17th CLUB PHASE 1 ANNUAL MEETING, 5 April 2018, Paris

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In silico tools for early phase side effect profiling and off target prediction of potential drug candidates

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Thierry Langer

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Outline

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- Introduction & technical backgroud
  - Rule-based approach
  - (Q)SAR-based approach
  - Molecular interactions-based approach
- Our own technology platform
- Success stories
- Conclusions

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Never Forget !

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- Risk of toxicity / unwanted side effects can also be related to drug metabolites
- All possible metabolites must therefore be enumerated and assessed
- For in silico prediction of metabolism, see e.g.

  Predicting Drug Metabolism: Experiment and/or Computation?
  Kirchmair et al., Nature Reviews Drug Discovery 14, 387–404 (2015)

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Rule-based Approach

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- Alerts based on substructure analysis and compound database knowlegde-based search
- For examples see e.g. Lhasa Limited
  - Derek Nexus

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About Us: Developing expert computer systems and facilitating data-sharing in the life science industries

Lhasa Limited is a not-for-profit organisation and educational charity that facilitates collaborative data sharing projects in the pharmaceutical,
cosmetics and chemistry-related industries.
Lhasa Limited specialises in the development of expert computer systems for toxicity and metabolism prediction.

Read more

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shared **knowledge** shared **progress**

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Initiatives > eTOXsys

- Initiatives
- AI/PDE
- Aromatic Amines
- Elemental Impurities
- eTOXsys
- EU-ToxRisk
- Excipients
- FDA RCA
- iPiE
- Lhasa Carcinogenicity Database
- Production Intermediates

eTOXsys

eTOXsys is an essential software solution that can deliver improved early drug candidate safety assessment through intuitive access to proprietary toxicology data and predictive models.

eTOXsys

The Models

Expert model developers have provided well-documented and verified predictive models for endpoints including ADME, organ toxicity and target safety pharmacology.

The Database

This data has been derived from proprietary data donated by the 13 pharmaceutical eTOX partners. The chemical space covered by the eTOX database is highly relevant for drug discovery and development.

Find Out More

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eTOXsys

Improved early drug candidate safety assessment

Home | The Platform | The Models | The Database | Features and Benefits | eTOX

You are in: Home

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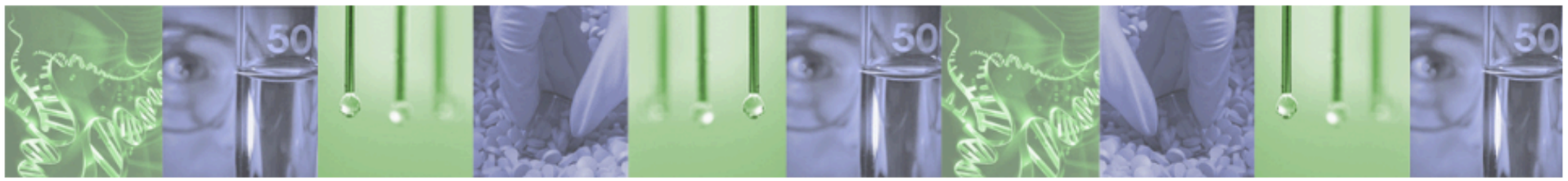

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Read more

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Read more

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Read more

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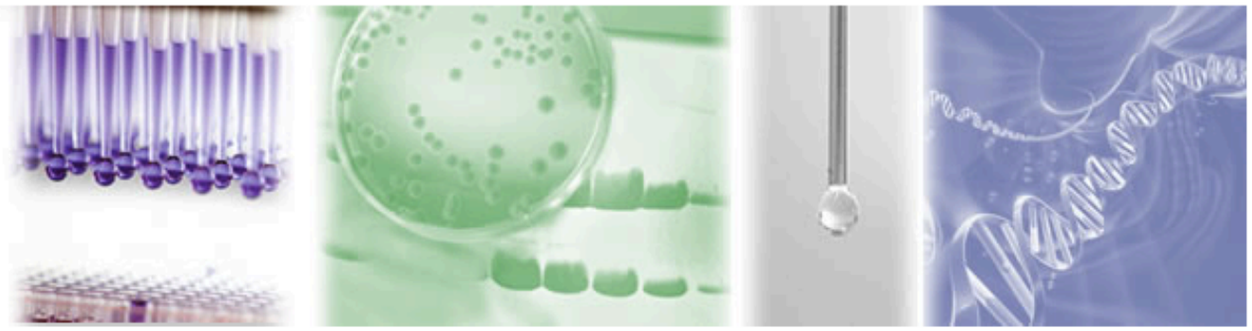

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LAST NEWS

February 2018
eTOX project close out meeting

On January 25th, eTOX Executive Committee members: François Pognan, Ferran Sanz, Thomas Steger-Hartmann and Carlos Díaz held the close out meeting of the eTOX project at the IMI´s offices in Brussels.

January 2018
Latest version of the histopathology ontology has been released

Histopathology Ontology was initially developed in the framework of the eTOX consortium, aiming at the standardisation of the histopathology findings, and it is now made

Welcome to the eTOX Website

This has been the main communication tool of the eTOX outcomes during the project's life, 2010-2016.

