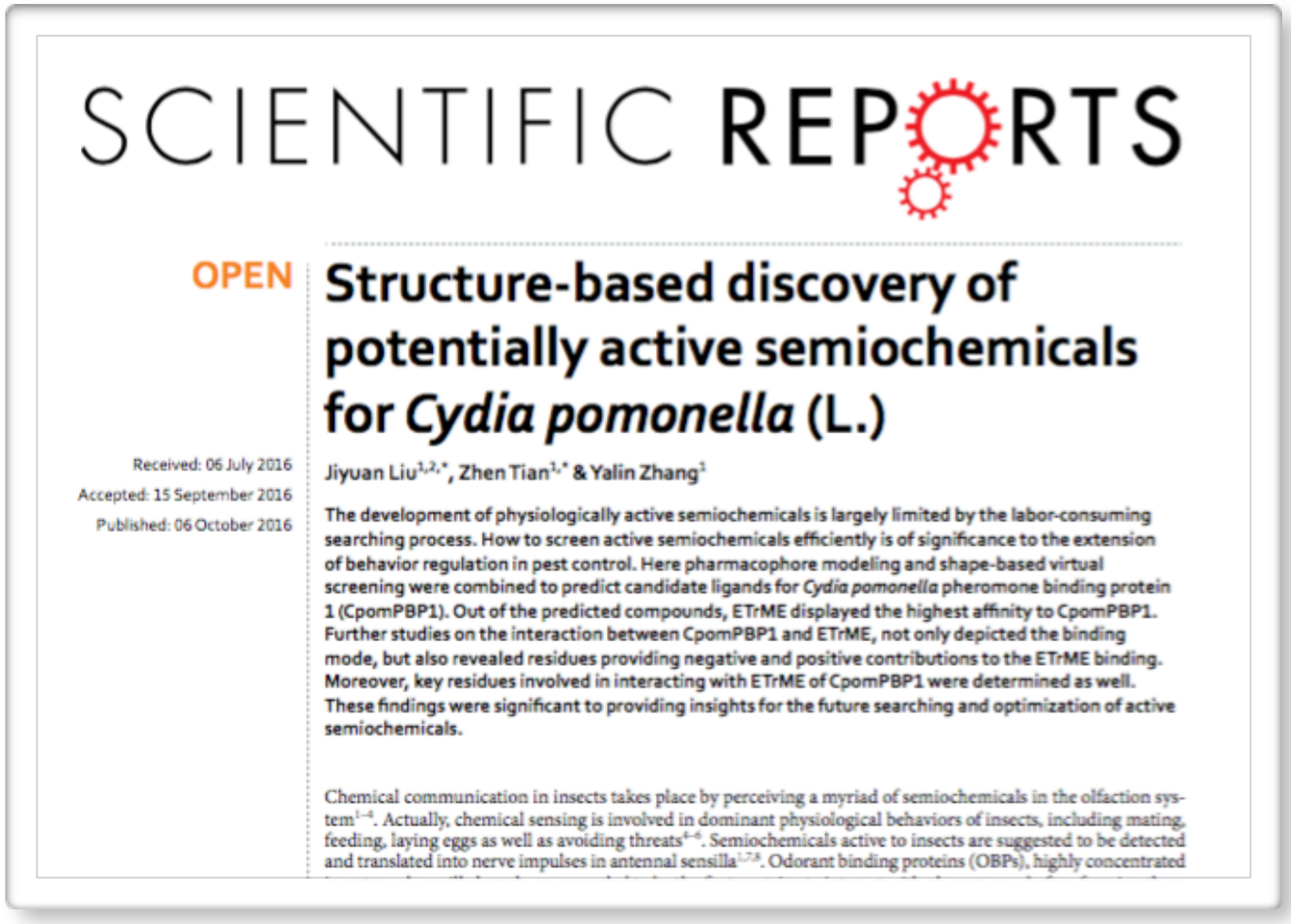
A Few Recent Success Stories (2)

- Active compound binds to pheromone binding proteins (PBPs) to modulate the behavior of Cydia pomonella
- Avoid damage to fruit production
- First use of pharmacophore modeling for discovery of semiochemicals



SCIENTIFIC REPORTS

OPEN

Structure-based discovery of potentially active semiochemicals for *Cydia pomonella* (L.)

Received: 06 July 2016
Accepted: 15 September 2016
Published: 06 October 2016

Jiyuan Liu[1,2,*], Zhen Tian[1,*] & Yalin Zhang[1]

The development of physiologically active semiochemicals is largely limited by the labor-consuming searching process. How to screen active semiochemicals efficiently is of significance to the extension of behavior regulation in pest control. Here pharmacophore modeling and shape-based virtual screening were combined to predict candidate ligands for *Cydia pomonella* pheromone binding protein 1 (CpomPBP1). Out of the predicted compounds, ETrME displayed the highest affinity to CpomPBP1. Further studies on the interaction between CpomPBP1 and ETrME, not only depicted the binding mode, but also revealed residues providing negative and positive contributions to the ETrME binding. Moreover, key residues involved in interacting with ETrME of CpomPBP1 were determined as well. These findings were significant to providing insights for the future searching and optimization of active semiochemicals.

Chemical communication in insects takes place by perceiving a myriad of semiochemicals in the olfaction system[1–4]. Actually, chemical sensing is involved in dominant physiological behaviors of insects, including mating, feeding, laying eggs as well as avoiding threats[4–6]. Semiochemicals active to insects are suggested to be detected and translated into nerve impulses in antennal sensilla[1,7,8]. Odorant binding proteins (OBPs), highly concentrated

Liu, J., et al., Nature Sci. Rep. 6, (2016); doi :10.1038/srep34600

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A Few Recent Success Stories (2)

- Active compound binds to pheromone binding proteins (PBPs) to modulate the behavior of Cydia pomonella
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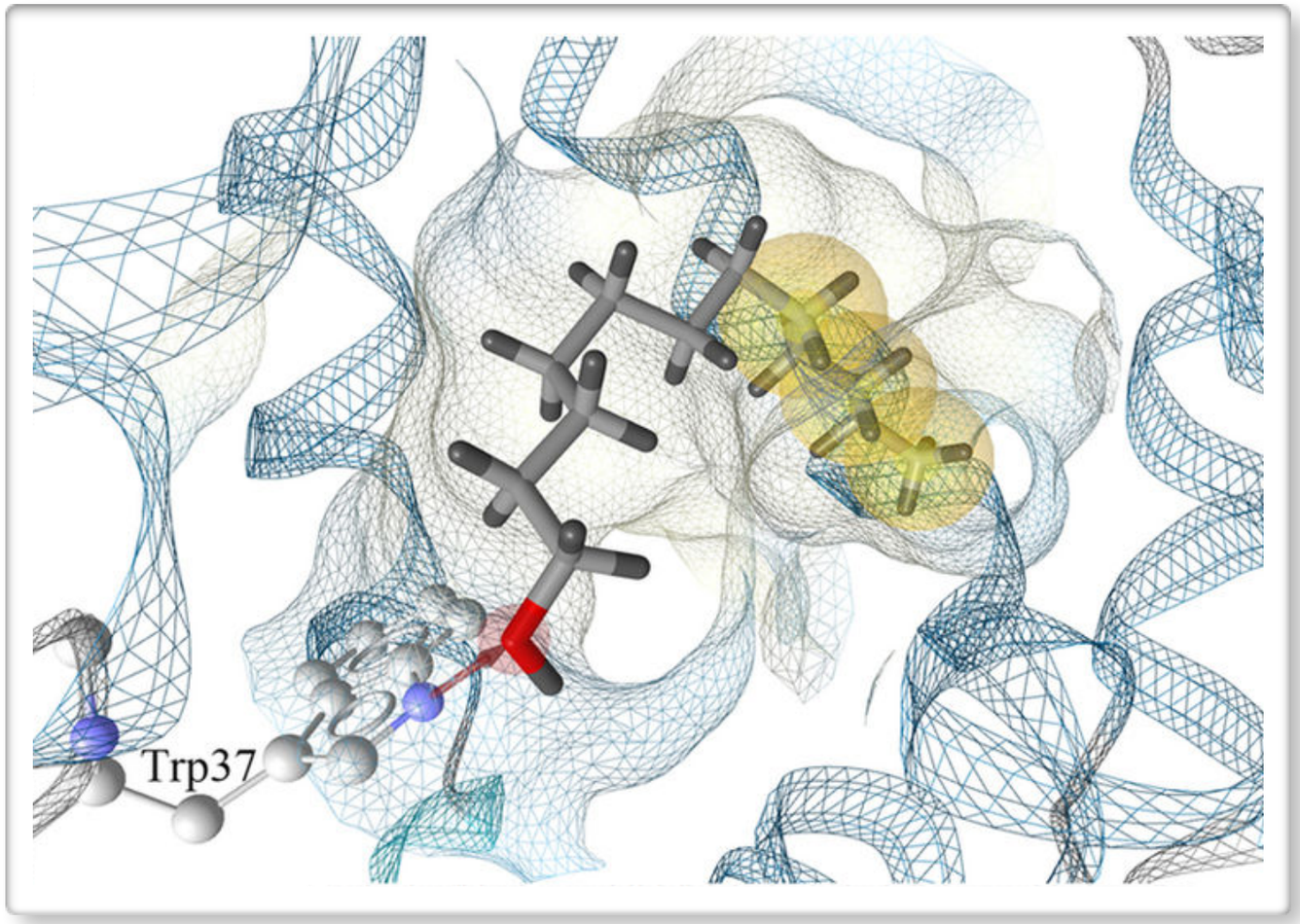

Liu, J., et al., Nature Sci. Rep. 6, (2016); doi :10.1038/srep34600

A Few Recent Success Stories (3)

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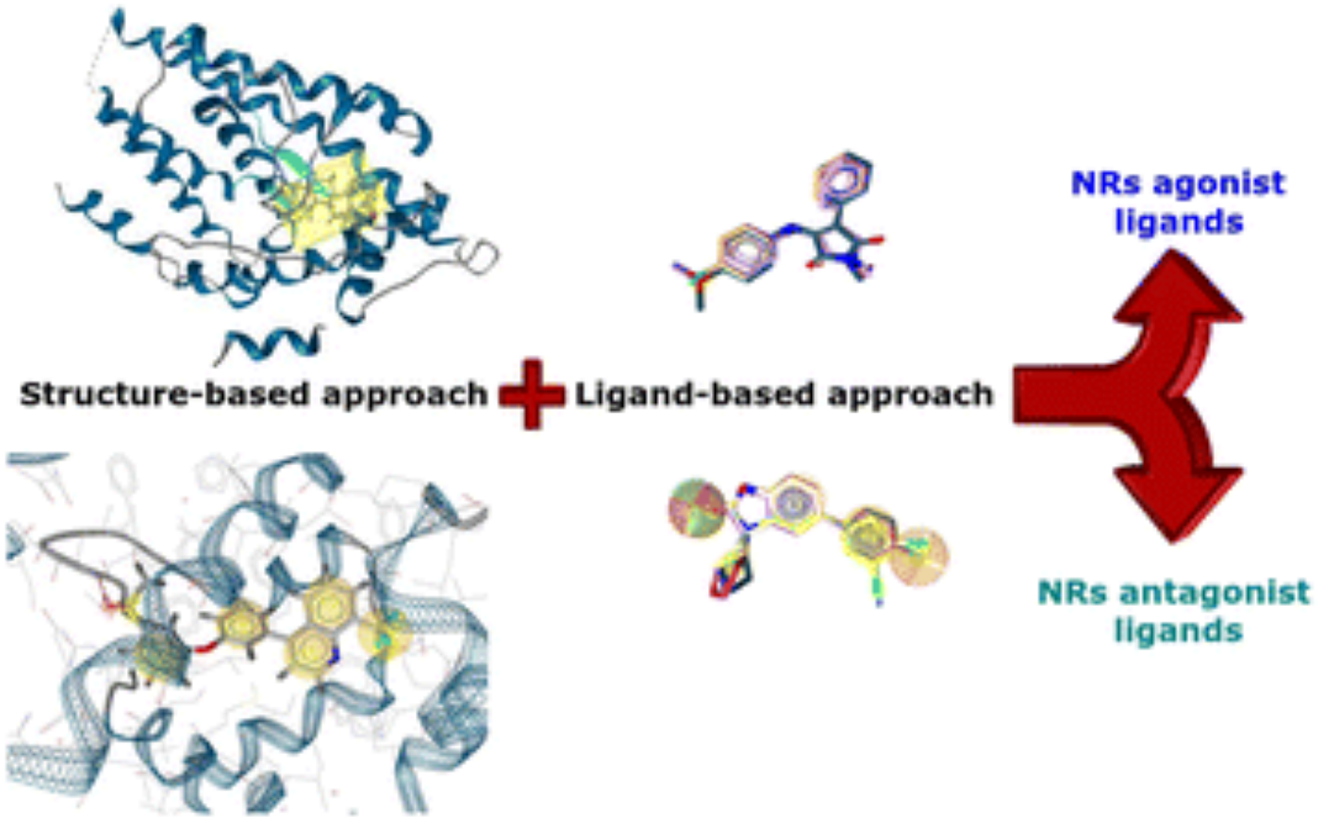
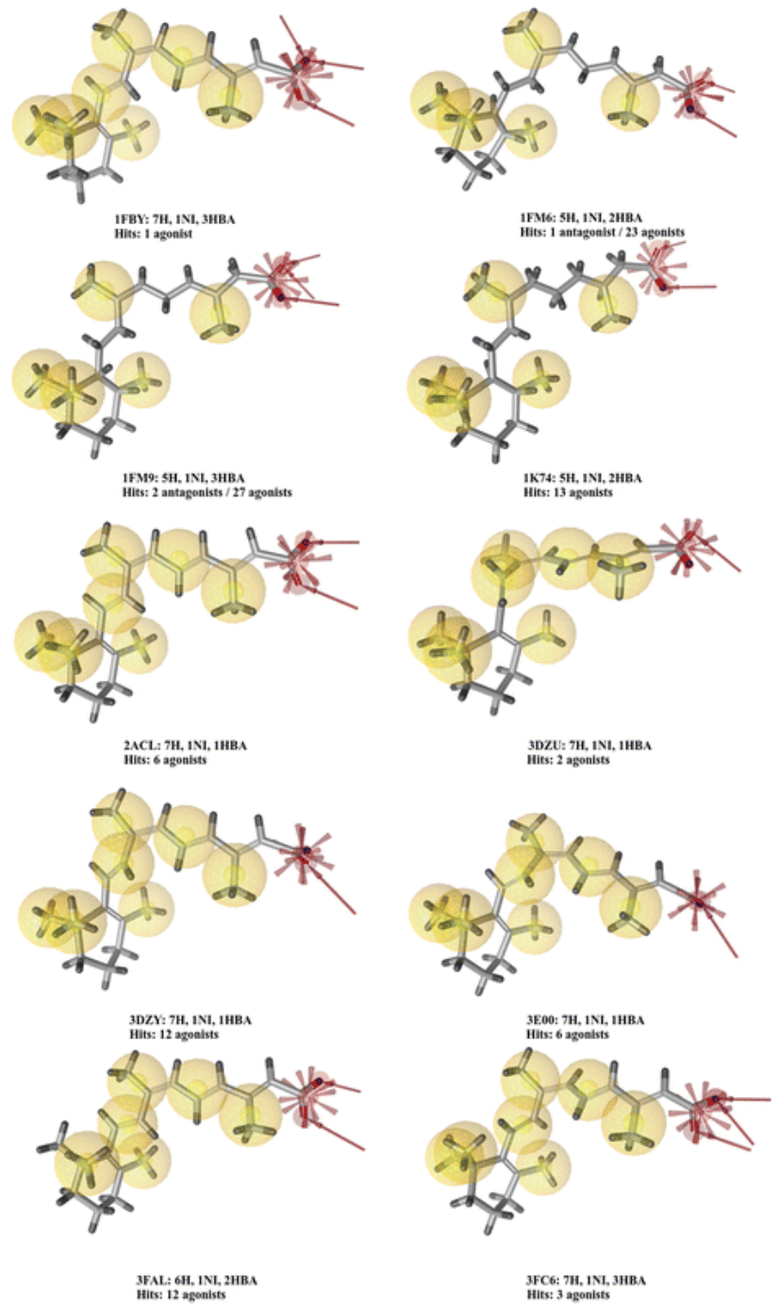
- Discriminating agonists and antagonist ligands of the nuclear receptors using 3D-pharmacophores





Lagarde, N. et al., J Cheminform (2016). DOI 10.1186/s13321-016-0154-2

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An Interesting Article To Read ...

JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

pubs.acs.org/jcim

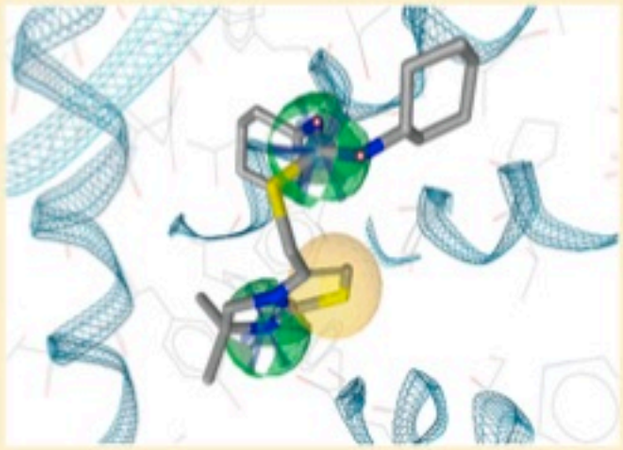
Highly Specific and Sensitive Pharmacophore Model for Identifying CXCR4 Antagonists. Comparison with Docking and Shape-Matching Virtual Screening Performance

Arnaud S. Karaboga,[†,§] Jesús M. Planesas,[‡,§] Florent Petronin,[†] Jordi Teixidó,[‡] Michel Souchet,*[,†] and Violeta I. Pérez-Nueno*[,†,‡]

[†]Harmonic Pharma, Espace Transfert, 615 rue du Jardin Botanique, 54600 Villers lès Nancy, France

[‡]Grup d'Enginyeria Molecular, Institut Químic de Sarrià (IQS), Universitat Ramon Llull, Barcelona, Spain

ABSTRACT: HIV infection is initiated by fusion of the virus with the target cell through binding of the viral gp120 protein with the CD4 cell surface receptor protein and the CXCR4 or CCR5 coreceptors. There is currently considerable interest in developing novel ligands that can modulate the conformations of these coreceptors and, hence, ultimately block virus−cell fusion. Herein, we present a highly specific and sensitive pharmacophore model for identifying CXCR4 antagonists that could potentially serve as HIV entry inhibitors. Its performance was compared with docking and shape-matching virtual screening approaches using 3OE6 CXCR4 crystal structure and high-affinity ligands as query molecules, respectively. The performance of these methods was compared by virtually screening a library assembled by us, consisting of 228 high affinity known CXCR4 inhibitors from 20 different chemotype families and 4696 similar presumed inactive molecules. The area under the ROC plot (AUC), enrichment factors, and diversity of the resulting virtual hit lists was analyzed. Results show that our pharmacophore model achieves the highest VS performance among all the docking and shape-based scoring functions used. Its high selectivity and sensitivity makes our pharmacophore a very good filter for identifying CXCR4 antagonists.



Karaboga et al.,
J. Chem. Inf. Model. 53
1043−1056 (2013)

LigandScout for VS

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Pharmacophore from PDB entry 3OE6

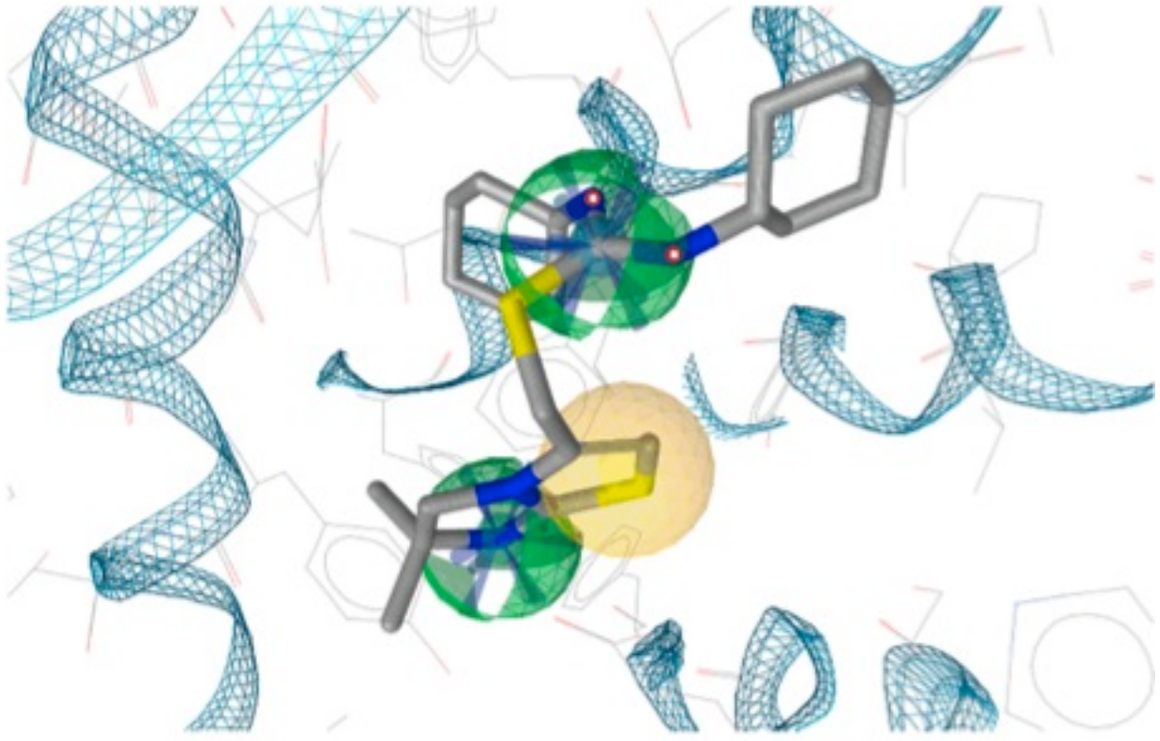

Figure 2. CXCR4 pharmacophore model with a high activity CXCR4 antagonist aligned. Five-featured manually refined final pharmacophore model. The pharmacophore hydrophobic features are shown in yellow. Positively charged features are shown in blue, and hydrogen bond donor features are shown in green.

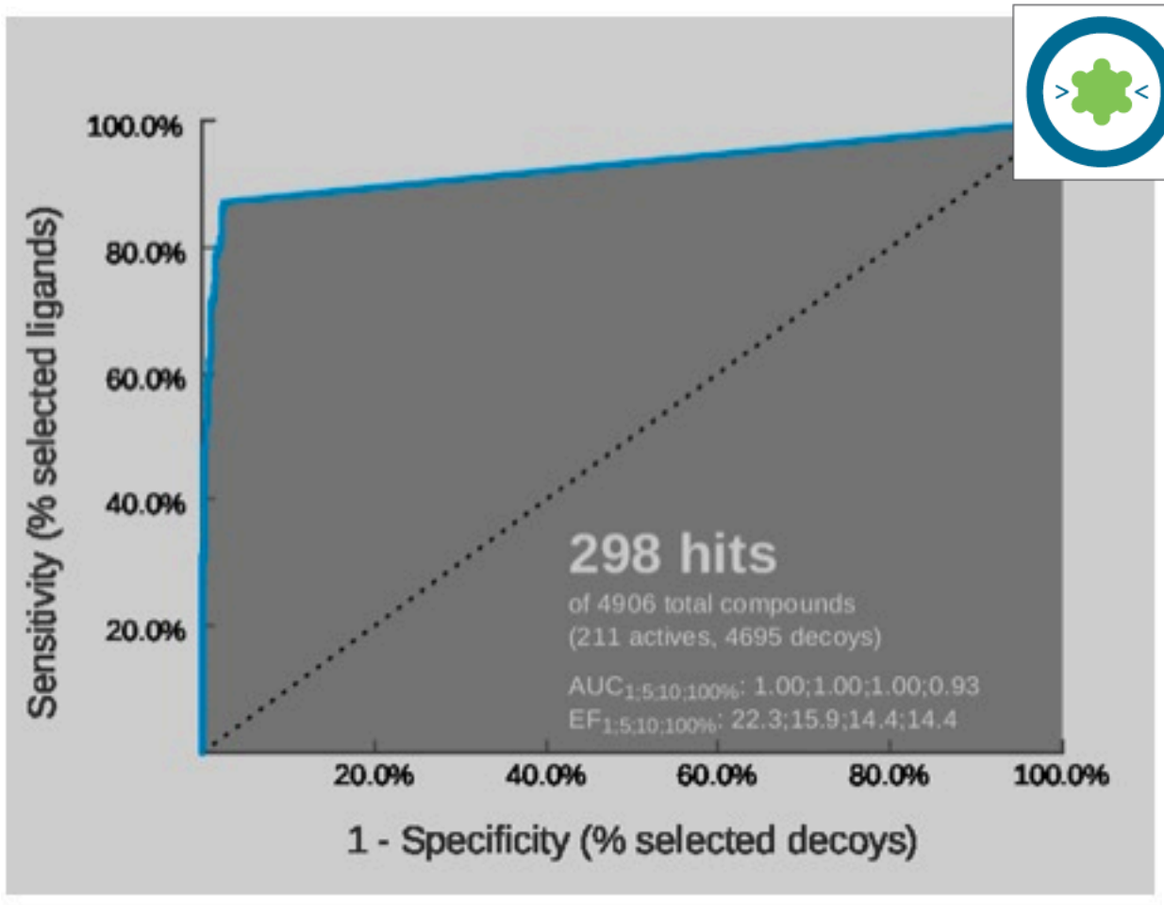

Figure 3. ROC plot validation of the pharmacophore model applied to CXCR4 antagonists. Values of area under the curve (AUC) and enrichment factor (EF) are displayed at 1, 5, 10, and 100% of screened database, respectively. These values highlight the high sensitivity and specificity of the designed pharmacophore model.

