Pharmacophore Modeling:
Approaches for Advanced Molecular Design and Profiling of Compounds

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Thierry Langer

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Perspectives in Drug Discovery and Design, **9/10/11:** 225–252, 1998.
KLUWER/ESCOM

Similarity and Dissimilarity: A Medicinal Chemist's View

Hugo Kubinyi
Drug Design, BASF AG, D-67056 Ludwigshafen, Germany

Several 3D approaches discussed in this volume describe methods for the analysis and quantitative description of chemical similarity. The underlying concept is that chemical similarity is reflected by similar biological activities — i.e. chemically closely related analogs should be related in their mode of action, as well as in their relative potencies. This fundamental assumption has, indeed, been used in medicinal chemistry research, and has led to many valuable drugs.

However, chemical similarity may have different facets if a computer chemist or a medicinal chemist look at the compounds. There is no argument that for maximal affinity a ligand of a biological macromolecule has to fit the binding pocket geometrically and that hydrophobic surfaces of the ligand and the binding site have to be com-

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https://www.kubinyi.de/dd-06.pdf

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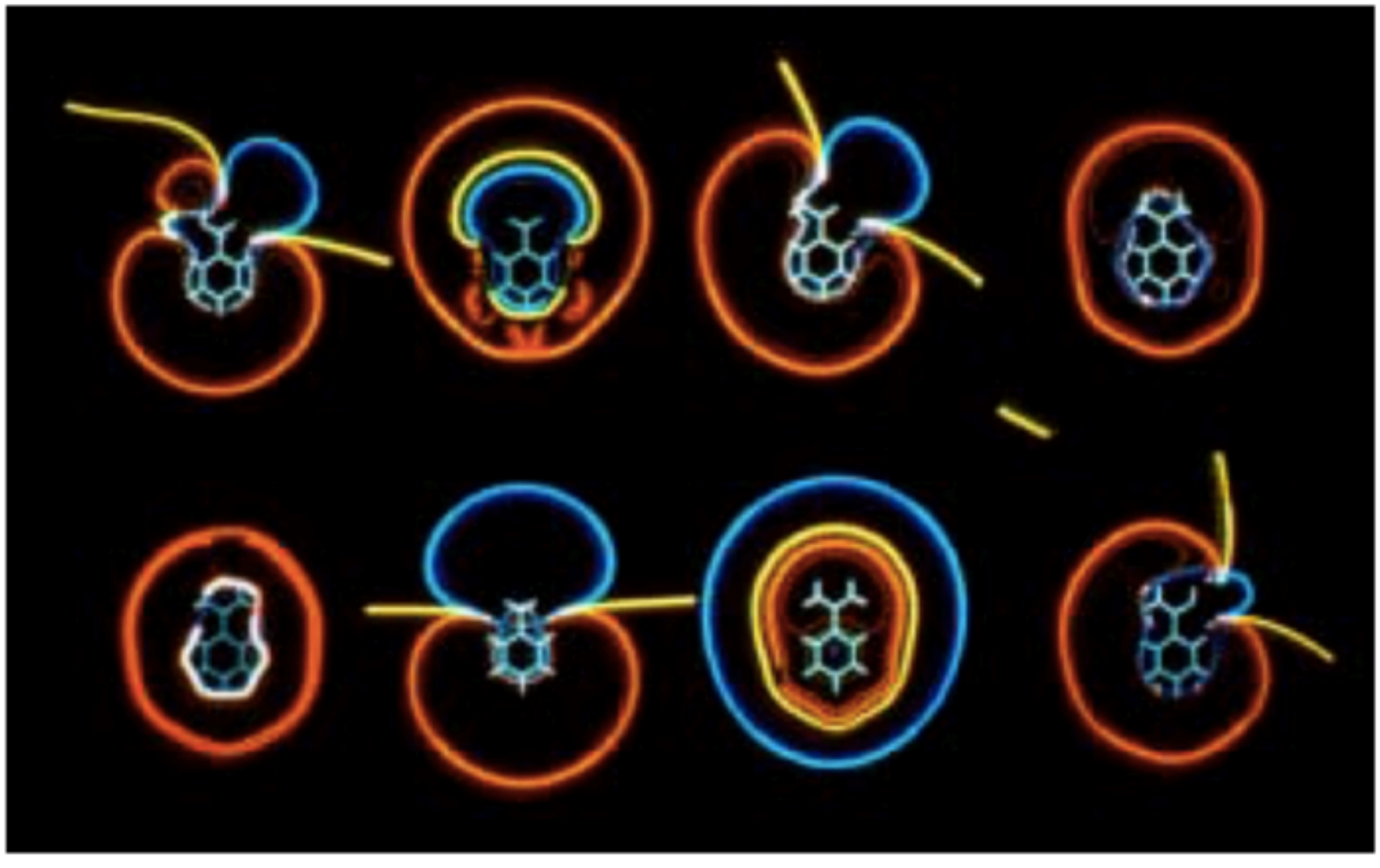
Hugo Kubinyi, www.kubinyi.de

Molecular Electrostatic Potentials (MEP)



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A Possible Solution

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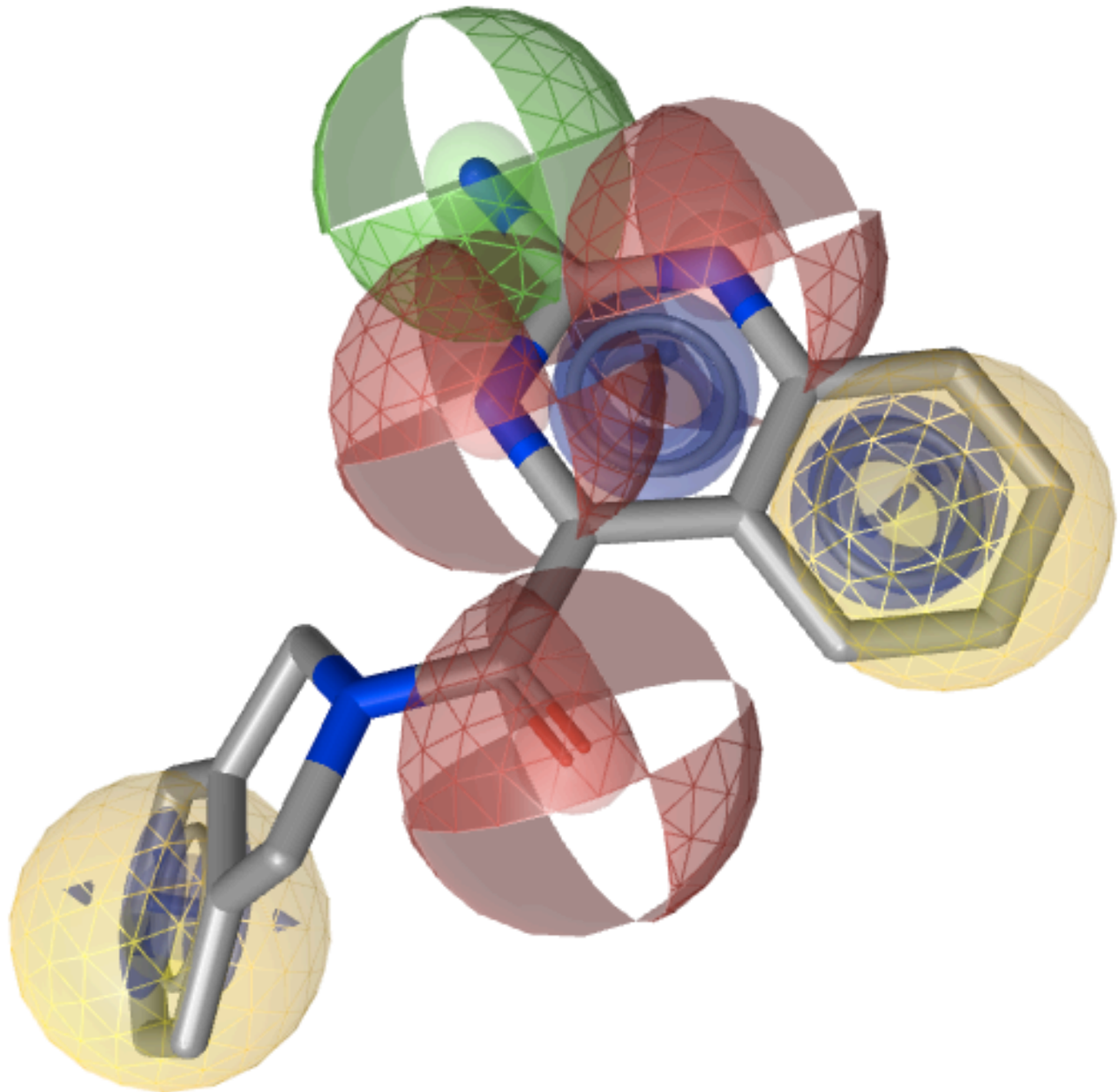
- Compare compound structures in view of their preferences for specific molecular interactions

- Annotate molecules with all interaction features possible
- Find out, which of them are the really important ones …



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A Possible Solution

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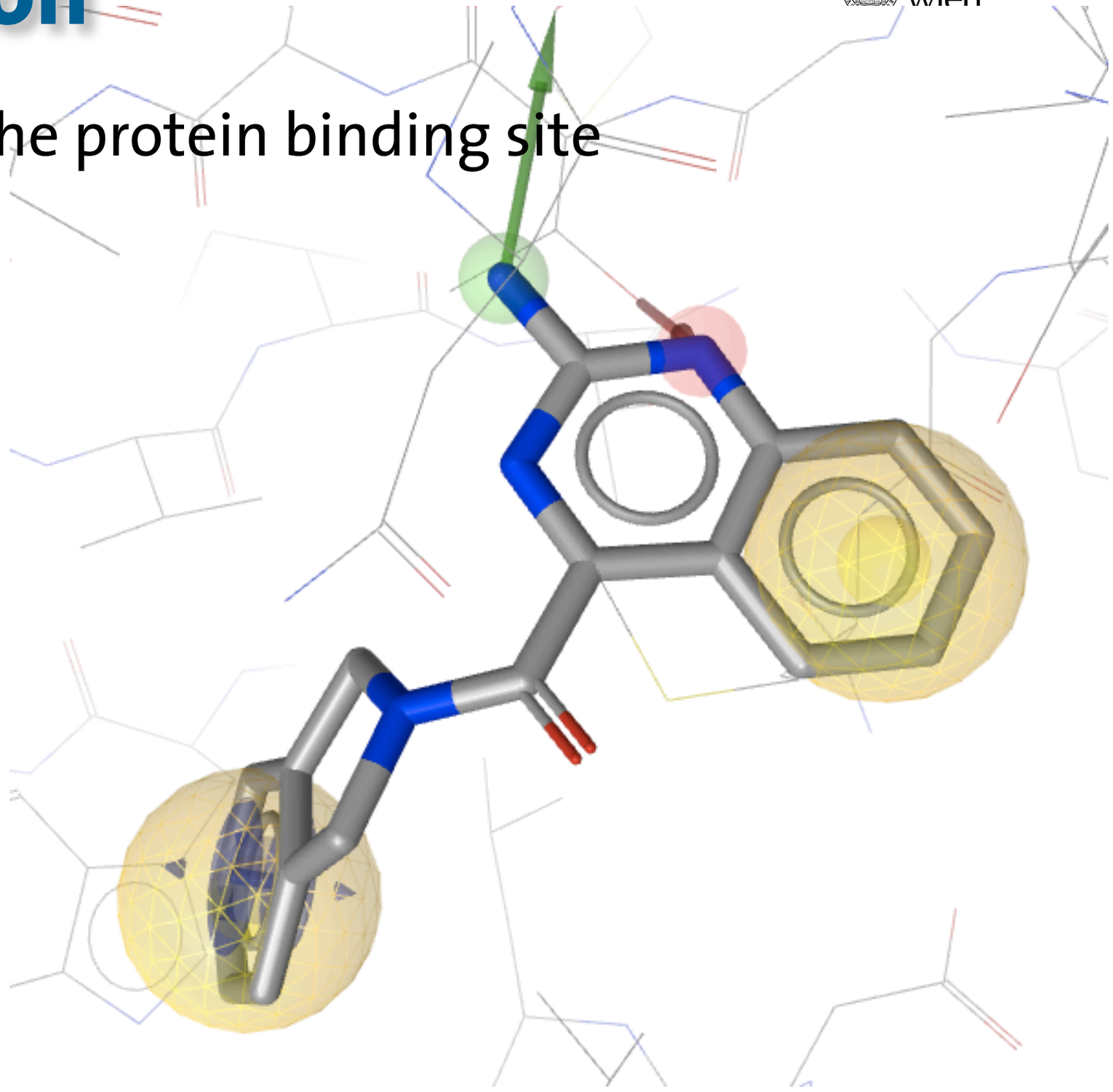
- Look at interactions in the protein binding site



Schütz D., PhD Thesis,
University of Vienna, 2018

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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."

1933 - 2015

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

Feature-based Pharmacophores

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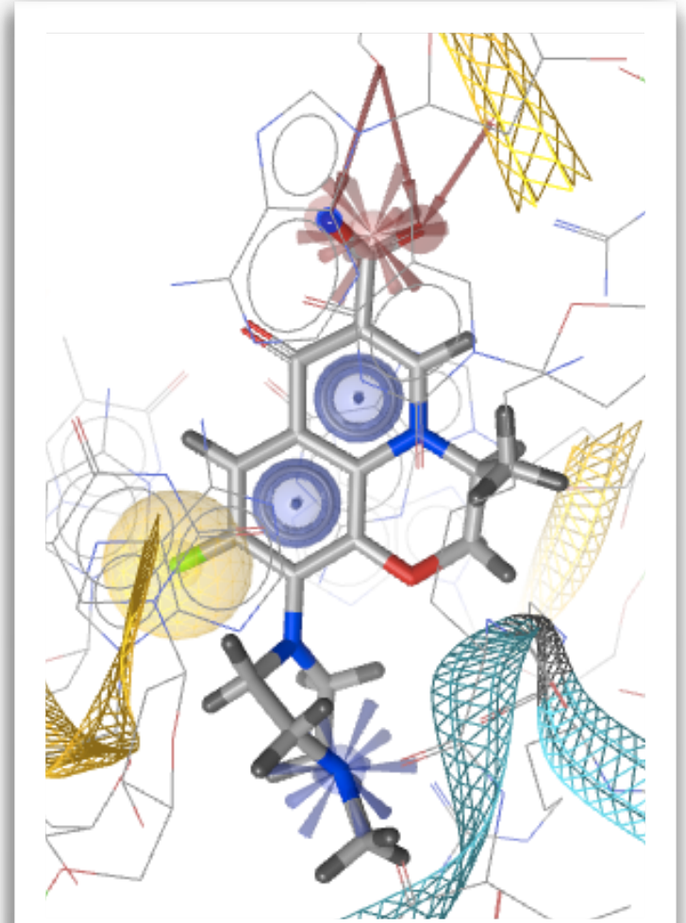
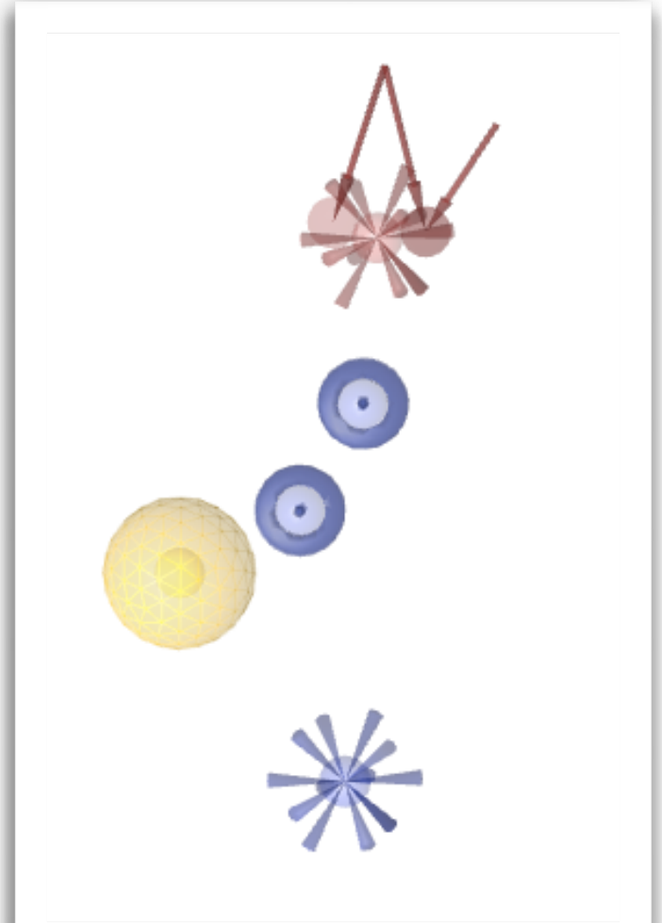
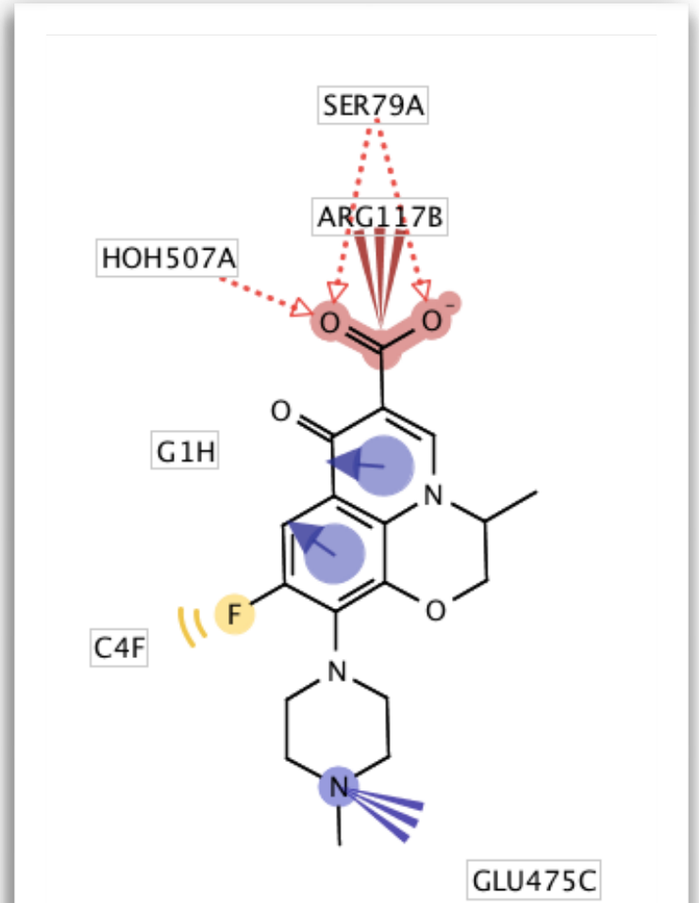
Totality of universal chemical features that represent a defined binding mode of a ligand to a bio-molecular target