The **eTOX project** was granted as one of the first IMI projects. It has successfully ended its consortium life after 7 years of collaboration between 13 pharma companies, 11 academia institutions and 6 SMEs.
The **eTOX project** as IMI consortium has been completed with the accomplishment of an effective synergic sharing of historical toxicological data within the pharmaceutical industry. It created a series of models to support toxicity prediction. Both data and models are integrated in the platform developed in the project, the **eTOXsys**™, which is a powerful system to access the **eTOX** data and the predictive models.

eTOX FACTS and FIGURES

* 15 Consortium meetings, 1 Mid-term Review, 7 **eTOXsys** user meetings, 1 modelling workshop and 2 Hackathons were celebrated.
* 15 releases of the Vitic Nexus **eTOX** database were delivered. The final version contains **1,947 substances** (483 labelled as confidential) and **8,047 study design records from 6,971 legacy reports; and 265,502 substances and 1,088,007 records** from public sources like ChEMBL, DrugMatrix and Open TG-GATES.
* Technical synchronization between **OntoBrowser, Vitic Nexus eTOX database** and **eTOXsys** regarding the Terminology (SEND codelists and INHAND controlled vocabularies) harmonization allowed the mapping of around **20 millions of verbatim terms to 7,262 preferred terms**, which highly improves the quality of read across analysis and data stratification for modelling challenges.
* **Several tools** were developed and are freely accessible for the scientific community benefit.
* 5 releases of the **eTOXsys** were launched. The final version includes the **2016.3 Vitic release**, a bunch of **200 predictive models**, and the **Human Outcomes Module integrated**, which was designed to support and open a door for translational research from preclinical to clinical research

http://etoxproject.eu

(Q)SAR-based Approach

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- Usually, activity is calculated as a function of molecular descriptors or physicochemical parameters
- Modification: Toxicity Index (Ti)
  - Lipophilicity
  - pKa
  - Molecular refractivity
  - Polarizability
  - Volume
  - …

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Dearden J., J. Comp.-Aided Mol. Des. 17, 119-127 (2003)

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(Q)SAR-based Approach

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It is rare to find human drug toxicity studies. One such was carried out by King and Moffat [6], who used as a toxicity index (TI) of barbiturates the number of U.K. deaths in a given year from a specified barbiturate divided by the number of prescriptions issued for that barbiturate:

$$\log TI = 1.48 \log P - 1.28 \qquad (2)$$

$$n = 5 \quad r^2 = 0.983 \quad s = 0.078$$

Although the data-set is very small, the statistics are remarkably high, reflecting probably the accuracy of the data. The limited log P range of the 5 barbiturates probably explains the lack of observed biphasic dependence on hydrophobicity.

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King L.A. et al., Med. Sci. Law, 23 (1983) 193.

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In silico prediction of dr

John C
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Summa

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Journal of Environmental Science and Health, Part C, 31:45–66, 2013
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ISSN: 1059-0501 print / 1532-4095 online
DOI: 10.1080/10590501.2013.763576

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Models
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ASAR, and SARpy
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inside and outside
ability domain tools
The predictive tools
on of both methods.

Advanced Review

In silico toxicology: computational methods for the prediction of chemical toxicity

Arwa B. Raies and Vladimir B. Bajic*

Determining the toxicity of chemicals is necessary to identify their harmful effects on humans, animals, plants, or the environment. It is also one of the main steps in drug design. Animal models have been used for a long time for toxicity testing. However, *in vivo* animal tests are constrained by time, ethical considerations, and financial burden. Therefore, computational methods for estimating the toxicity of chemicals are considered useful. *In silico* toxicology is one type of toxicity assessment that uses computational methods to analyze, simulate, visualize, or predict the toxicity of chemicals. *In silico* toxicology aims to complement existing toxicity tests to predict toxicity, prioritize chemicals, guide toxicity tests, and minimize late-stage failures in drugs design. There are various methods for generating models to predict toxicity endpoints. We provide a comprehensive overview, explain, and compare the strengths and weaknesses of the existing modeling methods and algorithms for toxicity prediction with a particular (but not exclusive) emphasis on computational tools that can implement these methods and refer to expert systems that deploy the prediction models. Finally, we briefly review a number of new research directions in *in silico* toxicology and provide recommendations for designing *in silico* models.