Karaboga et al., J. Chem. Inf. Model. 2013, 53, 1043−1056

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Virtual Screening Performance

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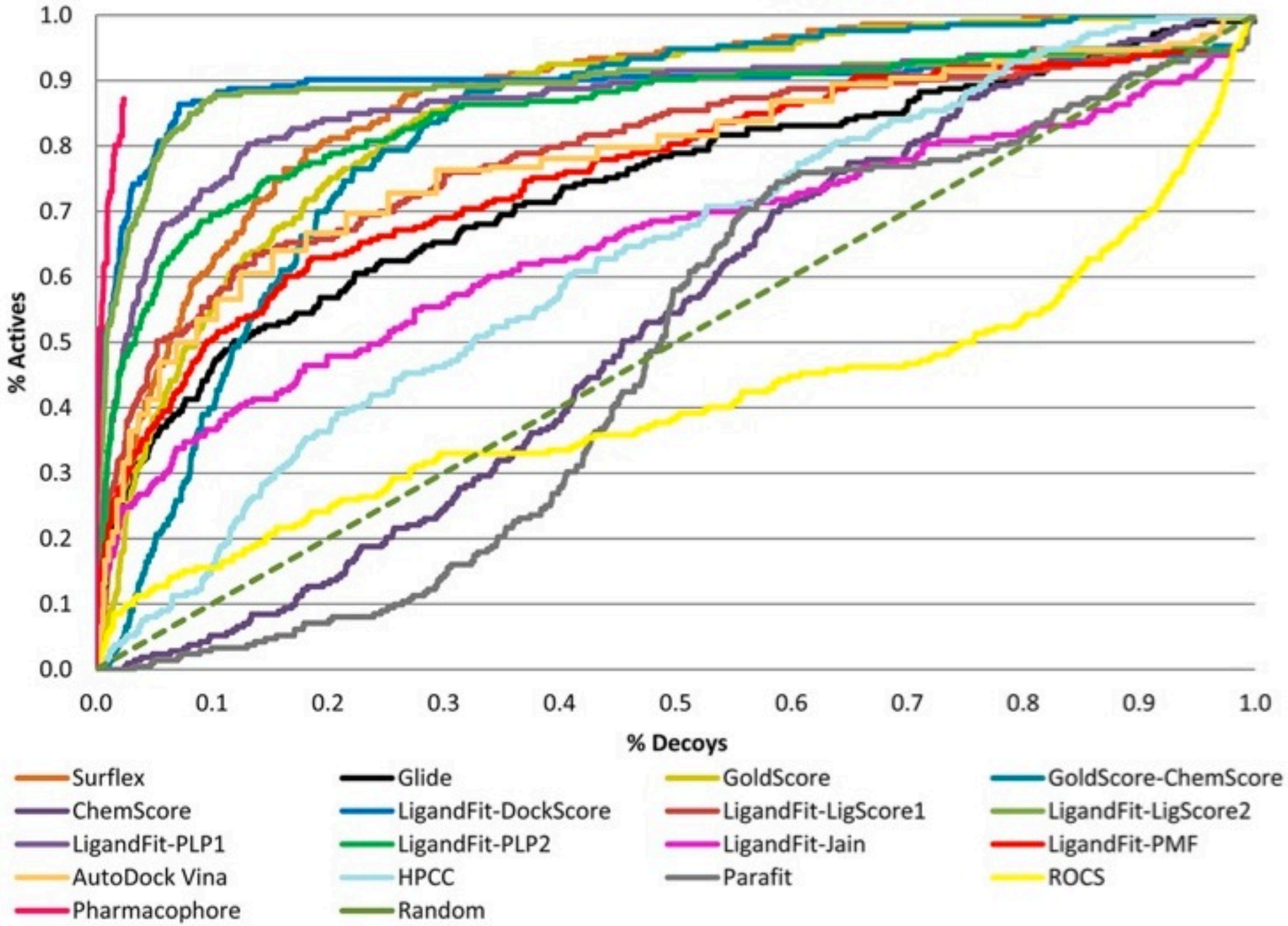

Karaboga et al., J. Chem. Inf. Model. 2013, 53, 1043−1056

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Virtual Screening Performance

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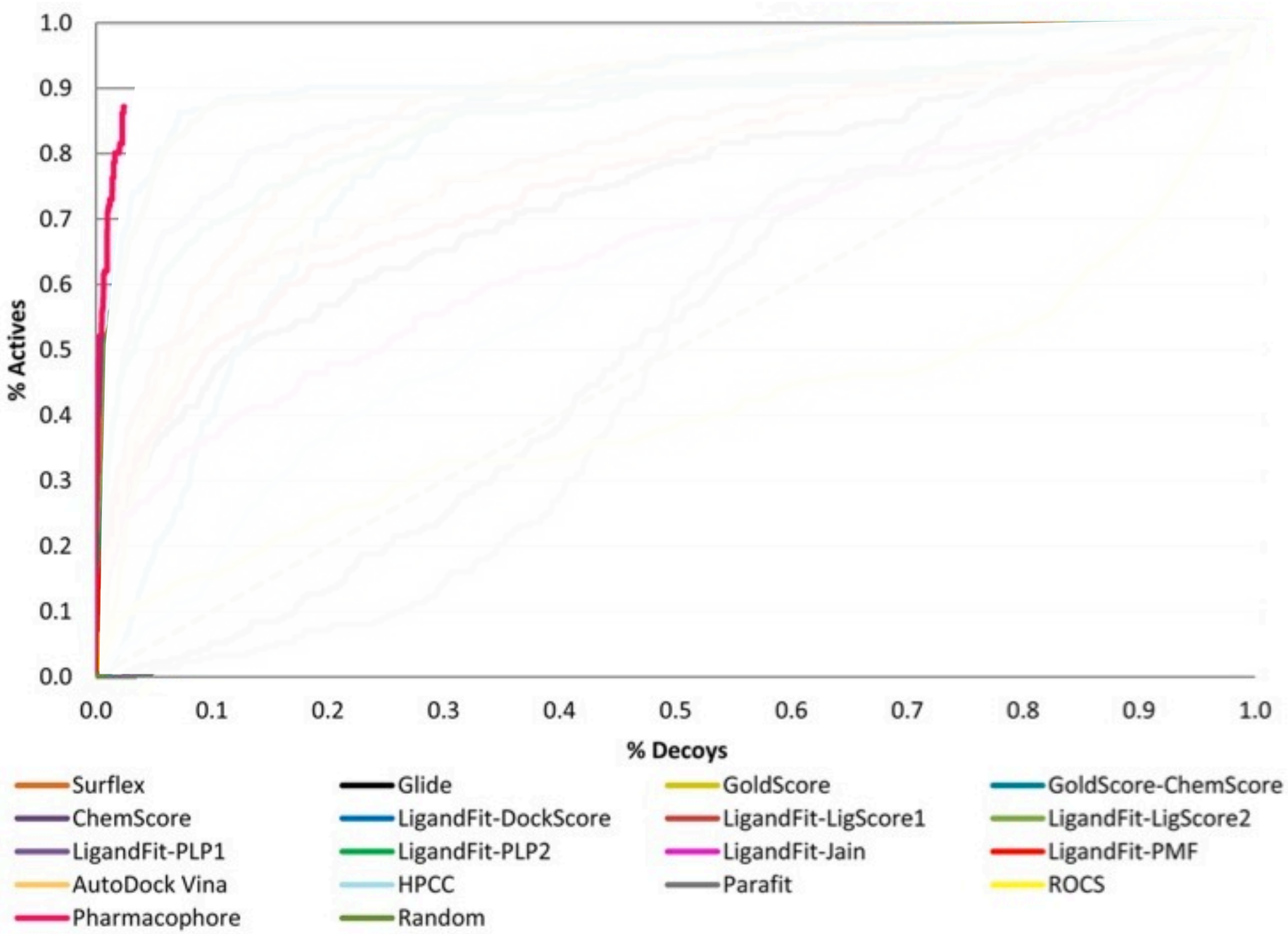

Karaboga et al., J. Chem. Inf. Model. 2013, 53, 1043−1056

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The Conclusions

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- Overall, the total area under de curve of the ROC plot and the early recovery results of the present pharmacophore model show that it is a highly specific and sensitive screening filter, which makes it very appropriate for identifying CXCR4 antagonists.

- Moreover, the scaffold retrieval analysis shows that the pharmacophore model is able to retrieve a diverse scaffold pool.

Karaboga et al., J. Chem. Inf. Model. 2013, 53, 1043−1056

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Fragment-based Drug Design

MedChemComm

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Med. Chem. Commun.*, 2016, 7, 506

Fragment pharmacophore-based *in silico* screening: a powerful approach for efficient lead discovery†

Laurence Deyon-Jung,*[a] Christophe Morice,*[a] Florence Chéry,[a] Julie Gay,[a] Thierry Langer,[ab] Marie-Céline Frantz,[c] Roger Rozot[c] and Maria Dalko-Csiba[c]

Received 5th October 2015,
Accepted 28th December 2015

DOI: 10.1039/c5md00444f

www.rsc.org/medchemcomm

Through a process of fragmentation, functionalization, and recombination of market approved molecules for cosmetic usage, we customized an *in-house* virtual library comprising molecules ideally suited for virtual screening. Computational pharmacophore-based screening of this virtual library followed by a 3 month optimization phase led to the identification of an optimized lead with all its expected properties in hand to be developed as a candidate molecule for skin care in cosmetic applications. The success of this pilot project paves the way for other cosmetic targets of interest.

Pharmacophores for FBDD

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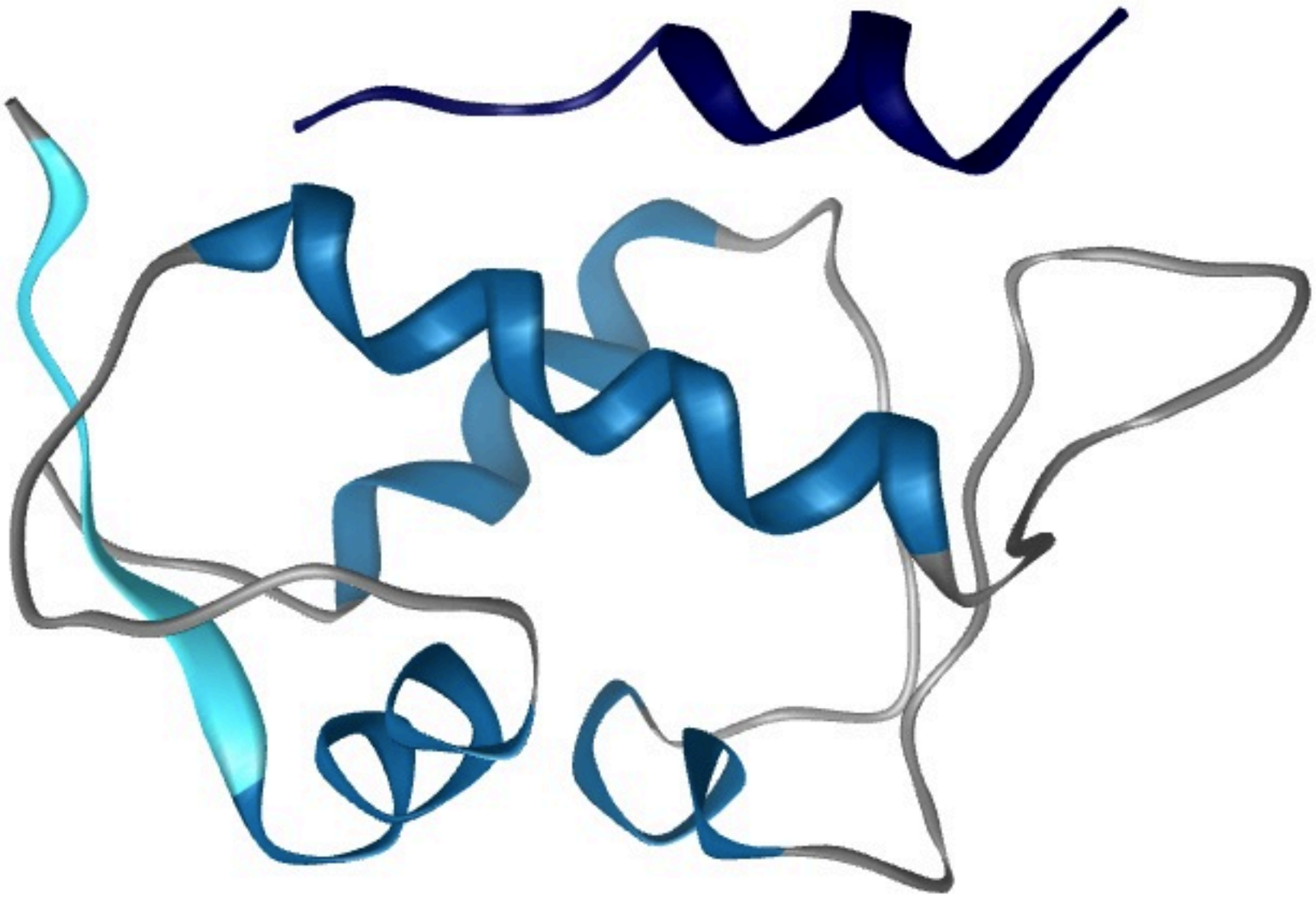

T. Langer, 2019-01-23

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A medicinal chemistry company

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Pharmacophores for FBDD

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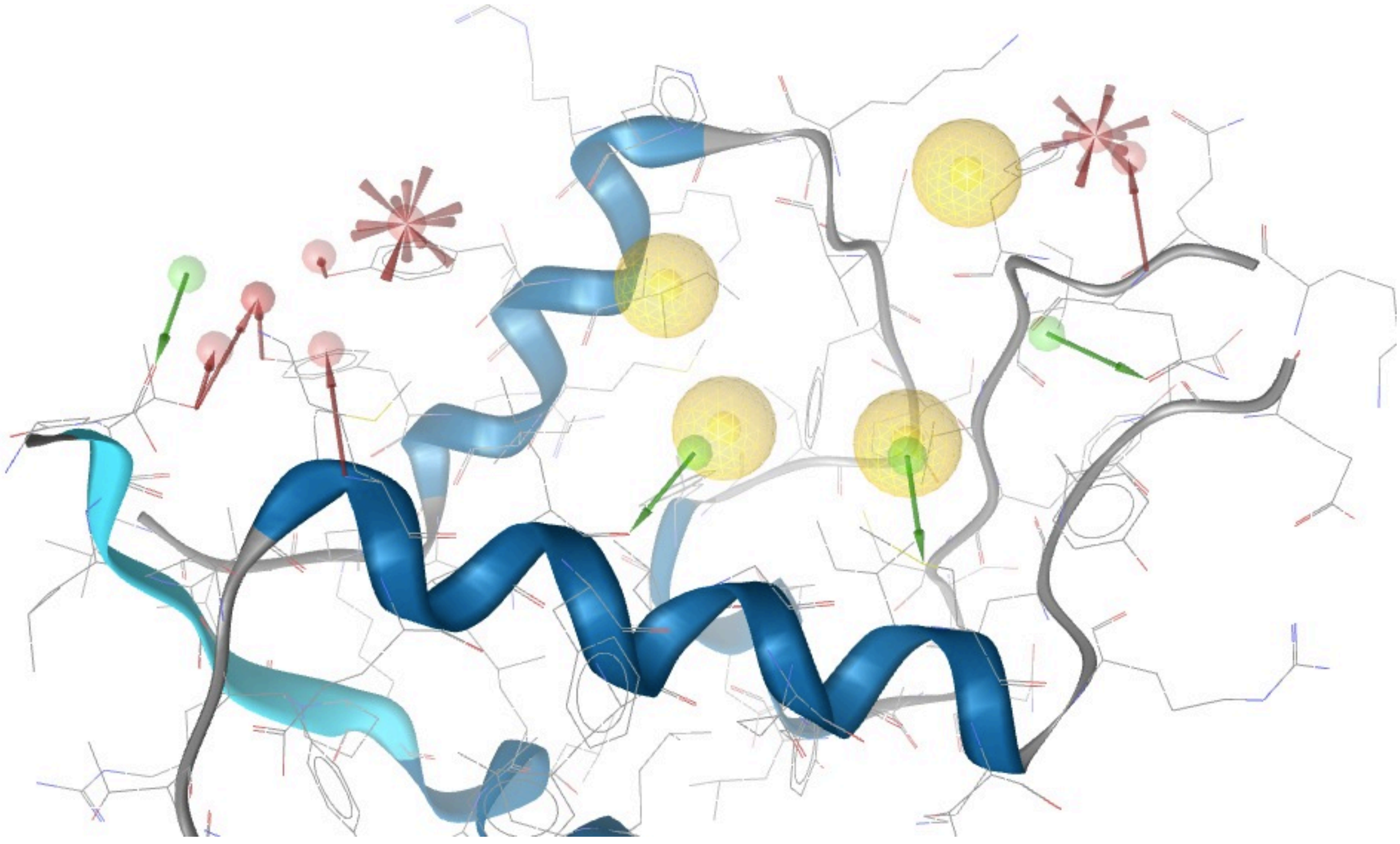

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Pharmacophores for FBDD

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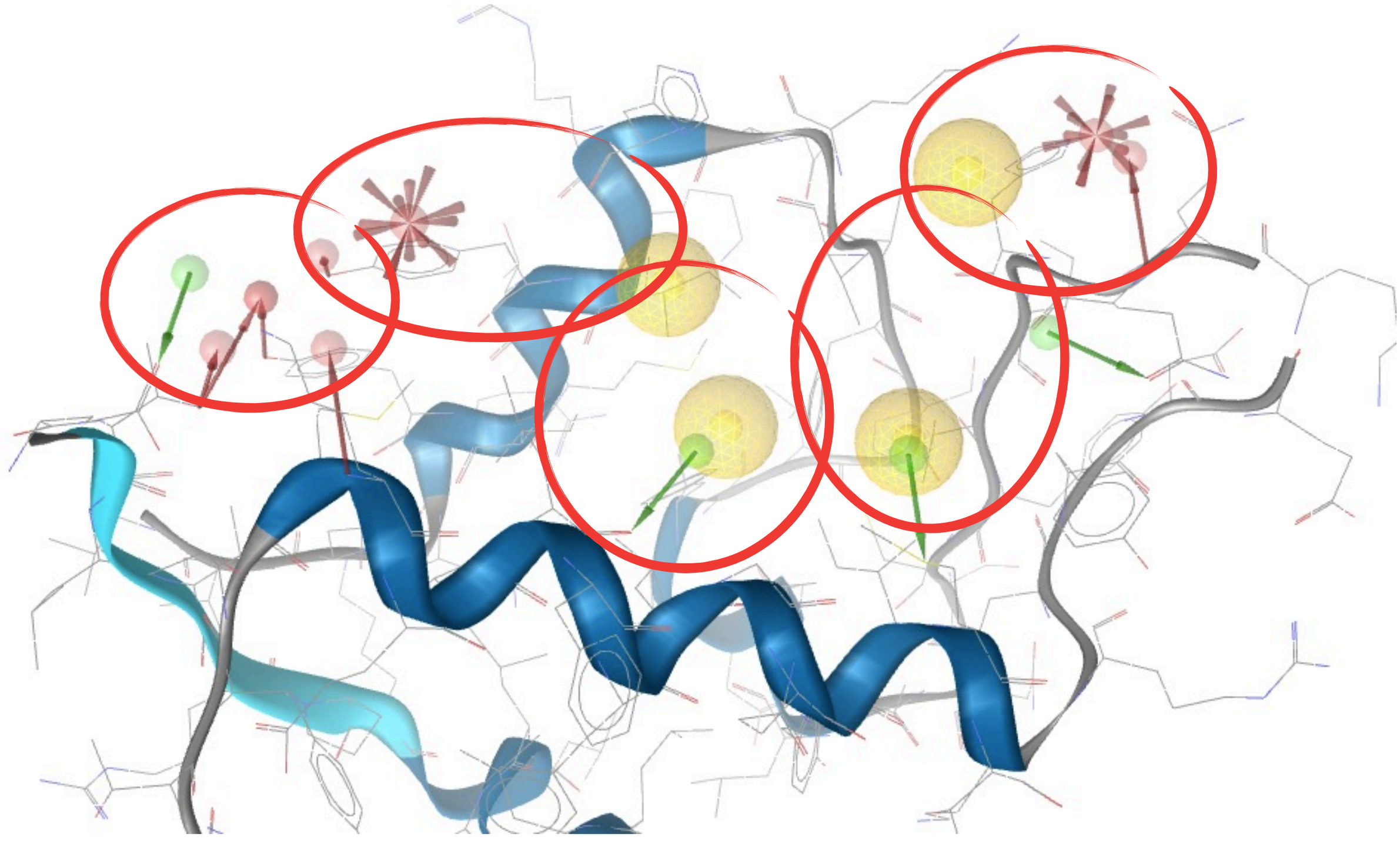

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In Silico FBDD Strategy

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- Use set of smart, recombinable fragments
- Perform pharmacophore-based screening
- Recombine fragments in silico
- Synthesize the highest ranked solutions
  - IP situation
  - Fit for the target
  - Chemical tractability
  - Physicochemical properties

Real Life - The Numbers

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- PPI target with known 3D structure (x-ray)
- Pharmacophore derived in direct approach
- Chemistry based fragment library design: 274 -> 837 -> 582
- Virtual combination of 2 fragments: 91k compounds
- LigandScout virtual screening delivered a reasonably small number of hits: 0.005% range
- Synthesis and biological testing: Novel IP, low µM hits

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Real Life - Timelines

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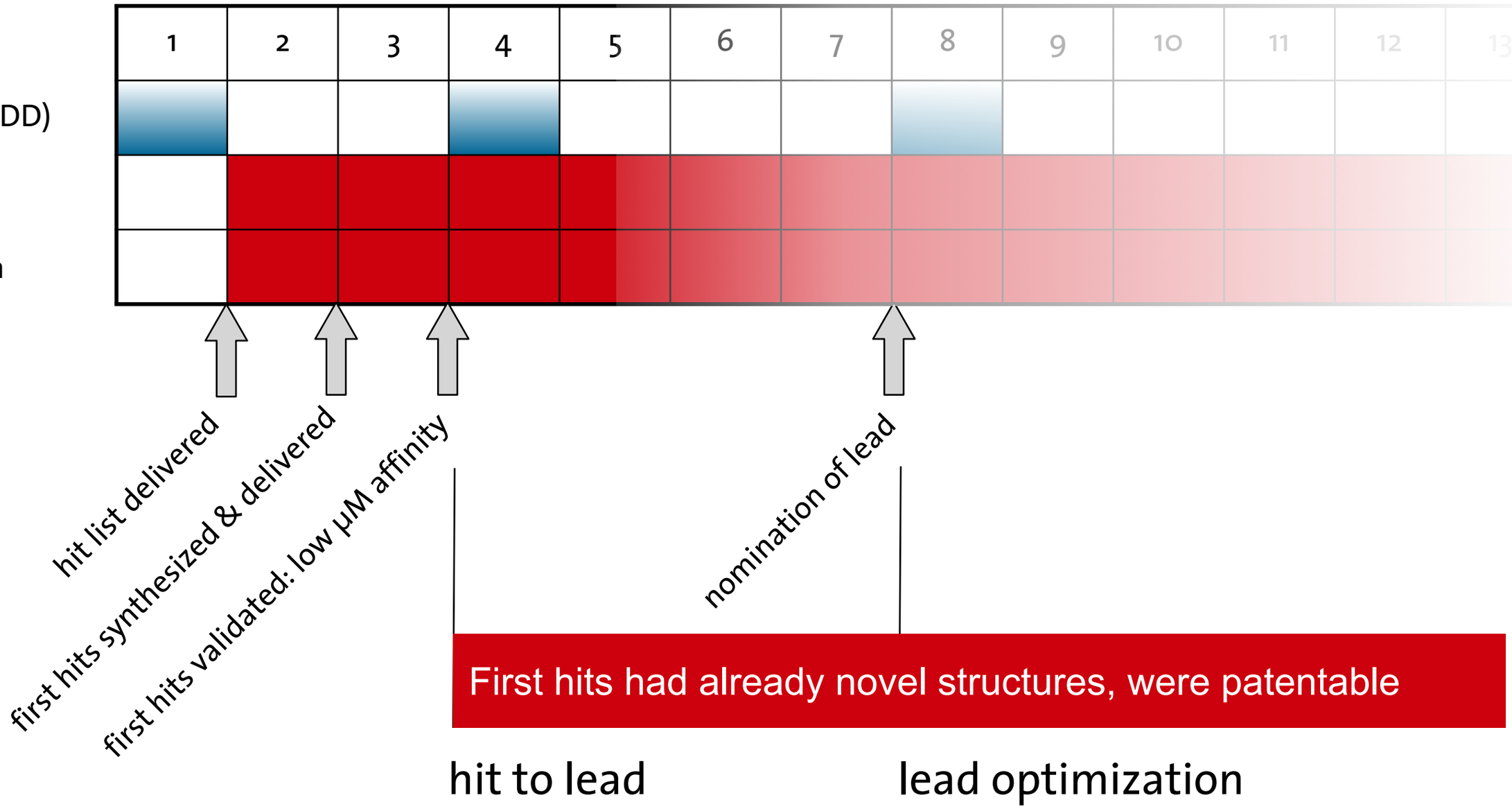

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First Summary

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- Universal and rapid method for accurate feature-based 3D-pharmacophore model generation now available
- Highly selective models will retrieve low number of false positives
- High enrichment factor will be obtained
- Where and how to apply such models in the drug discovery pipeline ?
- **What are the next steps to integrate ?**

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Statics & Dynamics

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Molecular Dynamics

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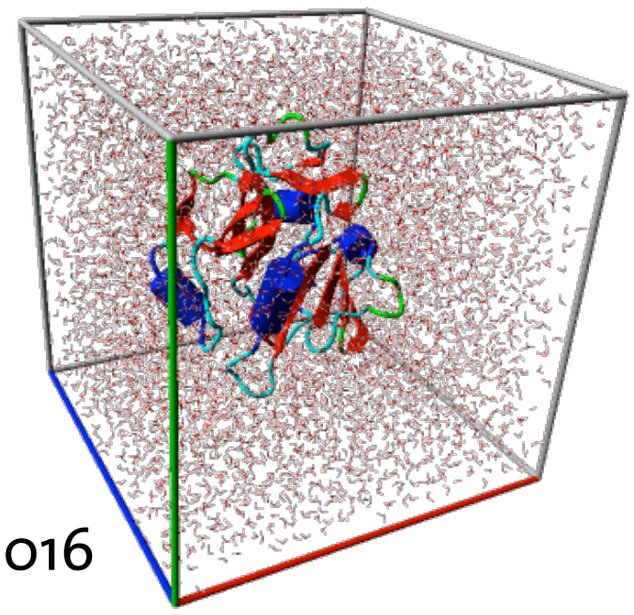
- MD approaches have gained substantial interest in early drug discovery due to parallel computing hardware options*
- Interpretation of MD trajectories still cumbersome
- Pharmacophores are a perfect solution



* J. Mortier et al., Drug Discov Today. 2015. 20(6):686-702. doi: 10.1016

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REVIEWS

Drug Discovery Today • Volume 20, Number 6 • June 2015

Teaser An overview on molecular dynamics (MD) studies illustrating the range of applications in the field of drug design.

Reviews • FOUNDATION REVIEW

The impact of molecular dynamics on drug design: applications for the characterization of ligand–macromolecule complexes

Jérémie Mortier[1], Christin Rakers[1], Marcel Bermudez[1], Manuela S. Murgueitio[1], Sereina Riniker[2] and Gerhard Wolber[1]

[1] Institute of Pharmacy, Freie Universität Berlin, Königin-Luise-Strasse 2+4, 14195 Berlin, Germany
[2] Laboratory of Physical Chemistry, ETH Zürich, Vladimir-Prelog-Weg 2, CH-8093 Zurich, Switzerland

Among all tools available to design new drugs, molecular dynamics (MD) simulations have become an essential technique. Initially developed to investigate molecular models with a limited number of atoms, computers now enable investigations of large macromolecular systems with a simulation time reaching the microsecond range. The reviewed articles cover four years of research to give an overview on the actual impact of MD on the current medicinal chemistry landscape with a particular emphasis on studies of ligand–protein interactions. With a special focus on studies combining computational approaches with data gained from other techniques, this review shows how deeply embedded MD simulations are in drug design strategies and articulates what the future of this technique could be.

Jérémie Mortier is a postdoctoral fellow in Gerhard Wolber's computer-aided drug design group at the Free University of Berlin, Germany. His main field of research is at the interface of biological and medicinal chemistry, with a particular focus on the prediction and understanding of molecular systems, their structures and interactions. After a Master in Chemistry in 2006, he was first introduced to computational chemistry during his PhD in pharmaceutical and biomedical sciences at the University of Namur, Belgium, in 2010. His position is currently funded by a fellowship from the Deutsche Forschung Gemeinschaft.