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







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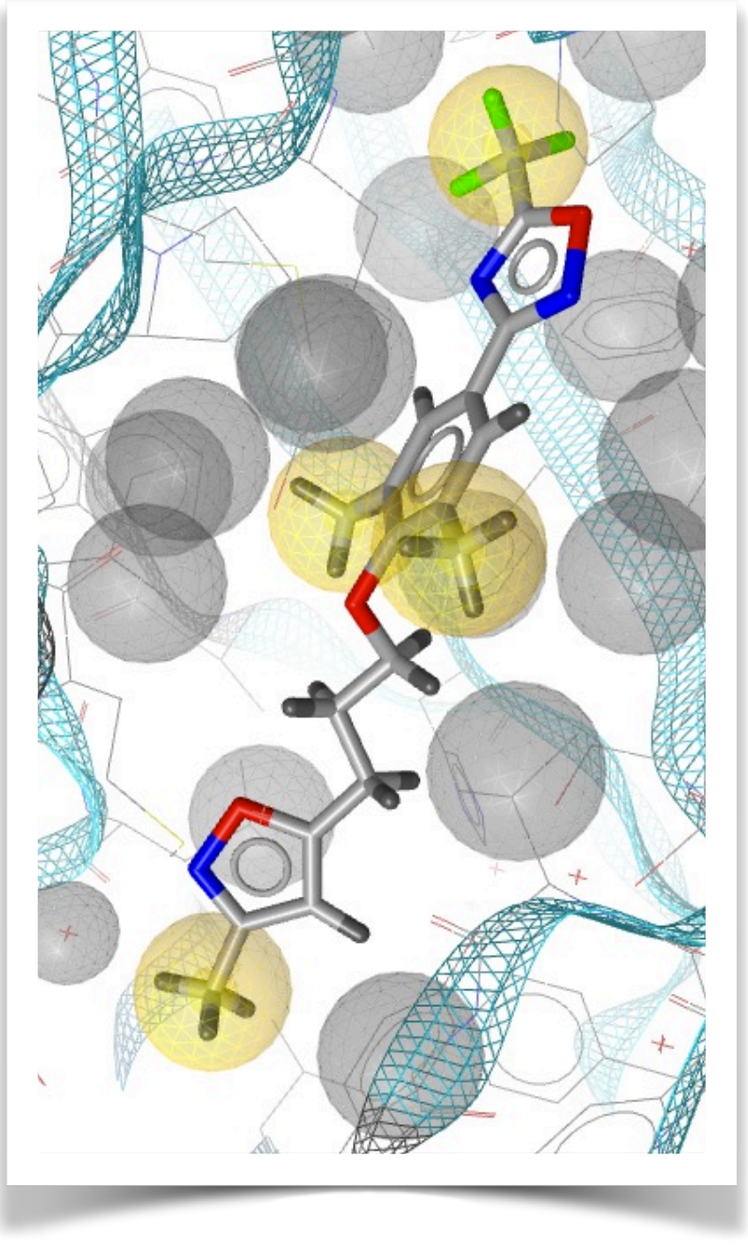
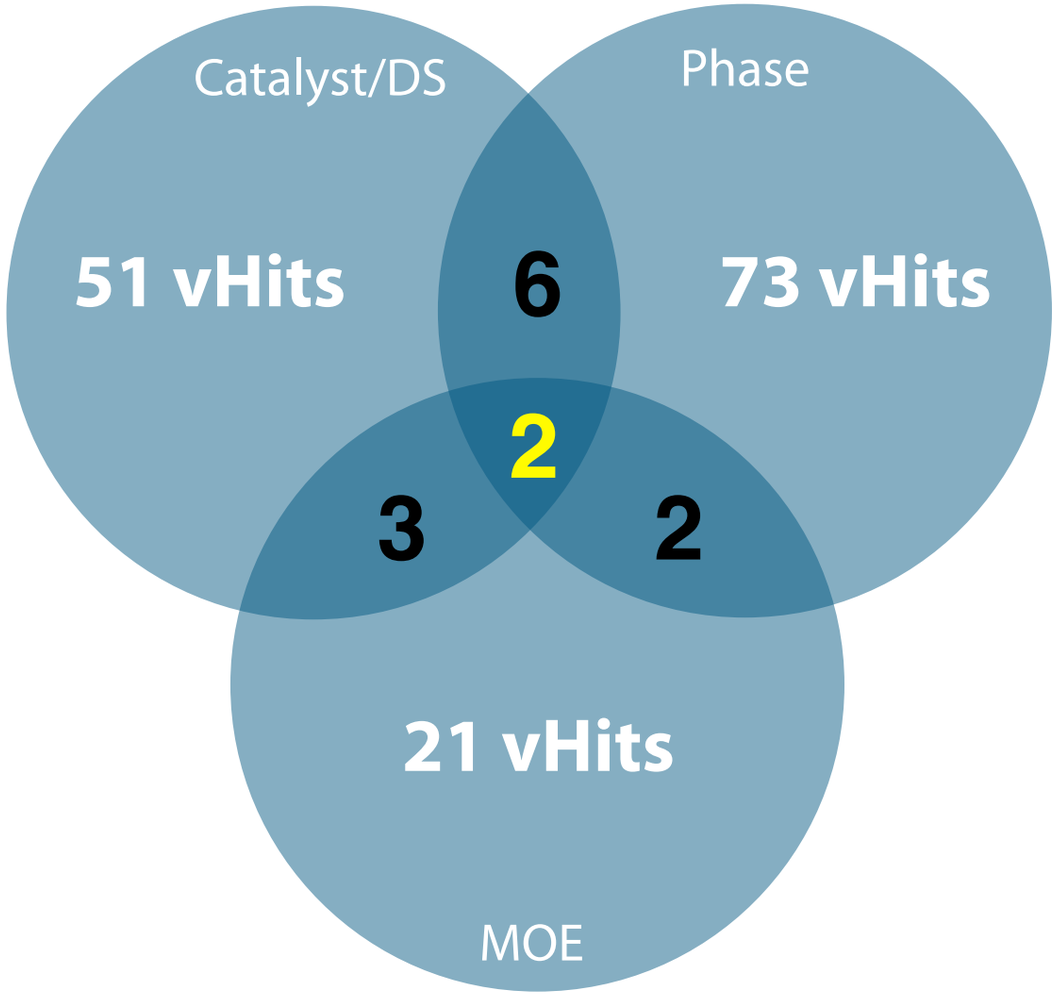
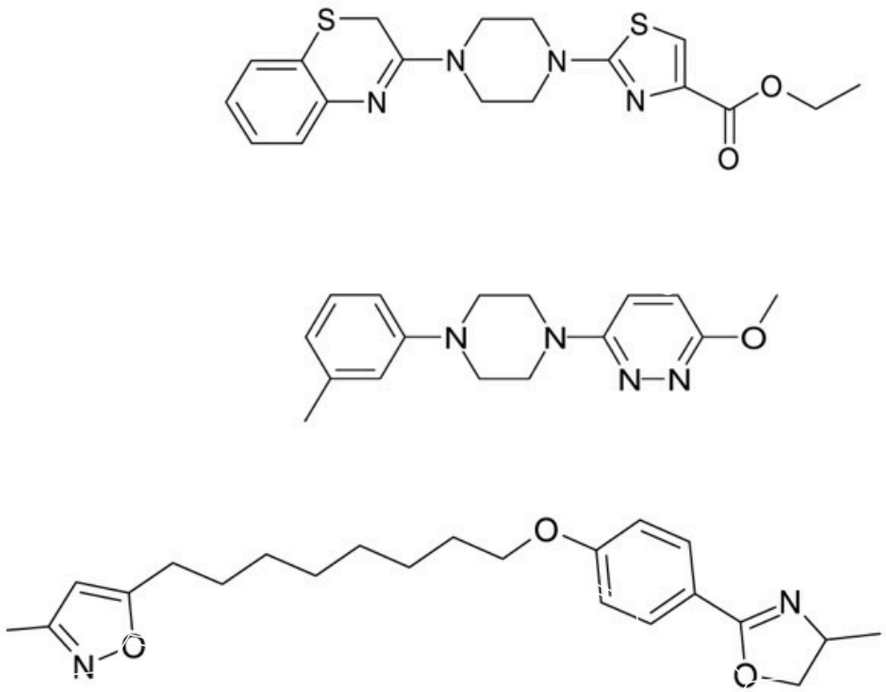
Pharmacophore Screening ...

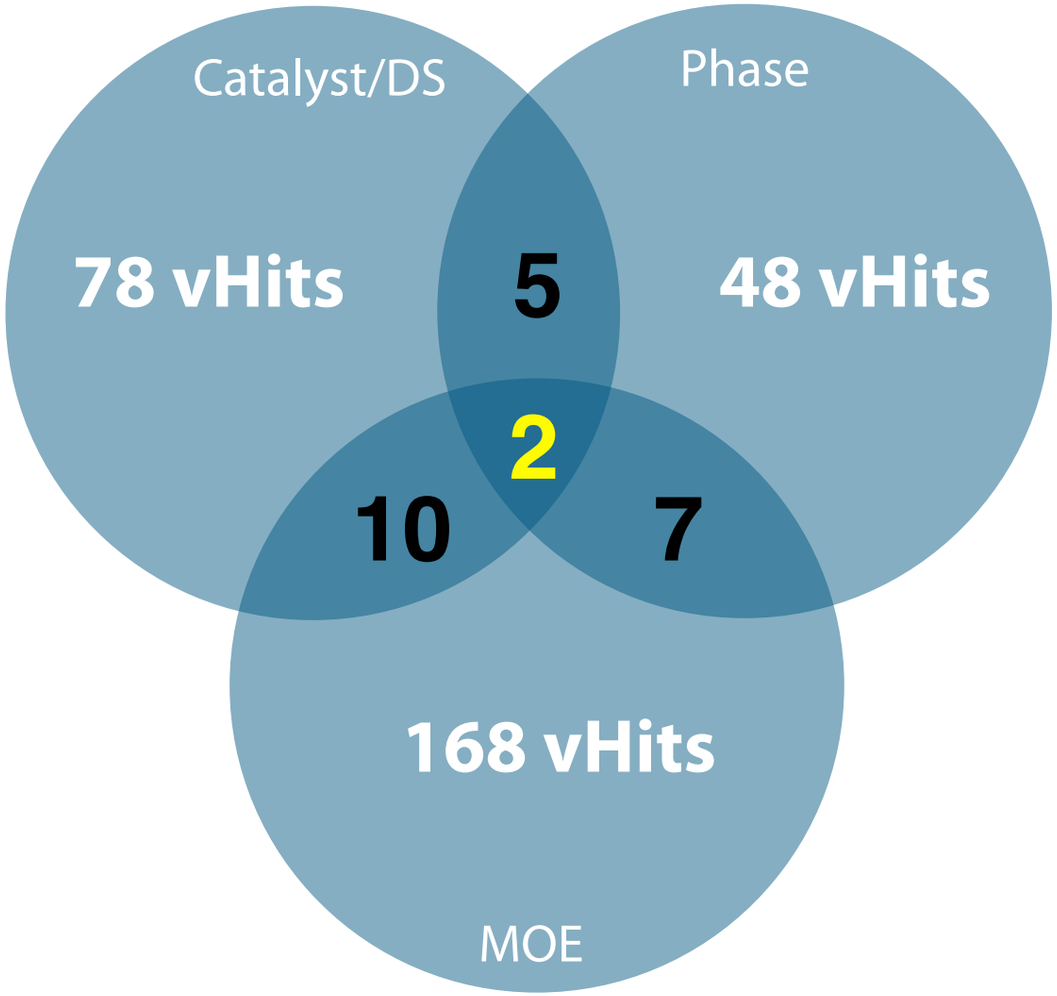




[Mangold 2006] Martina Mangold. *Human Rhinovirus Coat Protein Inhibitors - A Pharmacophore Modeling Approach.*
Master's thesis at the University of Innsbruck (2006)

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 was 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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We Need Speed & Accuracy

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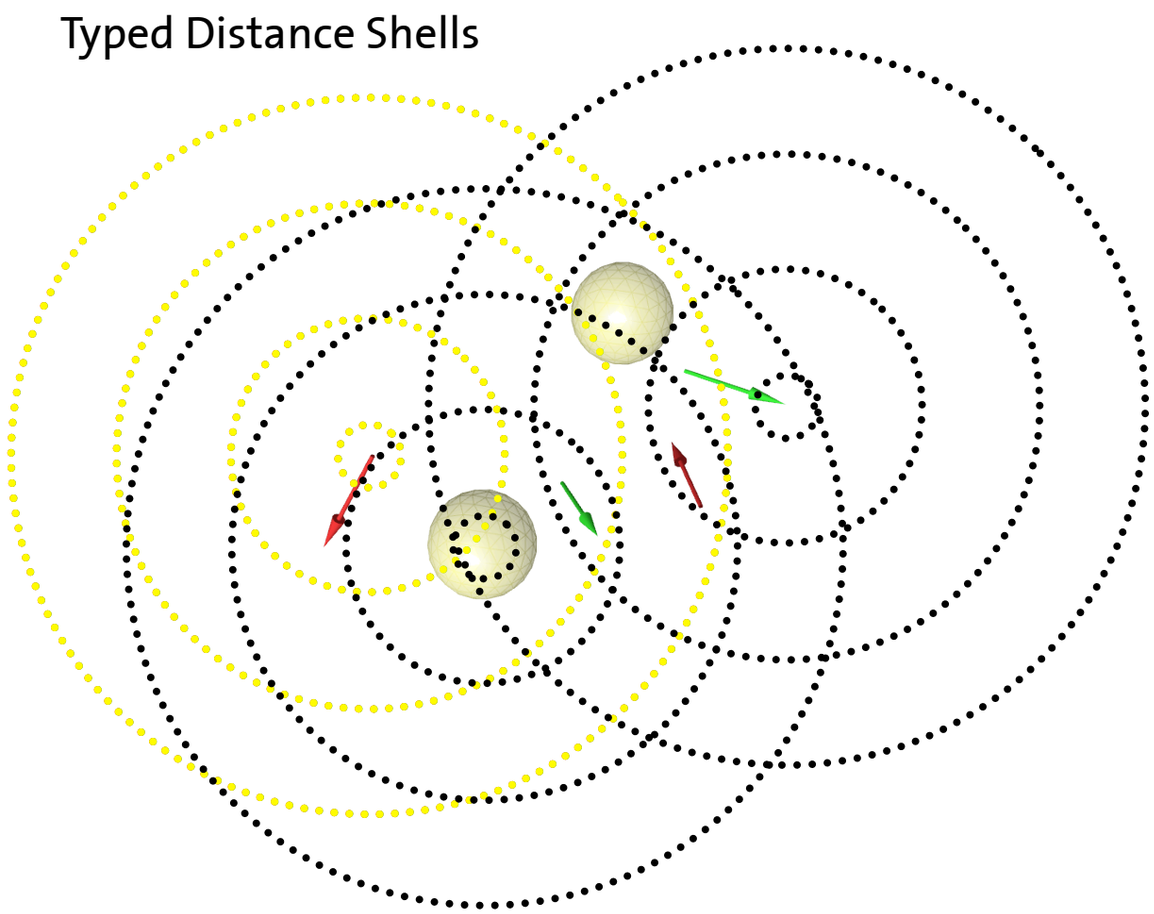
- Redesign the alignment algorithm
- Avoid computationally inefficient graph matching
- Create a pattern recognition based approach



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Pattern Recognition

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… Breaking the Code

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- Why Yuor Barin Can Raed Tihs

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… Breaking the Code

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… Breaking the Code

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- S1M1L4RLY, Y0UR M1ND 15 R34D1NG 7H15 4U70M471C4LLY W17H0U7 3V3N 7H1NK1NG 4B0U7 17

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

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Distance Characteristics

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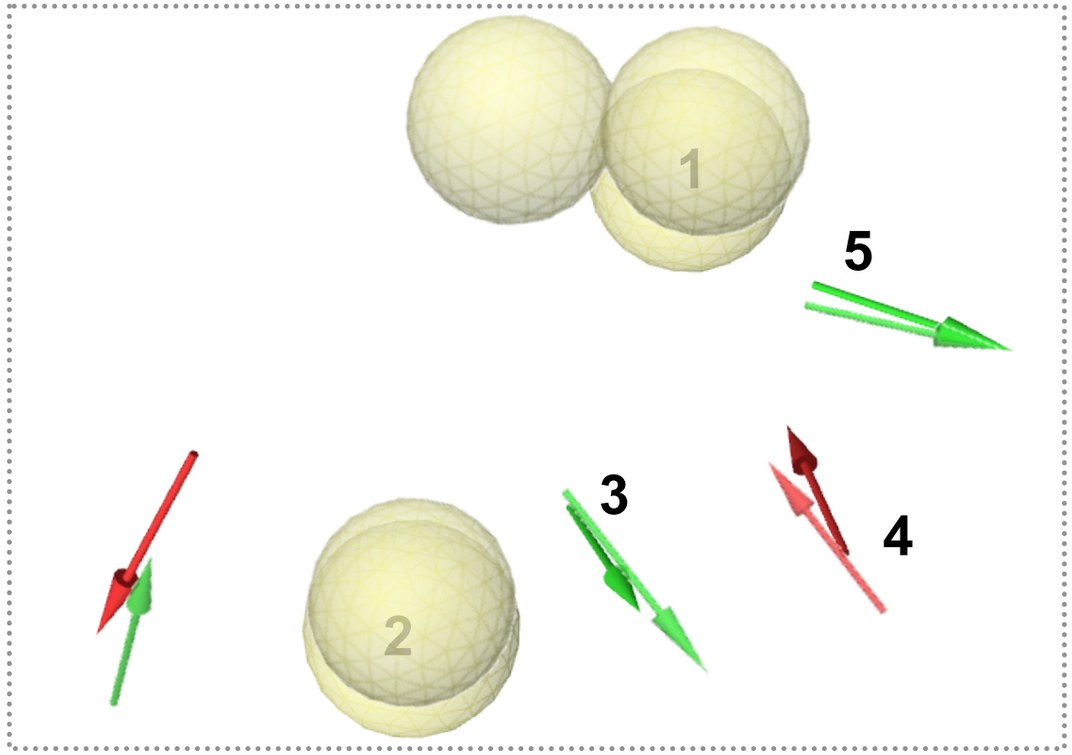
Result: Best matching pairs for each feature



Final step: 3D rotation using Kabsch algorithm

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LigandScout Prototype 2003

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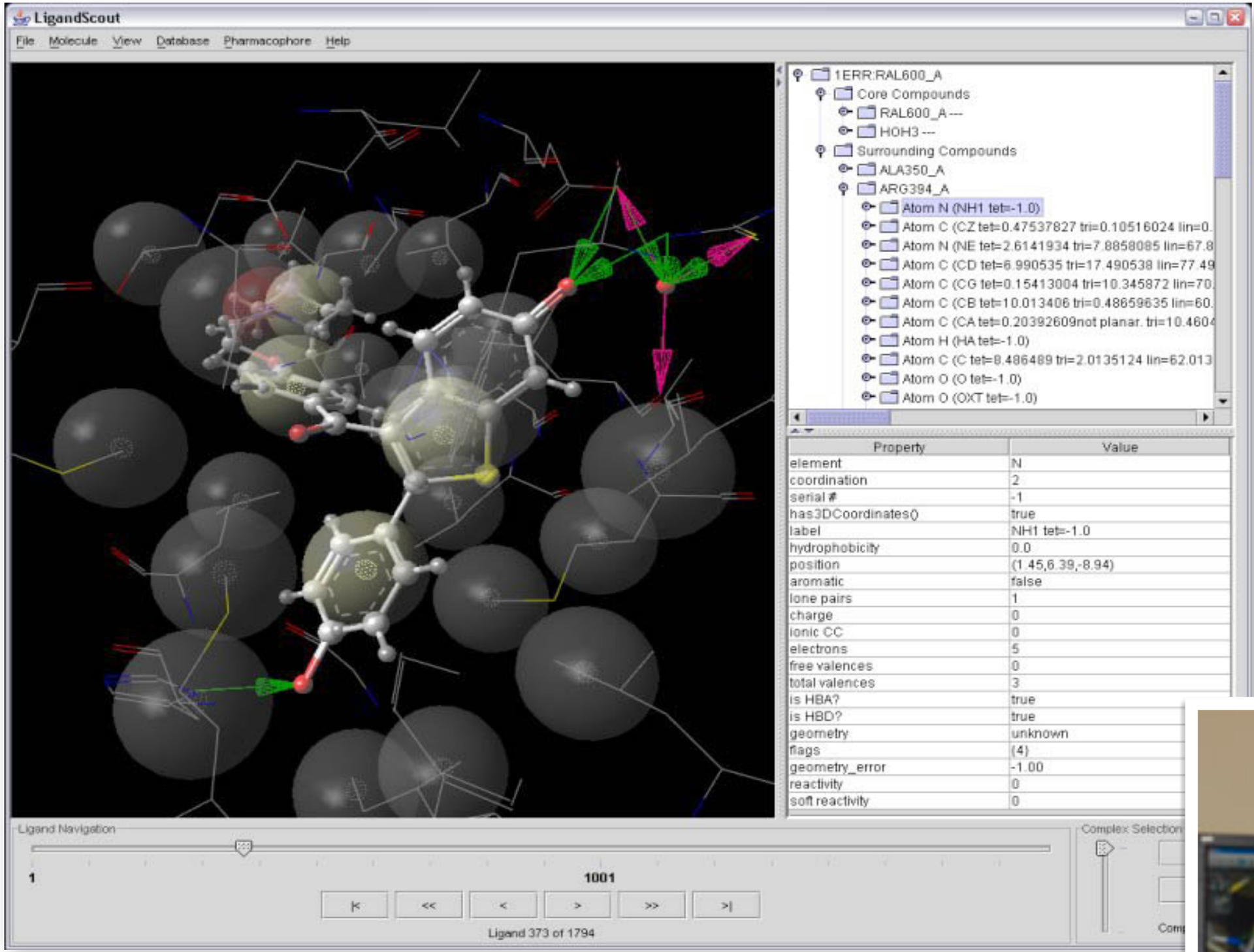

Gerhard Wolber
University of Innsbruck

T. Langer, 2023-01-31

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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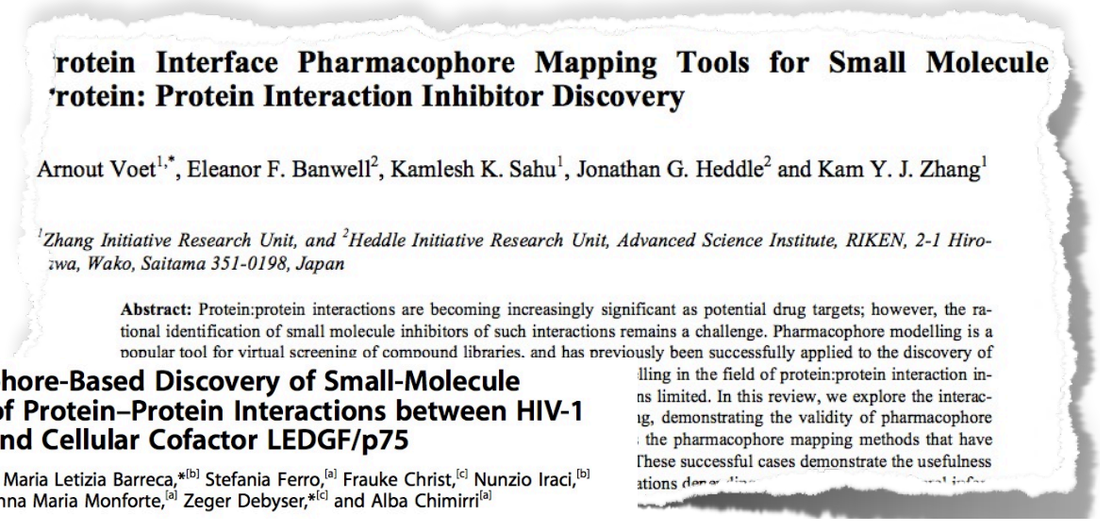
- More than 2800 papers*
  - structure-based modeling
  - ligand-based modeling
  - virtual screening
- Hit identification
- Fragment-based design
- Lead structure optimization
- Protein-Protein Interactions
- Drug repurposing
- Profiling (side-effects)



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 ra- tional 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
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ARTICL

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Therapeutic Discovery

Molecular Cancer Therapeutics

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 pharma- cokinetic 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, January 2023

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An Interesting Article To Read ...