How to cite this article:
WIREs Comput Mol Sci 2016, 6:147–172. doi: 10.1002/wcms.1240

General Workflow

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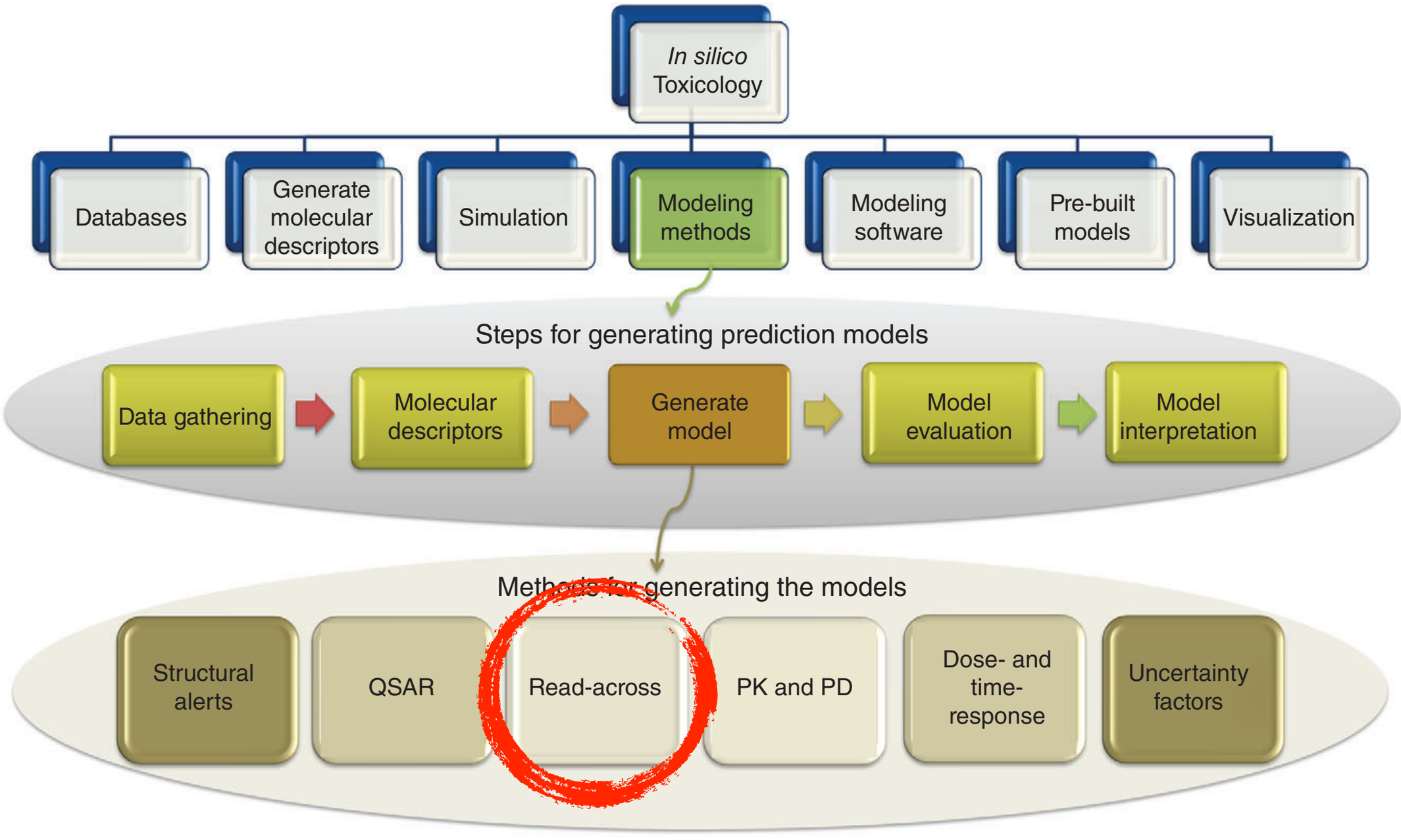

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Raies et al., WIREs Comput Mol Sci 6, 147–172 (2016)