Sereina Riniker received her PhD at ETH Zurich in the field of molecular dynamics simulations. In 2012, she moved on to take a postdoctoral position in cheminformatics at the Novartis Institutes for BioMedical Research in Basel as well as Cambridge, Massachusetts, before

MD and Pharmacophores

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- Analysing molecular dynamics trajectories
- Finding relevant pharmacophore models
- Defining ways to calculate similarities
- Sampling and identification of rare (but important) events
- Using pharmacophores as a way to abstract ligand-protein interactions in MD trajectories

Model POC Study

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- Data set: 40 Protein ligand complexes selected from PDB / DUD-E
  - single ligand, no metal ions involved in binding interaction, < 200k atoms
- MD Simulation: 10 x 20 ns, CHARMM, TIP3P water
  - 1 fs time steps, coordinate saved every 10 ps
- Pharmacophore generation & virtual screening analysis
  - 10 x 2.000 coordinate sets + 10 x 1 PDB structures = 20.010 P4 Models
  - Pharmacophore vector for feature frequency analysis
  - Parallel virtual screening with all models
  - Post screening processing for ranking the hits

Wieder M. et al., J. Chem. Inf. Model., 57, 365-385 (2017)

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Model POC Study

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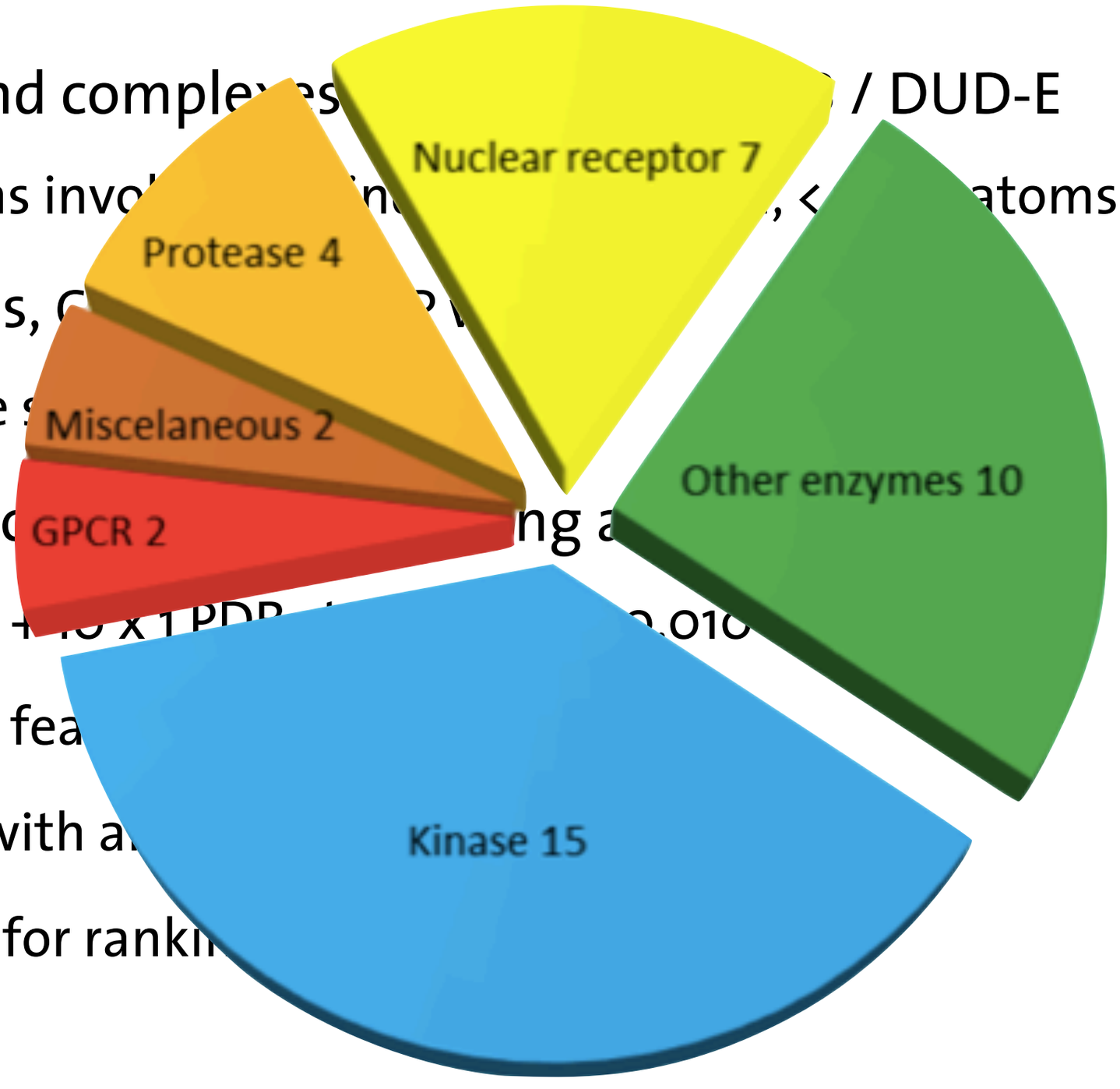

Wieder M. et al., J. Chem. Inf. Model., 57, 365-385 (2017)

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Sampling Pharmacophore Models

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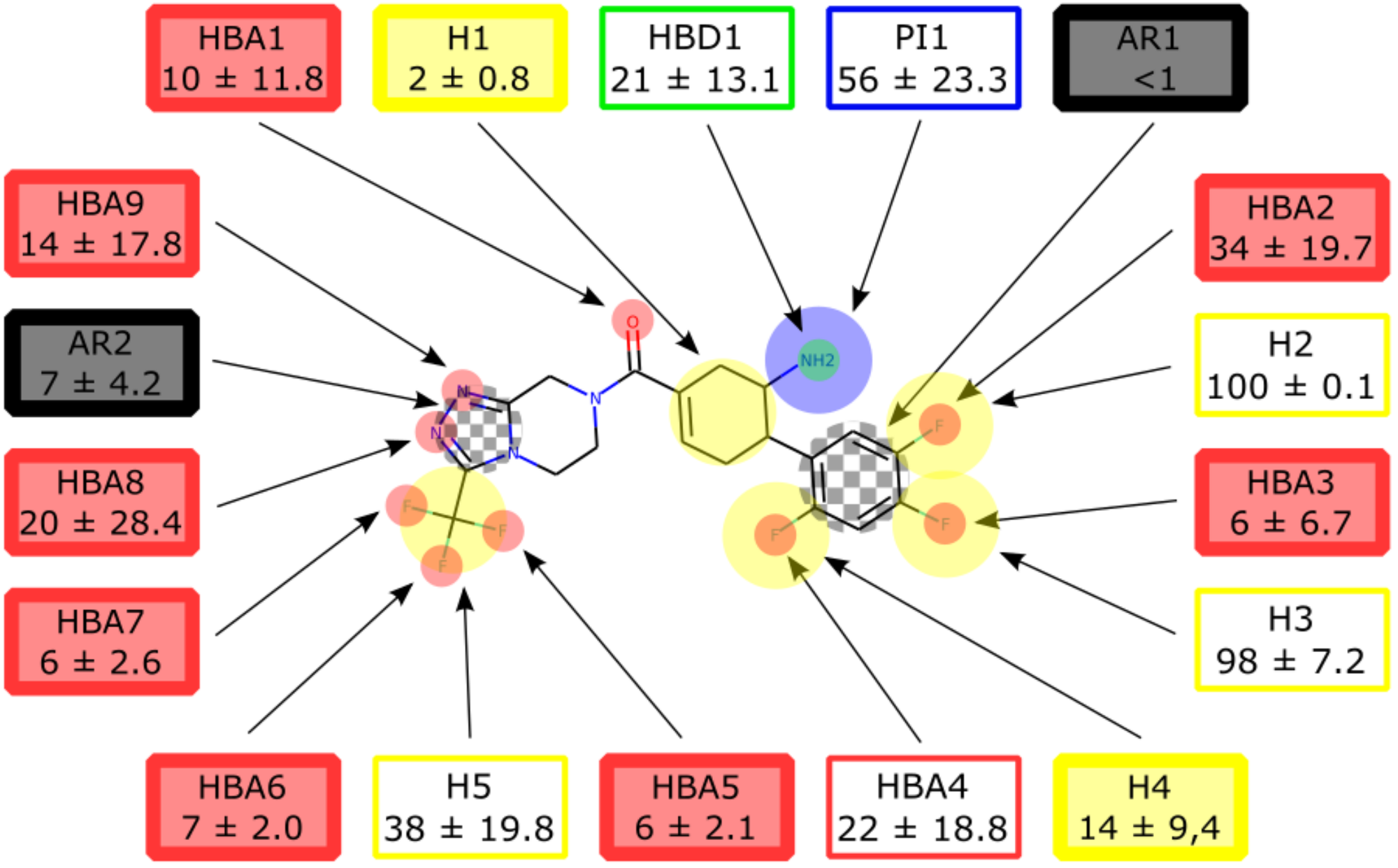

PDB ID 2I78: MD pharmacophore features, appearance in % of total frames

Wieder M. et al., J. Chem. Inf. Model., 57, 365-385 (2017)

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P4 Vector MD Analysis

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AR2	AR1	H1	H5	H6	H4	H3	H2	HBA1	HBA9	HBA8	HBA6	HBA7	HBA5	HBA4	HBA3	HBA2	HBD1	PI1	#p4	% tf
0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1818	9,1%
0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	0	1	826	4,1%
0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	1	1	805	4,0%
0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	683	3,4%
0	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	455	2,3%
0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	0	0	451	2,3%
0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	1	424	2,1%
0	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	384	1,9%
0	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	1	0	0	363	1,8%
0	0	0	1	0	0	1	1	0	1	1	0	0	0	0	0	0	0	0	353	1,8%
0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	1	1	332	1,7%
0	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	1	0	1	325	1,6%
0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	0	1	0	1	259	1,3%
0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	236	1,2%
0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	1	0	217	1,1%
0	0	0	1	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0	205	1,0%
0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	1	1	180	0,9%
1	0	0	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	176	0,9%
0	0	0	0	0	0	1	1	0	0	0	1	0	0	0	0	0	0	1	169	0,8%

****

0	0	0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	1	1	45	0,2%
0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	1	1	44	0,2%
0	**0**	**0**	**1**	**0**	**0**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**1**	**1**	**43**	**0,2%**
0	0	0	1	0	1	1	1	0	0	0	0	0	0	0	0	1	0	0	43	0,2%
0	0	0	1	0	1	1	1	0	1	1	0	0	0	0	0	1	0	0	41	0,2%
0	0	0	1	0	0	1	1	0	1	1	0	0	0	0	0	1	0	1	40	0,2%
0	0	0	1	0	0	1	1	0	0	1	0	0	0	1	0	0	0	1	40	0,2%
0	0	0	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	0	37	0,2%
0	0	0	1	0	1	1	1	0	1	1	0	0	0	0	0	0	0	0	37	0,2%
0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	1	1	1	36	0,2%

MD pharmacophore feature PDB pharmacophore feature PDB initial pharmacophore

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Sampling Pharmacophore Models

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- Out of a total of 260k possibilities, 50 - 400 combinations exist
- Many features are not present in the initial PDB-derived pharmacophore model
- Initial PDB model does not have the highest frequency
- Frequency does not seem to have an impact on quality of screening result

How to use all this information ?

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Post-screening Process

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- Underlying Principle
  - A true active molecule should have a higher chance to fit more than one model than a false positive one
  - A higher enrichment should be obtained when using a consensus fit approach

- Application: “Common Hits Approach (CHA)”
  - First, all hits from all models are considered
  - Then, the hits are ranked by the number models they fit

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VS Results Example: AUC (2i78)

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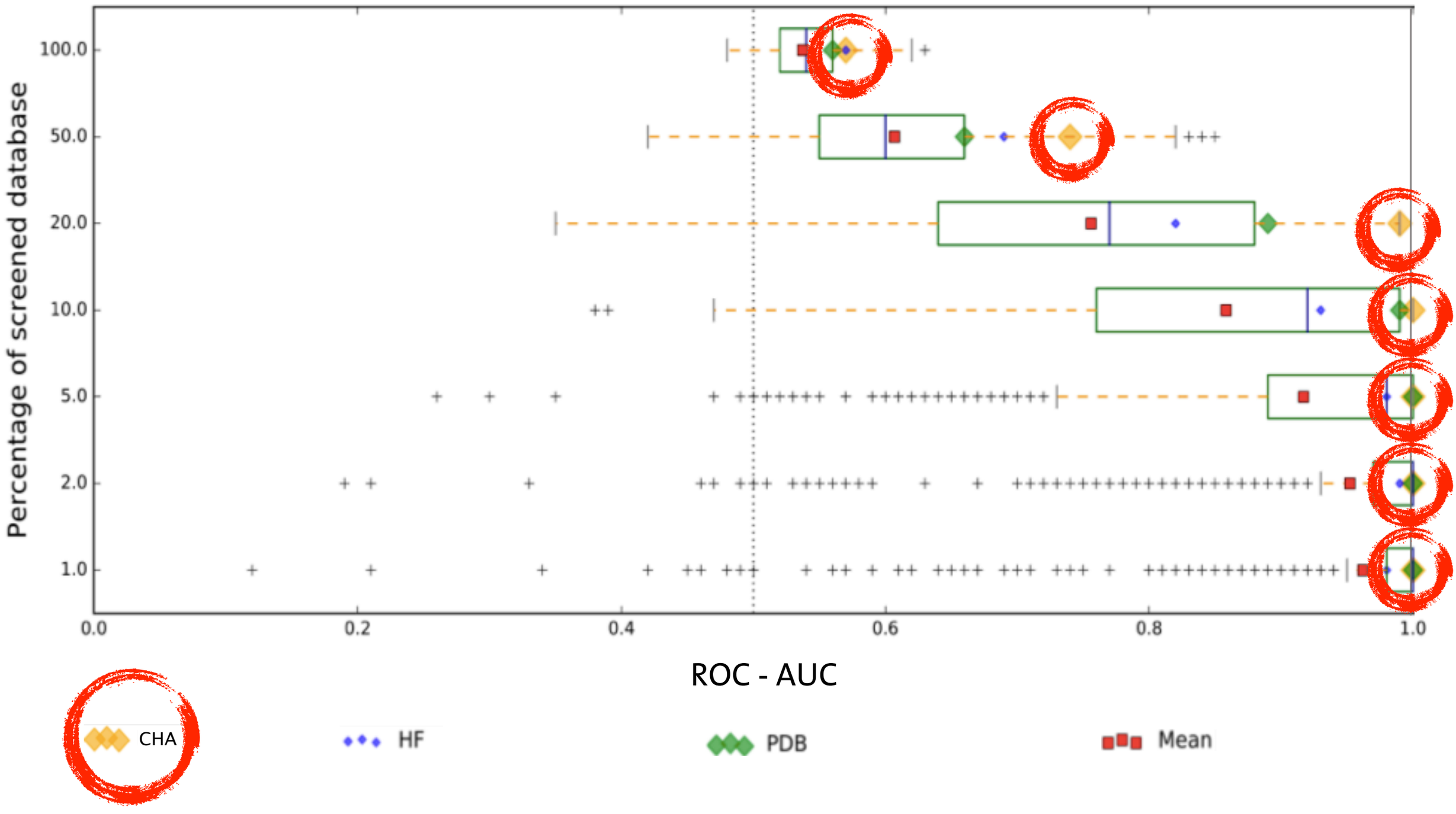

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How Diverse Are The Hits ?

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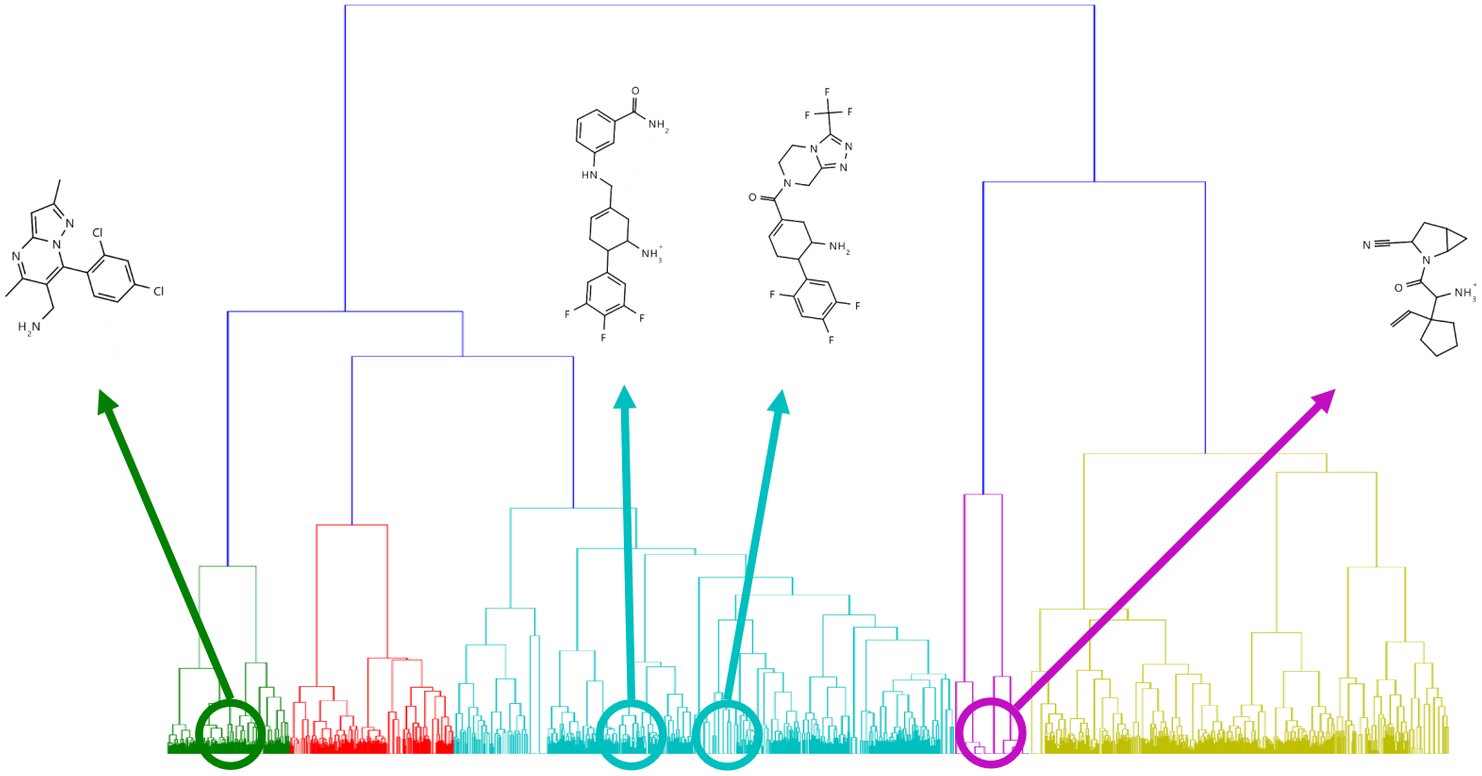

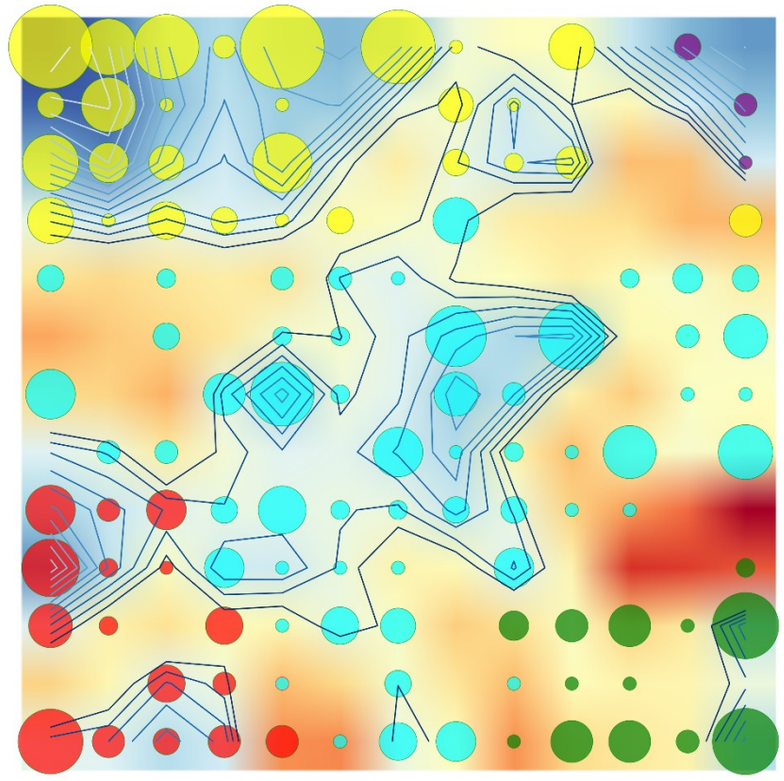

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Hit Structure Diversity Analysis

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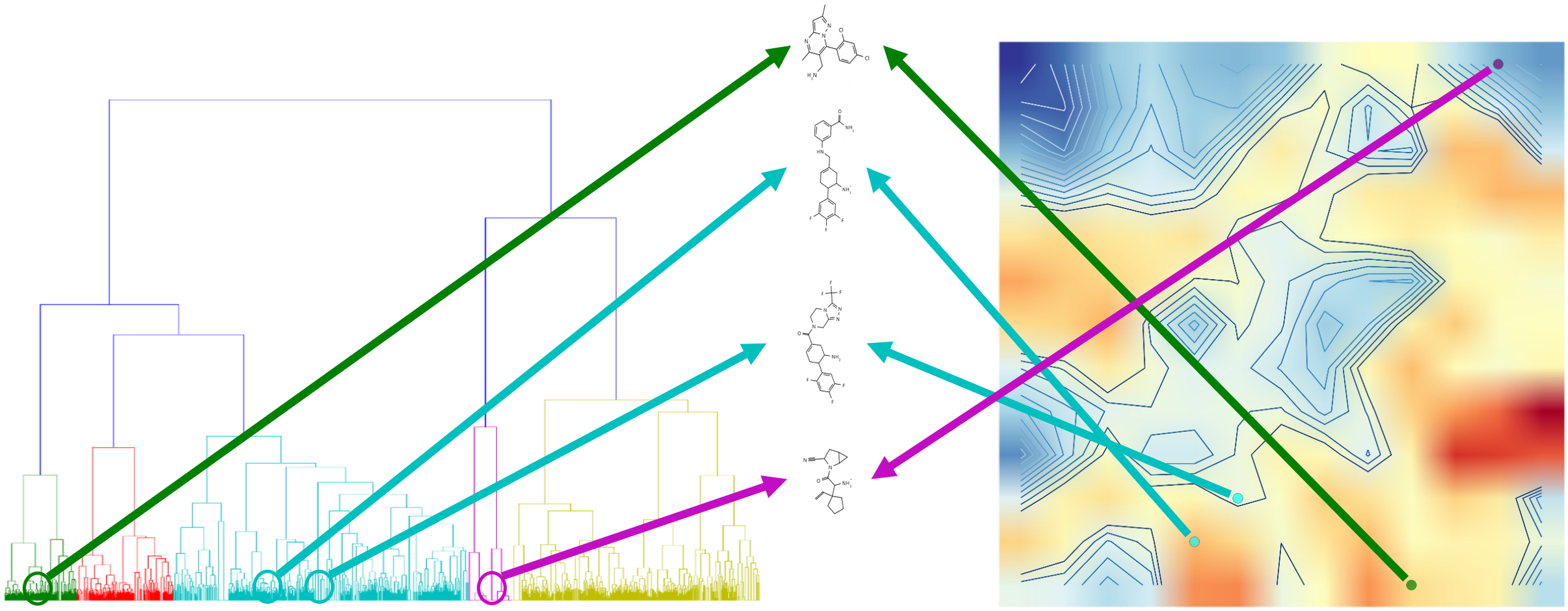

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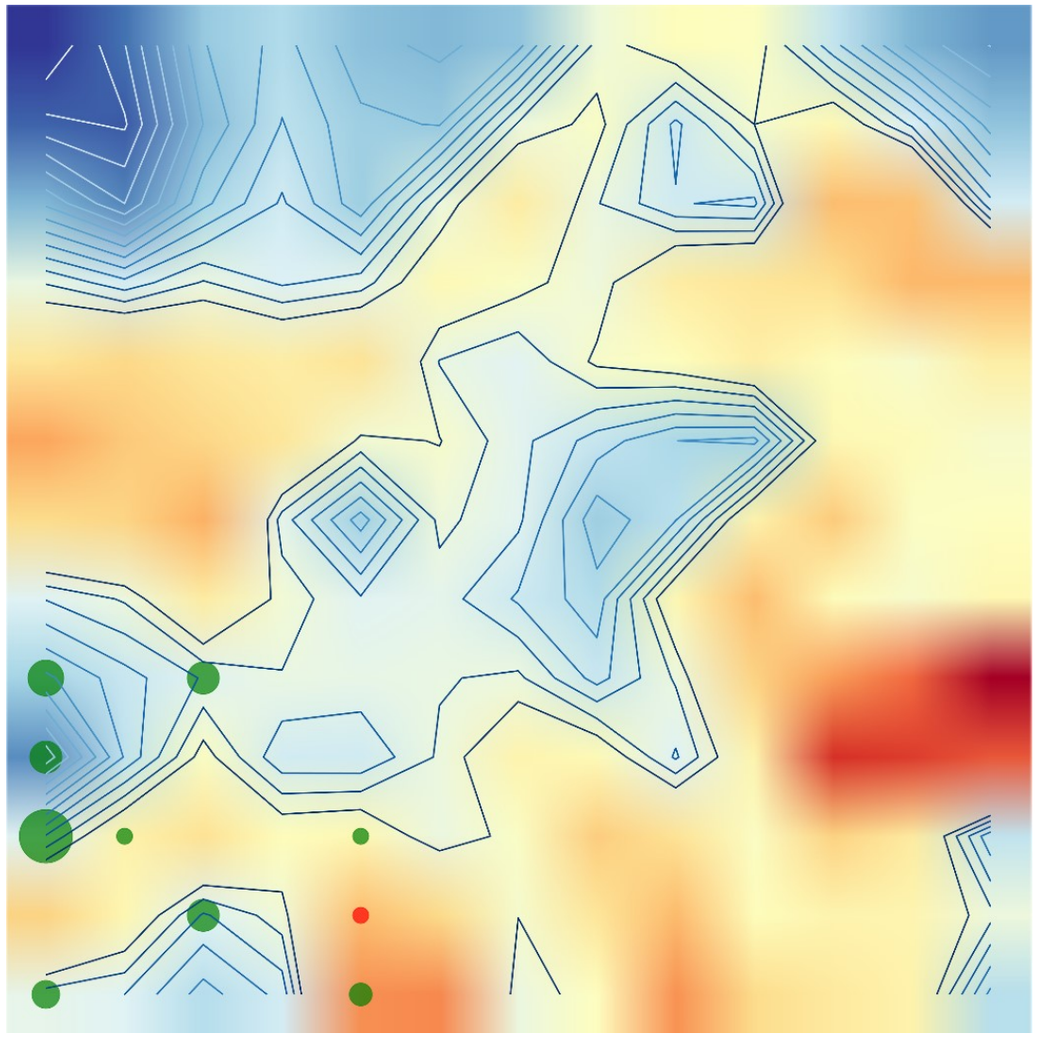
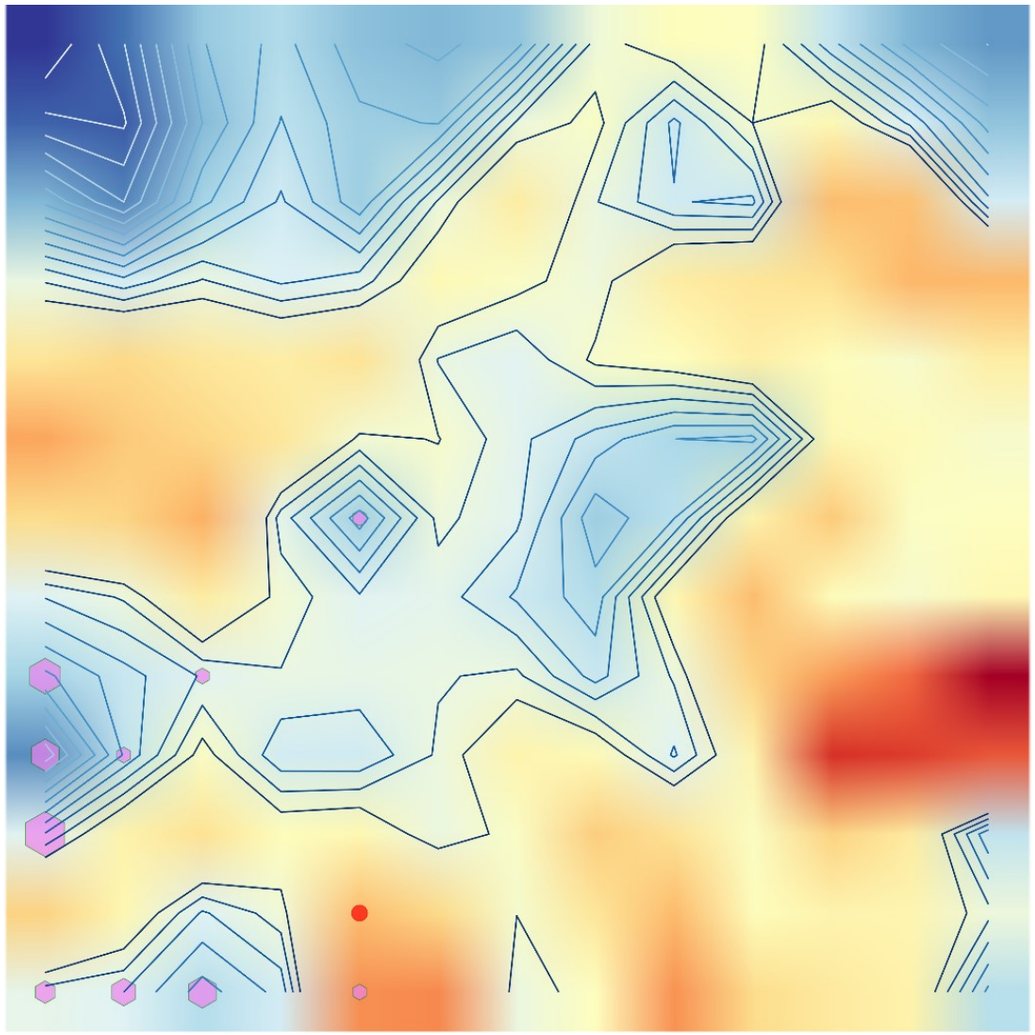