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JOURNAL OF CHEMICAL INFORMATION AND MODELING

Article

pubs.acs.org/jcim

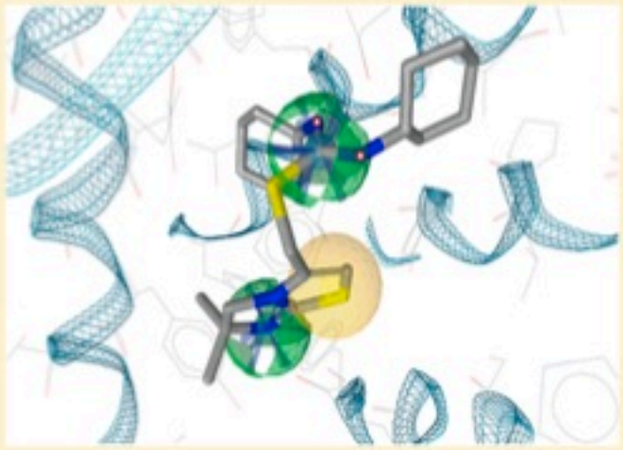
Highly Specific and Sensitive Pharmacophore Model for Identifying CXCR4 Antagonists. Comparison with Docking and Shape-Matching Virtual Screening Performance

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)

T. Langer, 2023-01-31

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LigandScout for VS

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Pharmacophore from PDB entry 3OE6

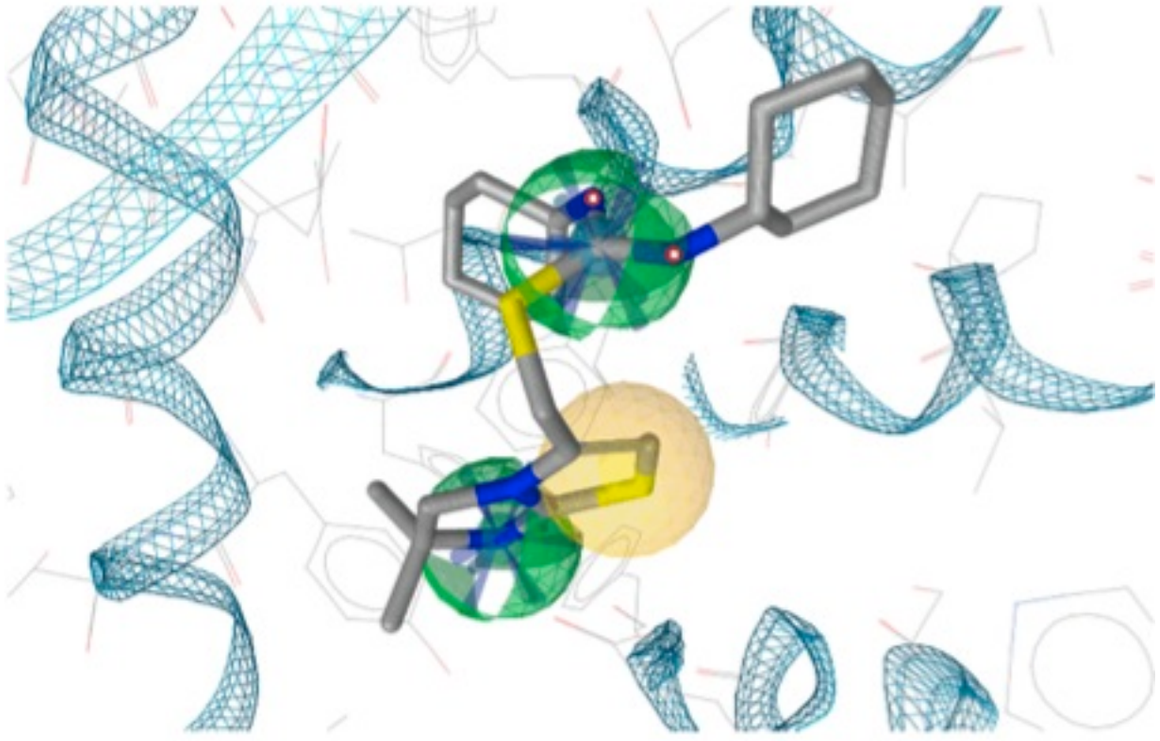

Figure 2. CXCR4 pharmacophore model with a high activity CXCR4 antagonist aligned. Five-featured manually refined final pharmacophore model. The pharmacophore hydrophobic features are shown in yellow. Positively charged features are shown in blue, and hydrogen bond donor features are shown in green.

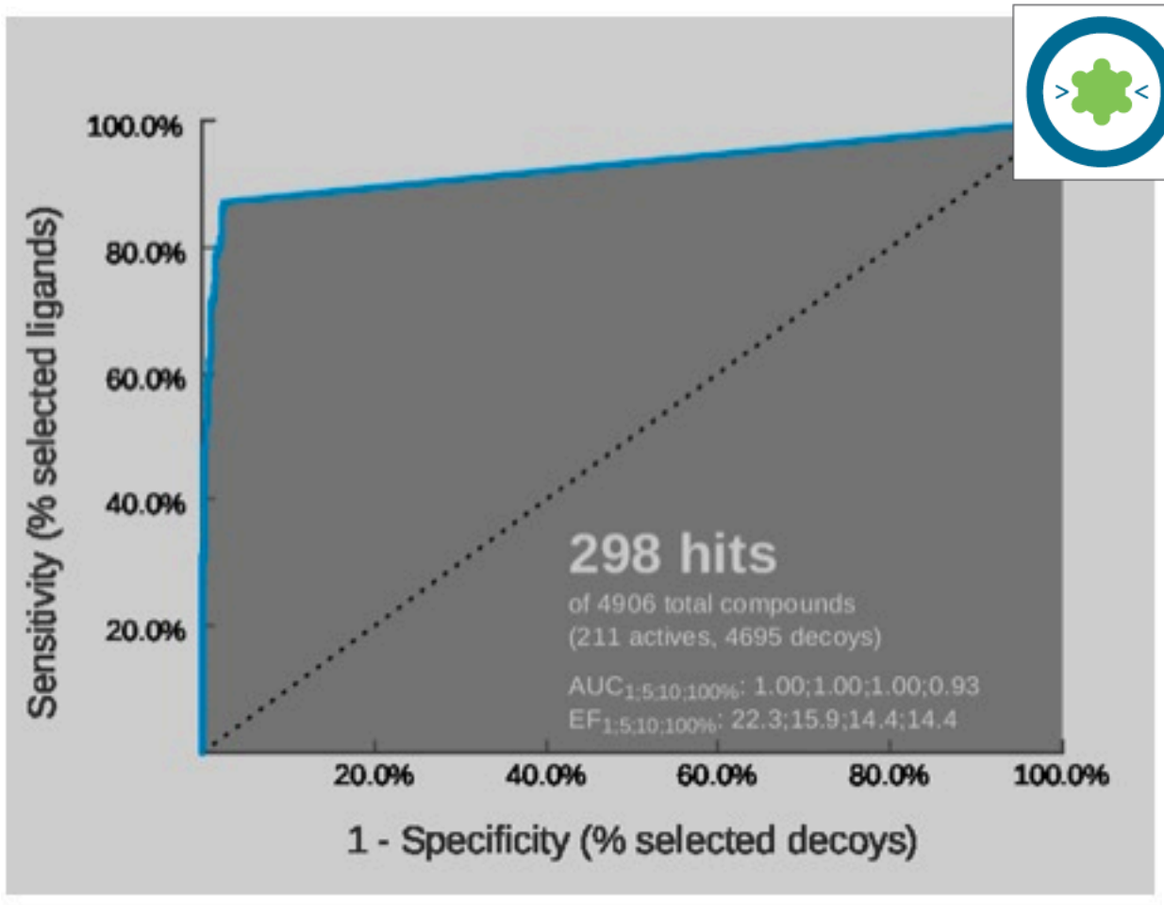

Figure 3. ROC plot validation of the pharmacophore model applied to CXCR4 antagonists. Values of area under the curve (AUC) and enrichment factor (EF) are displayed at 1, 5, 10, and 100% of screened database, respectively. These values highlight the high sensitivity and specificity of the designed pharmacophore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

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

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Virtual Screening Performance

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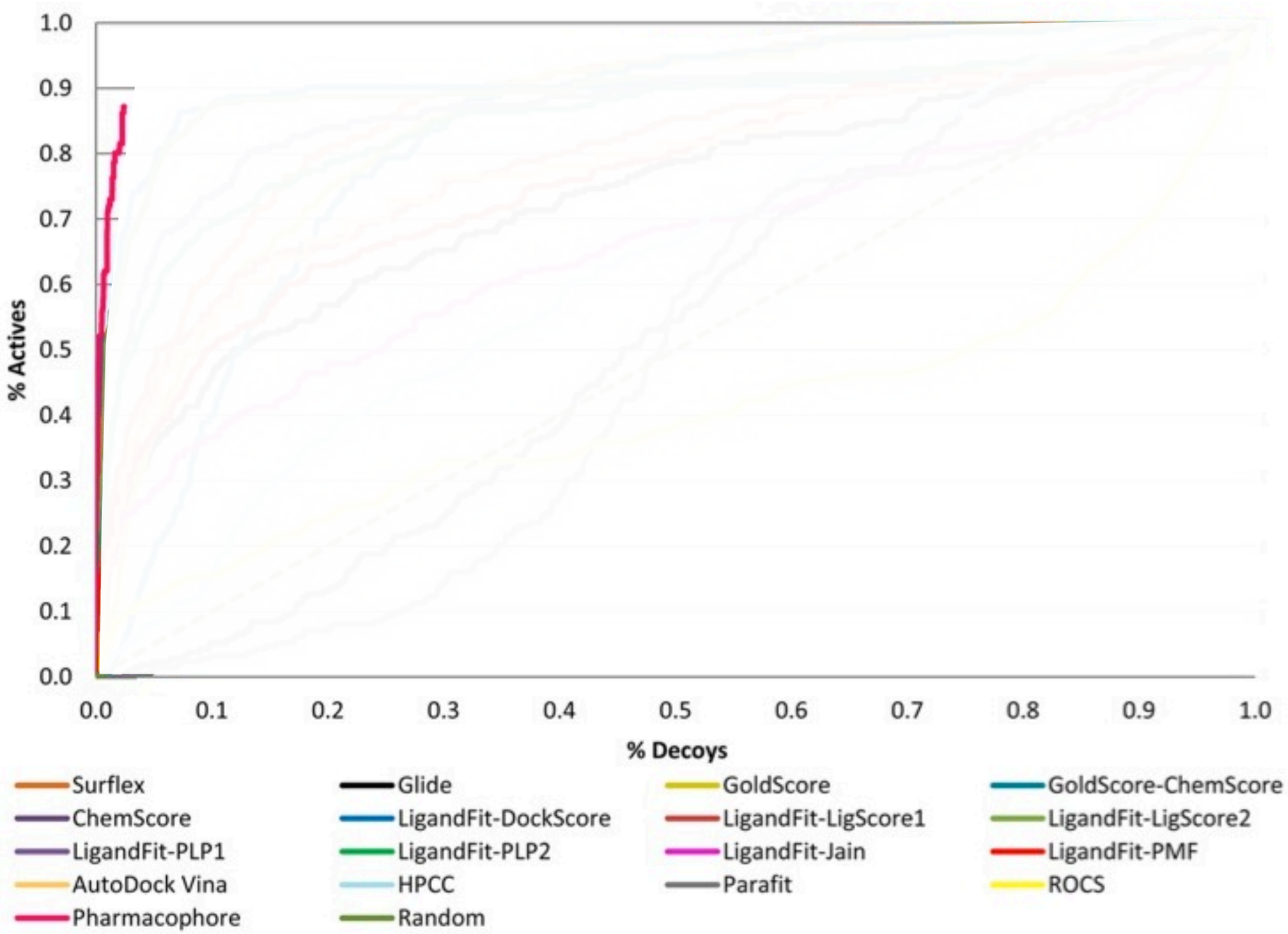

Karaboga et al., J. Chem. Inf. Model. 2013, 53, 1043–1056

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The Author's 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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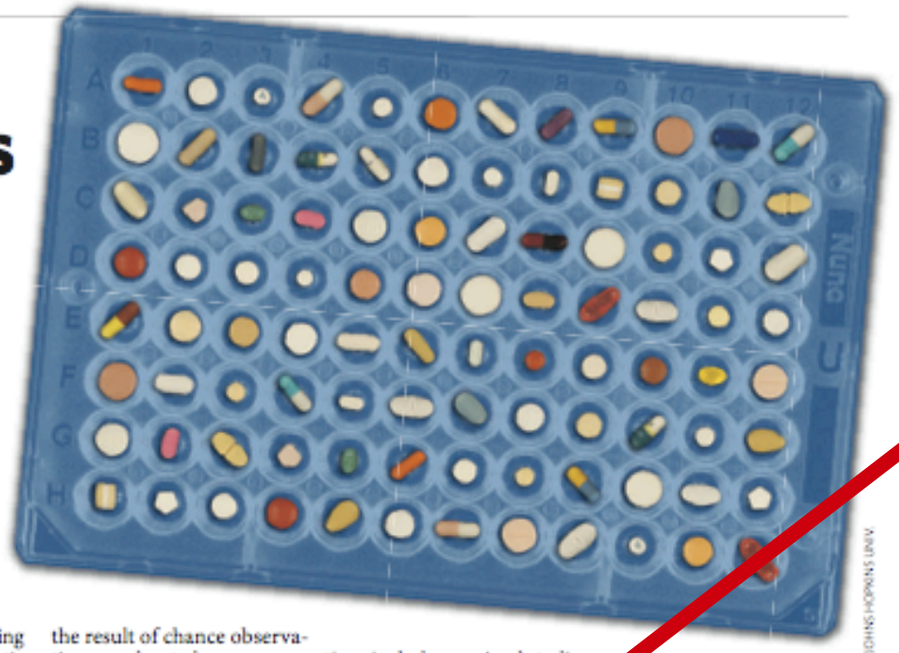
Vol 448|9 August 2007 nature

COMMENTARY

New uses for old drugs

It takes too long and costs too much to bring new drugs to market. So let's beef up efforts to screen existing drugs for new uses, argue **Curtis R. Chong** and **David J. Sullivan Jr.**



Fast, affordable drug development is a vision that contrasts sharply with the current state of drug discovery — which also neglects too many diseases of the poor. An analysis[1] of 68 approved drugs estimated that it takes an average of 15 years and US$800 million to bring a single drug to market. And despite a doubling in research spending by the US National Institutes of Health (NIH) to $27 billion in 2003, the number of new drugs approved by the US Food and Drug Administration (FDA) each year remains constant at 20–30 compounds[2]. At this rate it will take more than 300 years for the number of drugs in the world to double.

The current costly and time-consuming paradigm of drug discovery is ill-equipped to combat rapidly emerging diseases, such as avian flu, drug-resistant pathogens and diseases that have a small financial market. One solution is to identify new uses for existing drugs. As the pharmacologist and Nobel laureate James Black said, "the most fruitful basis for the discovery of a new drug is to start with an old drug." Because existing drugs have known pharmacokinetics and safety profiles and are often approved by regulatory agencies for human use, any newly identified use can be rapidly evaluated in phase II clinical trials, which typically last two years and cost $[illegible] million[1]. In this way, drug developers can bypass almost 40% of the overall cost of bringing a drug to market by eliminating much of the toxicological and pharmacokinetic assessments[1].

> "The most fruitful basis for the discovery of a new drug is to start with an old drug."

This back-to-basics approach is growing in popularity. At least 17 existing drugs are in various stages of clinical and animal testing for new uses (see Supplementary information), and a further 24 are already being remarketed by the pharmaceutical industry for new uses[3]. Although most successful crossovers have been the result of chance observations or educated guesses, exceptions include the antibiotic ceftriaxone, which is a potential treatment for amyotrophic lateral sclerosis[4], and whose new activity was discovered following the screening of 1,040 compounds from the National Institute of Neurological Disorders and Stroke (NINDS) custom collection in Gaylordsville, Connecticut. In the past, individual labs were limited to screening perhaps hundreds of compounds. Now, clinical drug collections like the NINDS library and the Prestwick Chemical Library in Washington DC offer more than 1,000 approved drugs for small-scale [illegible] screening. In our view, what is needed is a more systematic approach to drug rediscovery that takes the valuable resources to the next level.

Historically, 'repurposing' old drugs has proved successful in bringing new therapies to the developing world. Today, even with the billions of research dollars available to create new drugs through public–private partnerships, and the promise of genomic data, there remains an enormous unmet need for therapies for neglected diseases[5]. A recent example of a repurposed drug is miltefosine, initially developed for breast cancer but now used for treating visceral leishmaniasis[6]. This disease is caused by a sand-fly-transmitted parasite and kills an estimated 500,000 people each year. In fact, miltefosine failed phase II testing for tumour reduction and the drug was never approved by the FDA for cancer therapy. However, *in vitro* and animal studies indicated anti-infective activity, and phase II trials confirmed miltefosine as a viable treatment for visceral leishmaniasis[6].

Cost cutting

Cost is one reason to revisit existing drugs: roughly 1,000 of the 10,000 or so drugs ever tested in clinical medicine are covered by patents, so most drugs can affordably be redeployed in the developing world. Safety is another compelling reason. Phase IV clinical studies, which monitor post-marketing safety, cost around $100 million per drug to perform in developed countries[1] and are nearly impossible in countries without an established healthcare infrastructure. Because many existing drugs have undergone phase IV surveillance in millions of patients, the same stringent safety standards required by users in developed countries can be offered to patients with neglected diseases in the developing world.