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A New Trend: Read-across

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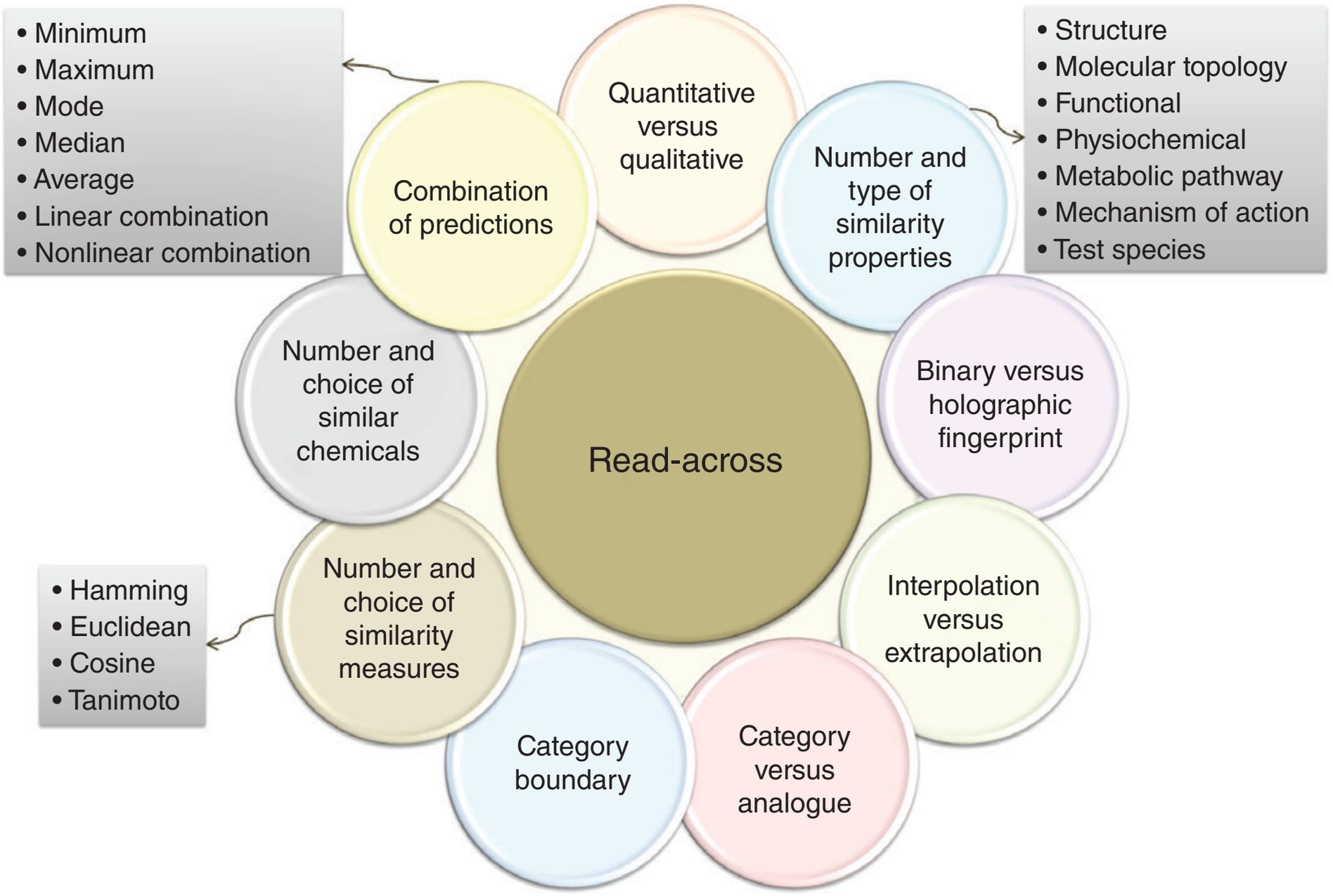

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Raies et al., WIREs Comput Mol Sci 6, 147–172 (2016)

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Molecular Interaction Approach

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- Assumption: toxicity / unwanted side effect is based on molecular interactions between drug and target
- Correlation between interaction pattern and effect
- Advantage: Bi-directional information flow possible
- Pharmacophore concept established