- Initial Ligand
- CHA retrieved active
- PDB retrieved active



0.1 % of database screened

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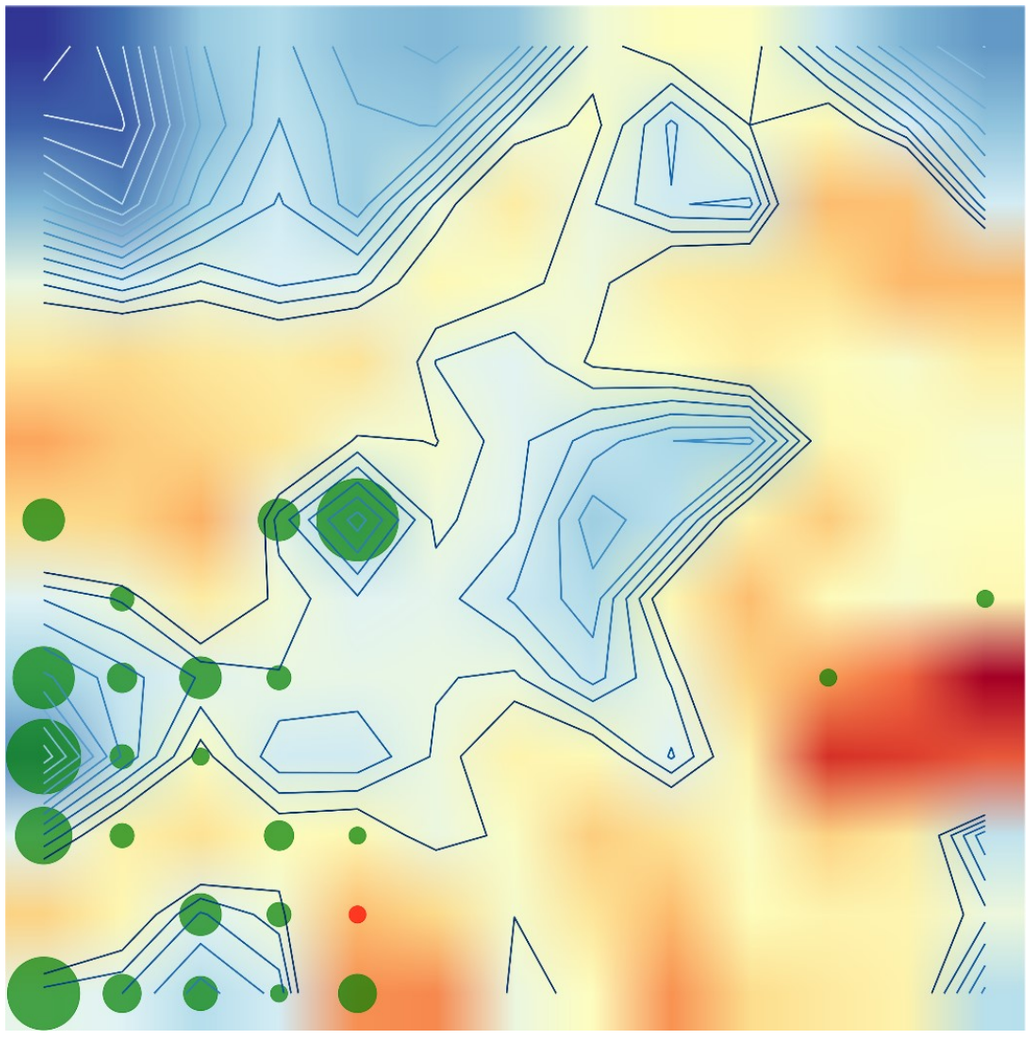
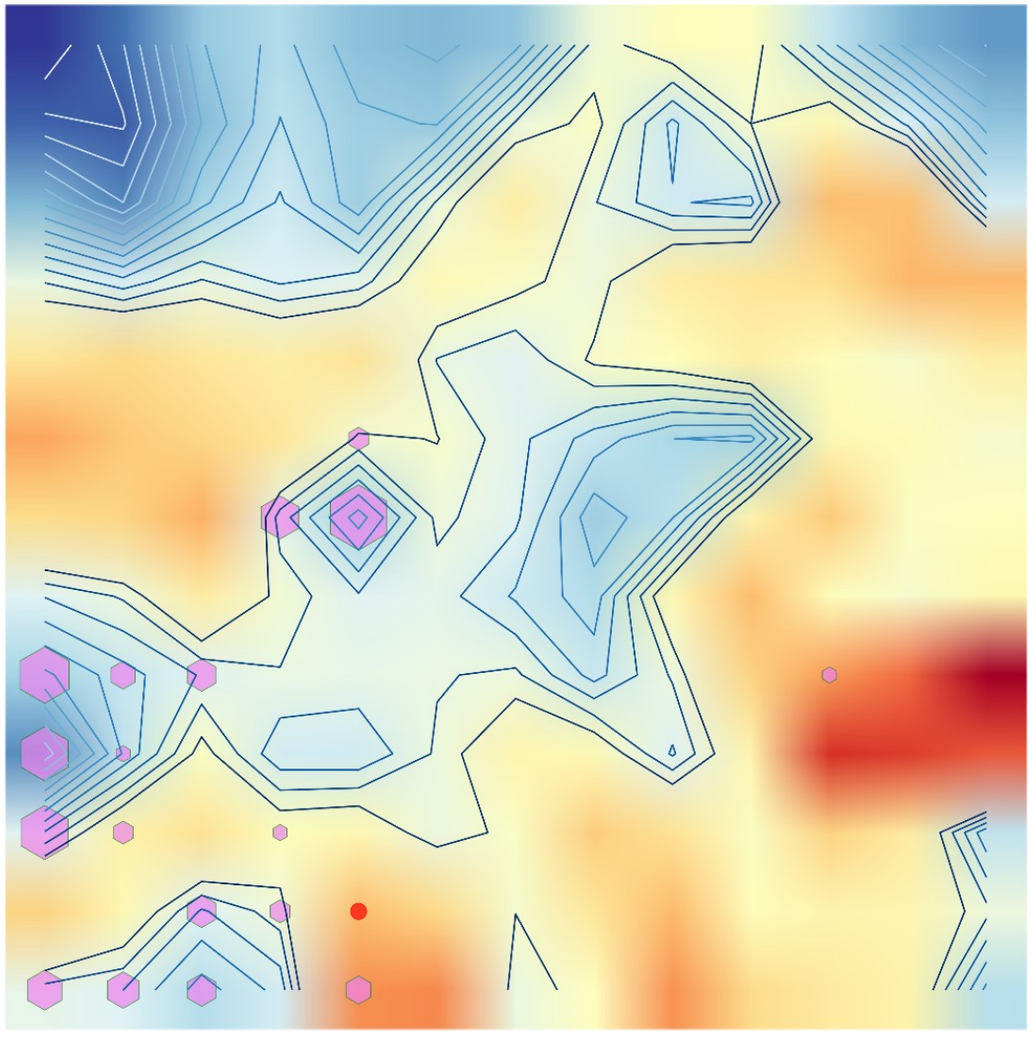


- Initial Ligand
- CHA retrieved active
- PDB retrieved active



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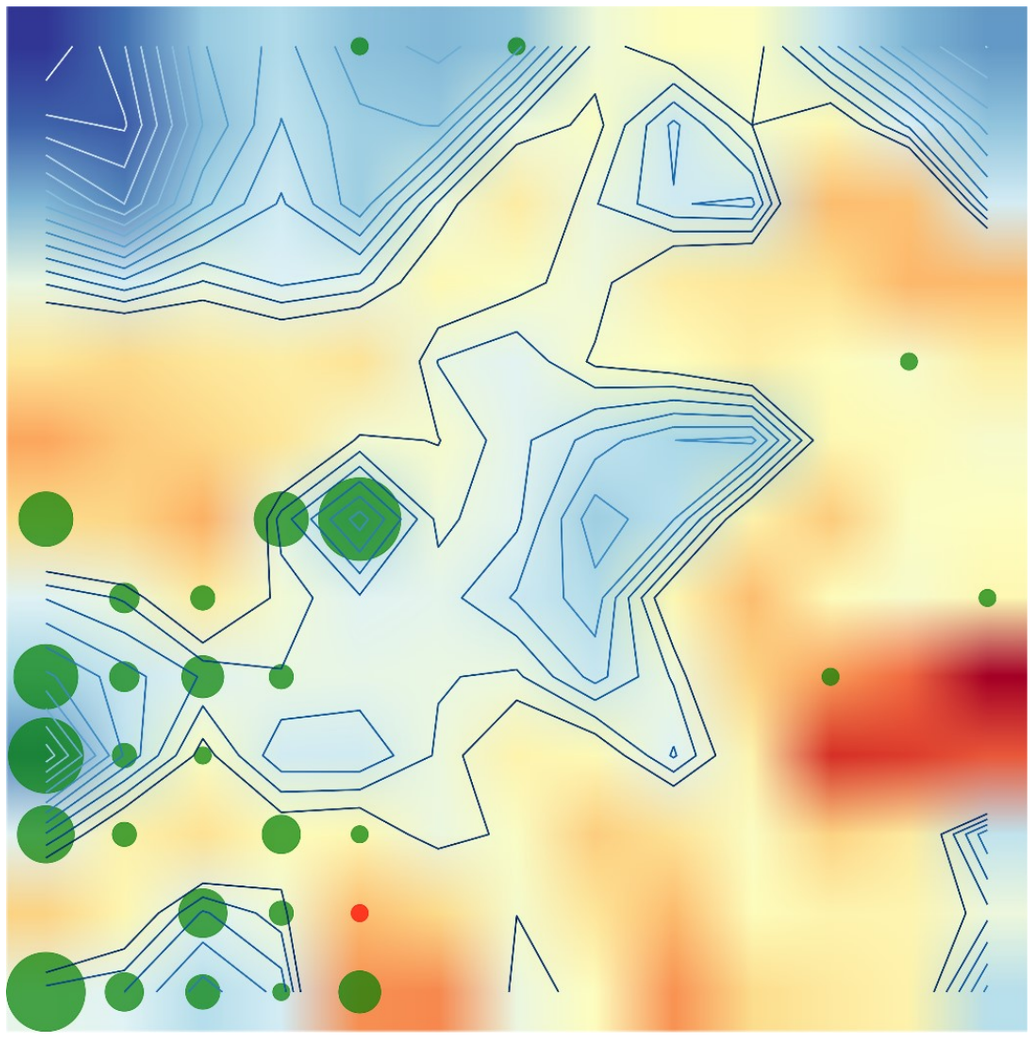
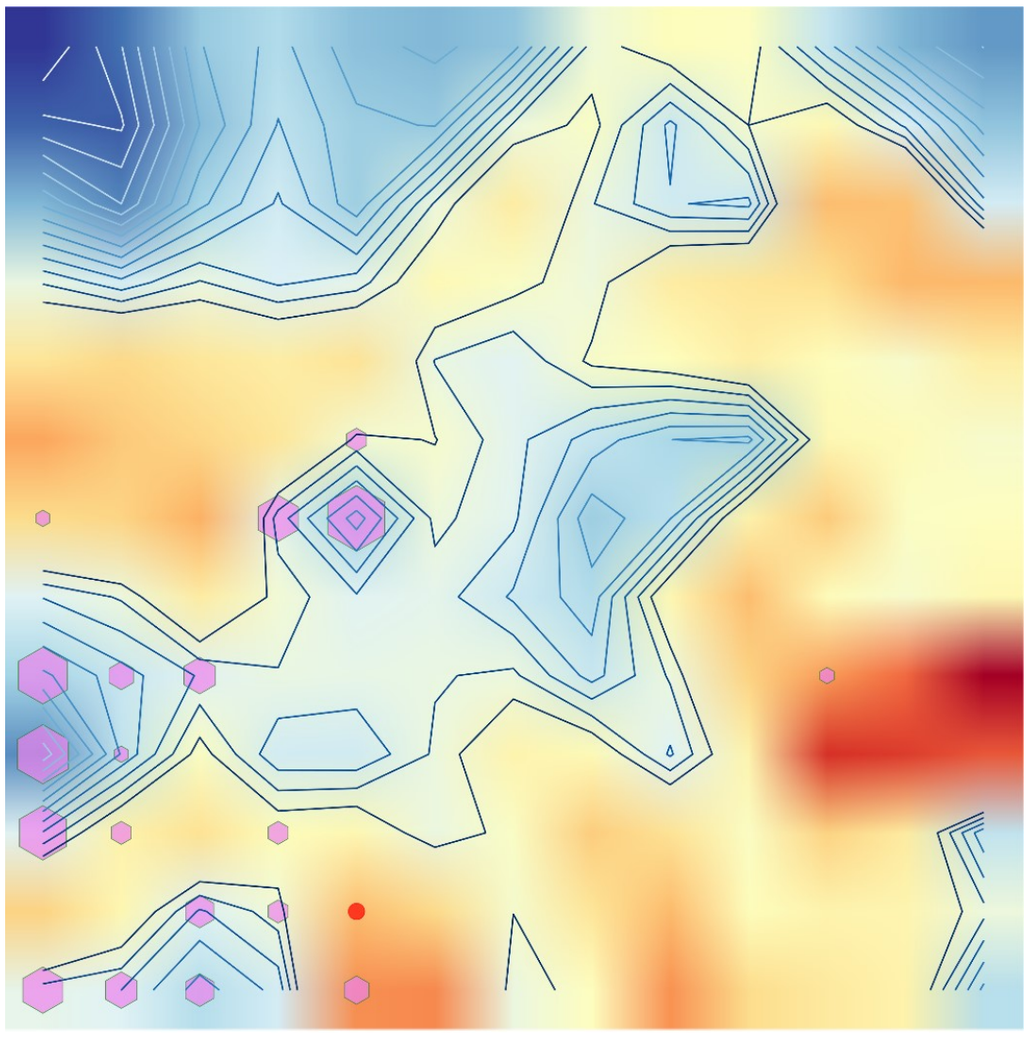


- Initial Ligand
- CHA retrieved active
- PDB retrieved active



1 % of database screened

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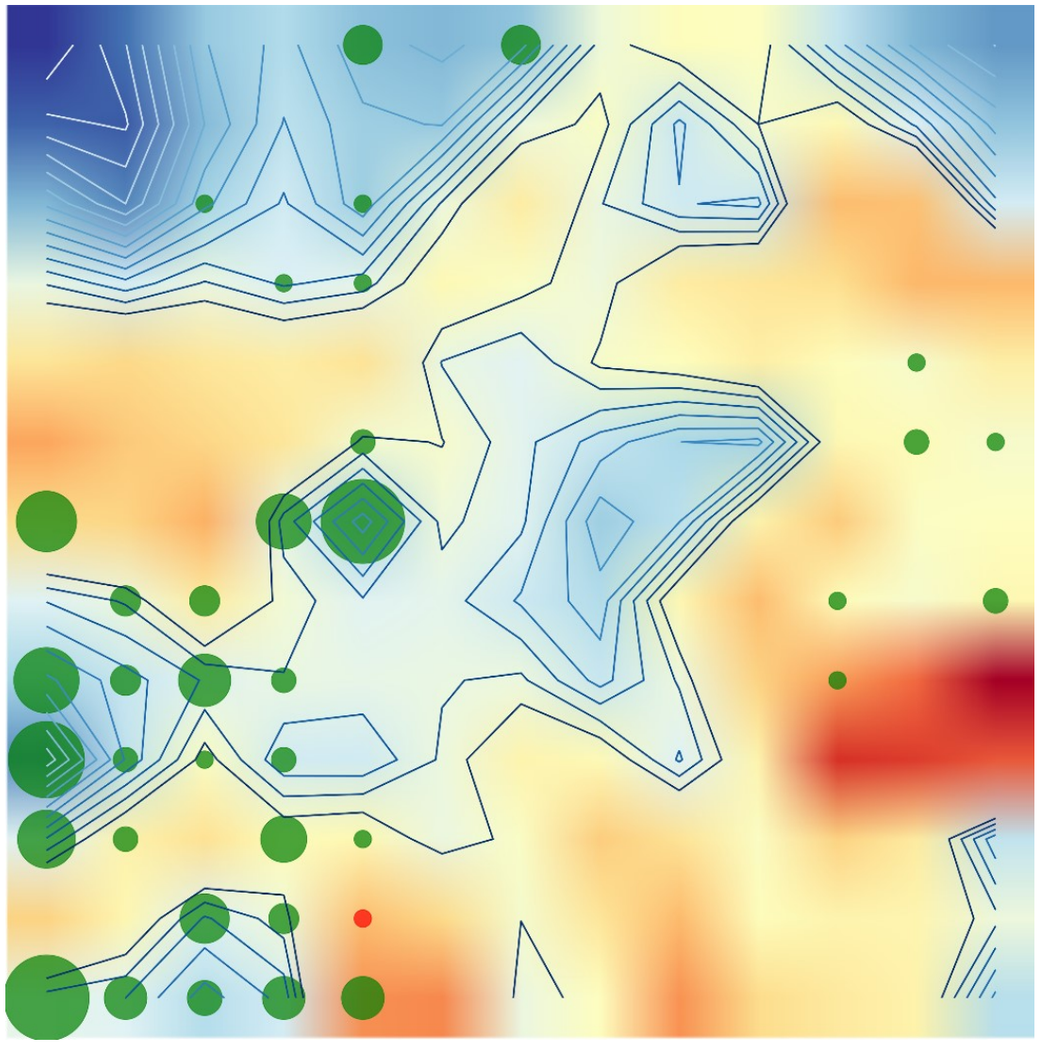
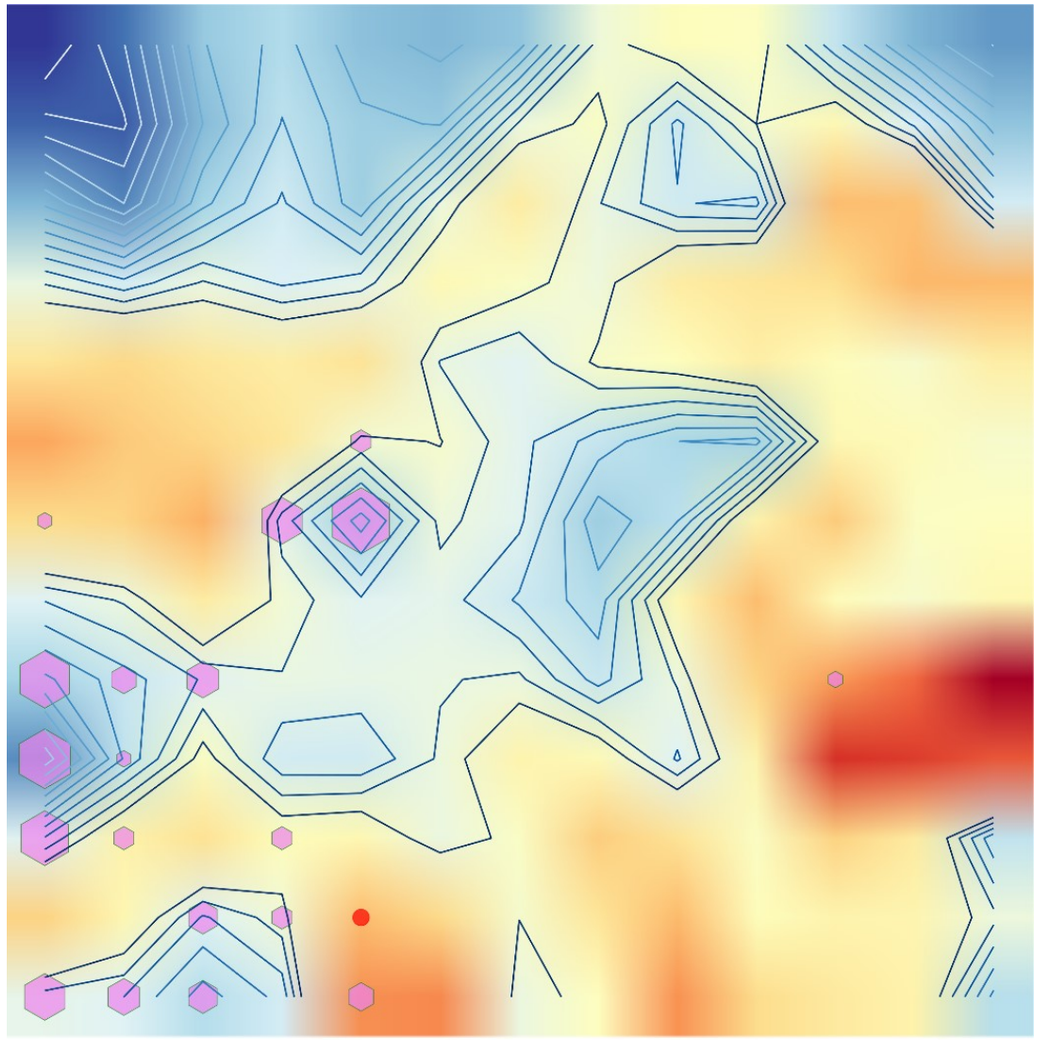


- Initial Ligand
- CHA retrieved active
- PDB retrieved active



5 % of database screened

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Enrichment & AUC

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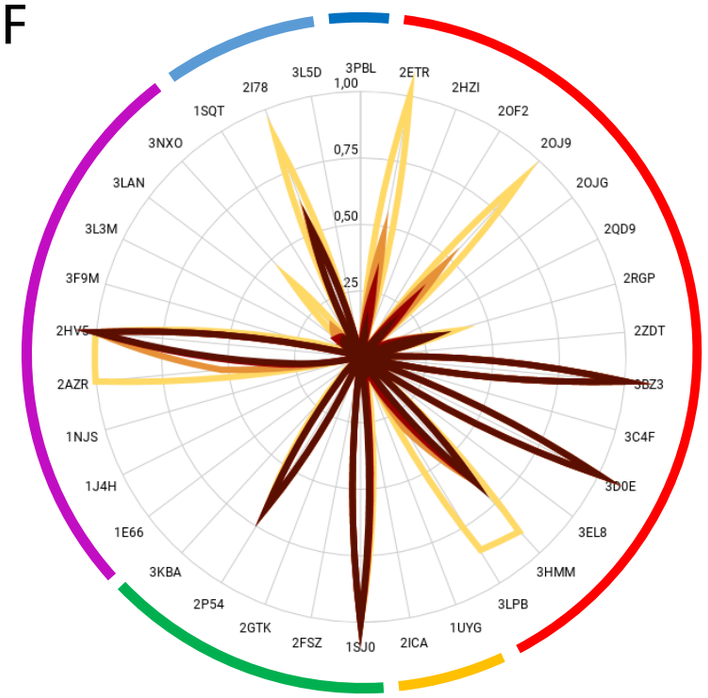
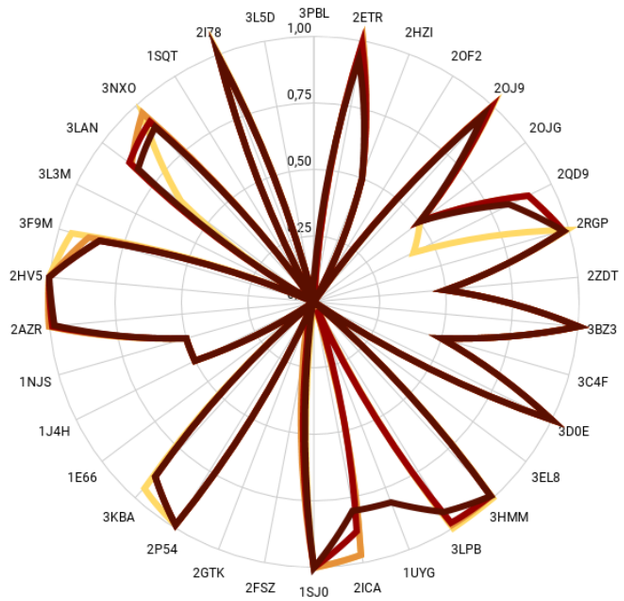
PDB EF