Despite the promise of finding new uses for existing drugs, a comprehensive collection of the approximately 9,990 drugs known to clinical medicine does not exist. This number includes 2,933 unique drugs approved by the FDA since 1938 (ref. 7), 1,107 drugs in the 2006 FDA Orange Book, 888 drugs in the 2006 Physician Desk Reference, and 7,057 drugs that are either approved abroad or have entered phase II clinical trials, as indicated by a US Adopted Name or International Non-proprietary Name[8]. Excluding antiseptics, pharmaceutical aids, therapeutic plant or animal extracts, and vaccines, we estimate that there are 8,850

1. Langer, 2023-01-31

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Sir James Black

Camille G. Wermuth:

SOSA: Selective Optimization of Side Activities (1993)

Chong & Sullivan,

Nat. Drug Discov. 2007, 448, 645-646

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An Example

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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 sorafenib, which has a dual-mode action by inducing ABCG2 degradation in lysosome in addition to inhibiting its function. Previously, we reported some novel dual-acting ABCG2 inhibitors that showed closer similarity to degradation-induced mechanism of action. On the basis of these ABCG2 inhibitors with diverse chemical structures, we developed a pharmacophore model for identifying the critical pharmacophore features necessary for dual-acting ABCG2 inhibitors. Sorafenib forms impressive alignment with the pharmacophore hypothesis, supporting the argument that sorafenib is a potential ABCG2 inhibitor. This is the first article that sorafenib may be a good candidate for chemosensitizing agent targeting ABCG2-mediated MDR. This study may facilitate the rediscovery of new functions of structurally diverse old drugs and provide a more effective and safe way of sensitizing MDR in cancer chemotherapy. *Mol Cancer Ther; 11(8); 1693–702. ©2012 AACR.*

An Example

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Molecular Cancer Therapeutics

Therapeutic Discovery

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Yinxiang Wei[1,3], Yuanfang Ma[3], Qing Zhao[1,4], Zhigu[illegible], Tingjun Hou[2], and Hui Peng[1]

T. Langer, 2023-01-31

Bernd Riedl, Bayer Pharma, Wuppertal

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LigandScout Model of ABCG2-I

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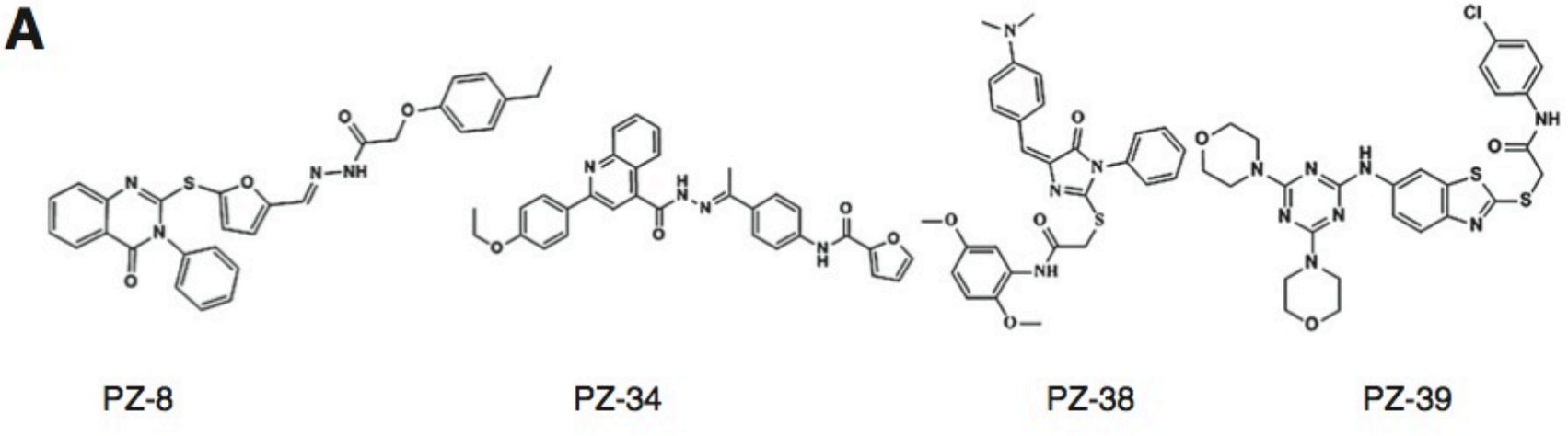

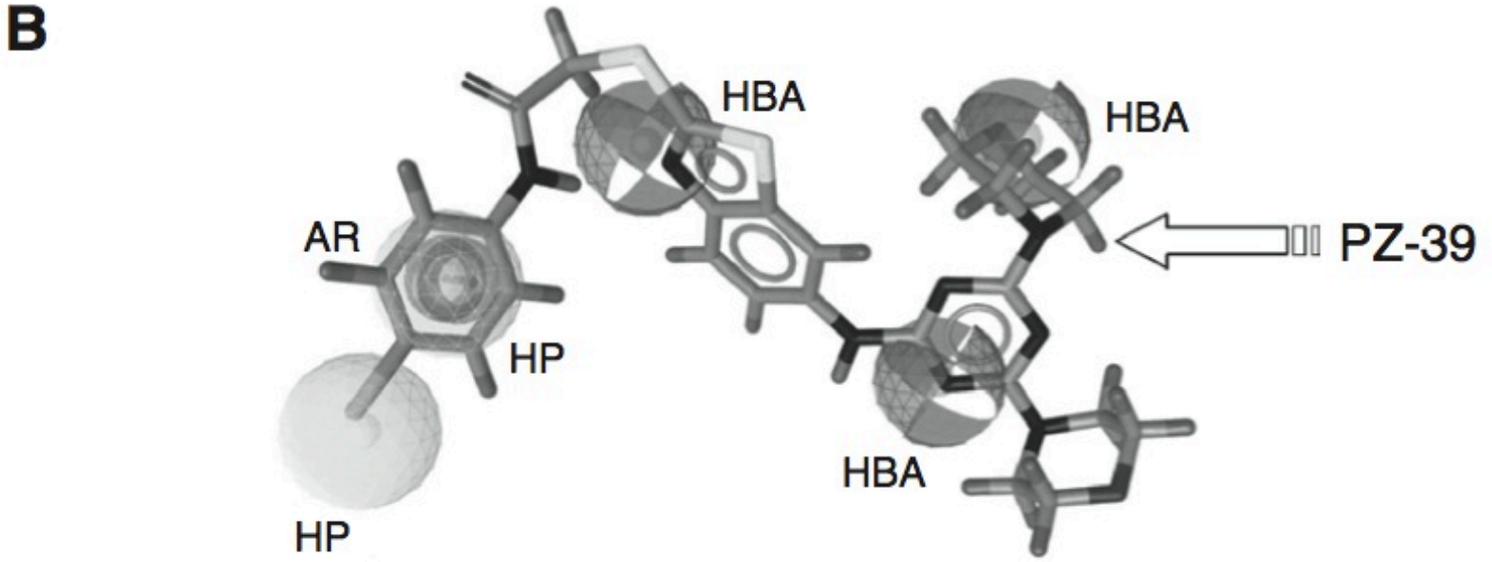

Yinxiang Wei et al., Mol. Cancer Ther.,11, 1693-1702 2012

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Inhibiting ABCG2 With Sorafenib

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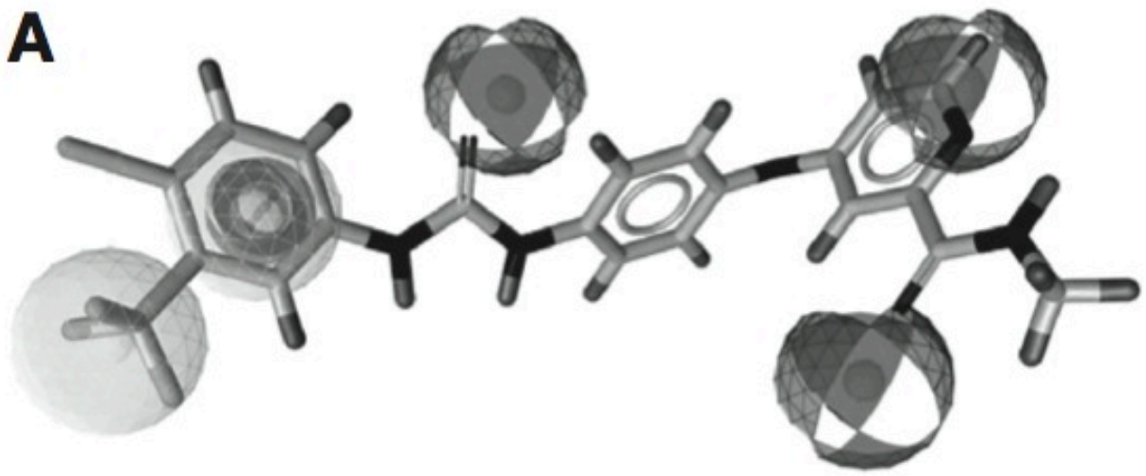

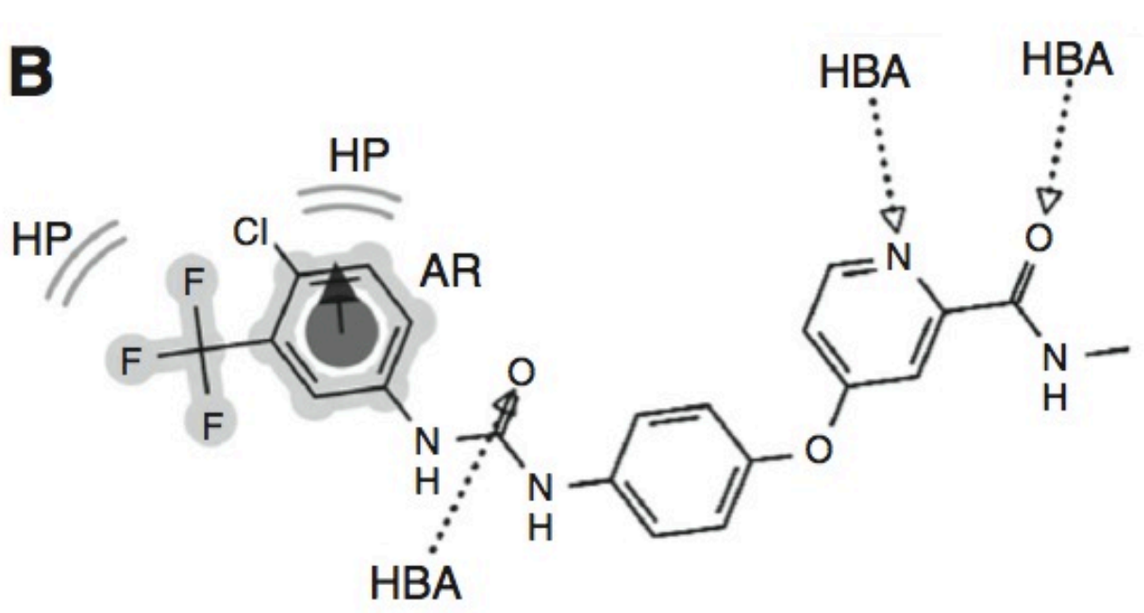

... at a concentration up to 2,5µM/L

no cytotoxic effect was observed ...

.... led us to conclude that sorafenib behaves like ABCG2 degradation-induced inhibitor. Sorafenib may, therefore, be a good candidate for MDR chemosensitizing agent.

Yinxiang Wei et al., Mol. Cancer Ther.,11, 1693-1702 2012

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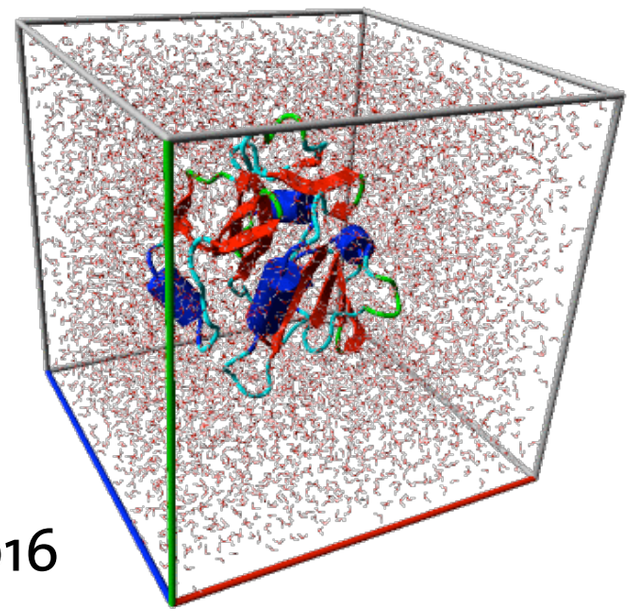
- MD approaches have gained substantial interest in early drug discovery due to parallel computing hardware options*
- Interpretation of MD trajectories still cumbersome
- Pharmacophores are a perfect solution



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

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

ELSEVIER

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

CrossMark

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

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MD Analysis by Pharmacophores

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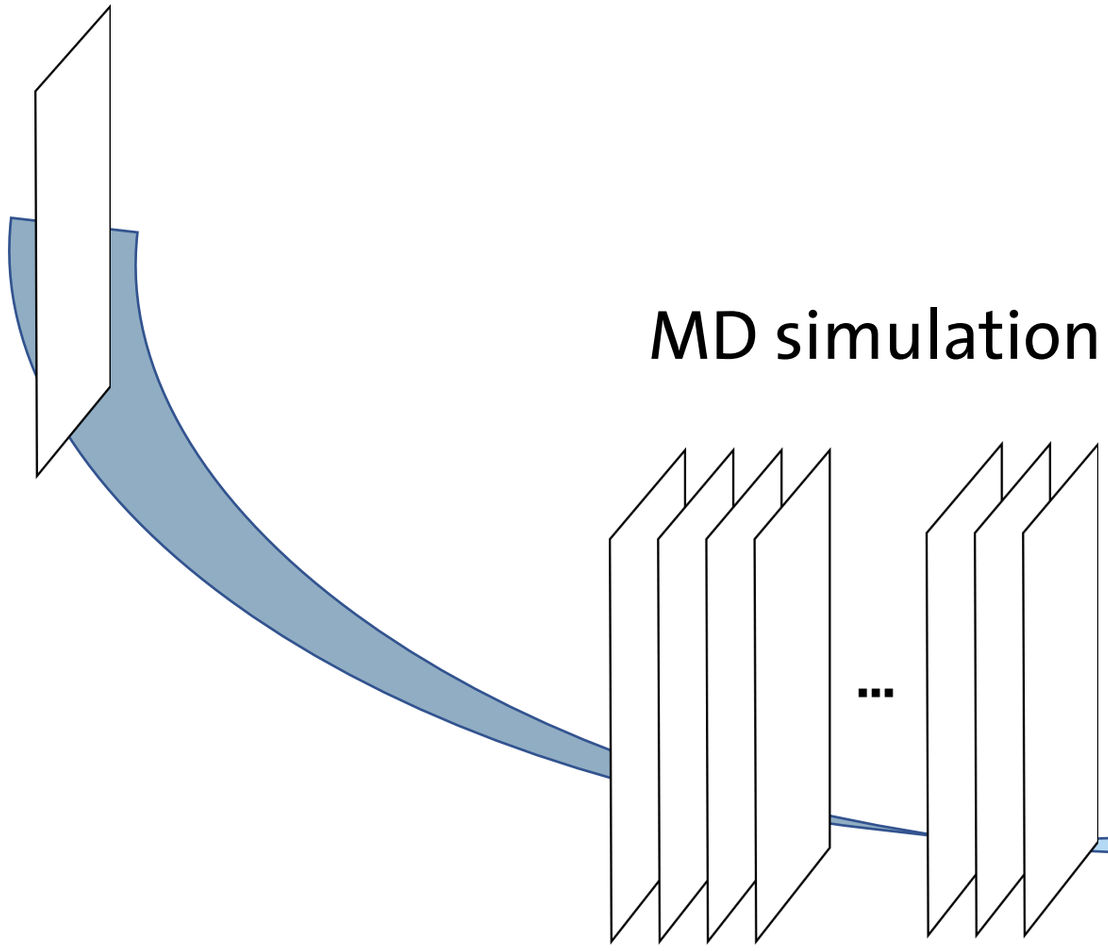
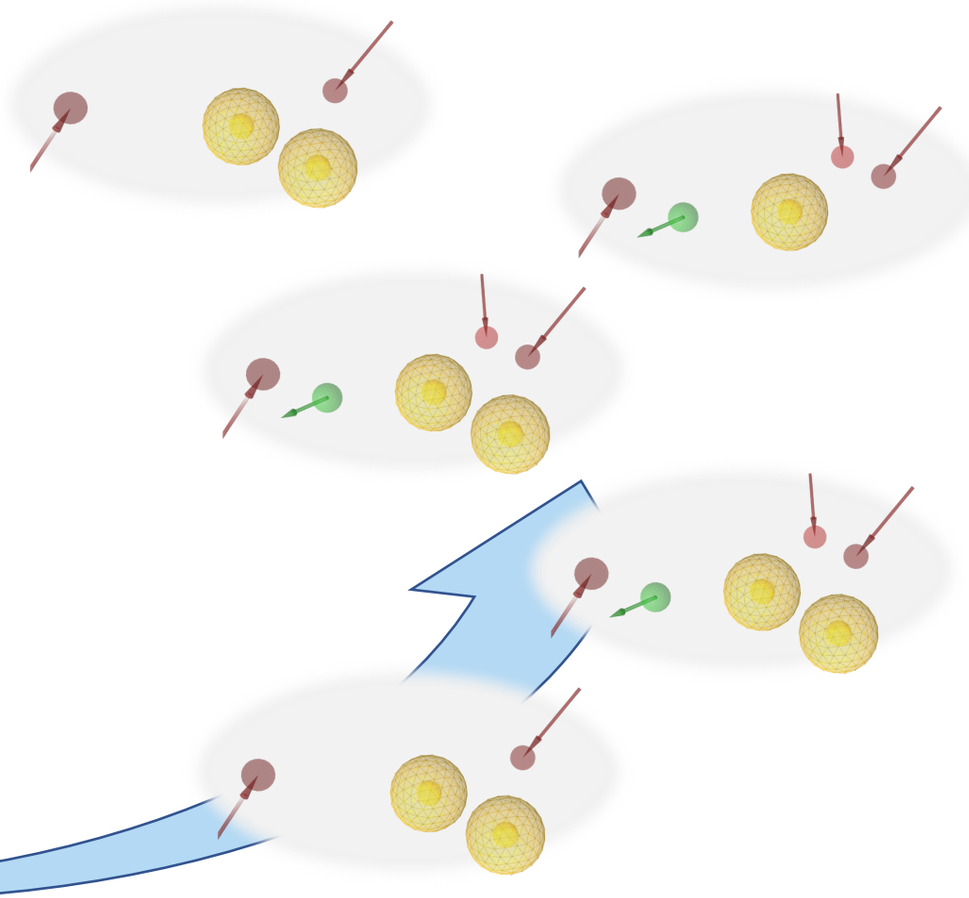
Crystallographic structure



MD simulation



3-D Pharmacophore Models

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LigandScout Trajectory Analysis

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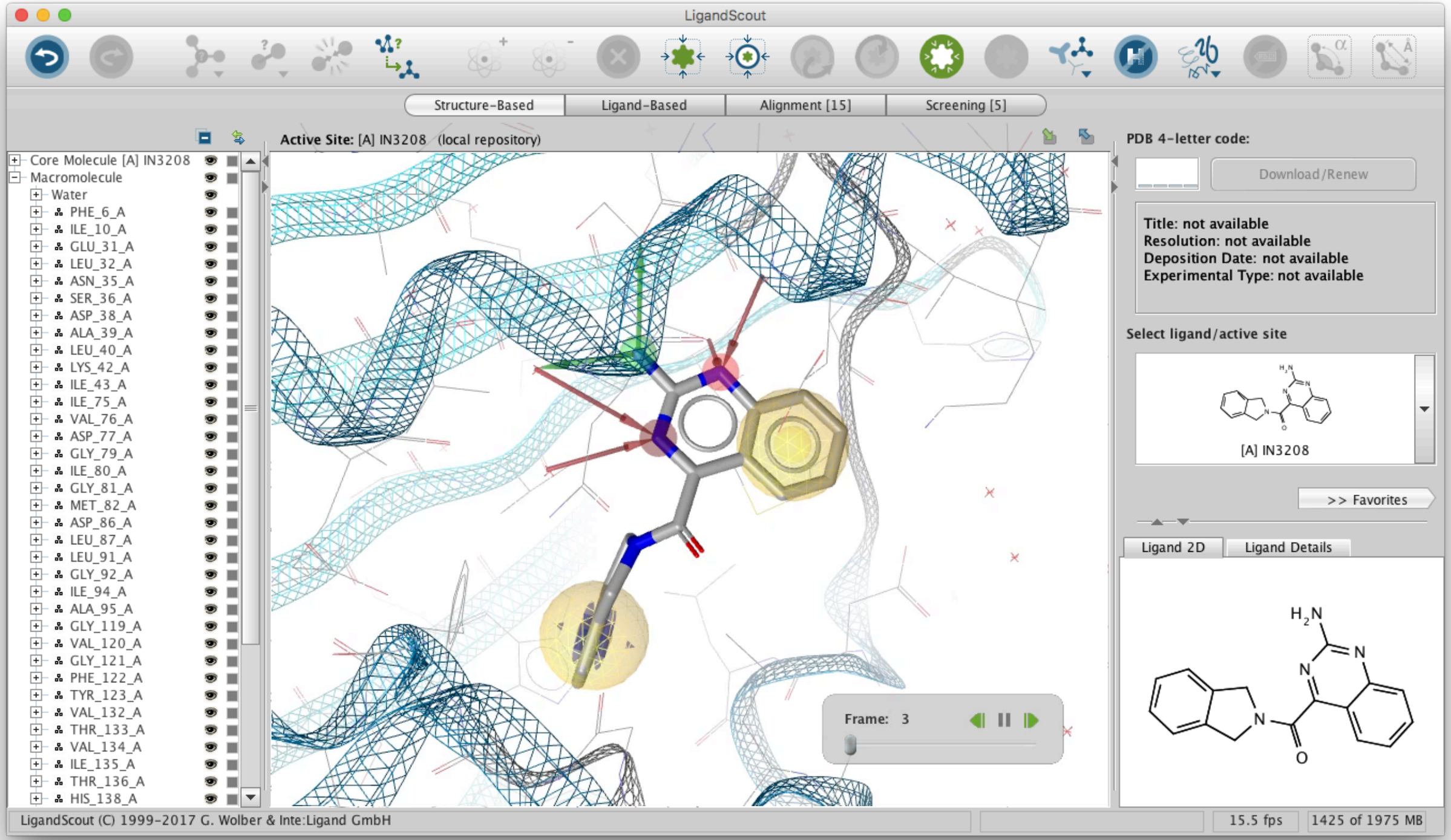

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MD Feature Frequency Analysis