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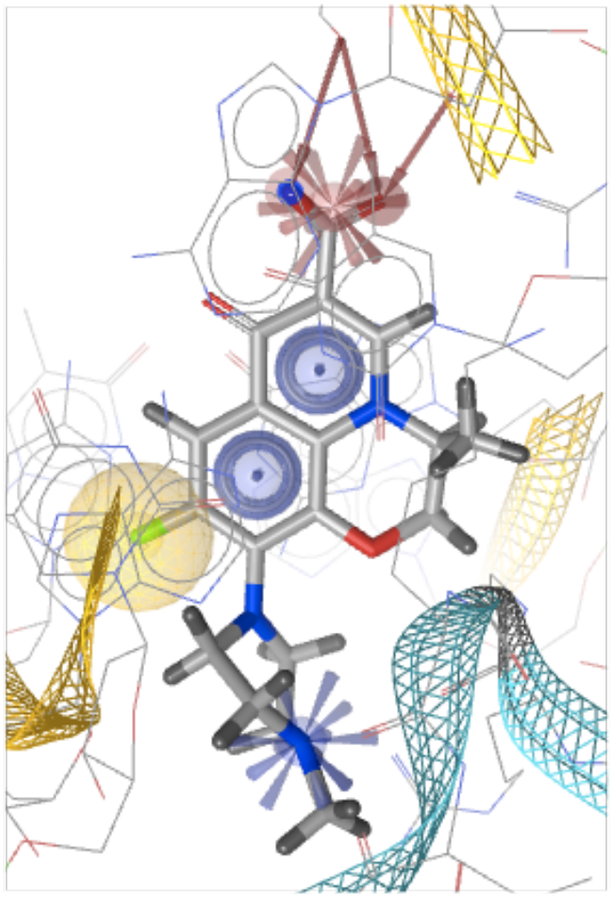
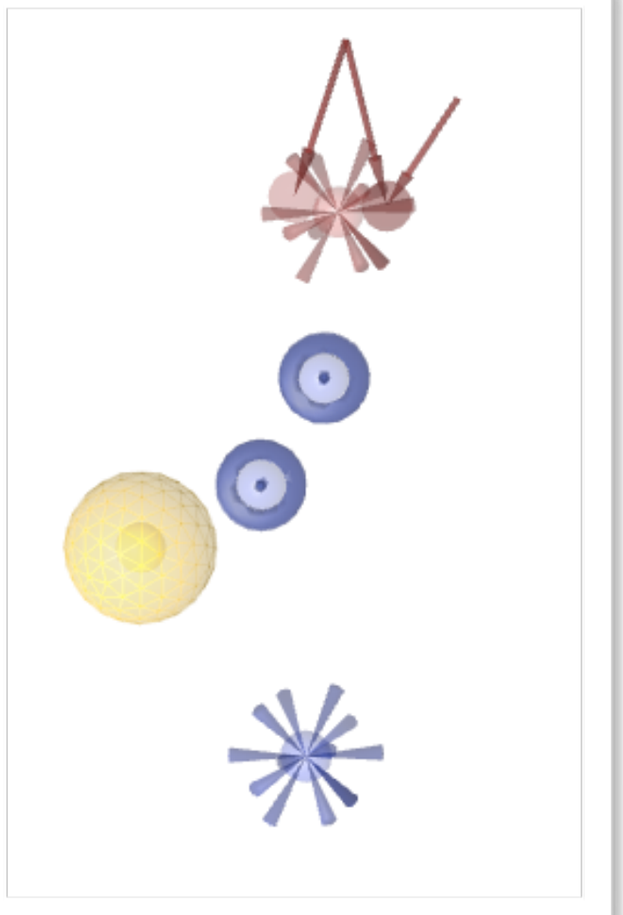
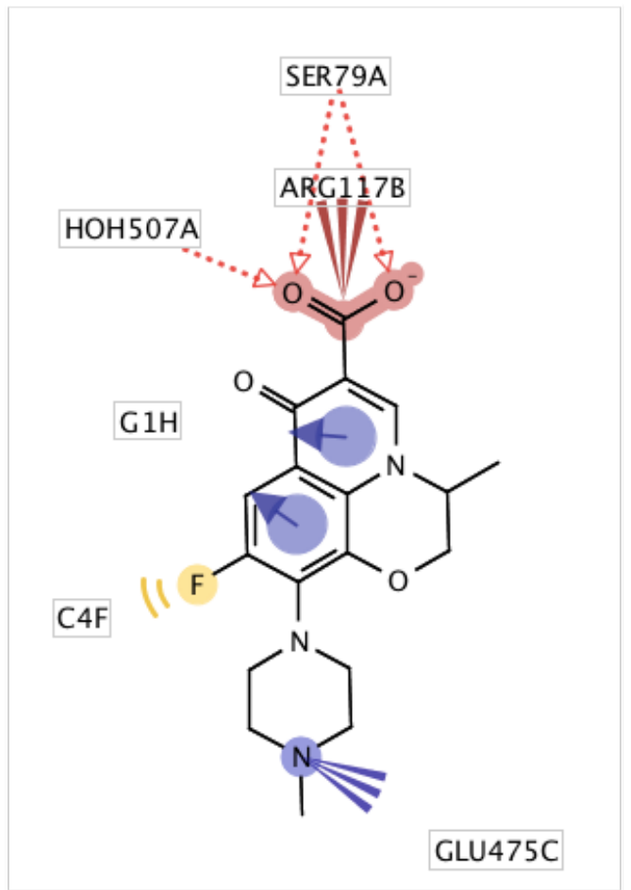
Totality of universal chemical features that represent a defined binding mode of a ligand to a bio-molecular target

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







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Pharmacophore-based Screening

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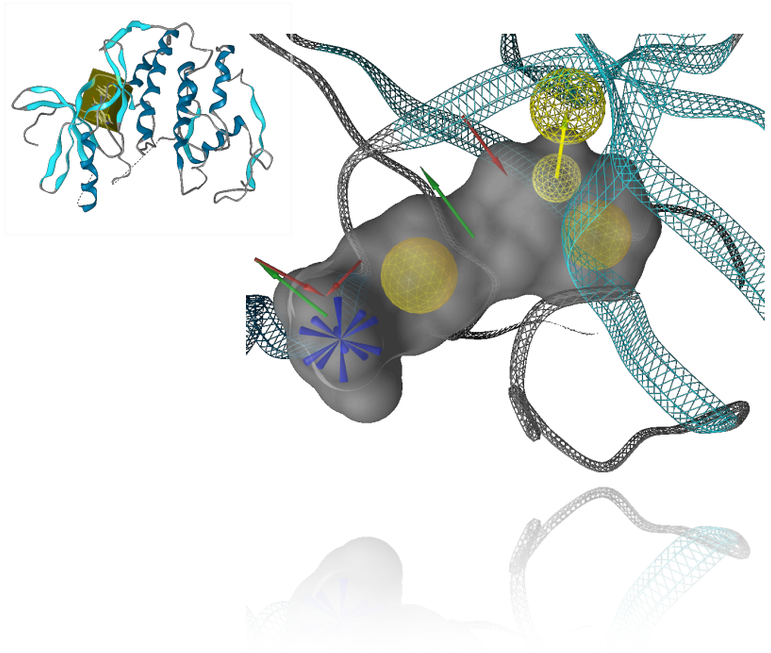
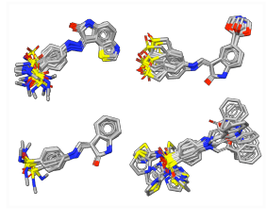
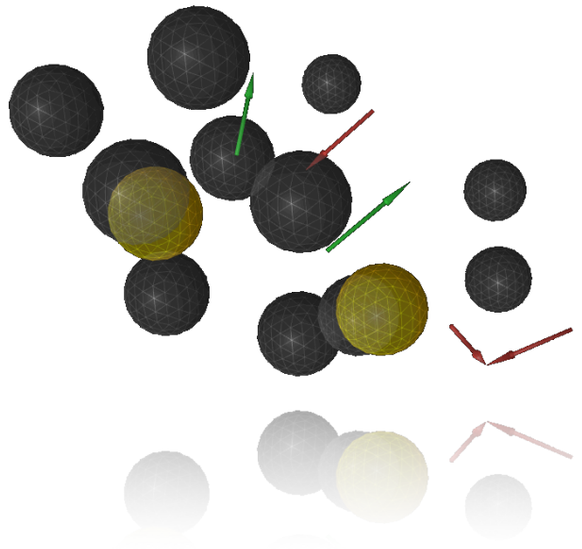
Structure-Based Pharmacophore