PDB AUC



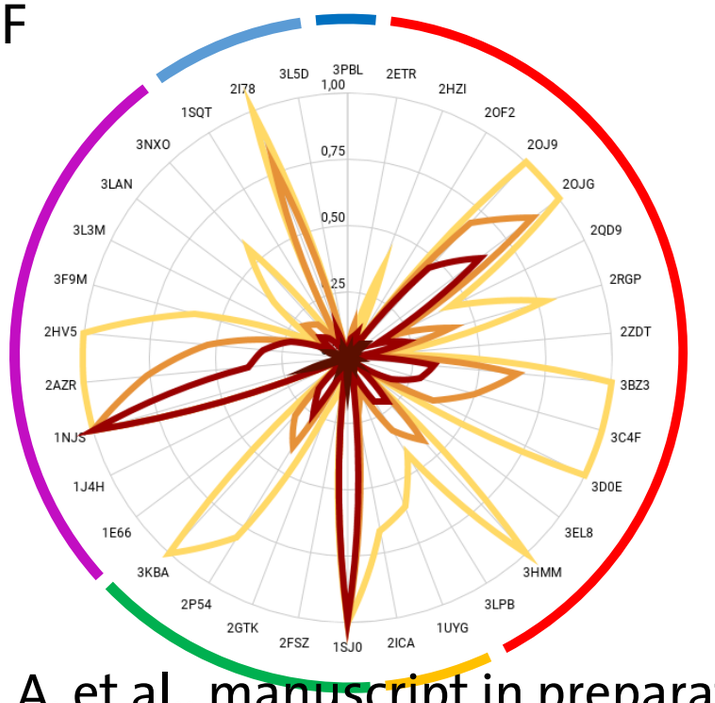
0.1 %

0.5 %

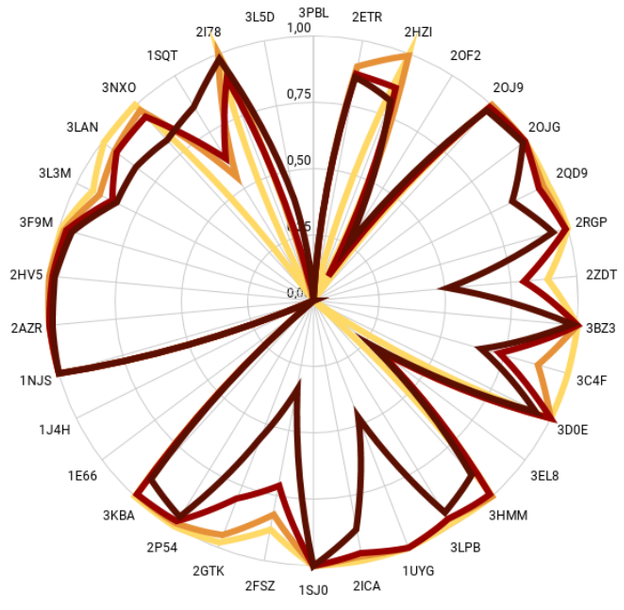
1 %

5 %

CHA EF



CHA AUC



GPCR

Kinase

Miscellaneous

Nuclear Receptor

Other Enzyme

Protease

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Hit Structure Diversity Analysis

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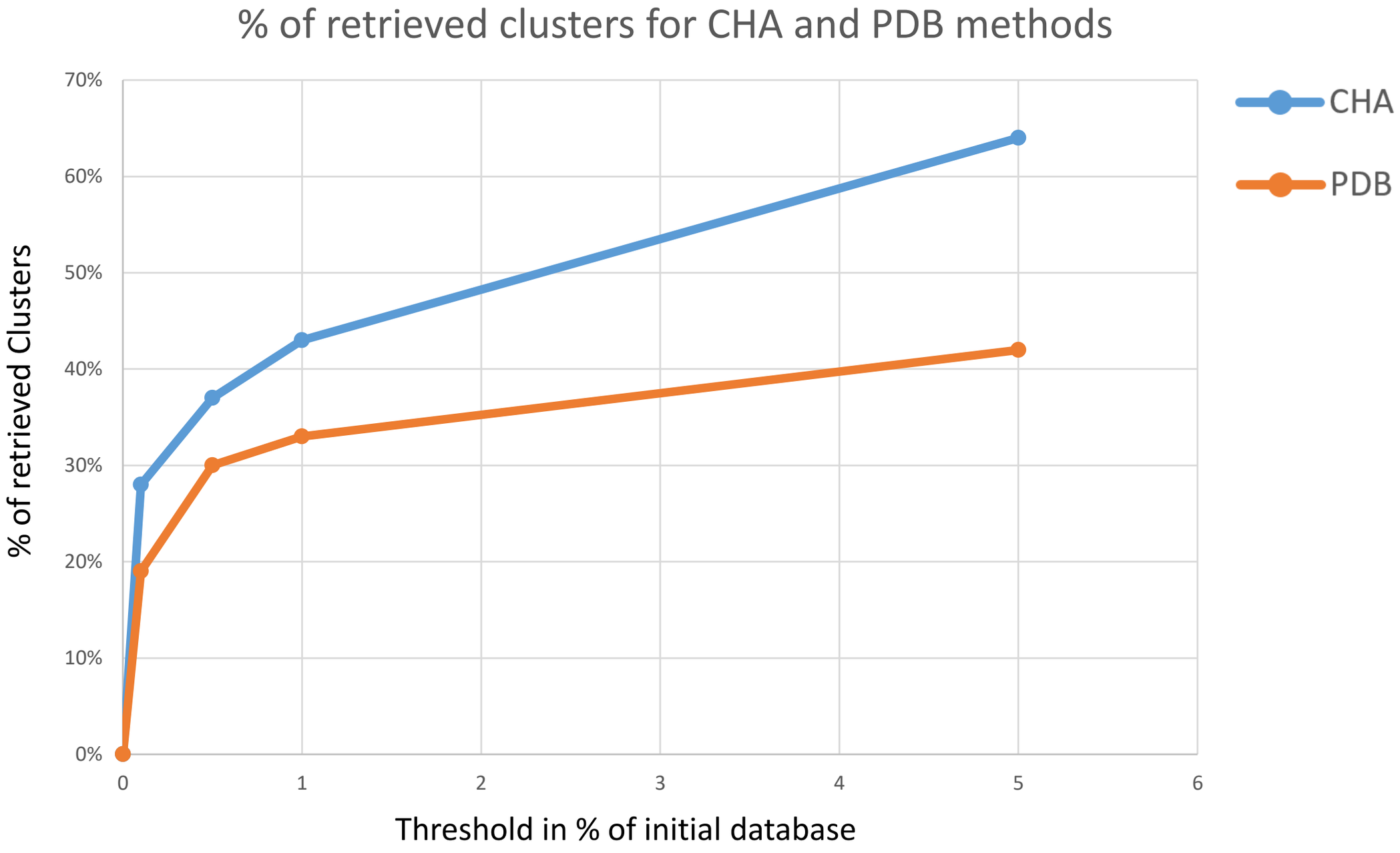

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MD in Optimization Strategy

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- A growing number of MD trajectories is available, however it is difficult to interpret them for design guidance
- Need for easy understandable interaction schemes

First Steps

- Focus on specific regions
  - e.g. looking for water mediated ligand-protein interactions
- Pharmacophore feature frequency analysis
  - for prioritising replacement of molecular substructures

Current Implementation

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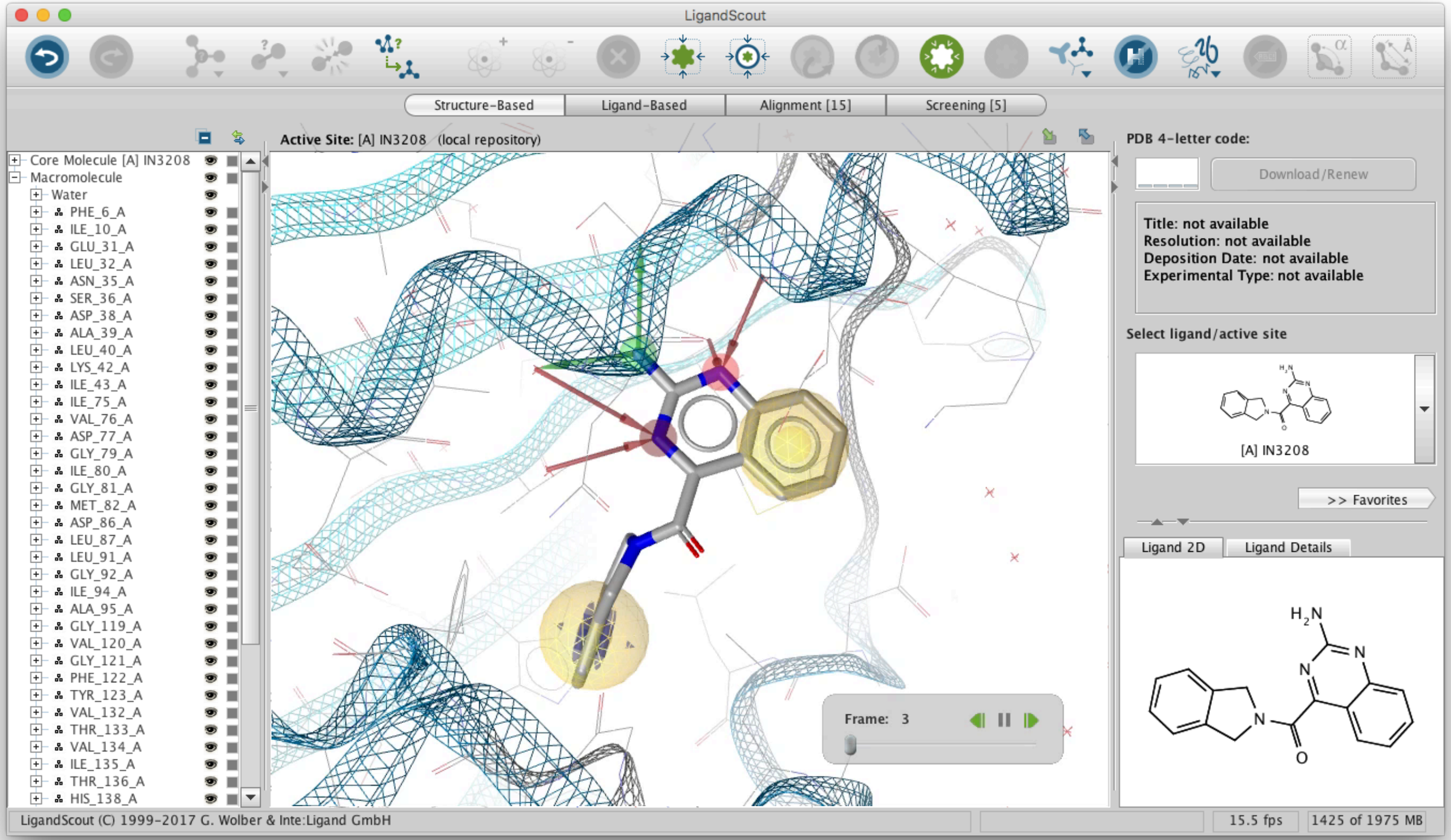

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MD Trajectory Analysis

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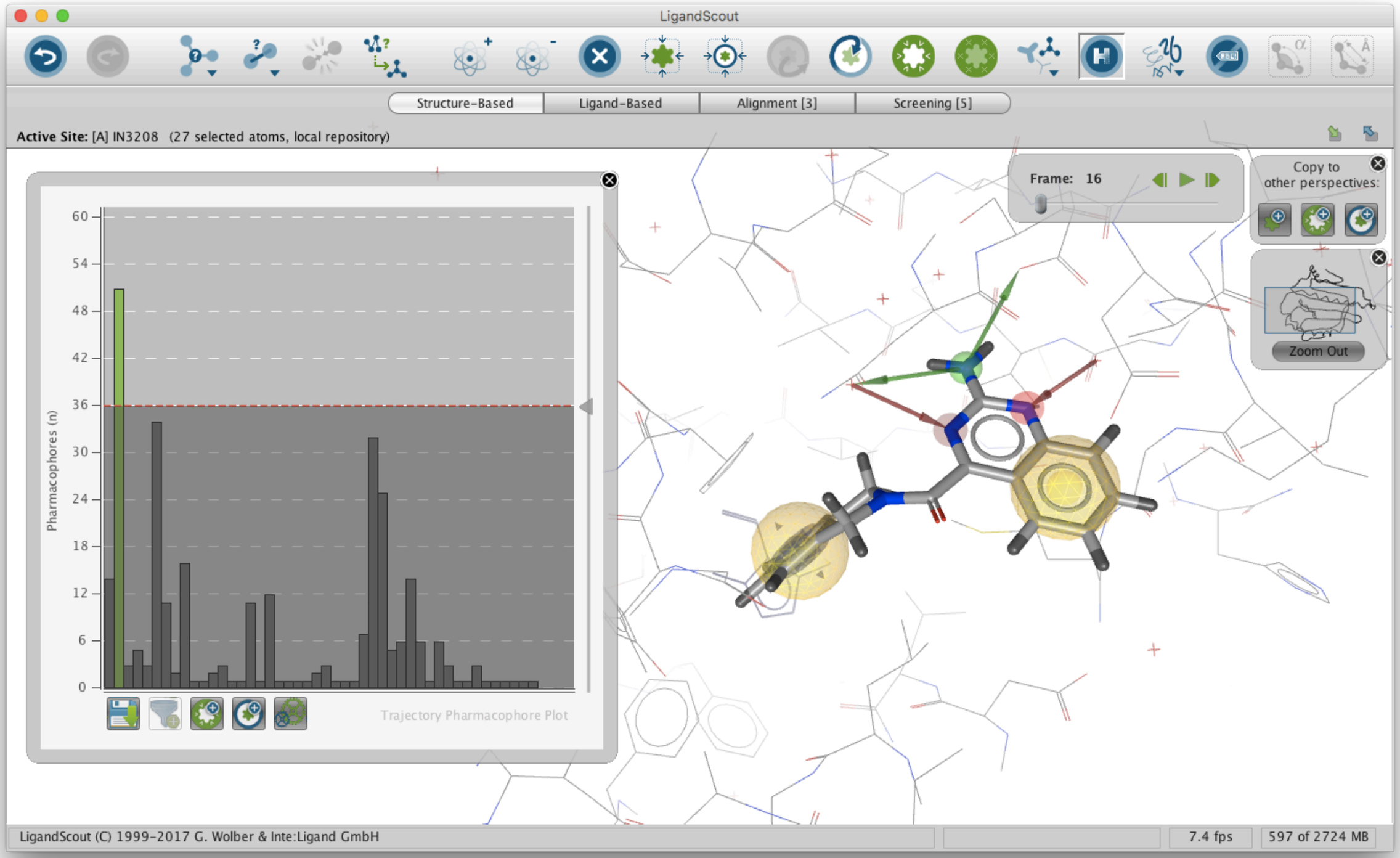

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Find Models With Specific Feature

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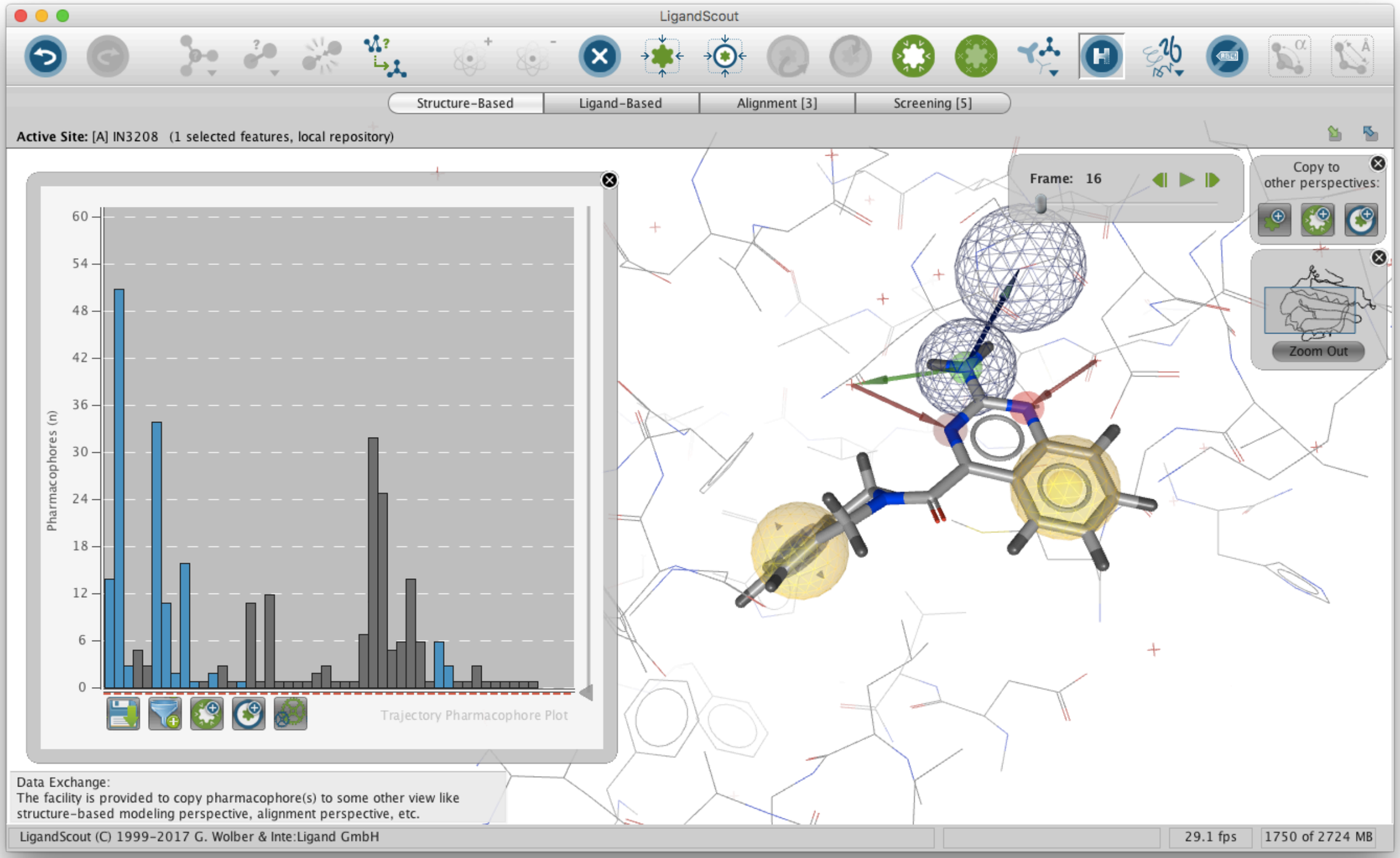

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Find Models With Specific Feature

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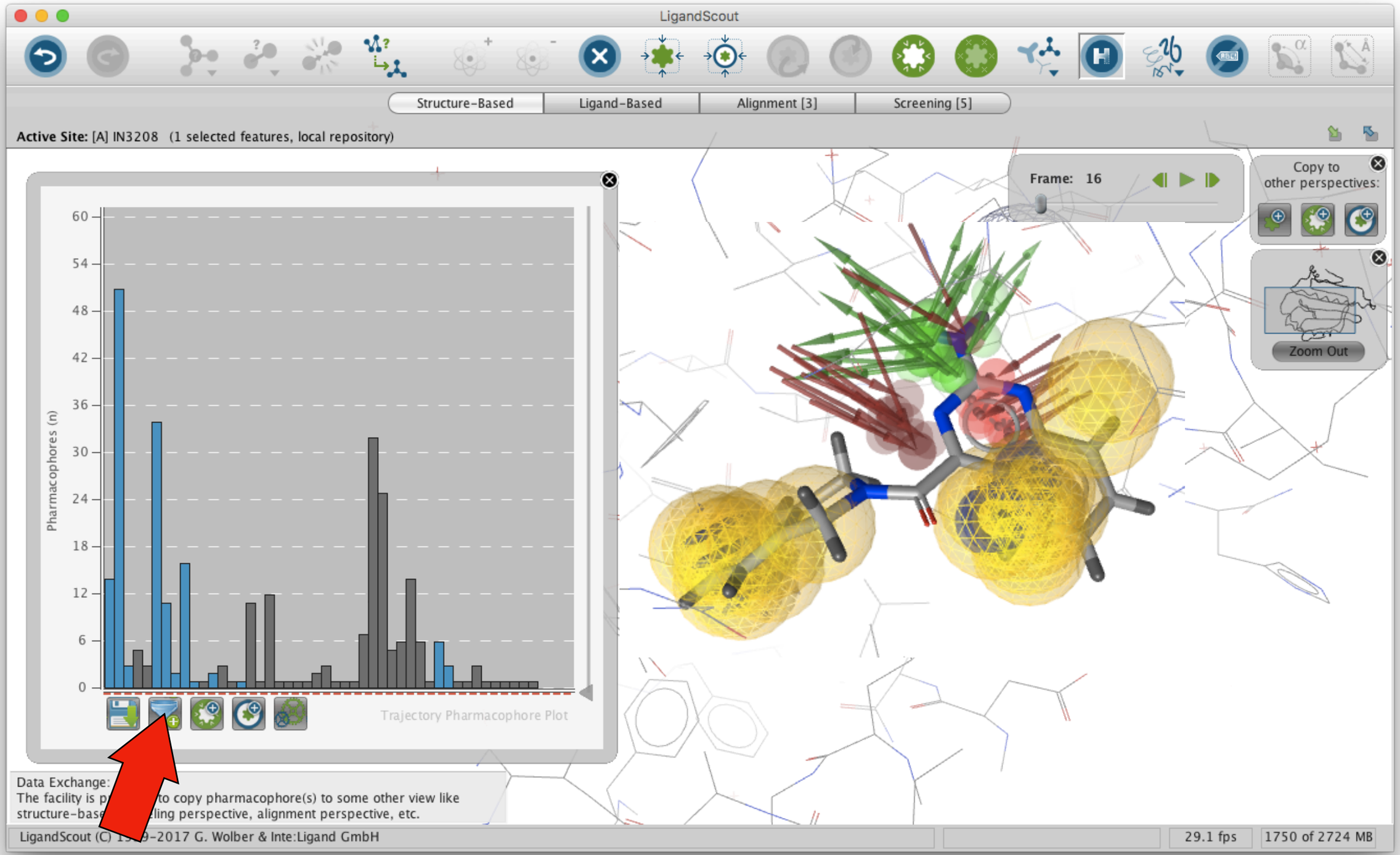

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Further Steps in the Procedure

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- Create for each frame a grid within the binding site
- Perform grid calculations
  - Buriedness and drugability threshold
  - Interaction probabilities for each grid point
- Align the grids
- Visualize and analyse
  - Look for emerging binding pockets
  - Hot spots for interactions
  - Water

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Visual Analysis

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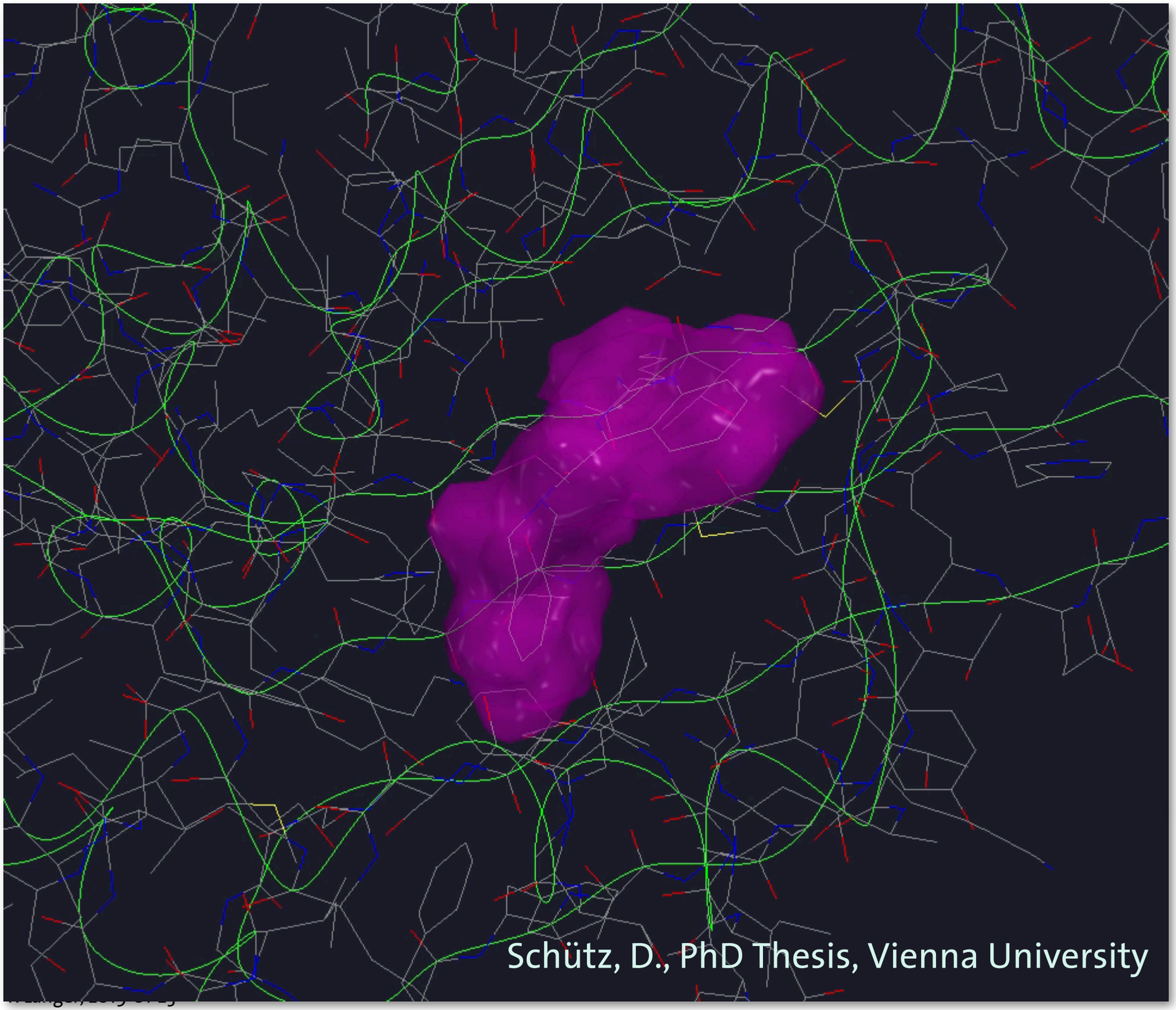

‘unhappy’ water molecules

‘happy’ water molecules

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Use in Lead Optimization

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- Easy understandable design guidance provided
- Focus on specific regions
  - e.g. replacing ‘unhappy’ water molecules with small hydrophobic substituent (“magic methyl positioning”)
- Pharmacophore hotspot feature frequency analysis
  - for prioritizing replacement/modifications of molecular substructures
  - providing interaction preference guidance
  - easily adaptable for automatization for de novo design