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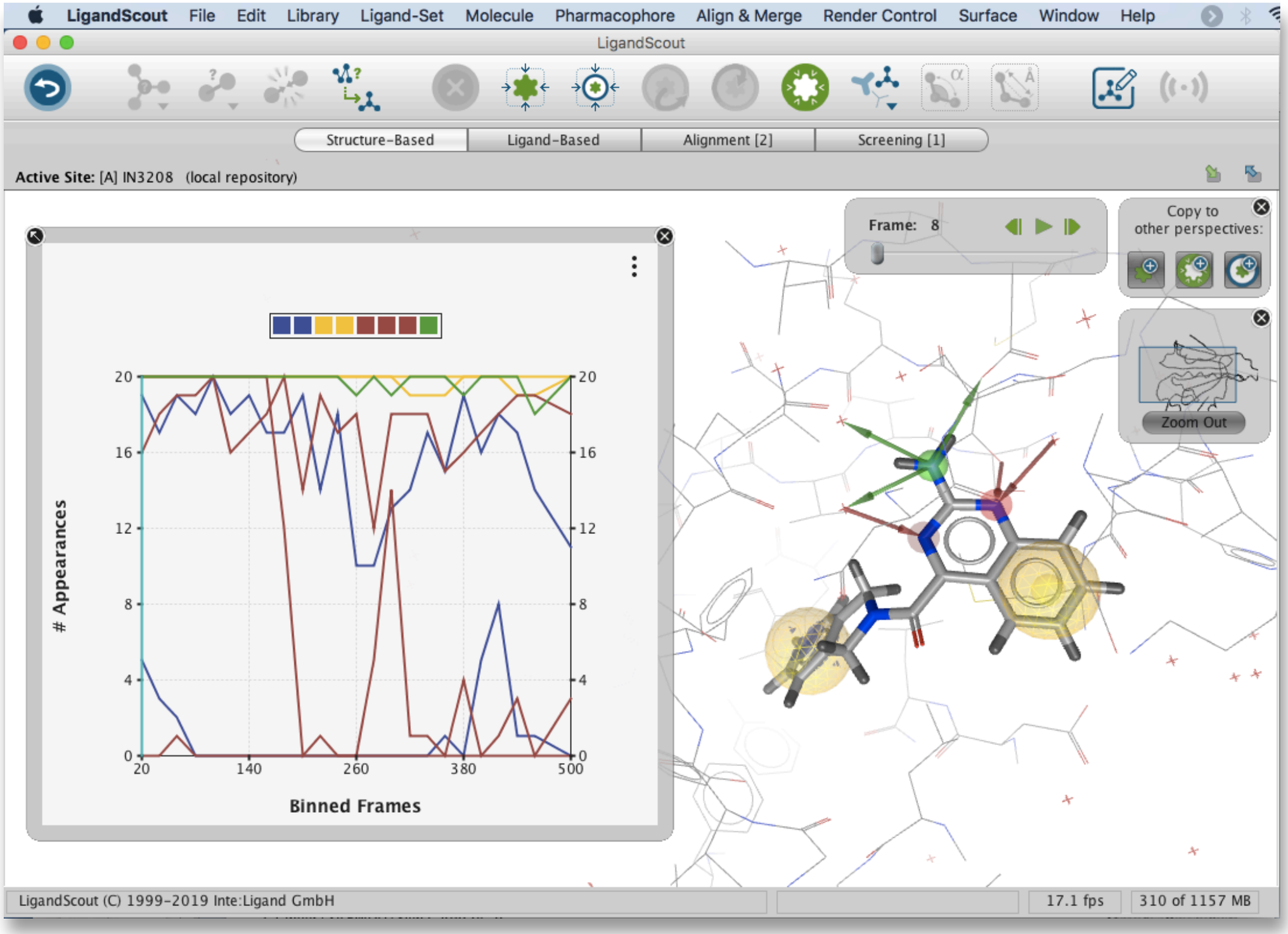

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Find Models With Specific Features

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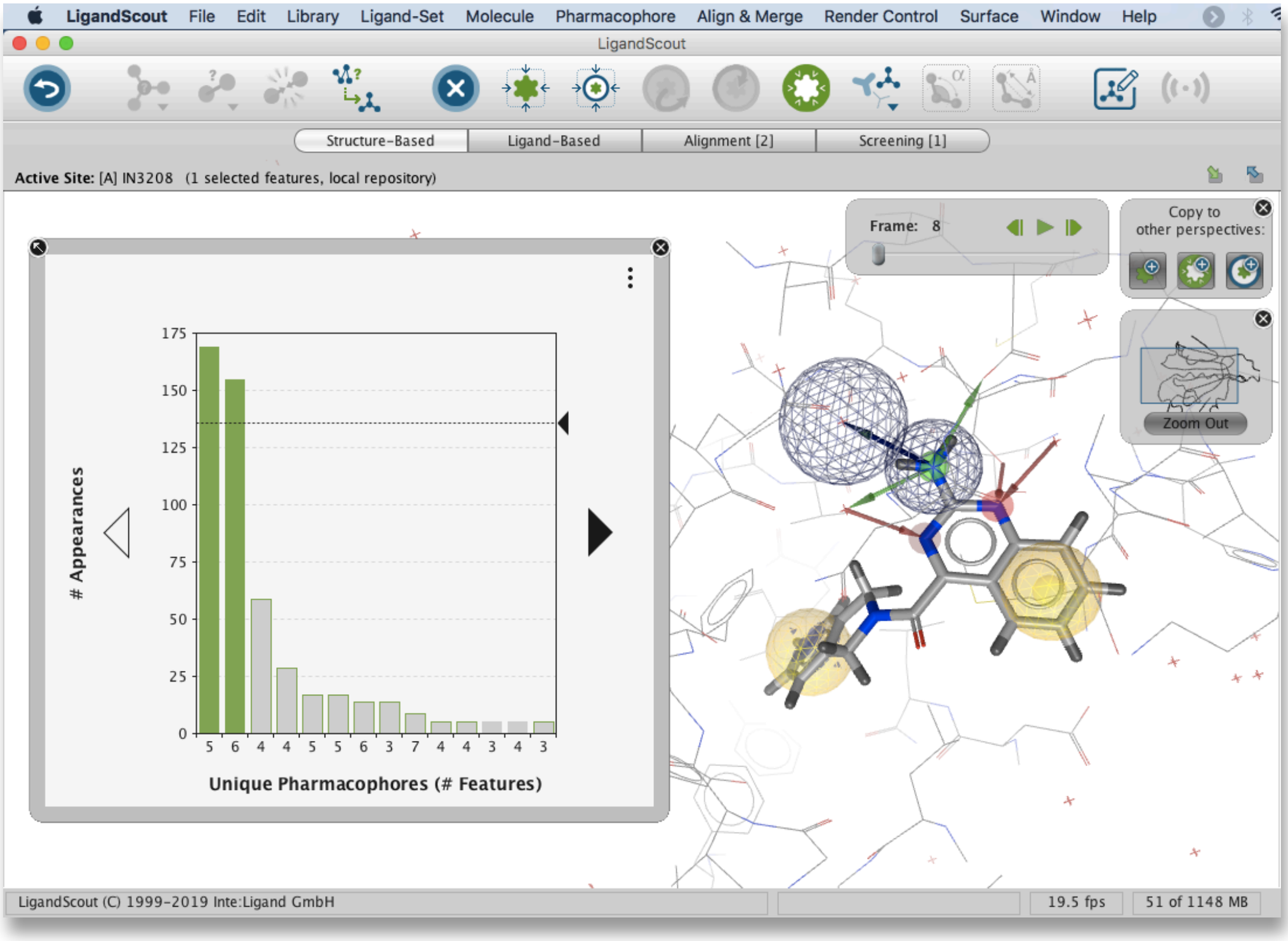

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Determine Interacting Amino Acids

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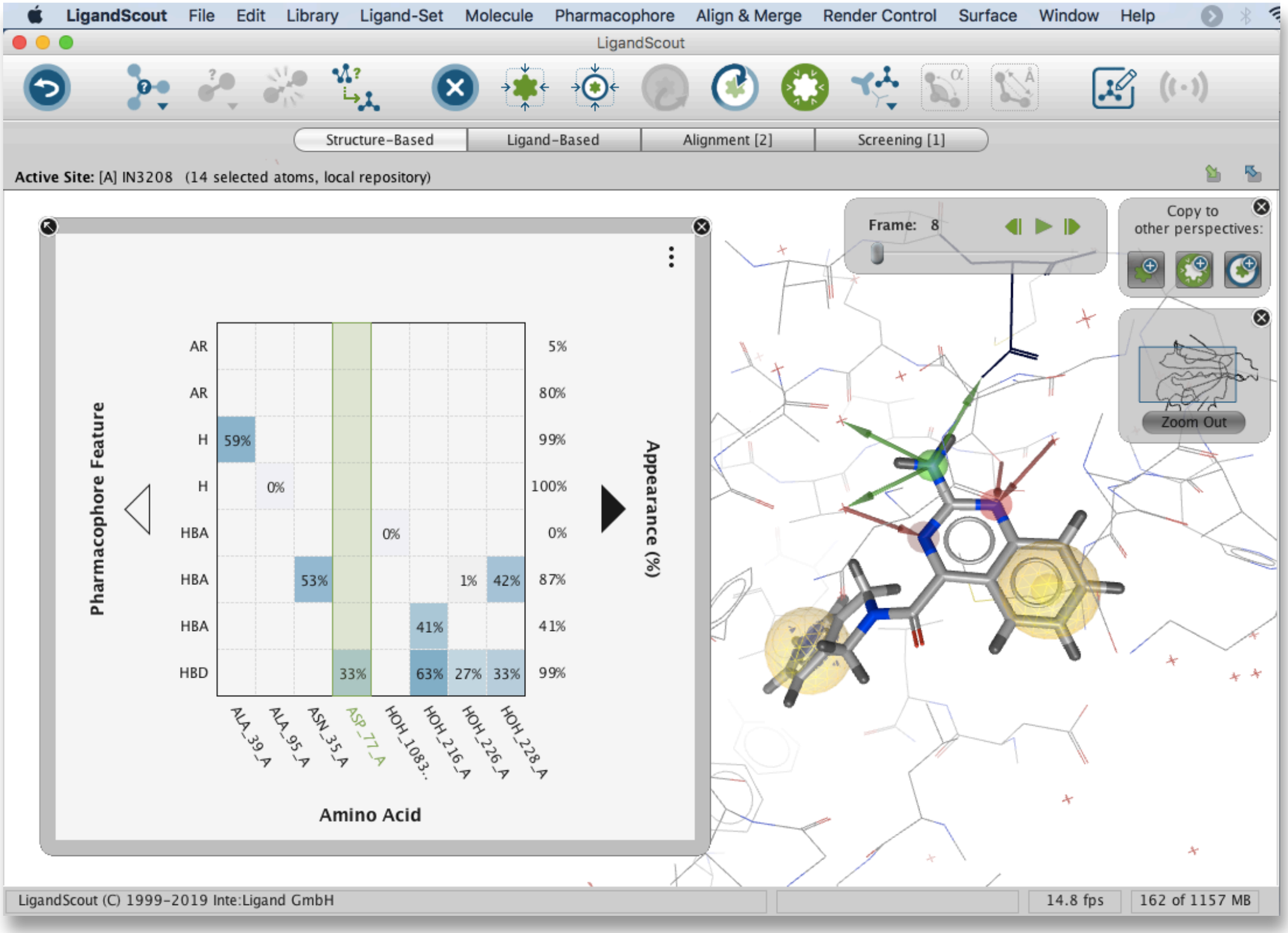

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Use in Lead Optimization

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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

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

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

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VS Results Example: AUC (2i78)

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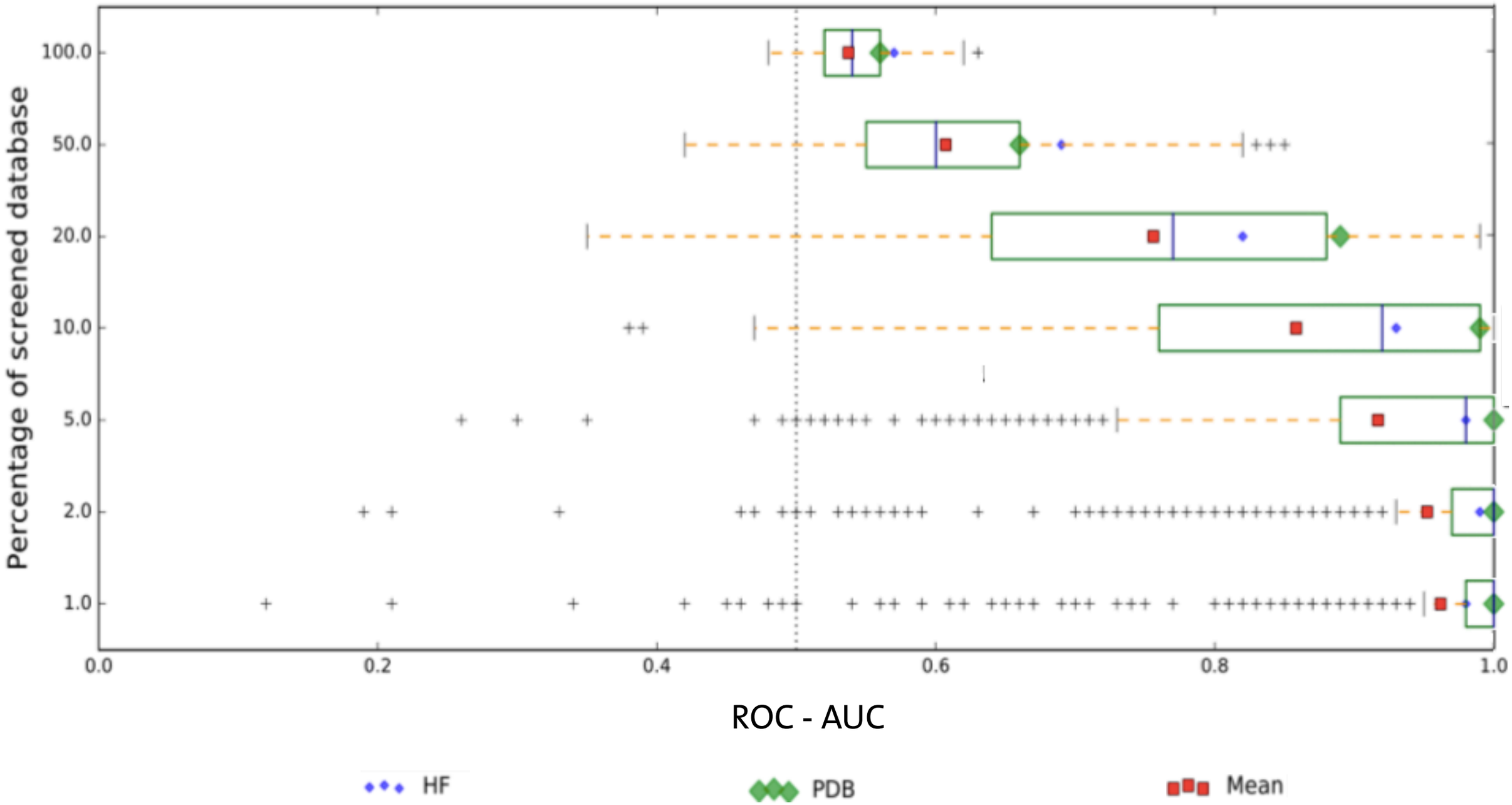

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VS Results Example: AUC (2i78)

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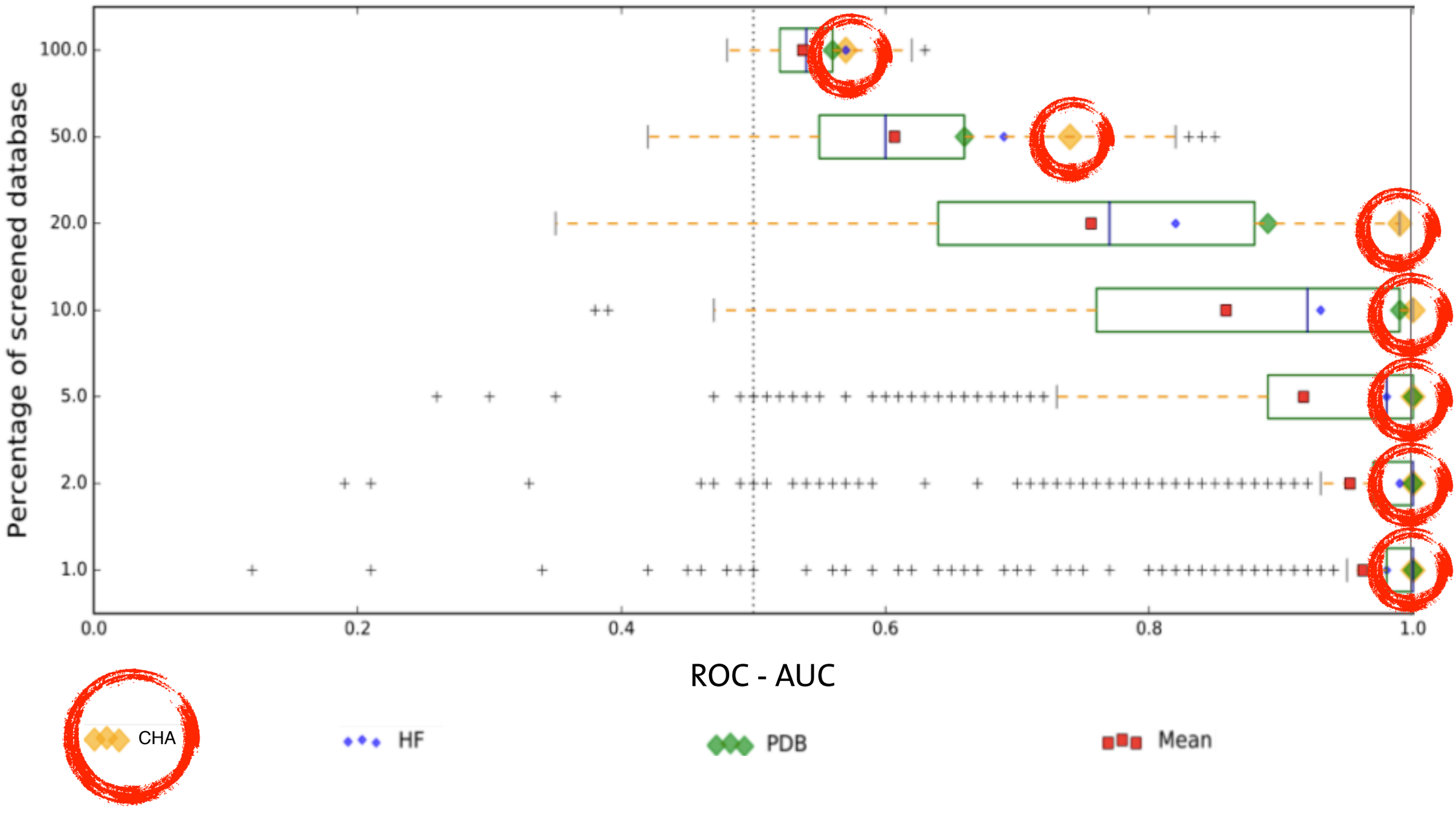

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Further Steps in the Procedure

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- Create a grid within the binding site for each MD frame
- Perform grid calculations
  - Buriedness and drugability threshold
  - Interaction probabilities for each grid point
- Align the grids
- Vizualize and analyse data
  - Look for emerging binding pockets
  - Find hot spots for potential ligand-protein interactions
  - Evaluate binding contribution of specific water molecules

https://github.com/aglanger/CDPKit

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JCTC Journal of Chemical Theory and Computation

Article

Cite This: J. Chem. Theory Comput. 2018, 14, 4958−4970

pubs.acs.org/JCTC

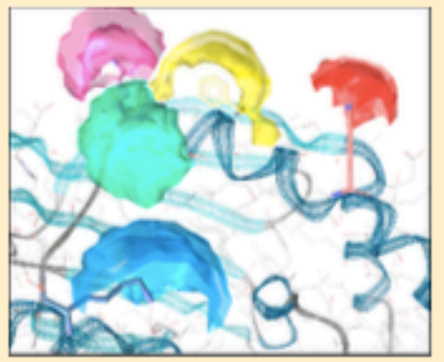
GRAIL: GRids of phArmacophore Interaction fieLds

Doris A. Schuetz,[†] Thomas Seidel,*[,‡] Arthur Garon,[‡] Riccardo Martini,[†,‡] Markus Körbel,[‡,∥] Gerhard F. Ecker,[‡] and Thierry Langer[†,‡]

[†]Inte:Ligand GmbH, Mariahilferstrasse 74B/11, A-1070 Vienna, Austria

[‡]Department of Pharmaceutical Chemistry, University of Vienna, UZA 2, Althanstrasse 14, 1090 Vienna, Austria

ABSTRACT: In the absence of experimentally derived, three-dimensional structures of receptors in complex with active ligands, it is of high value to be able to gain knowledge about energetically favorable interaction sites solely from the structure of the receptor binding site. For de novo ligand design as well as for lead optimization, this information retrieved from the protein is inevitable. The herein presented method called GRAIL combines the advantages of traditional grid-based approaches for the identification of interaction sites and the power of the pharmacophore concept. A reduced pharmacophoric abstraction of the target system enables the computation of all relevant interaction grid maps in short amounts of time. This allows one to extend the utility of a grid-based method for the analysis of large amounts of coordinate sets obtained by long-time MD simulations. In this way it is possible to assess conformation dependent characteristics of key interactions over time. Furthermore, conformational changes of the protein can be taken into account easily and information thus obtained well-guides a rational ligand design process. A study employing MD trajectories of the oncology target heat shock protein 90 showcases how well our novel approach GRAIL performs for a set of different inhibitors bound to their target protein and how molecular features of the inhibitors are subject to optimization.