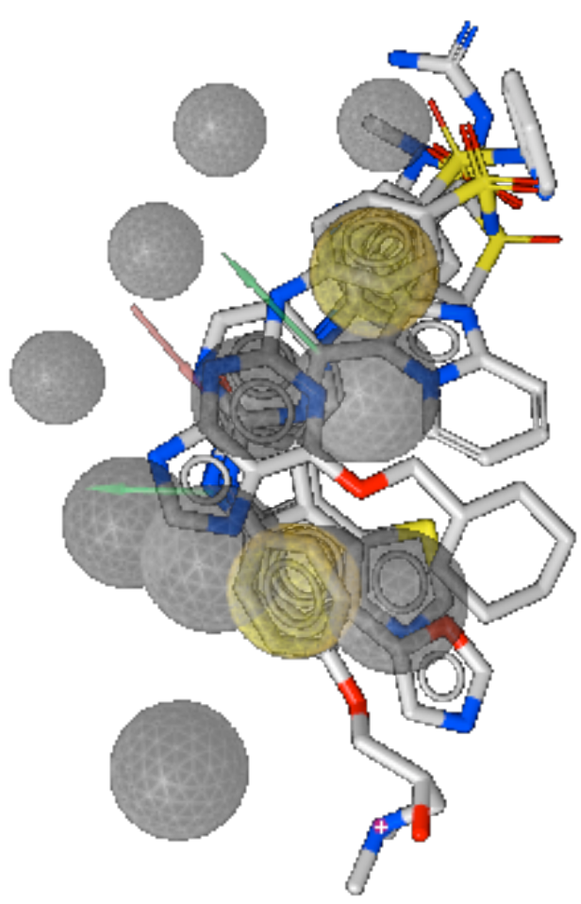


Ligand-Based Pharmacophore



3D Pharmacophore as a query





Screen rapidly large multi-conformational compound databases