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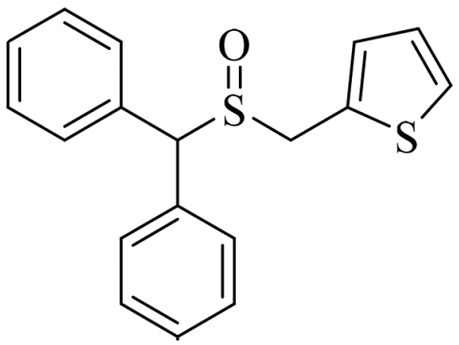
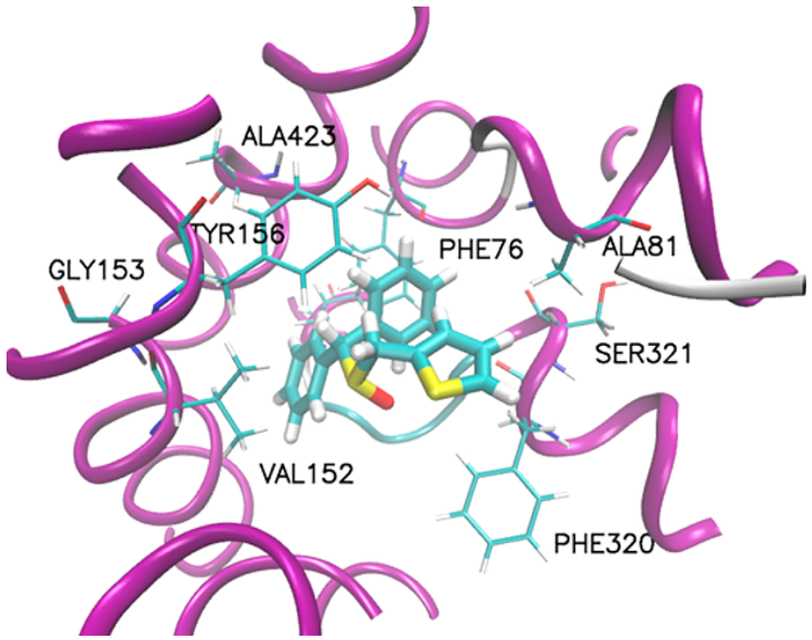
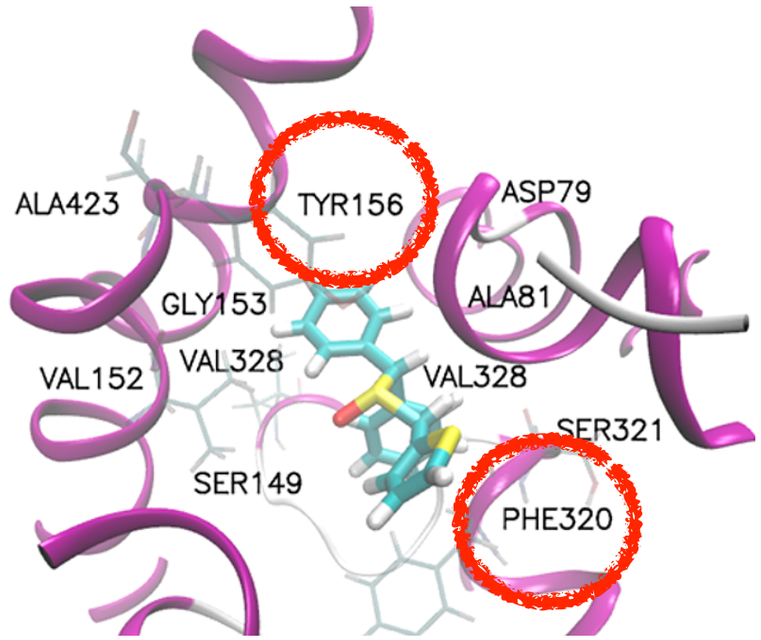
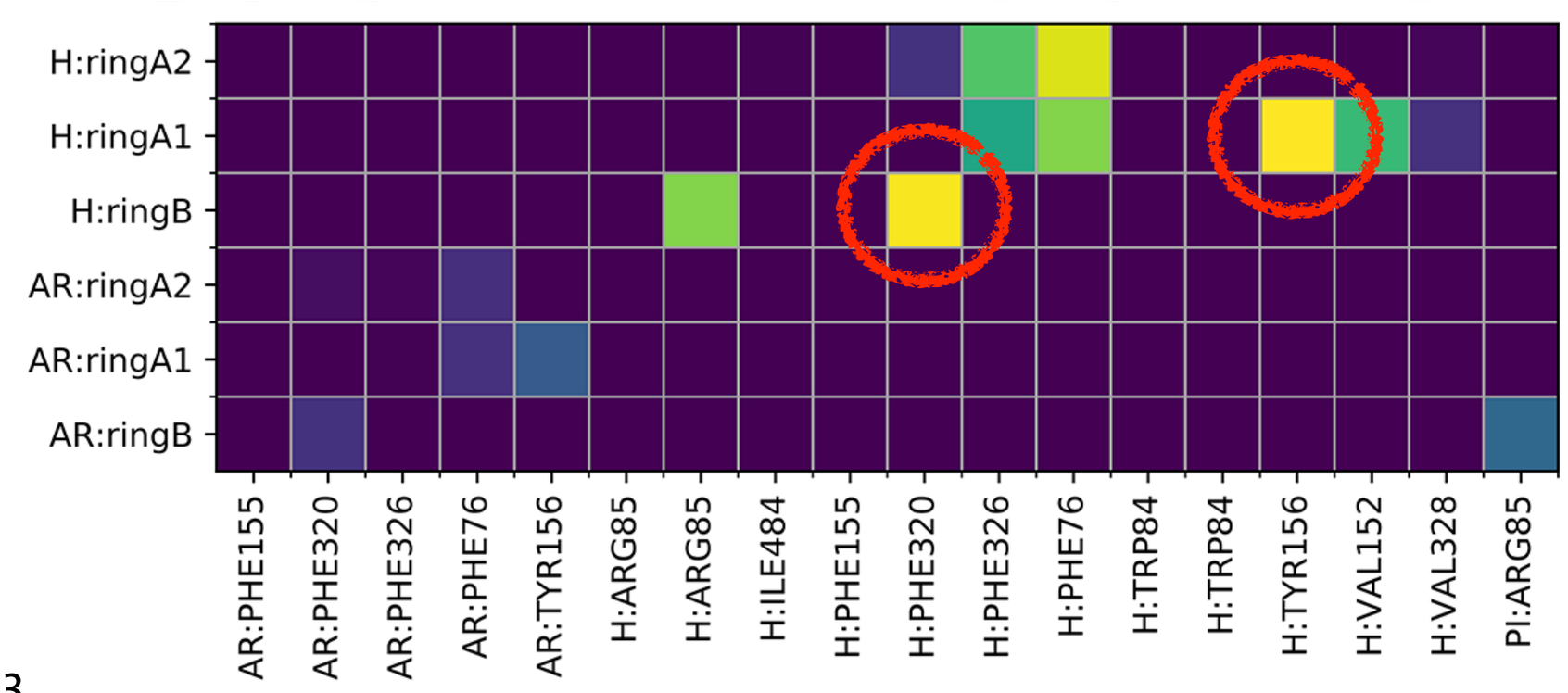
Example: Modafinil Analogs







Pharmacophore analysis of MD trajectory reveals predominant ligand-protein interactions



Kalaba, P. et al., 2017:
DOI 10.1021/acs.jmedchem.7b01313

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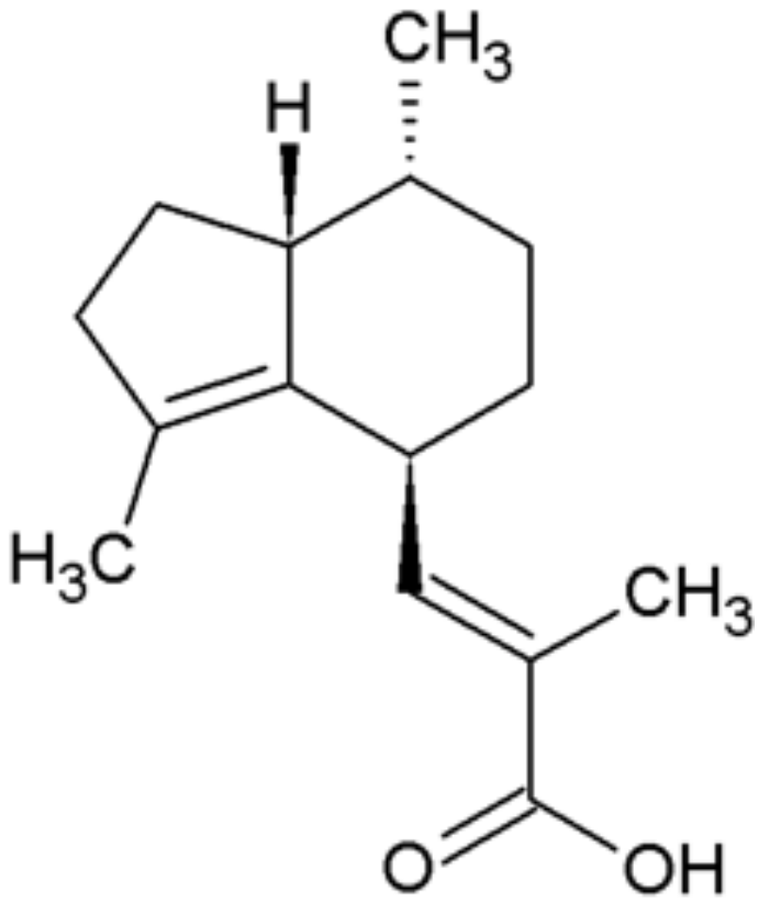
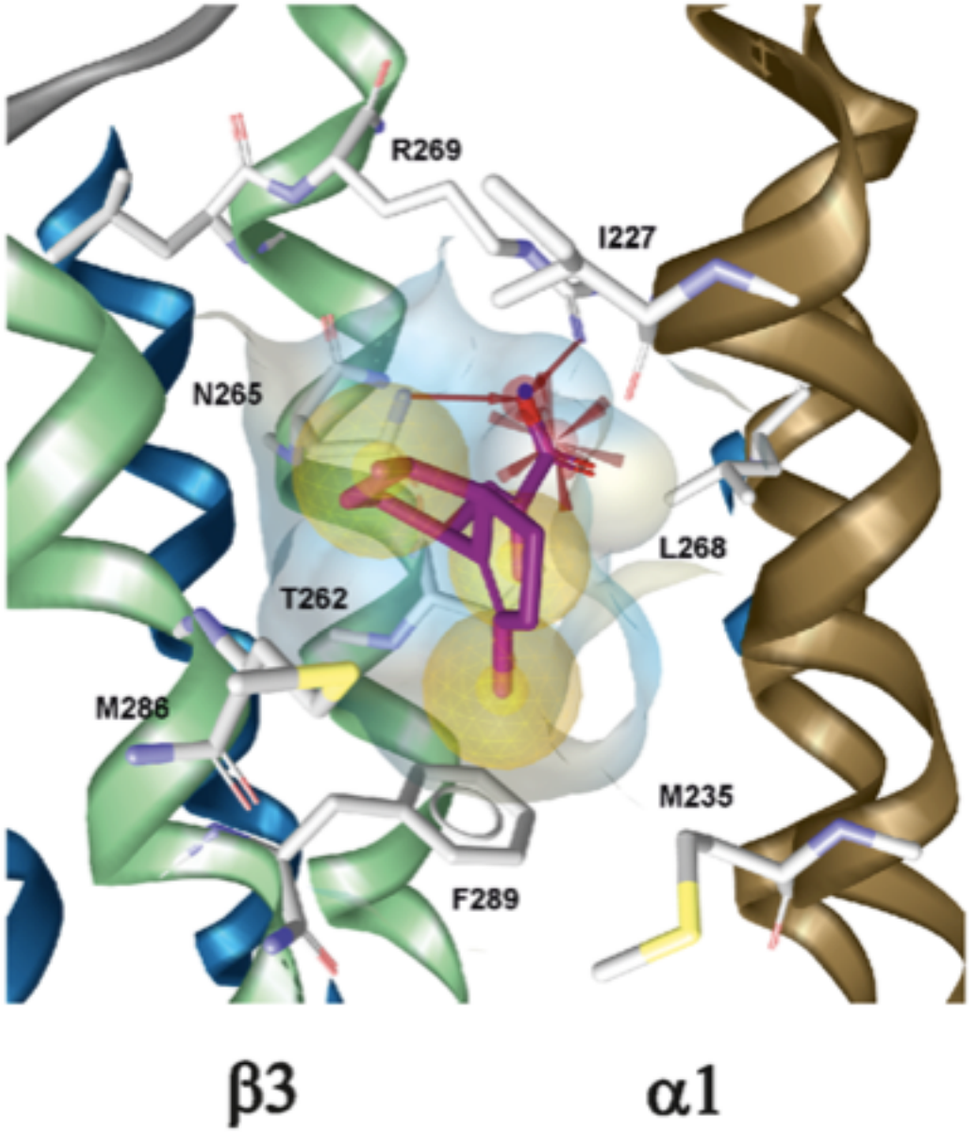
Example: Valerenic Acid Analogs

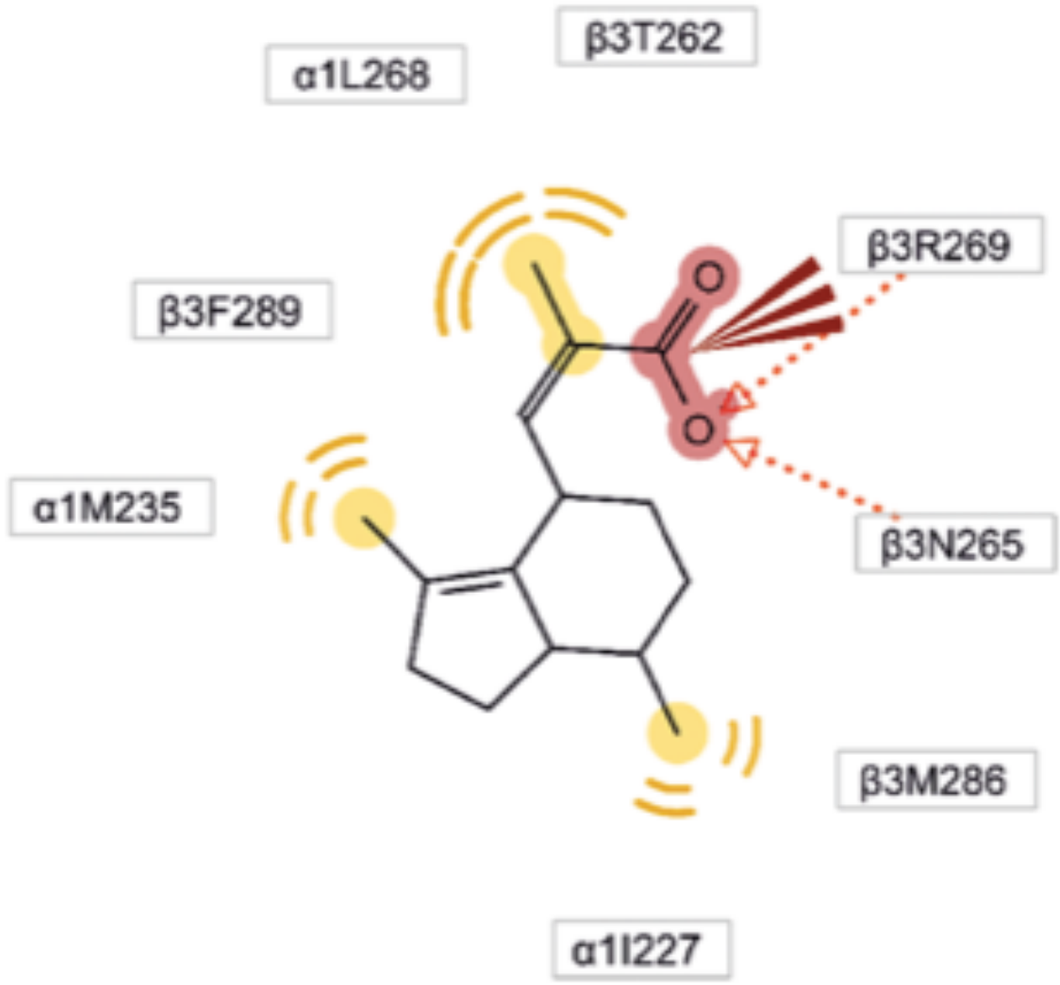
Designing ß$_{2/3}$ selective GABA$_A$ modulators, inspired by the natural product Valerenic Acid (VA)



- Identified in *Valeriana officinalis*
- GABA$_A$ receptor modulator
- ß$_{2/3}$-subunit selective
- anticonvulsant and anxiolytic
- hits also other interesting targets

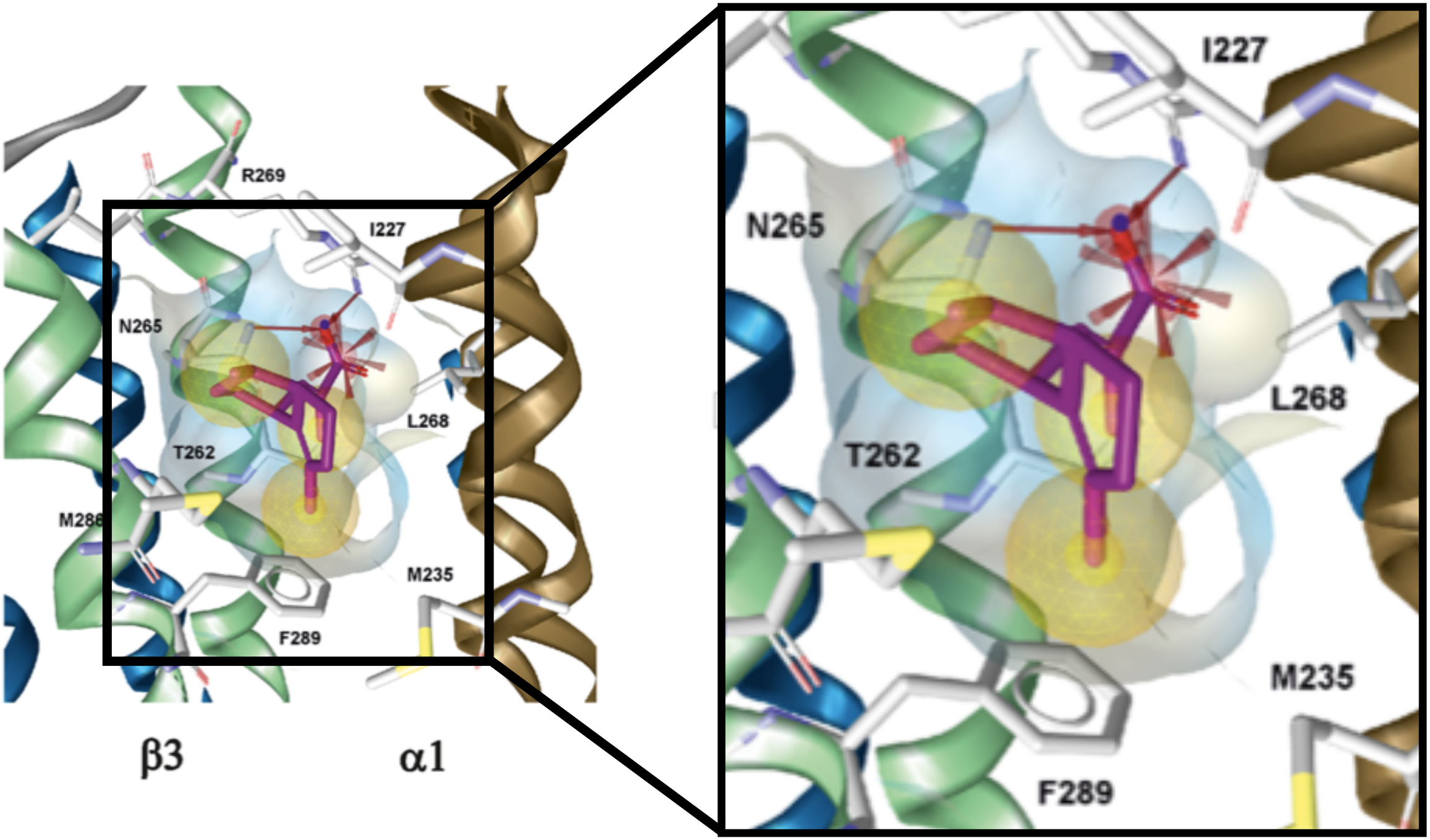
VA Putative Binding Mode





D. Luger et al., Brit. J. Pharmacol. (2015) 172 5403–5413

VA Putative Binding Mode



D. Luger et al., Brit. J. Pharmacol. (2015) 172 5403–5413

P4-based Scaffold Hopping

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- Total synthesis of VA by Ramhalter & Mulzer*:
  13 steps, overall yield 8%,
  starting from (R)-glycidol
- Optimized lead **VP-13**: 3 steps, overall yield > 80%**


The United States of America

The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this 5,860,492

United States Patent

Grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America for the term set forth below, subject to the payment of maintenance fees as provided by law.

If this application was filed prior to June 8, 1995, the term of this patent is the longer of seventeen years from the date of grant of this patent or twenty years from the earliest effective U.S. filing date of the application, subject to any statutory extension.

If this application was filed on or after June 8, 1995, the term of this patent is twenty years from the U.S. filing date, subject to any statutory extension. If the application contains a specific reference to an earlier filed application or applications under 35 U.S.C. 120, 121 or 365(c), the term of the patent is twenty years from the date on which the earliest application was filed, subject to any statutory extension.

Acting Commissioner of Patents and Trademarks

Attest

* J. Ramhalter, J. Mulzer, Org. Lett. (2009) 11, 1151 - 1153

** M. Stadler et al., J. Med. Chem. (2019) 62, 317-341

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Chloride Current Enhancement

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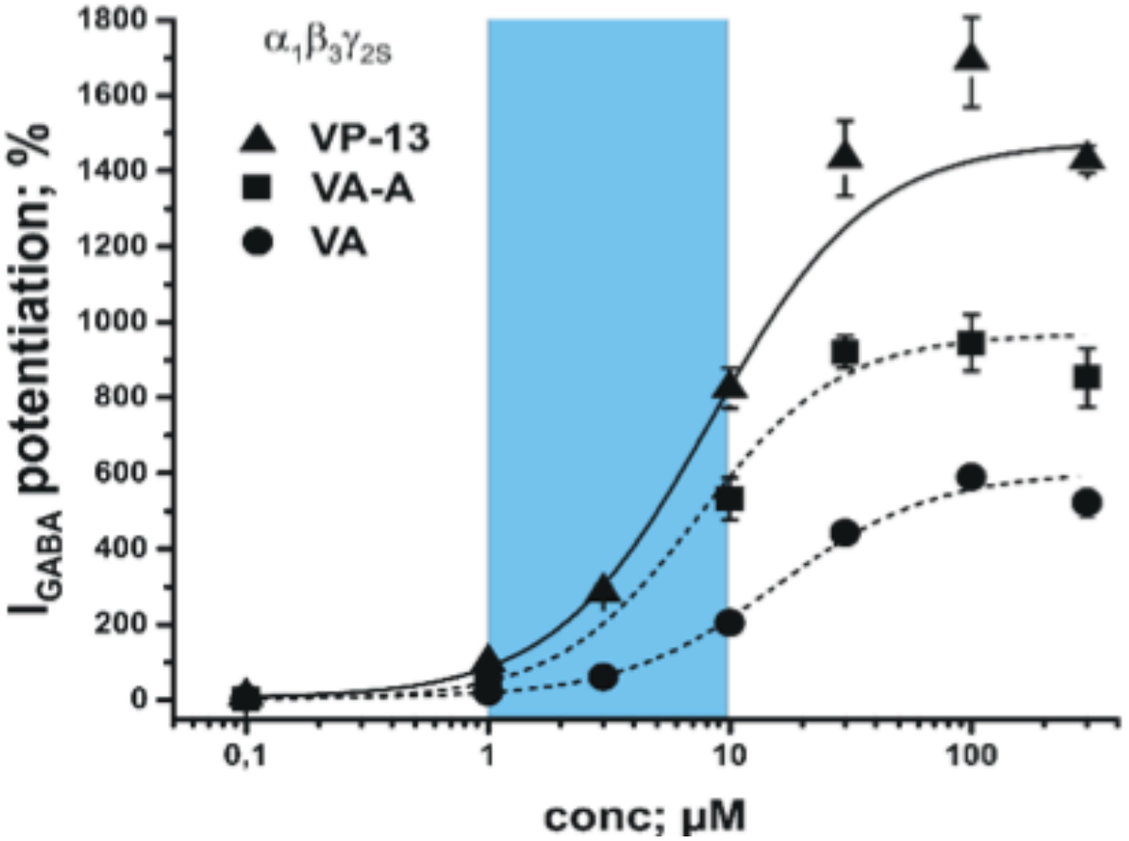
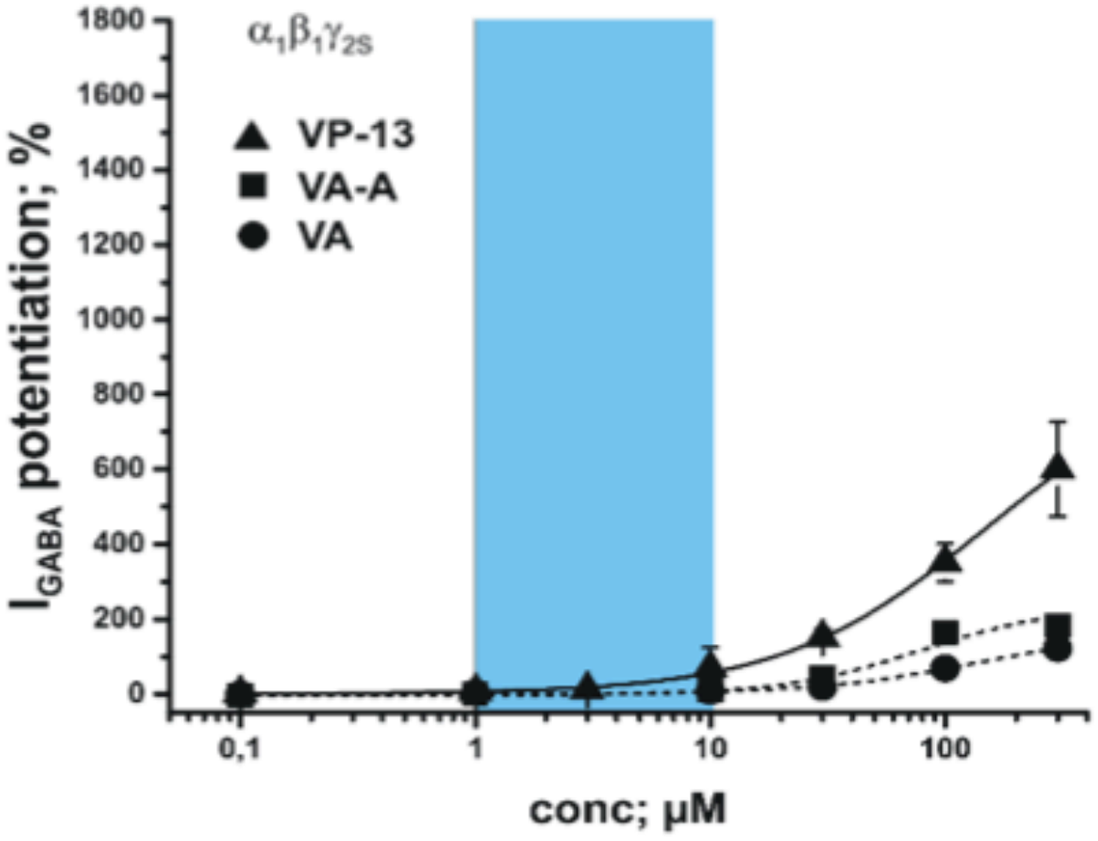
VP-13 is more efficient in modulating $\alpha_1\beta_3\gamma_2$ than VA and VA-A