Vizualisation (1)

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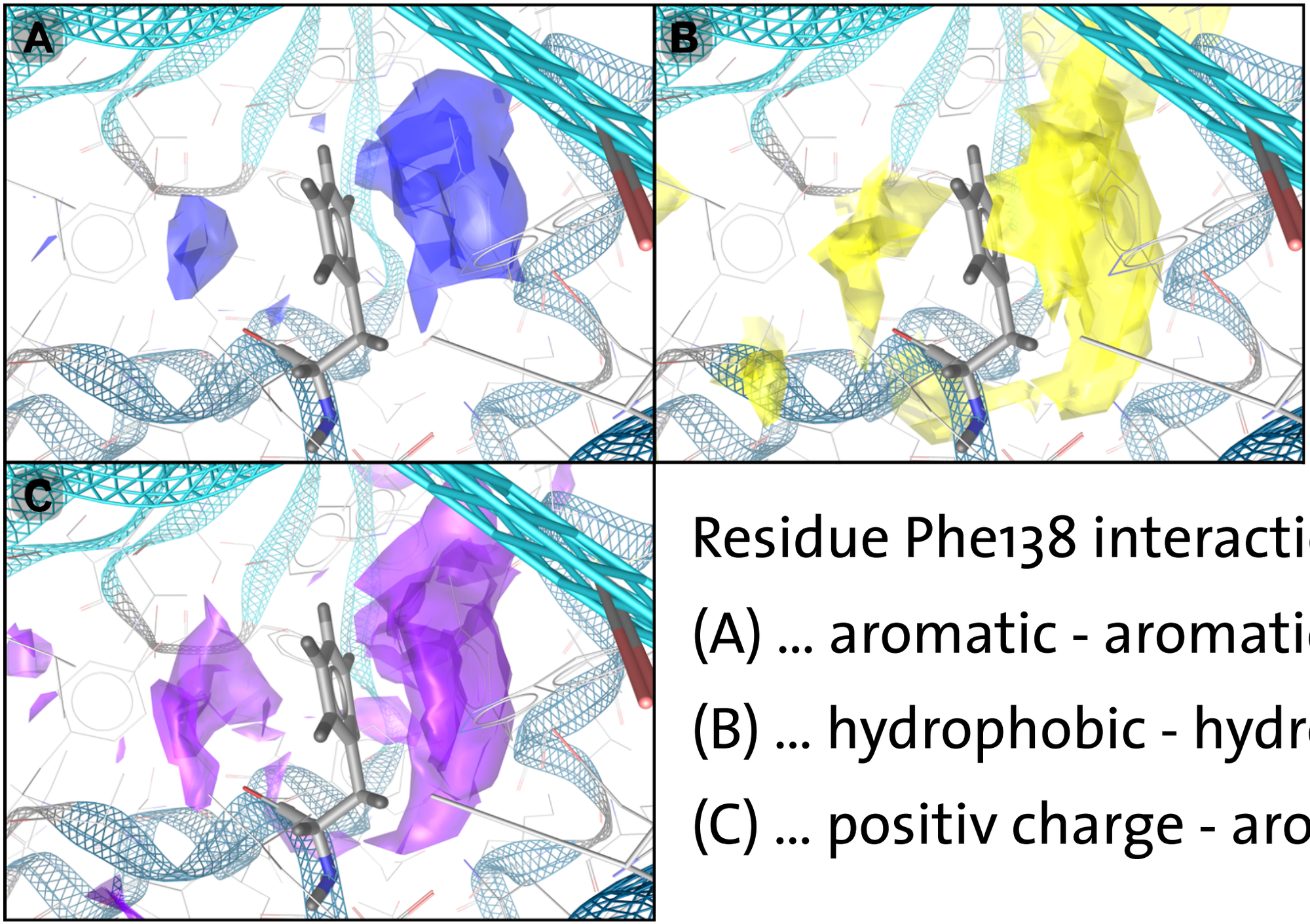

Residue Phe138 interactions:

(A) ... aromatic - aromatic

(B) ... hydrophobic - hydrophobic

(C) ... positiv charge - aromatic

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Vizualisation (2)

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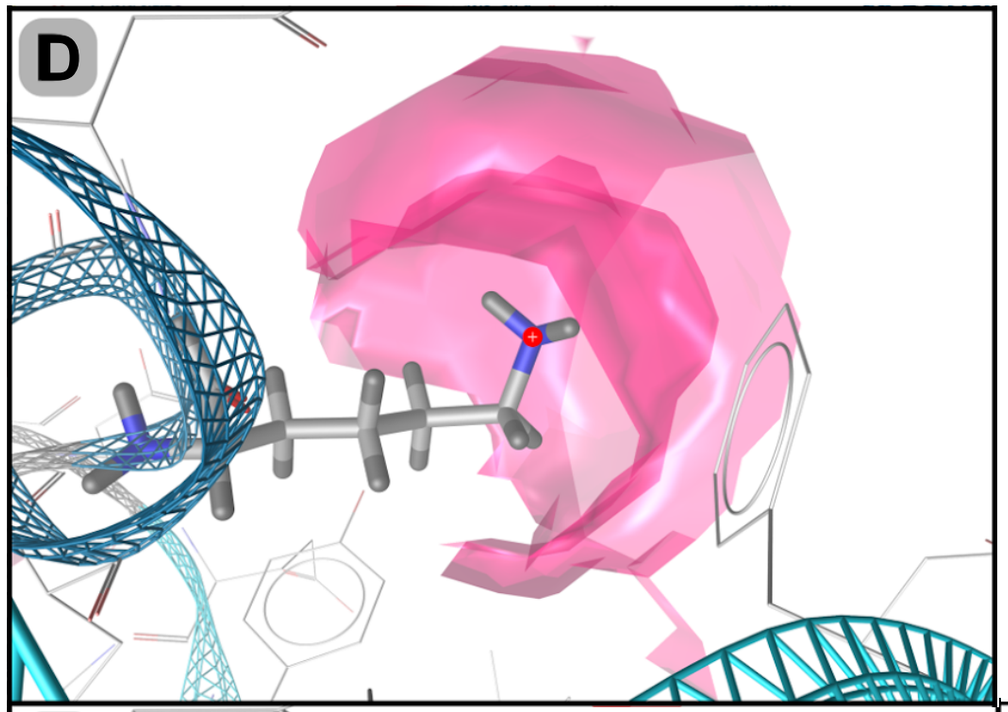
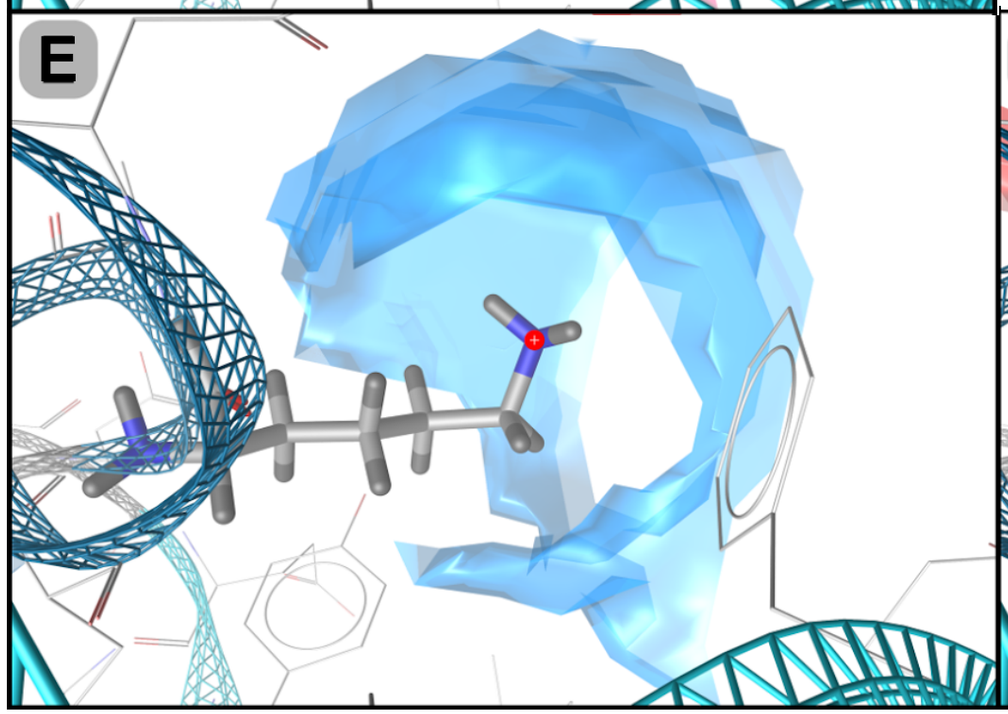


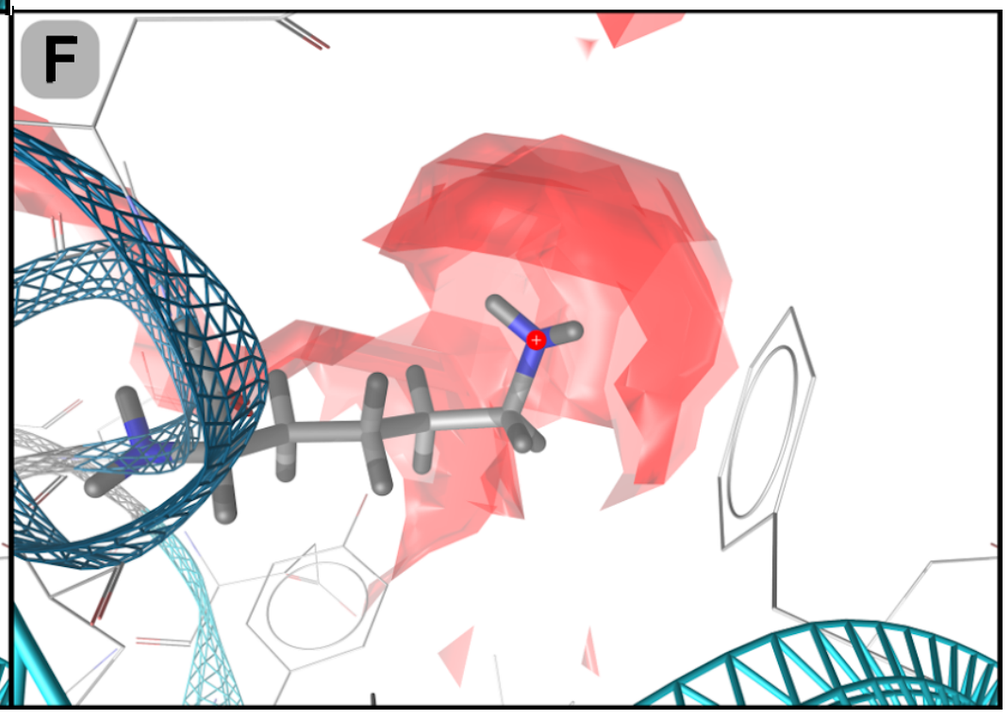
Residue Lys100 interactions:

(D) ... negative - positive charge

(E) ... aromatic - positive charge

(F) ... HBA - HBD





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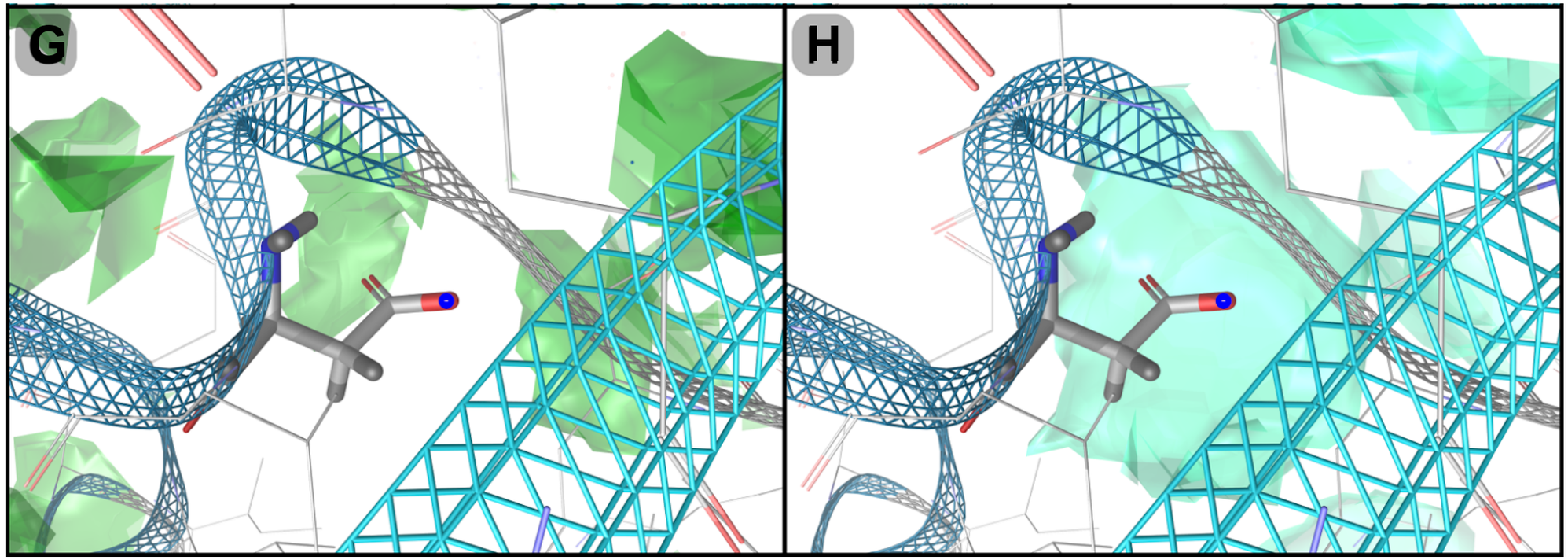
Vizualisation (3)



Residue Asp85 interactions:

(G) ... HBD -> HBA

(H) ... hydrophobic - hydrophobic

Further Steps in the Procedure

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- Create grid covering the binding site for each frame of the MD
- Perform calculations at grid points:
  - Buriedness and drugability threshold
  - Interaction probabilities for each feature at each point
- Align the grids and vizualize
- Further analysis
  - Look for emerging binding pockets
  - Find hot spots for interactions
  - Evaluate water molecules

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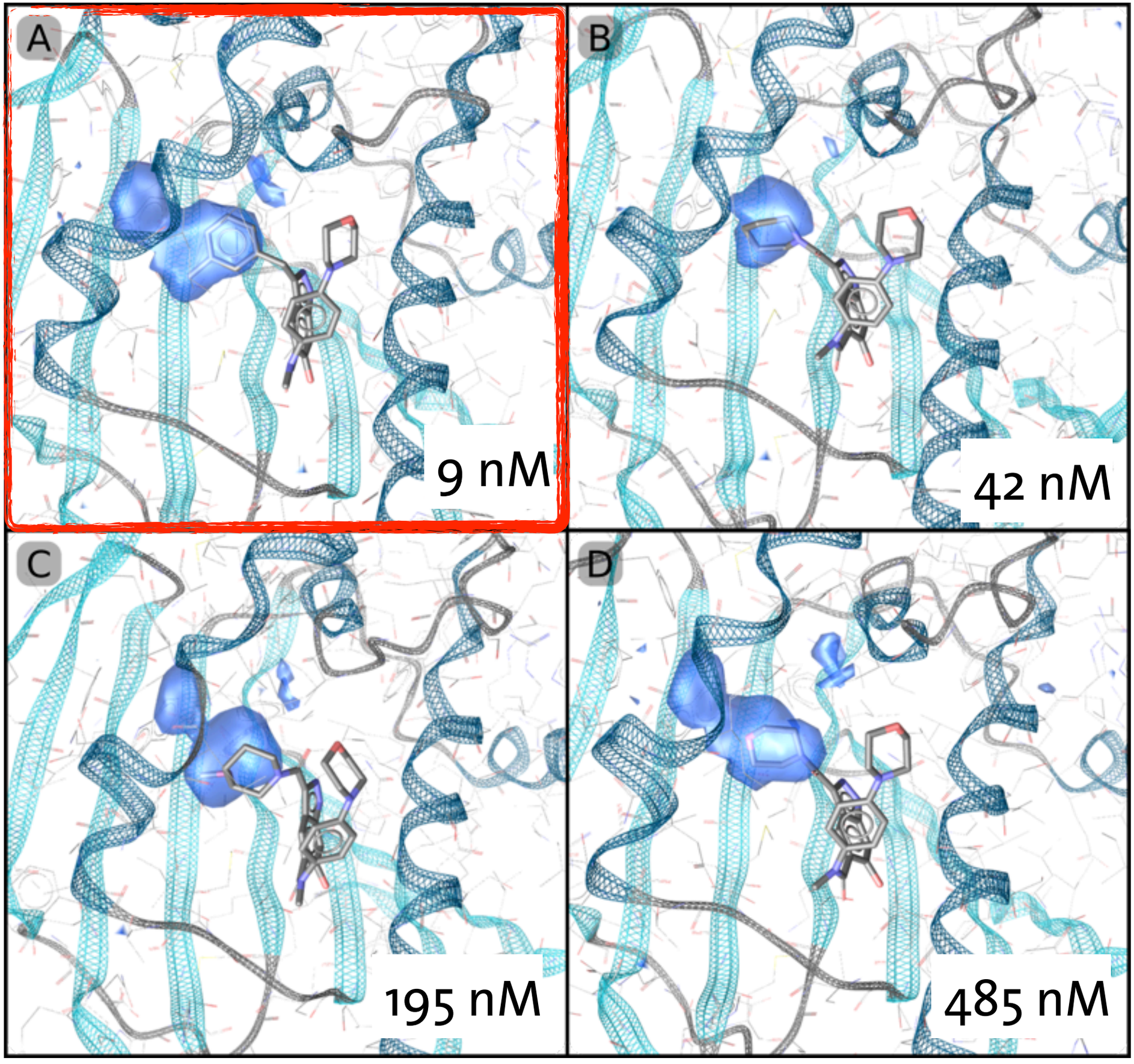

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Use in Lead Optimization

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- Easy understandable design guidance provided
- Focus on specific regions
  - e.g. replacing entropically disfavored 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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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**

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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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NEURODERISK

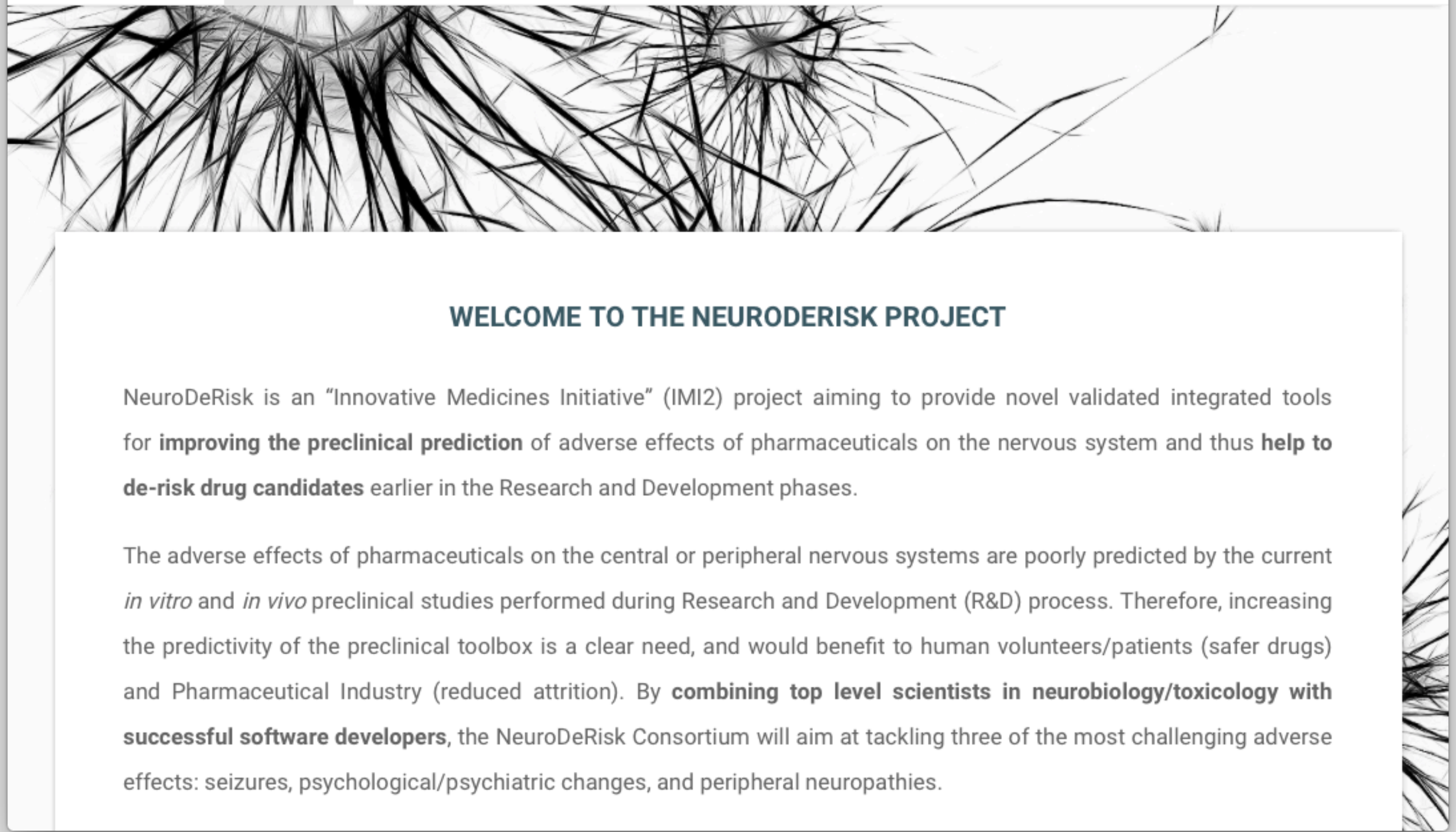
DERISKING NEUROTOXICITY

The NeuroDeRisk project has received funding from the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking under grant agreement No 821528.