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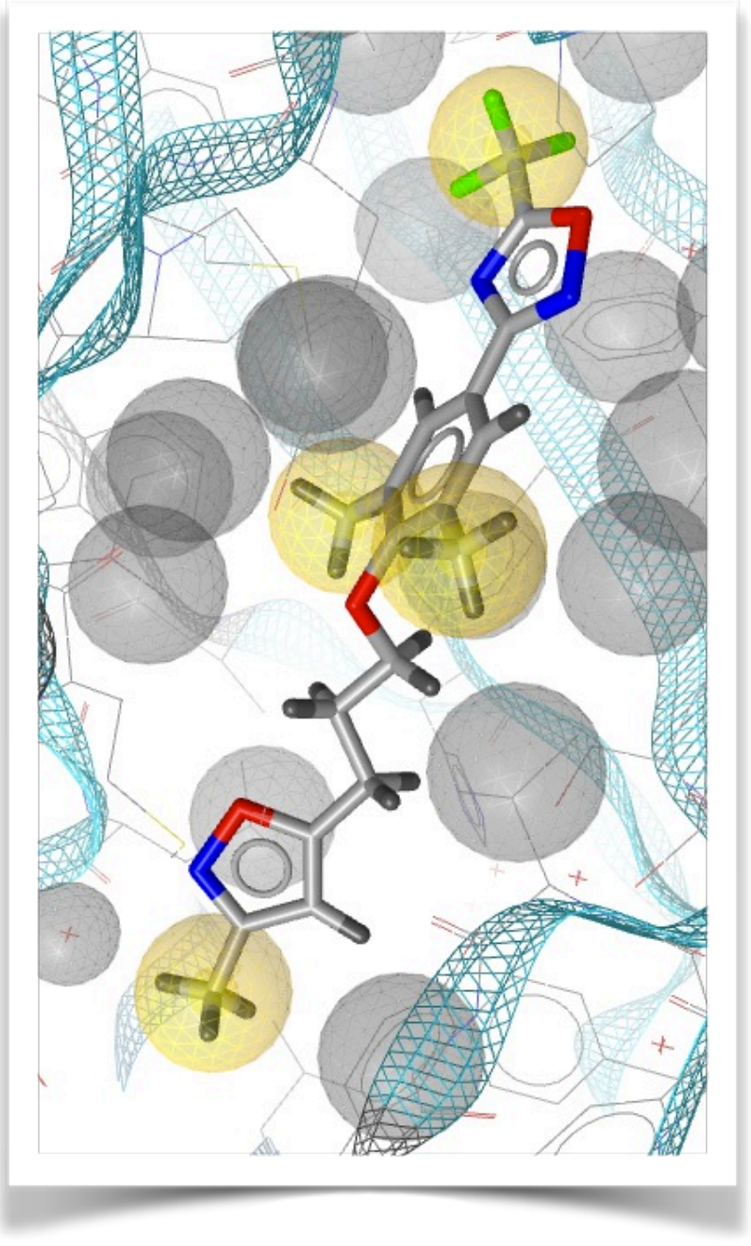
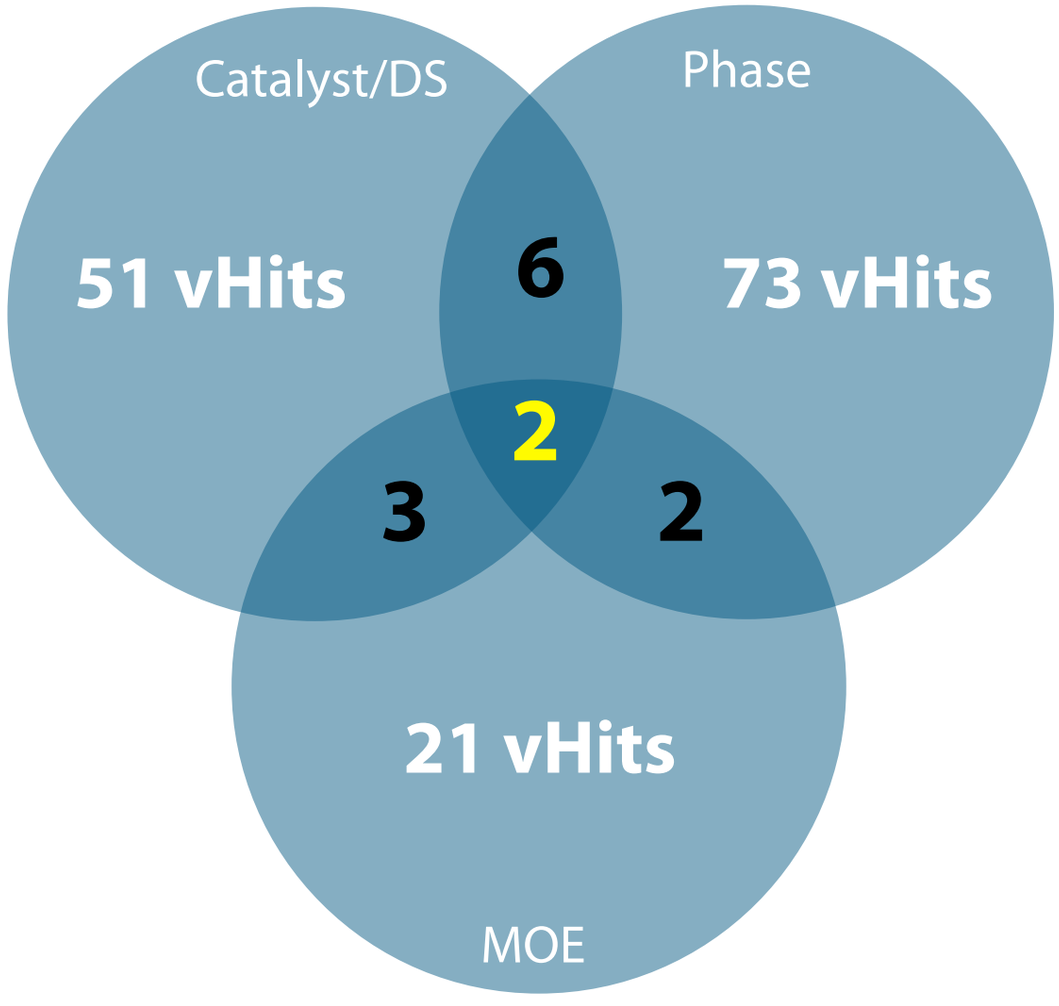
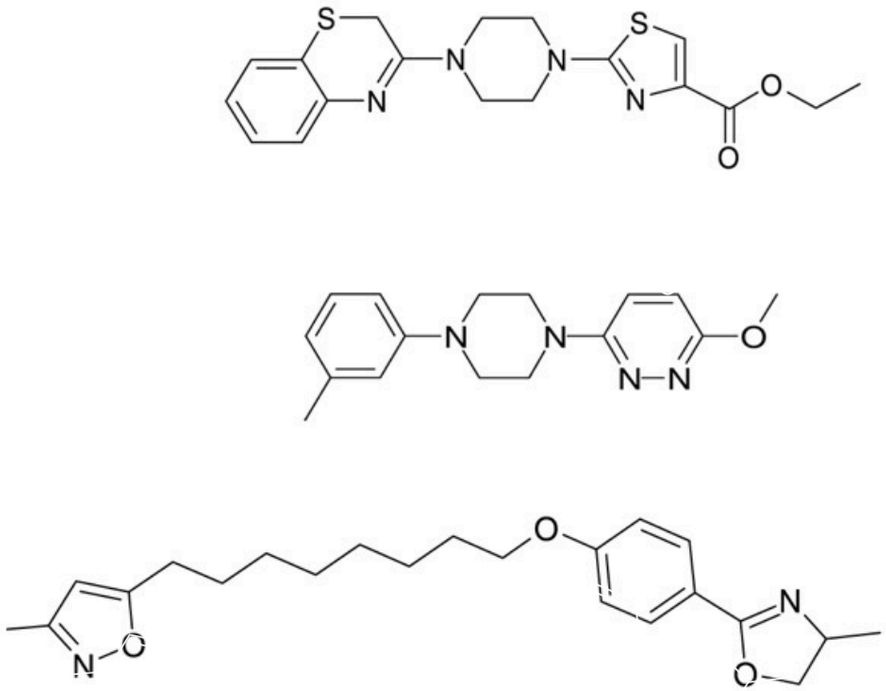
Pharmacophore Screening ...