VP-13: Emax 1477.7 ± 71.1 %; EC50: 8.4 ± 1.5 µM

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Anticonvulsant Activity

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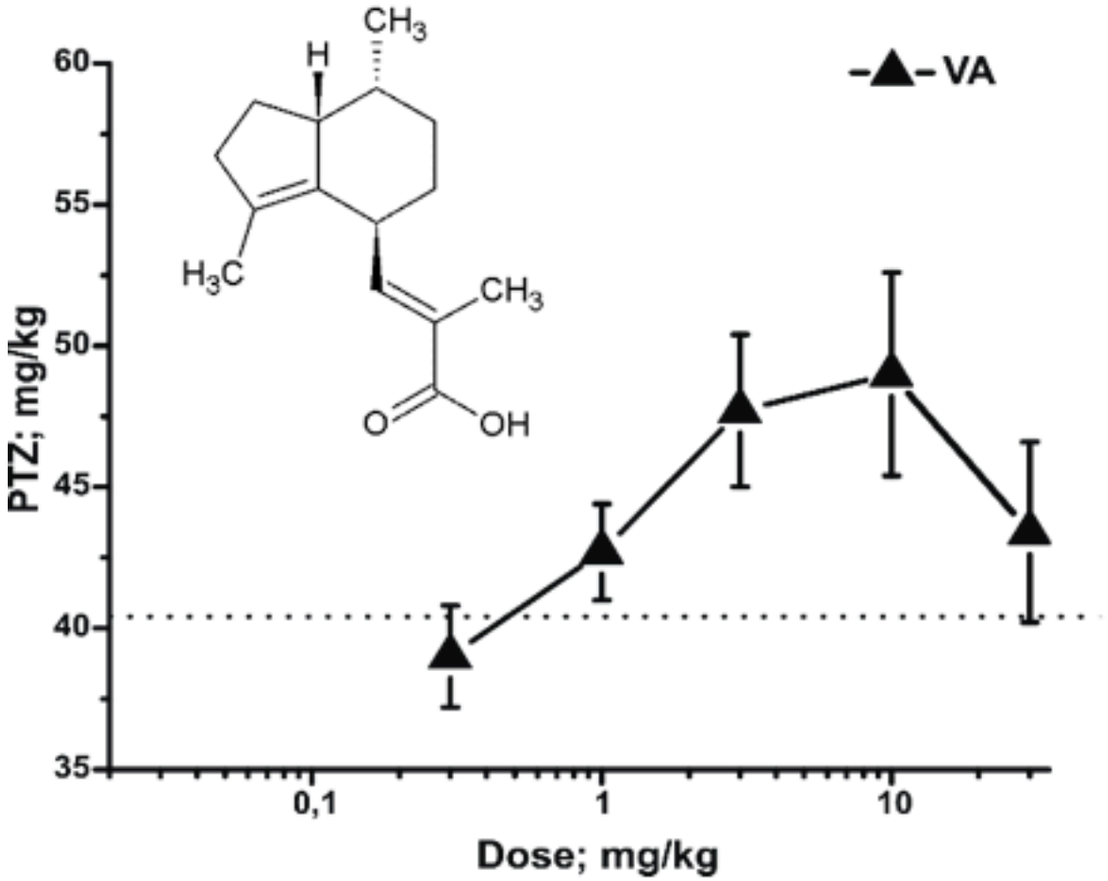
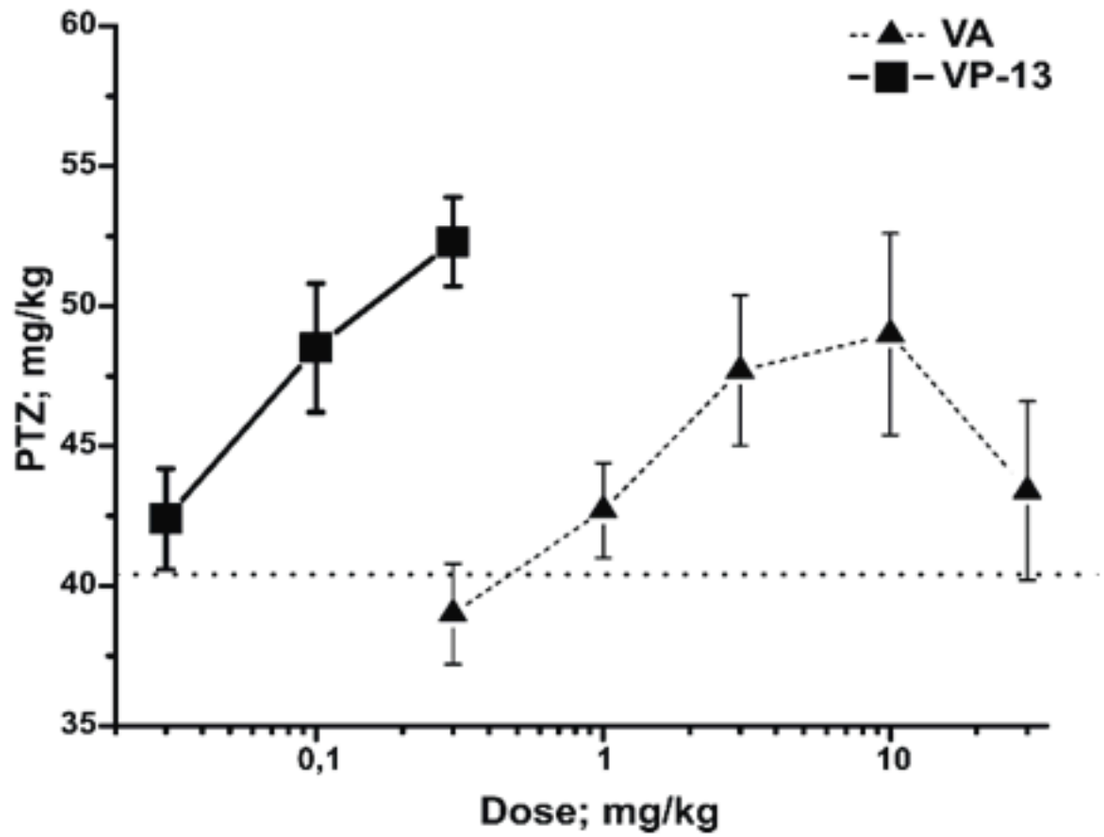
VP-13 is more potent in elevation of seizure threshold in male C57BL/6N mice induced by PTZ (tail vein infusion, same conditions) than VA





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Conclusions

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- Our pattern recognition-base pharmacophore technique is superior to all previous P4 methods with respect to speed and accuracy

➡ **Highly useful for hit identification**

- The pharmacophore interaction analysis concept is no more limited to static observation but is available in a convenient dynamic approach

➡ **Highly useful for lead structure optimization**

Conclusions (2)

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- On average, the CHA retrieved more structurally diverse actives than the PDB method
- The higher the number of considered molecules, the more diverse the retrieved actives
- Next steps: Comparison with pharmacophore fingerprint methods

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Thank you for your attention

LigandScout: Introduction

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- Fully integrated molecular design package
- High end GUI & command line tools
- Workflow integration into KNIME

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LigandScout: Unique Features

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Structure-based pharmacophore modeling

- Automated recognition of ligand-protein interactions
- User-friendly analysis of tautomers & side chain rotamers

Ligand-based pharmacophore modeling

- Pharmacophore-based ligand clustering
- Automated creation of exclusion volume for ligand-based pharmacophores
- Unlimited number of features per pharmacophore

Virtual screening

- Speed & accuracy increases with the number of features

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What's New in LigandScout 4.4 ?

- 2D Molecule editor for convenient structure editing
- Binding affinity prediction and atom contribution display
- Automated protein binding site alignment
- Radar plot for interactive graphics-based data analysis
- New features in scatter & parallel coordinate plots

  - colouring points, reversing axes, ready to use math functions ...

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What's New in LigandScout 4.3 ?

- Remote execution from the GUI:
  - iScreen on local HP clusters or on the Amazon Cloud*
  - idbgen on local HP clusters or on the Amazon Cloud*
- Halogen bond acceptor feature
- New fully searchable online help system

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Remote Execution from the GUI

LigandScout Remote: A New User-Friendly Interface for HPC and Cloud Resources

Thomas Kainrad,[*,†,‡] Sascha Hunold,[*,†] Thomas Seidel,[§] and Thierry Langer[§,‡]

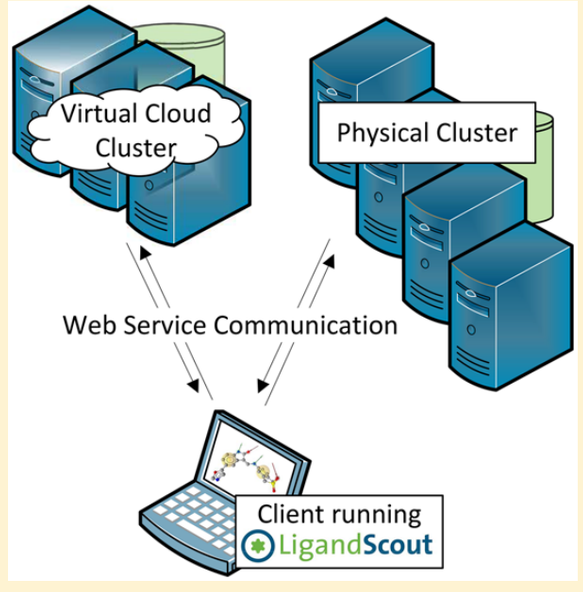
[†]Faculty of Informatics, TU Wien, A-1040 Vienna, Austria

[‡]Inte:Ligand Software Development and Consulting GmbH, A-1070 Vienna, Austria

[§]Department of Pharmaceutical Chemistry, University of Vienna, A-1090 Vienna, Austria

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

ABSTRACT: High-performance computing (HPC) clusters play a major role in scientific research. However, working with these clusters is often cumbersome, especially for researchers without a formal background in computer science. It requires preparation and transfer of the input data, manual gathering of results, and command-line expertise. Current approaches for improving accessibility to remote HPC clusters are focused on providing web-based graphical front-ends that allow jobs to be submitted to the distributed resource management system running on the cluster. This comes with significant usability benefits over command-line usage but does not circumvent the need for manual handling of the input and output files. With `LigandScout Remote`, we propose a different solution. Our software enables the seamless integration of HPC resources into the `LigandScout` desktop application that scientists use also in their day-to-day work. By handling necessary data conversion and network communication transparently to the user, this approach completely evades any HPC usability barriers. We show that the developed software combines the usability of local graphical desktop applications with the performance of HPC clusters.



https://doi.org/10.1021/acs.jcim.8b00716

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What's New in LigandScout 4.2 ?

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- User interactive charts for analyzing and filtering tables
- Fully editable tables, import & export from and to Excel
- Fully editable parameter sets for library filtering
- Find ligands present in the PDB database in any table
- Remodelled workflow for ligand-based pharmacophore generation
- Visualization of multiple superimposed binding sites
- MD trajectory import from AMBER & Gromacs, in addition to Charmm
- Automated creation of pharmacophores from MD trajectories
- Tools for analysis of pharmacophores derived from MD

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LigandScout Expert: KNIME Integration

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LigandScout functionality in KNIME workflows

- Molecular structure data input and output
- Data set manipulation
- Conformational analysis
- LigandScout 3D database generation
- Query builder for ChEMBL online databank
- Patent searching in SureChEMBL
- Virtual screening & Activity profiling
- MD trajectory analysis using pharmacophores
- Toxicity prediction

Deploy easy-to-use workflows to co-workers

Open for Innovation KNIME®

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The Inte:Ligand KNIME Extensions

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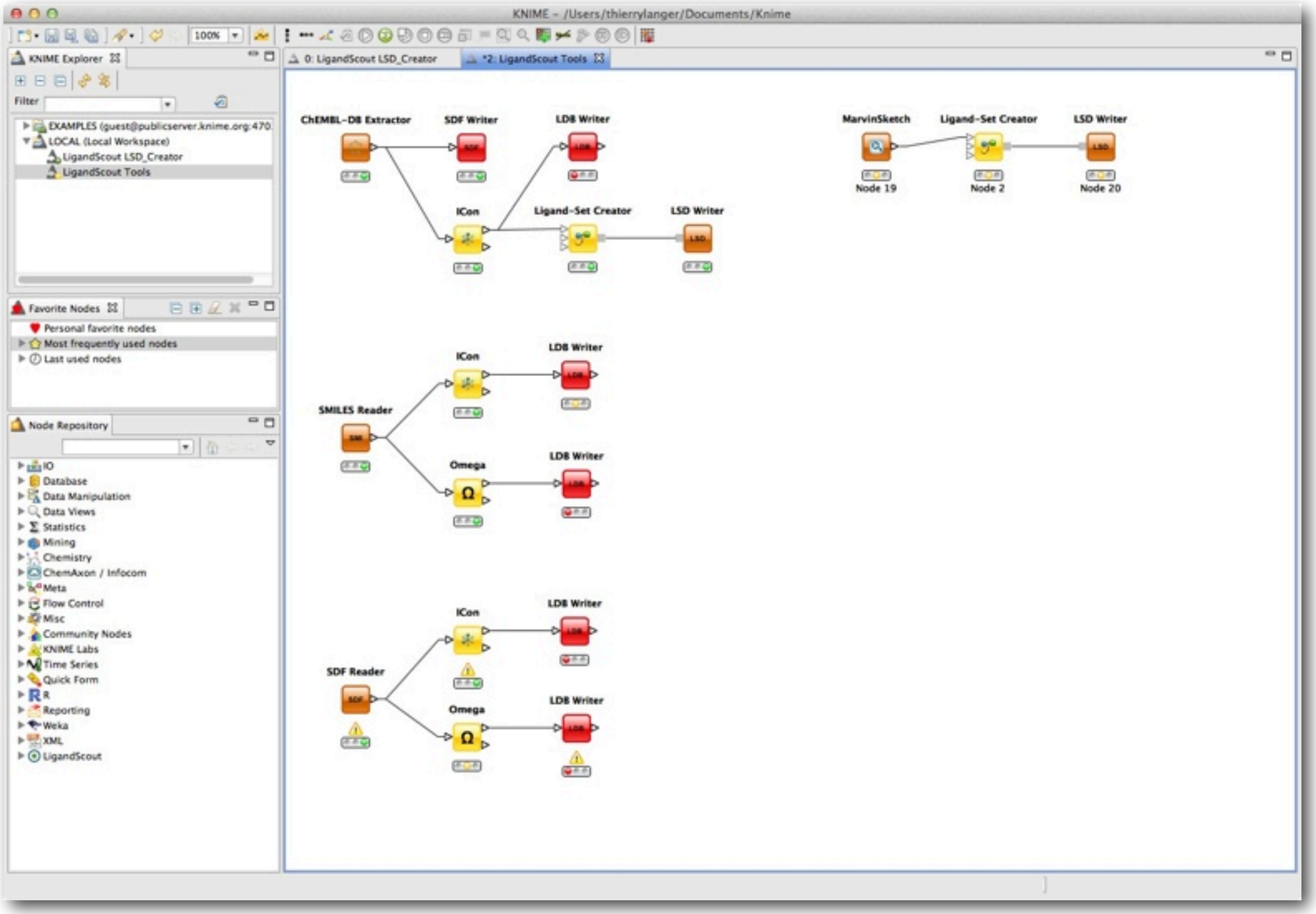

T. Langer, 2019-01-23

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The Inte:Ligand KNIME Extensions

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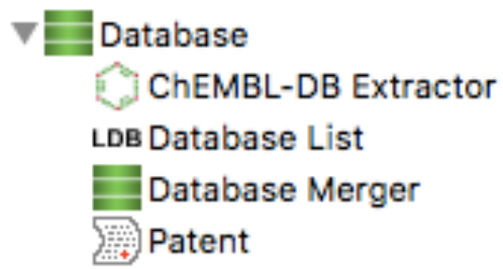
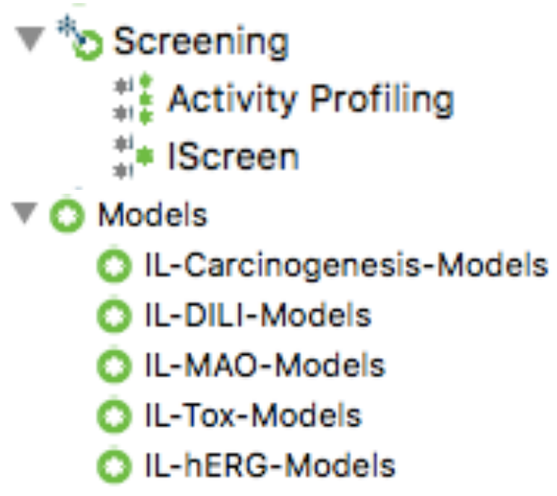
LigandScout functionality available in KNIME

- Batch data extraction from ChEMBL
- Conformational analysis & 3D database generation
- Batch mode for pharmacophore model building (LB & SB)
- Pharmacophore-based analysis of MD trajectories
- Virtual screening & activity profiling
- Validated toxicity models from eTox Consortium
- Patent searching using SureChEMBL





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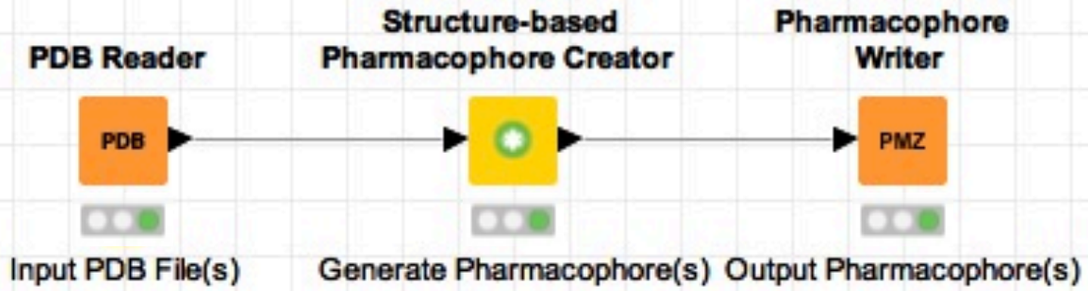
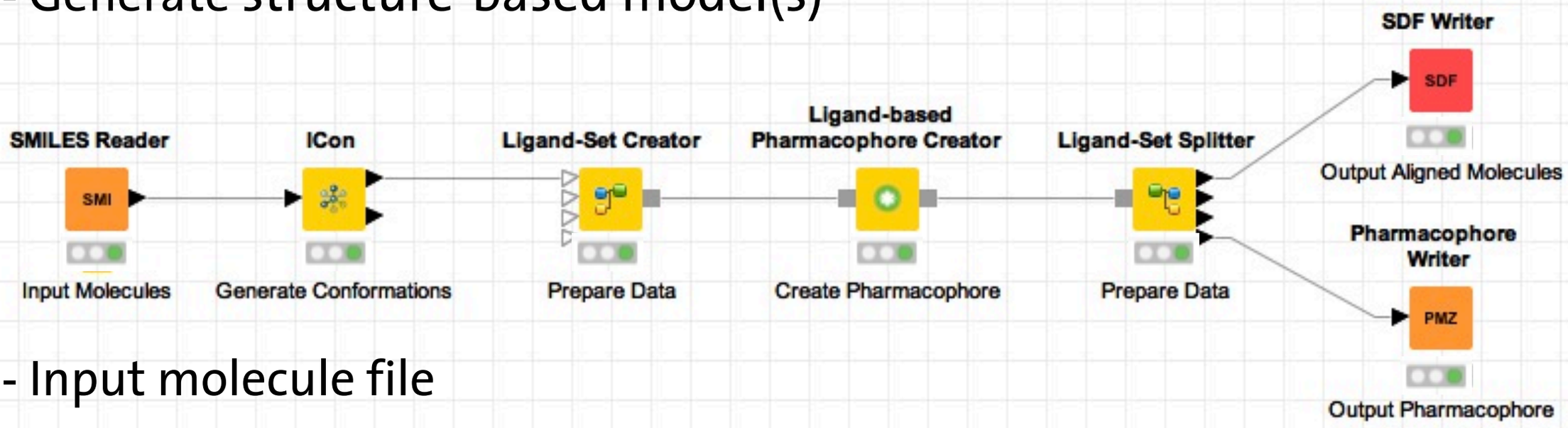
Batch Mode Pharmacophore Generation

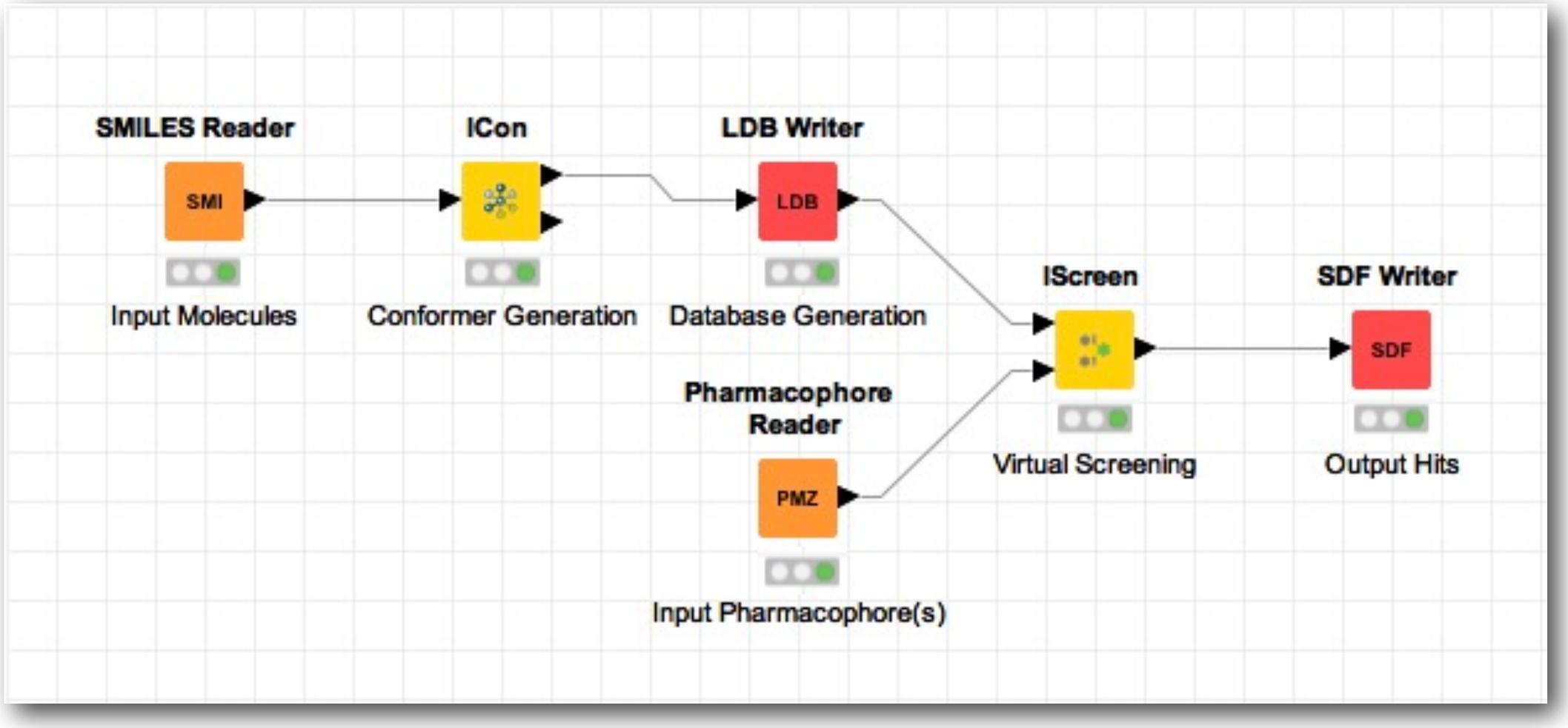


- Input pdb protein-ligand complex file(s)
- Generate structure-based model(s)



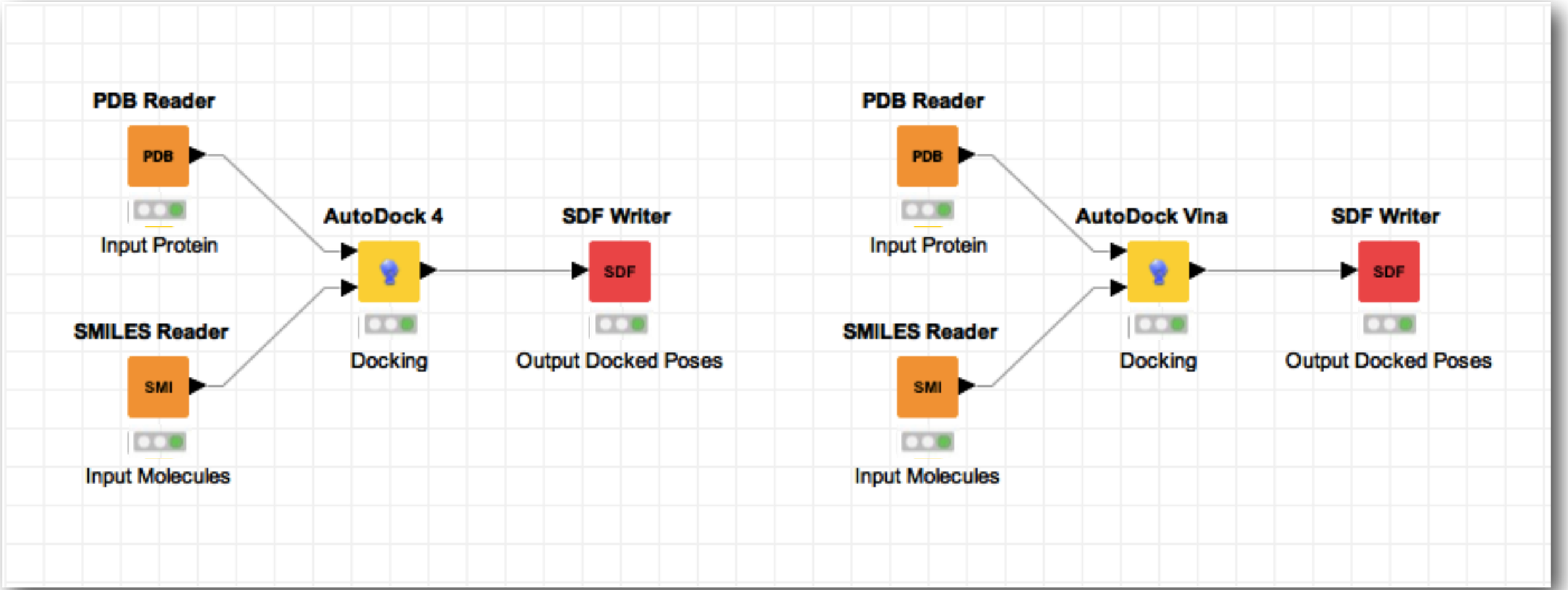
- Input molecule file
- Generate ligand-based model(s)

LigandScout VS in KNIME



- Input molecule files (smiles/sdf/mol2)
- Screen with your favourite pharmacophore model(s)
- Retrieve ranked hits

LigandScout Docking in KNIME



- Input PDB protein structure & list of molecules (smiles/sdf/mol2)
- Perform docking experiment
- Output sdf file of docked poses for further ranking

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Search for Patented Structures