This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

imi innovative medicines initiative

efpia



WELCOME TO THE NEURODERISK PROJECT

NeuroDeRisk is an “Innovative Medicines Initiative” (IMI2) project aiming to provide novel validated integrated tools for **improving the preclinical prediction** of adverse effects of pharmaceuticals on the nervous system and thus **help to de-risk drug candidates** earlier in the Research and Development phases.

The adverse effects of pharmaceuticals on the central or peripheral nervous systems are poorly predicted by the current *in vitro* and *in vivo* preclinical studies performed during Research and Development (R&D) process. Therefore, increasing the predictivity of the preclinical toolbox is a clear need, and would benefit to human volunteers/patients (safer drugs) and Pharmaceutical Industry (reduced attrition). By **combining top level scientists in neurobiology/toxicology with successful software developers**, the NeuroDeRisk Consortium will aim at tackling three of the most challenging adverse effects: seizures, psychological/psychiatric changes, and peripheral neuropathies.

De-risking Neurotoxicity

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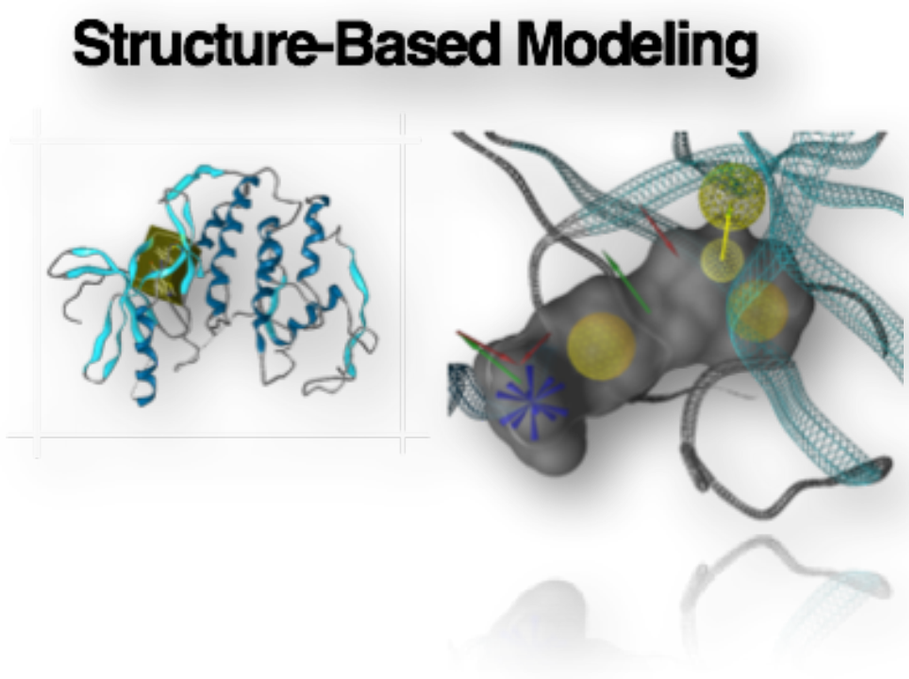
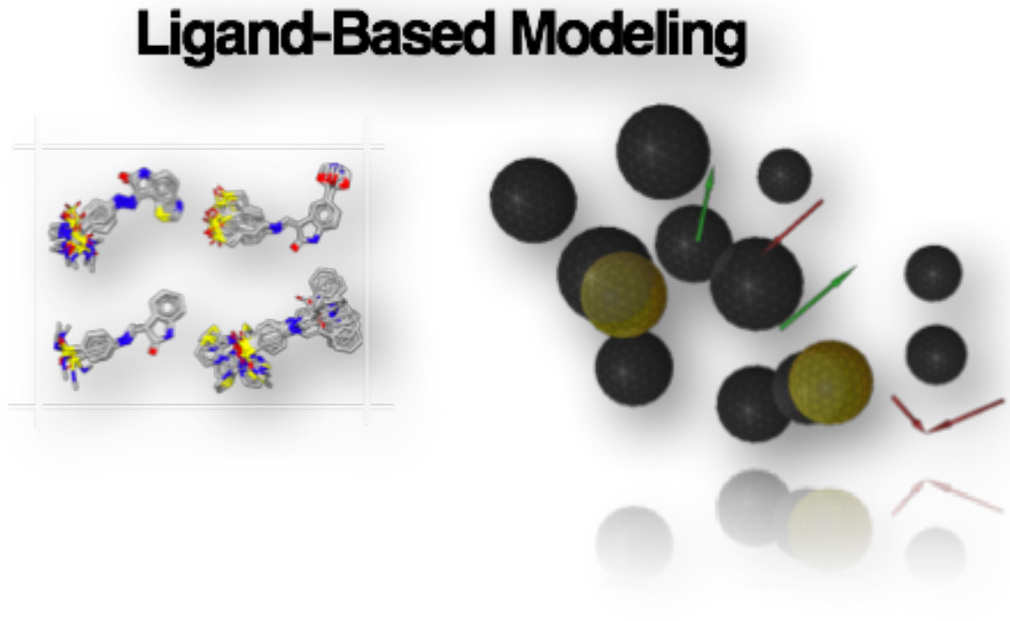
Target Based Approach

- Seizure Risk / Pharmacology
- GABA-A Antagonist
- GABA-A NAM
- GABA-A Channel Blocker
- GABA-A PAM
- GABA-A Agonist
- GABA-A Neurosteroid

Outcome Based Approach

- Suicidal Ideation
- Drugs associated with reported outcomes (pharmacovigilance)
- RNA Editing (Alcediag)





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De-risking Neurotoxicity

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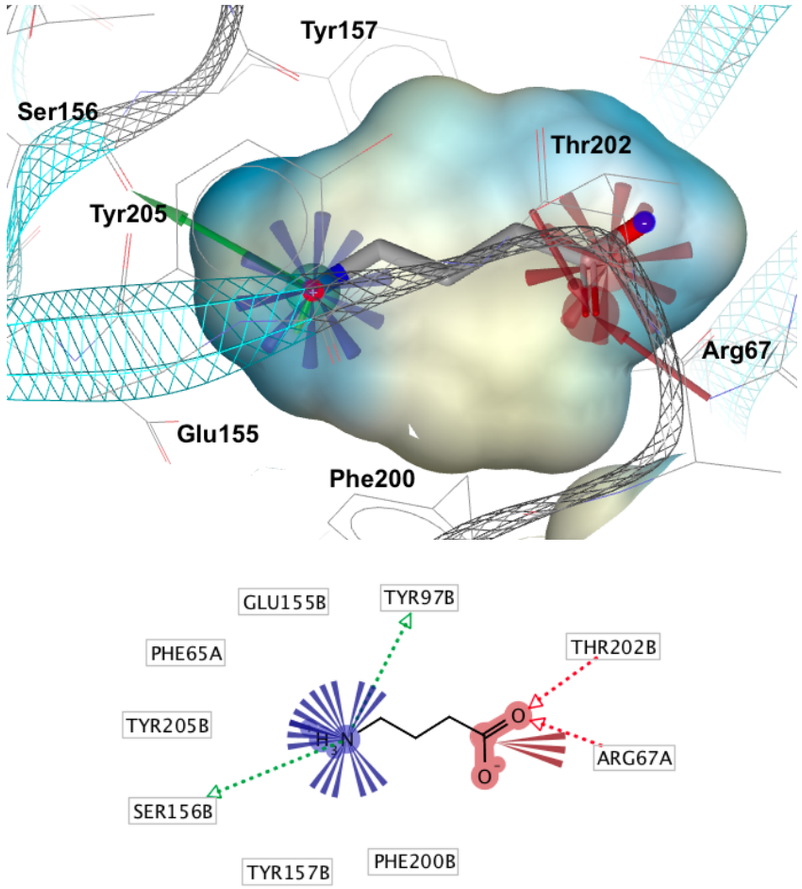
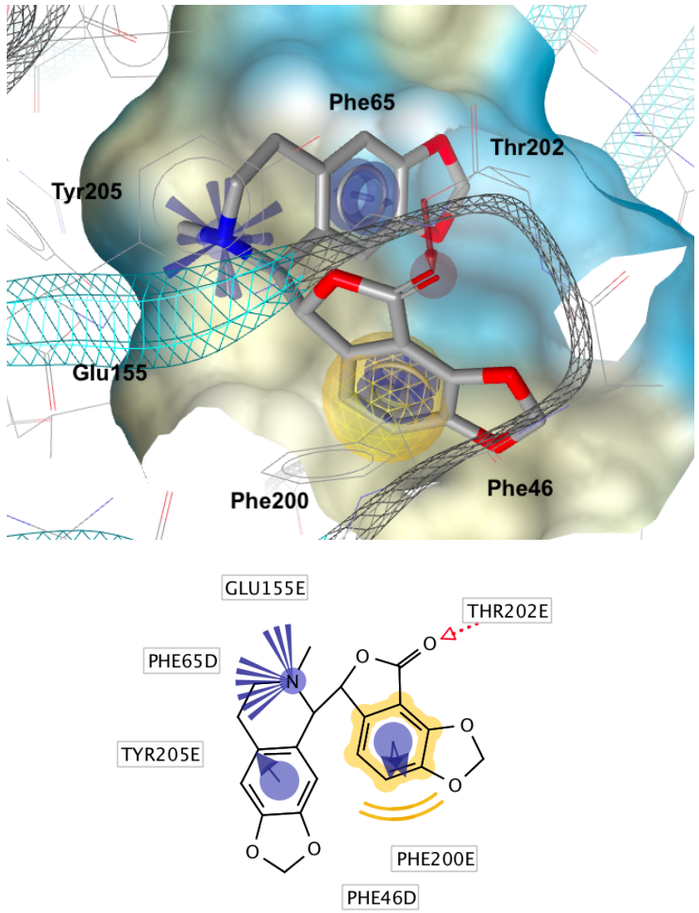
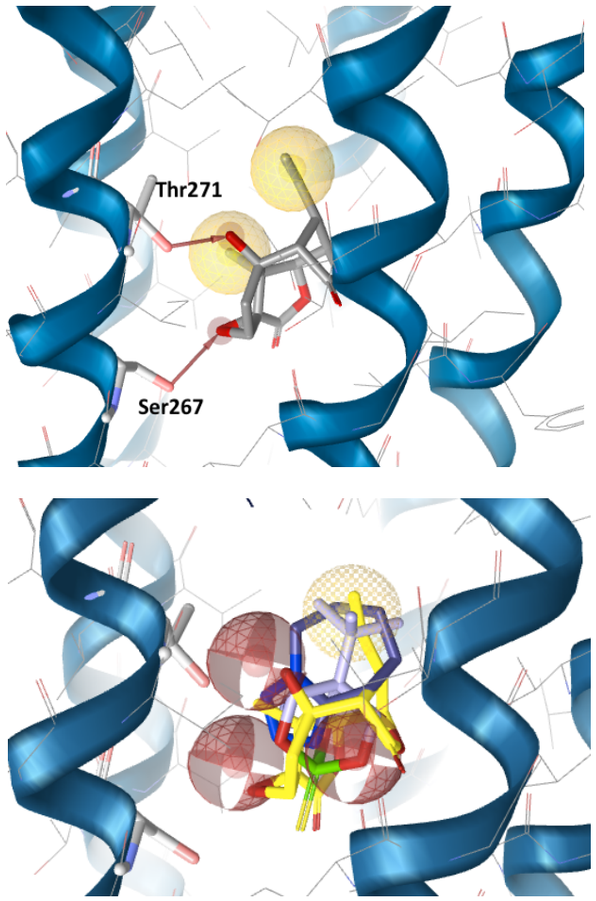
GABA-A orthosteric site, channel SB-modeling examples



GABA-GS-Agonist
(PDB ID:6huj)



Bicuculline-GS-Antagonist
(PDB ID:6huk)



Picrotoxinin-Channel
(PDB ID:6huj)

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De-risking Neurotoxicity

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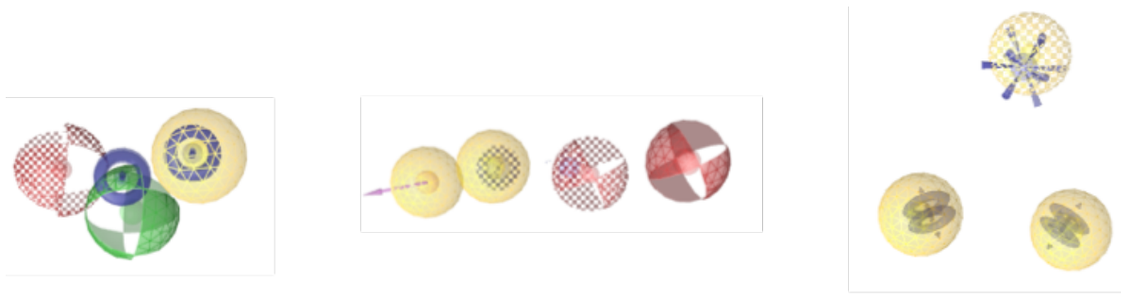
Can we identify chemical features in 3D-space associated with suicidal ADEs?

- Outcome Based Approach – No Target
- Suicidal Ideation (5 terms)
- 1492 drugs with suicidal annotations from FAERS, Meta ADEDB and NIH databases (pharmacovigilance)
- Clustering; > 45 LB models created and tested
- Models also generated using confidential experimental data from Alcediag
- Editox – unambiguous IFNa like RNA editing profiles (Alcediag)



Name	#	Matching Features
Bifeprunox	2	
Hydralazine	1	
Reserpine	3	
Rimonabant	1	
Ketoconazole	5	
Sertindole	3	
Taranabant	4	
Aripiprazole	2	
Imipramine	4	
Clomipramine	5	
Diphenhydramine	1	
Fluoxetine	2	
Nortriptyline	3	

Promising results with the IFNα like RNA editing (Editox) datasets

Van der Laan, S, et. al., (2017) Emerging RNA editing biomarkers will foster drug development. Drug Discovery Today, 22(7), 1056. doi:10.1016/j.drudis.2017.01.017

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De-risking Neurotoxicity

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- >60 3D-pharmacophore models have so far been incorporated and deployed in the toolbox for profiling of molecules

5 AMPA

- NDR-IL-AMPA-Agonist-LB
- NDR-IL-AMPA-Antag-Fanapel-6ruq
- NDR-IL-AMPA-Kainate-4u2q-a
- NDR-IL-AMPA-PAM-HI-LB-2
- NDR-IL-AMPA-PAM-Thiazides-LB

6 NMDA N2A

- NDR-IL-NMDA-Agonist-Glu-7eu7
- NDR-IL-NMDA-Agonist-Gly-7eu7
- NDR-IL-NMDA-Antag-Glu-LB
- NDR-IL-NMDA-Antag-Gly-1pbq
- NDR-IL-NMDA-Antag-Gly-LB
- NDR-IL-NMDA-Channel-LB-2

7 Suicidality

- NDR-IL-Suicidality-2
- NDR-IL-Suicidality-3
- NDR-IL-Suicidality-3v1
- NDR-IL-Suicidality-4
- NDR-IL-Suicidality-5
- NDR-IL-Suicidality-SE-ed-1
- NDR-IL-Suicidality-SE-sd-6

23 GABA-AR

- NDR-IL-GABA-A-Barbiturate-LB
- NDR-IL-GABA-A-Channel-LB-6
- NDR-IL-GABA-A-gs-Agonist-6huj-4
- NDR-IL-GABA-A-gs-Agonist-LB
- NDR-IL-GABA-A-gs-Antag-6huk-3
- NDR-IL-GABA-A-gs-Antag-LB
- NDR-IL-GABA-A-NAM-Flumazenil-6d6t
- NDR-IL-GABA-A-NAM-Flumazenil-LB
- NDR-IL-GABA-A-NSteroid-Pregnanolone-5O8f
- NDR-IL-GABA-A-PAM-BDZ-LB-3
- NDR-IL-GABA-A-PAM-Diazepam-6hup-2
- NDR-IL-GABA-A-Z-drug-LB
- NDR-IL-GABA-A-a1-BDZ-site-EFPIA-C24
- NDR-IL-GABA-A-a1-BDZ-site-EFPIA-C38
- NDR-IL-GABA-A-a1-BDZ-site-EFPIA-C42
- NDR-IL-GABA-A-a1-BDZ-site-EFPIA-Cmix-2
- NDR-IL-GABA-A-a2-Flumazenil-site-EFPIA-C8-2
- NDR-IL-GABA-A-a3-Flumazenil-site-EFPIA-C61
- NDR-IL-GABA-A-a3-Flumazenil-site-EFPIA-C74
- NDR-IL-GABA-A-a4-Ro154513-site-EFPIA-C5
- NDR-IL-GABA-A-a5-Flumazenil-site-EFPIA-C47
- NDR-IL-GABA-A-a5-Flumazenil-site-EFPIA-C51
- NDR-IL-GABA-A-a6-Ro154513-site-EFPIA

4 GlyRa3

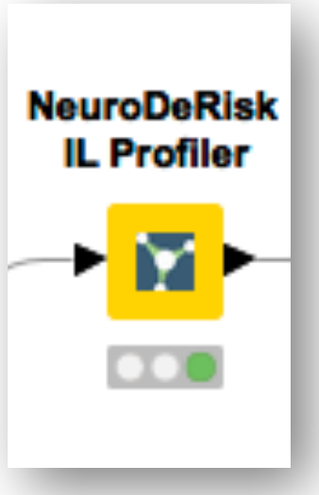
- NDR-IL-GlyRa3-Antag-LB
- NDR-IL-GlyRa3-Antag-Strychnine-5cfb-d3
- NDR-IL-GlyRa3-Channel-LB
- NDR-IL-GlyRa3-os-Agonist-5vdh-c

3 BBB Transporter

- NDR-IL-BBB-H+CO-Antiporter-C13C11-LB-2
- NDR-IL-BBB-OATP1A2-C18-LB
- NDR-IL-BBB-OATP1A2-C19-LB

15 PNS

- NDR-IL-PNS-Anthra-C3
- NDR-UV-PNS-Bendam-LB
- NDR-UV-PNS-CarfilTacrol-LB
- NDR-UV-PNS-Conazols-LB
- NDR-UV-PNS-EribEto-LB
- NDR-UV-PNS-Ixabepil-LB
- NDR-UV-PNS-M18-LB
- NDR-UV-PNS-M6-LB
- NDR-UV-PNS-M9-LB
- NDR-UV-PNS-Mefloq-LB
- NDR-UV-PNS-Omibs-LB
- NDR-UV-PNS-Procarb-LB
- NDR-UV-PNS-Snibs-LB
- NDR-UV-PNS-Taxels-LB
- NDR-UV-PNS-VincaA-LB



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Neurotox Off Target Prediction

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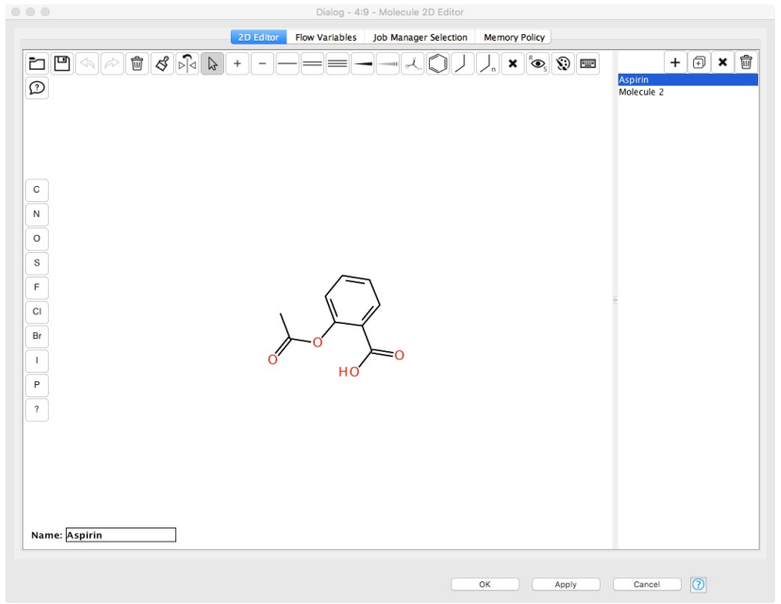
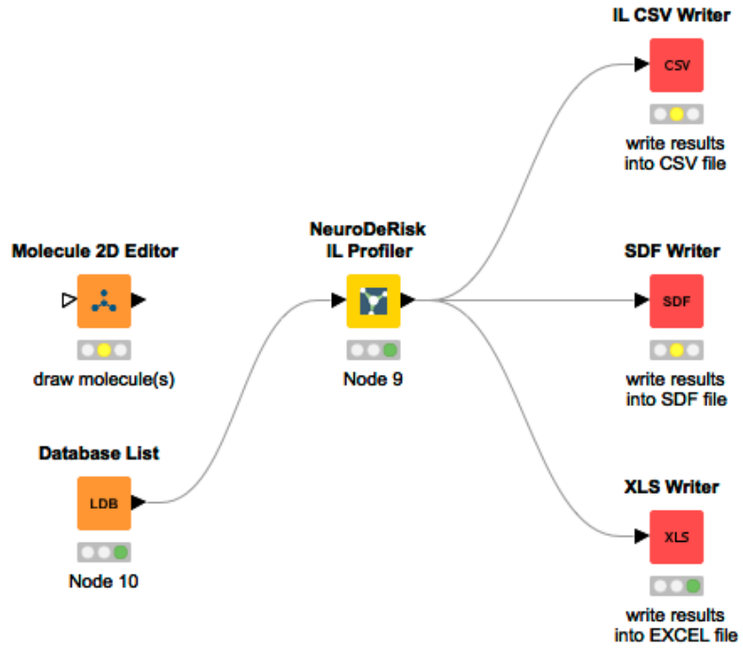
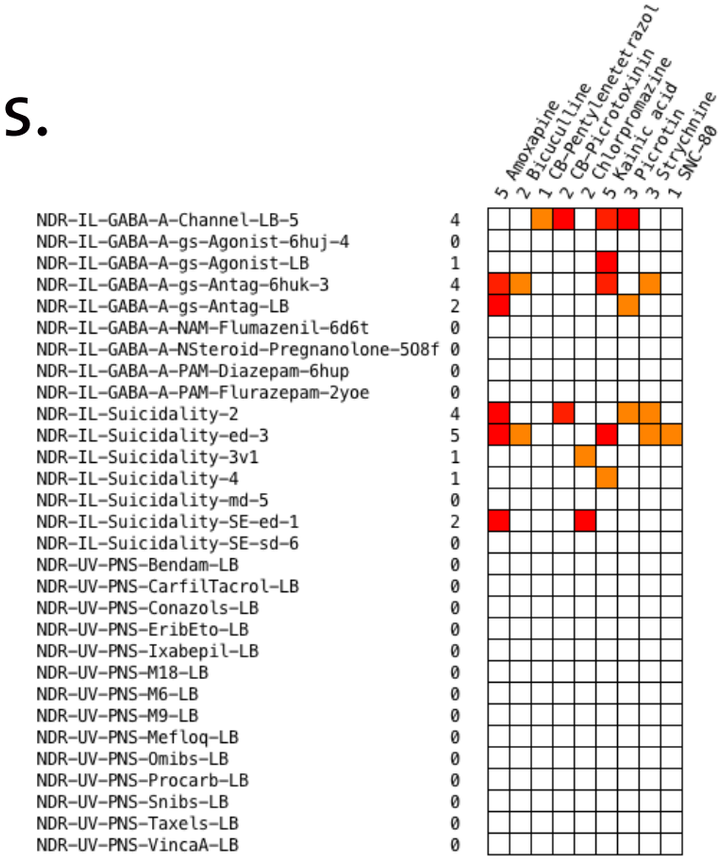
- Profile chemical structures (queries) using 3D-pharmacophore models.
- All compounds nominated for studies (WPs 1, 2, 3) have been profiled.
- 30 Models and LigandScout algorithms for profiling are coded into the NeuroDeRisk IL Profiler node.
- Multiple inputs supported including a 2D-editor.
- Visualize and export (PNG, CSV, XLS, SDF, etc) results.







https://neuroderisk.eu/in-silico-toolbox/

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Next Gen Pharmacophores: QPhAR

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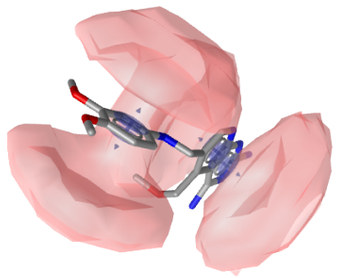
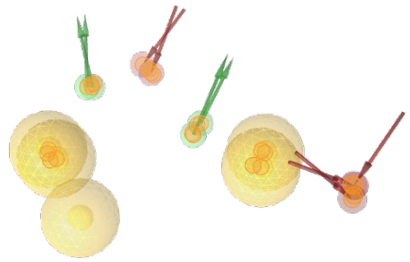


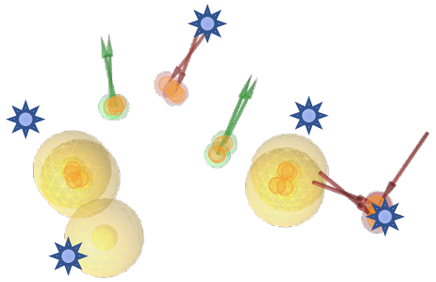
GRAIL* Based Pharmacophore



LigandScout Merged Pharmacophore

Cross Validation

Novel Quantitative Pharmacophore Methodology



Mo. 6

Today

* GRAIL: GRids of phArmacophore Interaction fieLds. Schütz D. et al., J. Chem. Theory Comput. 2018, 14, 9, 4958.

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Training Steps in QPhAR

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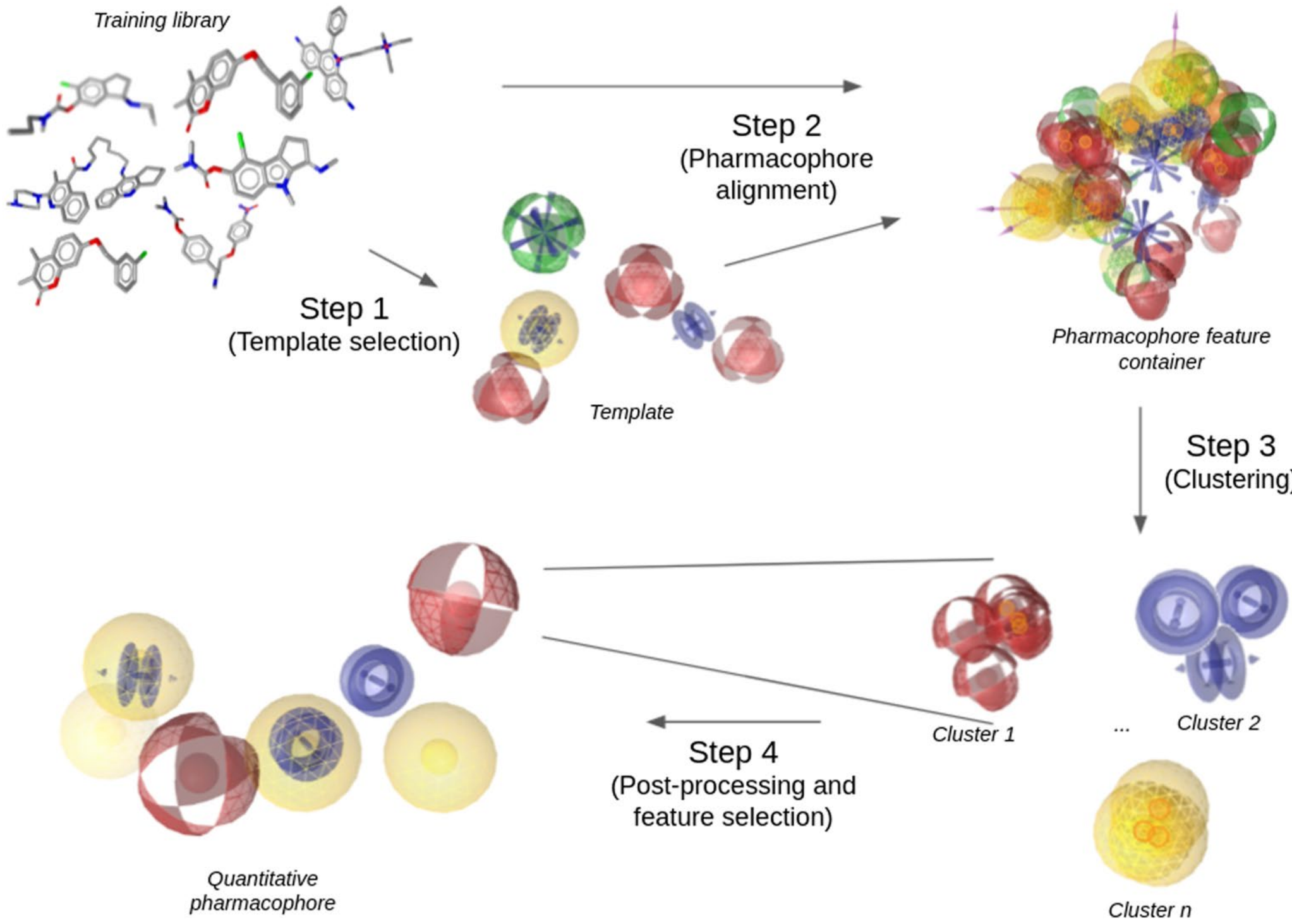

Kohlbacher SM et al., J Cheminform 13, 57 (2021)
https://doi.org/10.1186/s13321-021-00537-9

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QPhAR Workflow

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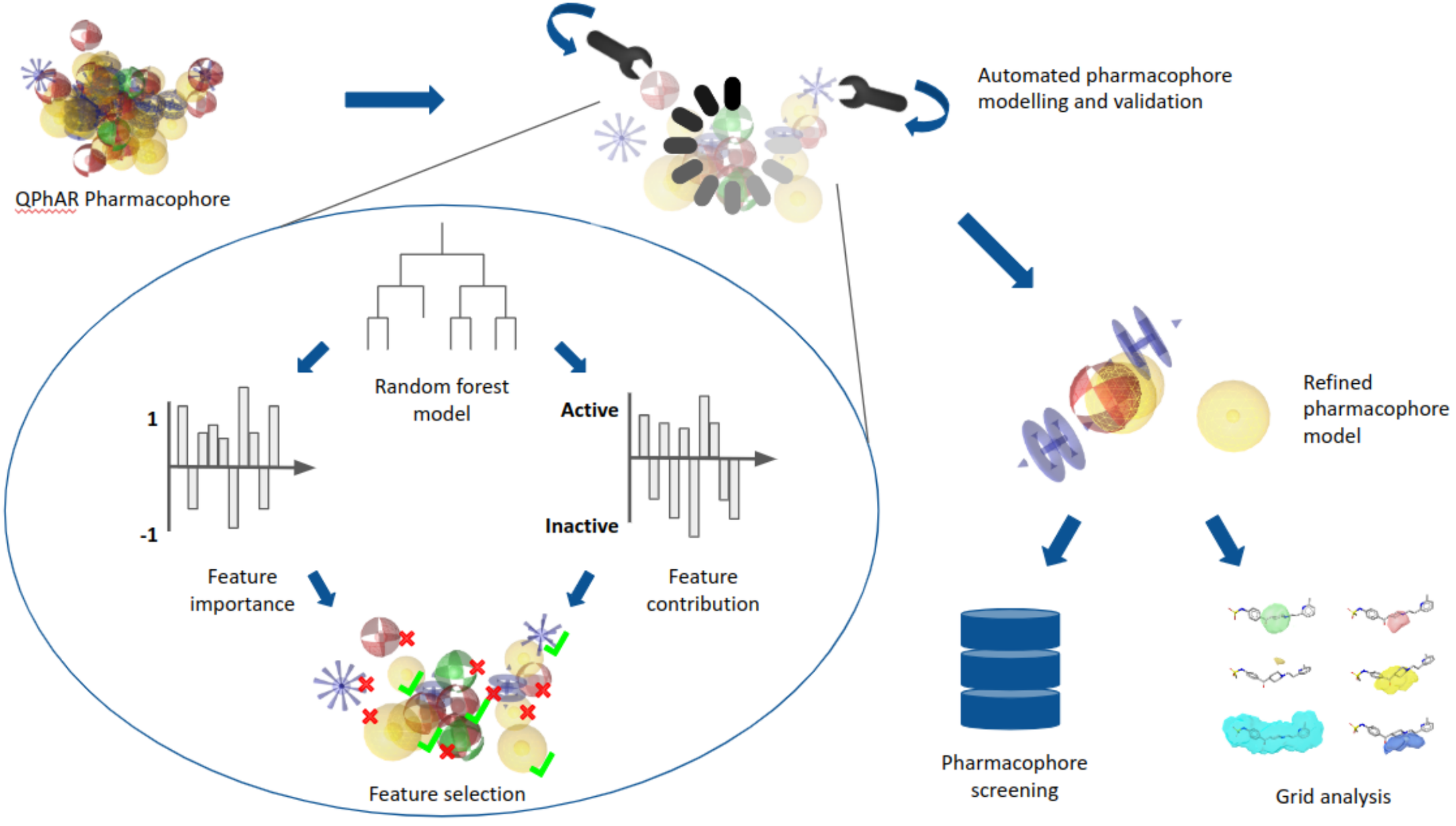

Kohlbacher SM et al., Pharmaceuticals 2022, 15, 1122. https://doi.org/10.3390/ ph15091122

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QPhAR in KNIME Platform

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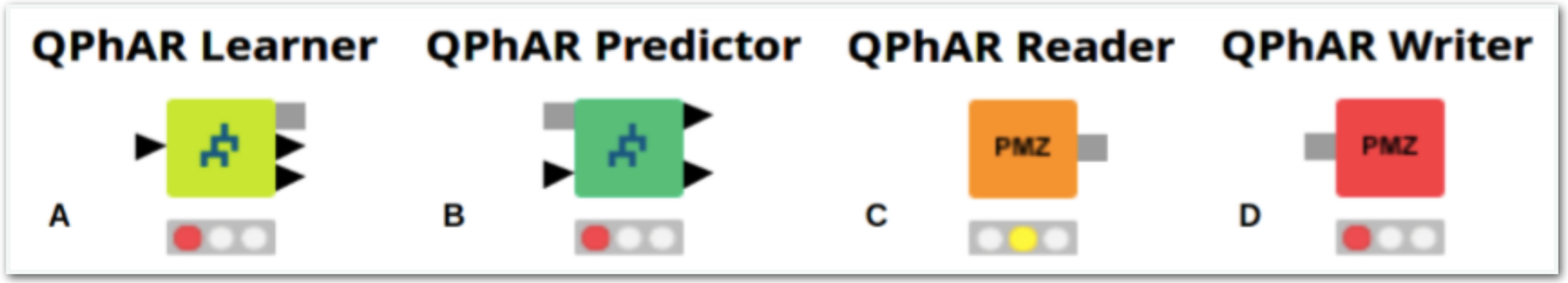

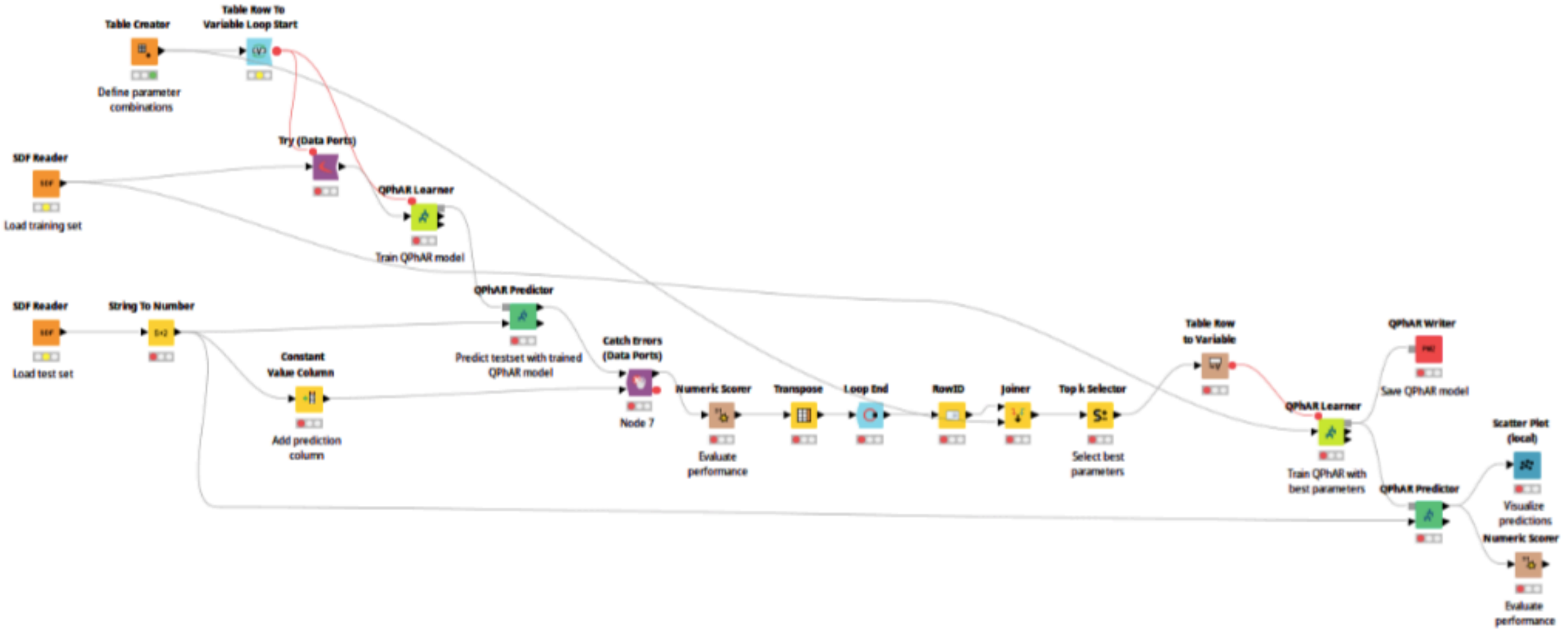

https://github.com/StefanKohlbacher/qphar-knime-nodes

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LigandScout 5 Sneak Preview

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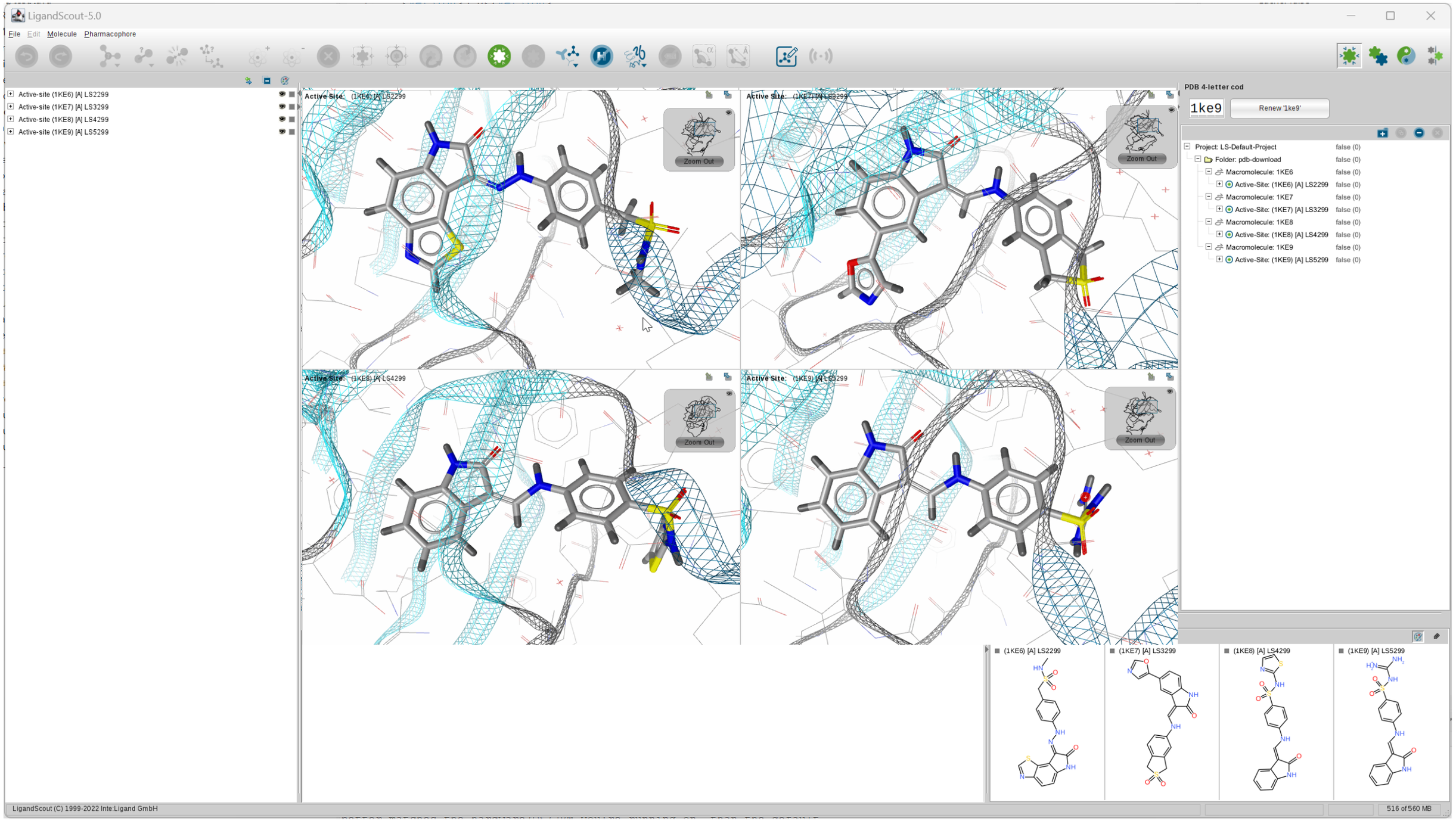

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Thank you for your attention

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https://www.inteligand.com

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