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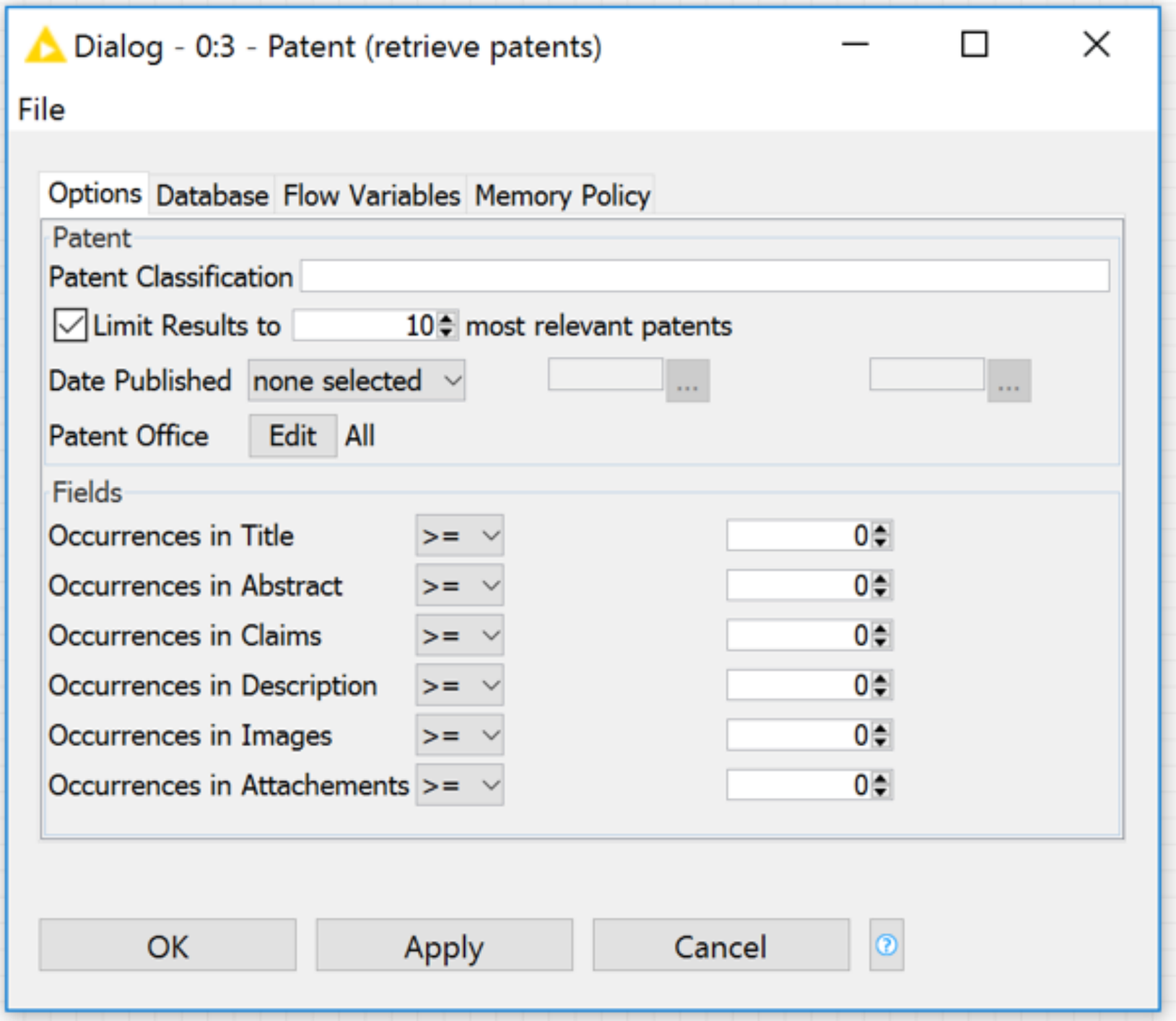

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3D Visualizer within Knime

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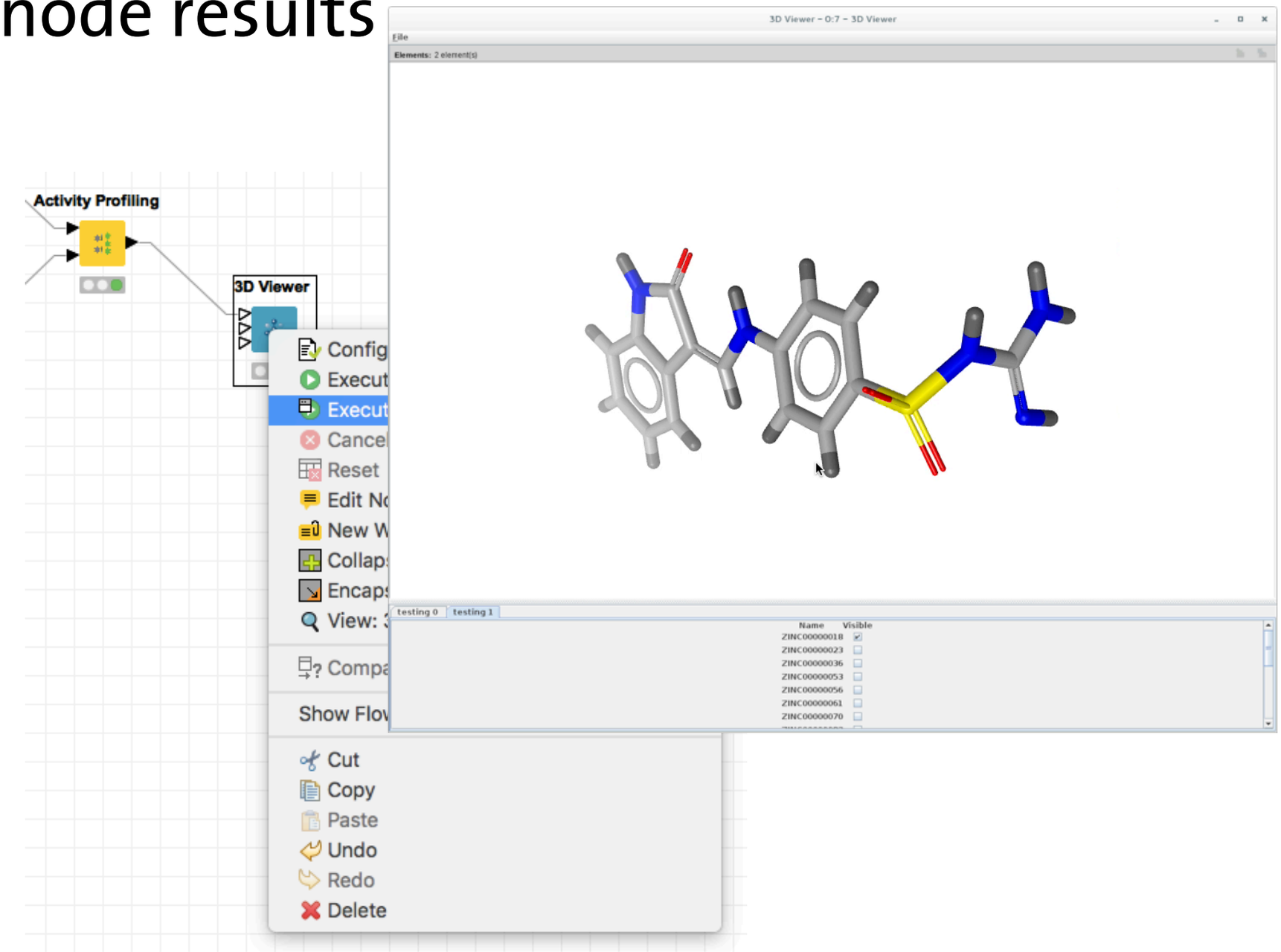
Visualization of node results

- Pharmacophores
- Ligands
- Macromolecules



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Activity Profiling

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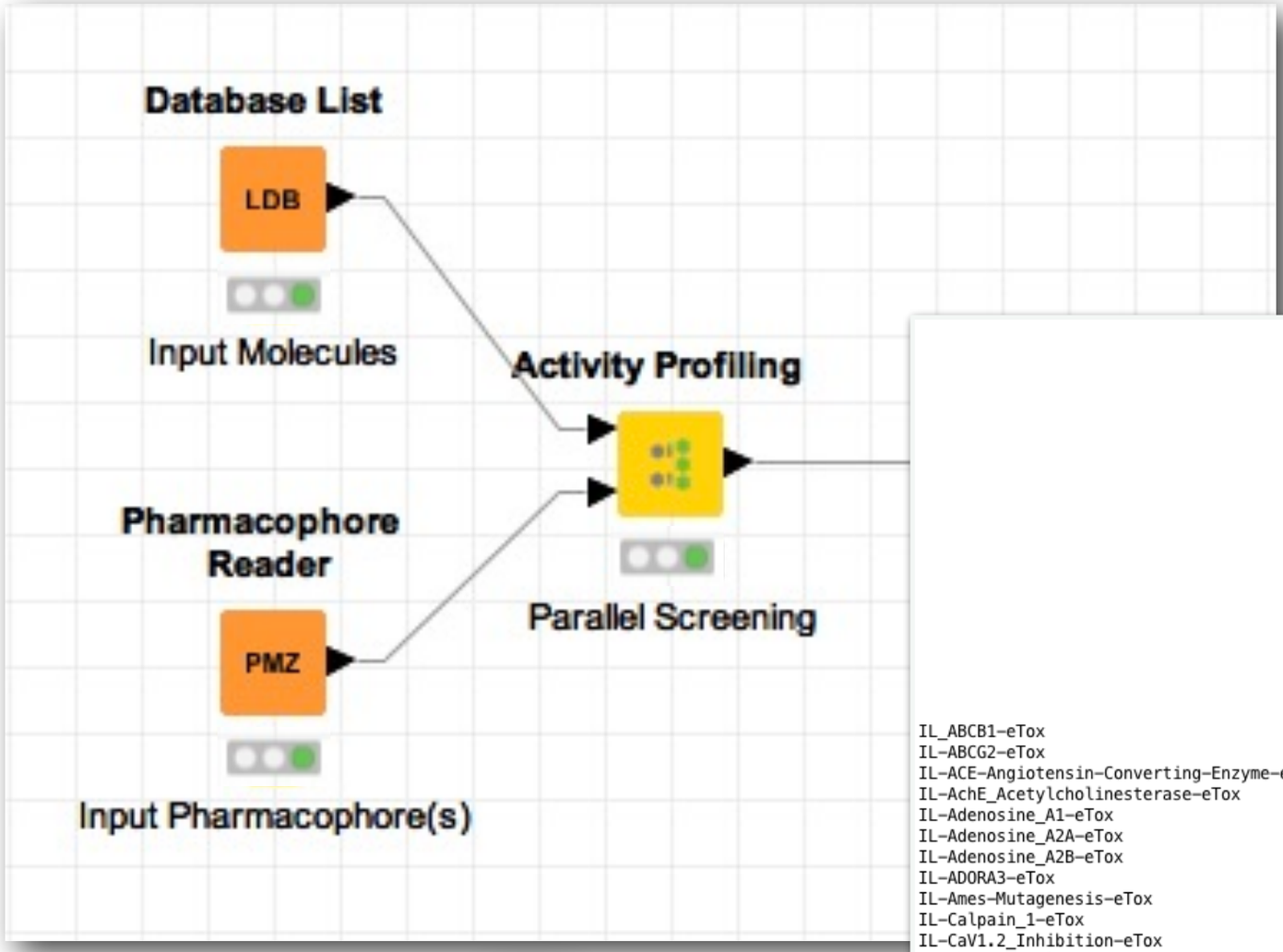

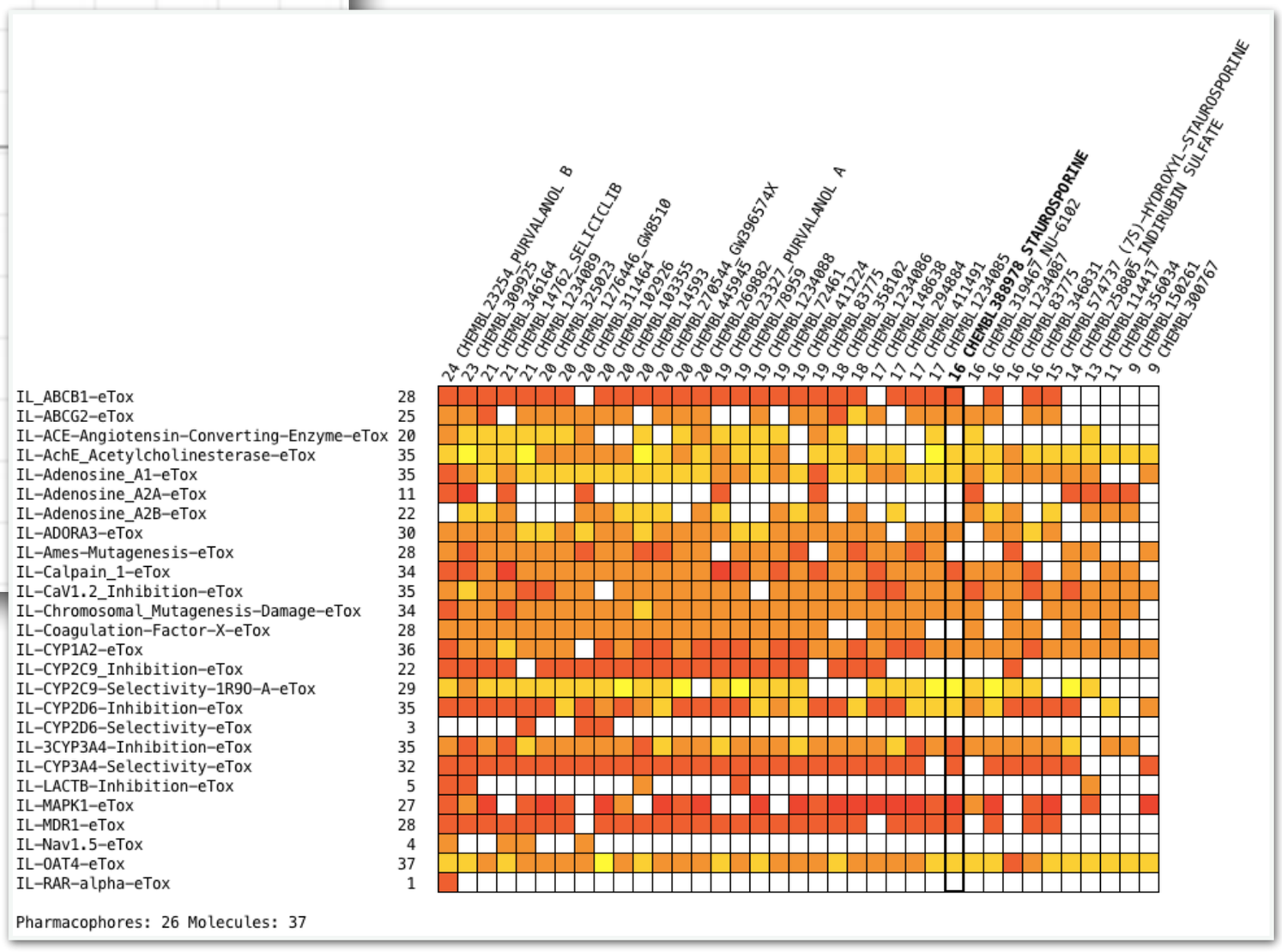

T. Langer, 2019-01-23

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Toxicity Assessment Models

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7 year collaborative EC Project on Toxicity Prediction

Executive Committee

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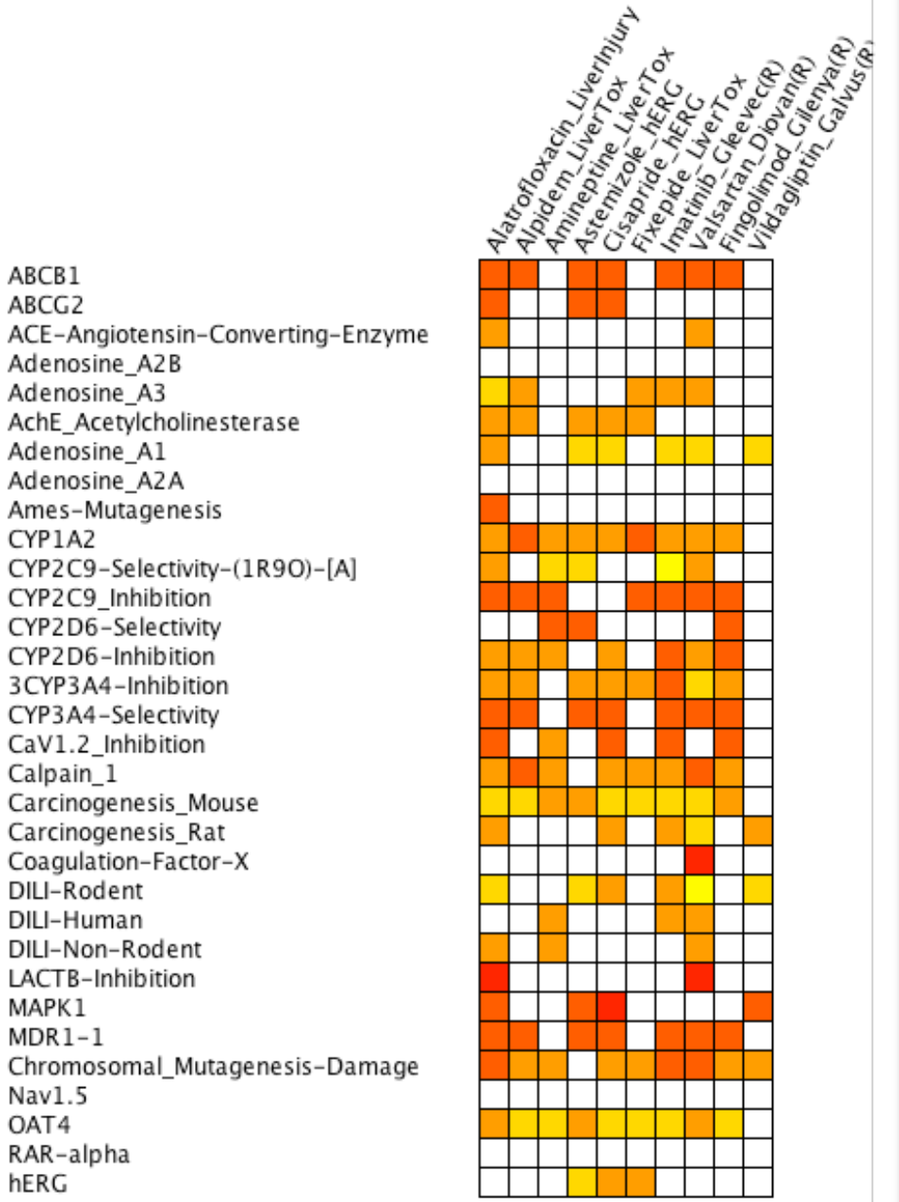
Chemotargets · inte:ligand · LMD Lead Molecular Design s.l. · Lhasa Limited · Molecular Networks Inspiring Chemical Discovery



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KNIME Nodes Available for ...

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- LigandScout
  - Alignment
    - Pharmacophore/Molecule Alignment
  - Clustering
    - Diversity Picker
    - Fingerprint Clustering
    - Pharmacophore/Molecule Clustering
  - Conformer Generation
    - ICon
  - Data Manipulation
    - Ligand-Set Creator
    - Ligand-Set Splitter
  - Database
    - ChEMBL-DB Extractor
    - Database List
    - Database Merger
    - Patent
  - Docking
    - AutoDock 4
    - AutoDock Vina
  - Filtering
    - Duplicate Remover
    - Library Filter

- I/O
  - Database List
  - GRO Reader
  - LDB Reader
  - LDB Writer
  - LSD Reader
  - LSD Writer
  - Mol Reader
  - Mol Writer
  - Mol2 Reader
  - Mol2 Writer
  - PDB Reader
  - PDB Writer
  - Pharmacophore Reader
  - Pharmacophore Writer
  - SDF Reader
  - SDF Writer
  - SMILES Reader
  - SMILES Writer

- Minimization
  - MMFF94 Library Minimizer
  - MMFF94 Minimizer
- Models
  - IL-Carcinogenesis-Models
  - IL-DILI-Models
  - IL-MAO-Models
  - IL-Tox-Models
  - IL-hERG-Models
- Molecular dynamics
  - AMBER Trajectory Reader
  - CHA Filter
  - CHA Re-Score
  - DCD Trajectory Reader
  - MD Pharmacophore Creato
  - TRR Trajectory Reader
  - XTC Trajectory Reader

- Molecule Property
  - Chiralator
  - Fingerprint Calculator
  - Fingerprint Similarity Calculator
  - InChI Generator
  - Property Appender
  - Standard Properties
- Pharmacophore
  - Ligand-based Pharmacophore Creator
  - Merged Pharmacophore Creator
  - Shared Pharmacophore Creator
  - Structure-based Pharmacophore Creator
- Screening
  - Activity Profiling
  - IScreen
- Tautomerization
  - Tautomer Generation
- Tools
  - 3D Viewer
  - ChartView
  - Table Merger

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KNIME Tutorial Workflows

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Inte:Ligand KNIME EXTENSION TUTORIAL CARD 2

Create Ligand Based Pharmacophore Models

Experience level: intermediate

Time needed: 15 minutes

Node Repository	Sequence
○ I/O - PDB Reader ○ Pharmacophore - Ligand-based Pharmacophore Creator	○ Read a SMILES file by using "SM ○ Connect the output of "SMILES Conformer Generator" node ○ Configure "Icon Conformer Gen ○ Connect the first port of "Icon C with the second input port of " Clustering" node and execute it ○ Connect the second output po "Pharmacophore/Molecule Clus port of "Ligand-based Pharmac ○ Configure "Ligand-based Pharm selecting the "Treat cluster ind ○ Connect "Ligand-based Pharma "Pharmacophore Writer" node "Export all pharmacophores t ○ Choose the folder in which sa execute the node

Description

In the Node Repository panel, open the "I/O" drop do the "SMILES Reader"[1] node and drag and drop it into F6.[2] A pop-up window for configuration will appear the traffic light underneath the node, which was red right click on it and press "Execute" from the pop-up visit the Node Repository panel again and open the " Look for the "Icon Conformer Generator" node and dr node (black triangle) with the input port of the "Icon node and configure it. In the pop-up window, click o (F7). In the "Clustering" drop down menu select the ' connect the first output of the "Icon Conformer Gene "Pharmacophore" drop down menu, drag and drop ' second output port of "Pharmacophore/Molecule Clu configure it selecting the "Treat cluster individually" the first output port of the "Ligand-based Pharmacop pharmacophores to a single file" and choose a nam Press OK and execute the node (F7). [4] The program the pharmacophore model(s) you have generated.

Where to go from here:

- Screening database(s) against pharmacophore
- Use generated pharmacophores for Activity Pr

Inte:Ligand KNIME EXTENSION TUTORIAL CARD 1

Create Structure Based Pharmacophore Models

Experience level: basic

Time needed: 10 minutes

Node Repository	Sequence	Advanced controls (opt.)
○ I/O - PDB Reader - Pharmacophore Writer ○ Pharmacophore - Structure-based Pharmacophore Creator	○ Read a PDB file by using "PDB Reader" node ○ Connect the output of "PDB Reader" node with "Structure-based Pharmacophore Creator" node ○ Configure "Structure-based Pharmacophore Creator" node and execute it ○ Connect "Structure-based Pharmacophore Creator" node with "Pharmacophore Writer" node ○ Configure "Pharmacophore Writer" node selecting "Export all pharmacophores to a single file" ○ Choose the folder in which save my_model.pmz, then execute the node	○ Prepare batch mode processing: - Configure "PDB Reader" node to read multiple PDB files at the same time ○ Modify pharmacophore creation parameters - Configure "Structure-based Pharmacophore Creator" node to add the exclusion volume coat to the model ○ Explore the options of the "Pharmacophore Writer" node (e.g. pharmacophore models saved as separate files)

Description

In the Node Repository panel, open the "I/O" drop down menu in the LigandScout section to see all the Input/Output nodes. Look for the "PDB Reader" [1] node and drag and drop it into the workspace. Configure the "PDB Reader" node by using a left double click or by pressing F6. [2] A pop-up window for configuration will appear and you enter the path to the PDB file you want to load. Press the "Add" button. You can add multiple PDB files. After pressing OK, the traffic light underneath the node, which was red before, will turn to yellow. Press F7 to execute the node (alternatively, you can right click on it and press "Execute" from the pop-up menu). The traffic light will turn green once the node has finished the task. Now, visit the Node Repository panel again and open the "Pharmacophore" drop down menu in the LigandScout drop down menu. Look for the "Structure-based Pharmacophore Creator" node and drag and drop it into the workspace. Connect the output port of the "PDB Reader" node (black triangle) with the input port of the "Structure-based Pharmacophore Creator" node (black triangle) [3]. Select the "Structure-based Pharmacophore Creator" node and configure it. In the pop-up window, select the minimum number of features necessary or creating the model (3) and the set the flag for adding an exclusion volume coat. After pressing OK, execute the node as before (F7). Once the task is finished the traffic light underneath the "Structure-based Pharmacophore Creator" node will turn green. In the "I/O" drop down menu select the "Pharmacophore Writer" node and drag and drop it in the workspace, connect the output of the "Structure-based Pharmacophore Creator" node with it and start the configuration as before. In the pop-up windows select "Export all pharmacophores to a single file" and choose a name for the output (you can also browse for the folder). [4] Press OK and execute the node (F7). The program will save a file in the specified directory containing the pharmacophore model(s) you have generated.

Where to go from here:

- Screening database(s) against pharmacophore model(s)
- Cluster pharmacophores
- Use generated pharmacophores for Activity profiling

Inte:Ligand KNIME EXTENSION TUTORIAL CARD 3

Calculate Physicochemical Properties and Filter a Database

e level: basic

ed: 5 minutes

	Advanced controls (opt.)
by using "SDF Reader" node tput of "SDF Reader" node with "Standard dard Properties" node and execute it d Properties" node with "Library Filter" node y Filter" node and execute it output port of "Library Filter" node with d output port of "Library Filter" node with	○ Calculate physicochemical properties: - Configure "Standard Properties" node to compute different sets of properties ○ Modify filtering parameters: - Add other text and/or numeric filters in "Library Filter" node - Configure the "Library Filter" node adding multiple properties to your filter - Explore all the filtering operators (equal, different, smaller than, greater than)

grop down menu in the LigandScout section to see all the Input/Output nodes. Look for
nto the workspace. Configure the node as showed in previous tutorial cards (by pressing
e Repository panel again and open the "Molecule properties" drop down menu in the
tandard Properties" node and drag and drop it into the workspace. Connect the output
ort of the "Standard Properties" node. Select the "Standard Properties" node and configure
chemical properties you want to compute (these properties will be used in the next
ll at once by pressing the corresponding "Select all" button. After pressing OK, execute
u select the "Library Filter" node and drag and drop it in the workspace, connect the
and continue with its configuration. In the pop-up windows, the "Library Filter" node
s by string (pressing the "+abc" button)[1 red circle] or numeric property (pressing the
utton[2] until "<" symbol appears. Configure the row by choosing "MolWt" in the
, the node will filter out molecules with molecular weight smaller than 400. Explore
Writer" node and drag and drop two of them in the workspace. Connect them with
respectively. The "SDF Writer" node connected to the first output port of the
lecular weight smaller than 400, while the one connected to the second output
greater than 400. Configure the "SDF Writer" nodes choosing the name for the
failed_molecules.sdf for the second). Execute them with F7.[4]

Inte:Ligand KNIME EXTENSION TUTORIAL CARD 4

Perform Vi

ced controls (opt.)

e Ligand parameters:
Figure "SDF Reader" node to extract name
a different column
ge "Icon Conformer Generator" settings (e.g.
BEST settings)
parameters for "iScreen" node:
ge the scoring function
o fragment screening mode
different retrieval modes
ure the node in order to not check the
on volumes
tch mode processing:
e "Pharmacophore Reader" node to read
files at the same time
oolean expression with "iScreen" node
d 2) not 3. Numbers are referred to the
phores ranking in the "Pharmacophore
ode]

tion into the workspace. Configure the
drop the "Icon Conformer Generator"
put port of the "SDF Reader" node
tor" node. In the pop-up window,
e "I/O" drop down menu ,select the
s "Icon Conformer Generator" node
he LDB file.[3] Execute and then
g" drop down menu. Add the
pharmacophore model you want to
the second input port of the
g the name for the output file.
molecules as a sdf file.

T. Langer, 2019-01-23

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