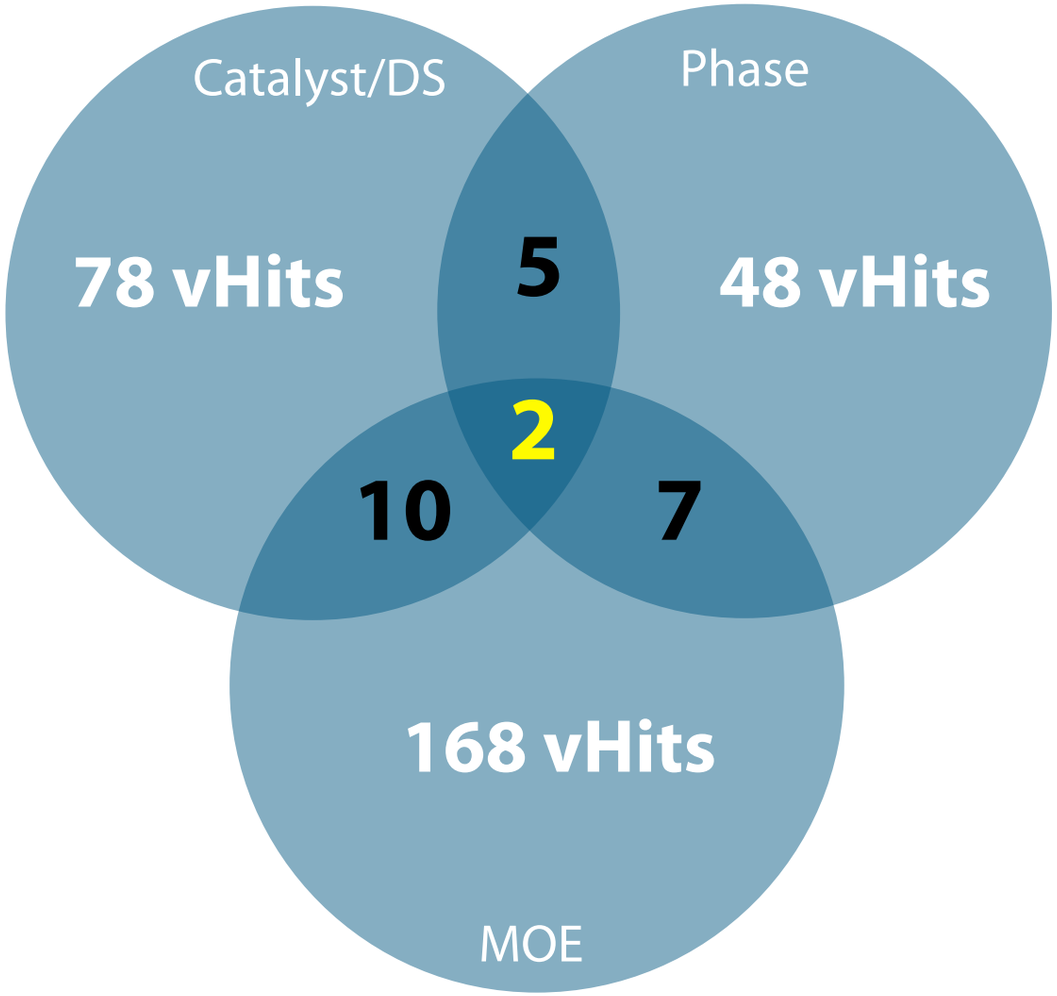




[Mangold 2006] Martina Mangold. *Human Rhinovirus Coat Protein Inhibitors - A Pharmacophore Modeling Approach.* Master's thesis at the University of Innsbruck (2006)

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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… Breaking the Code

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… Breaking the Code

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What Are We Looking At ?

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It’s all about pattern recognition !

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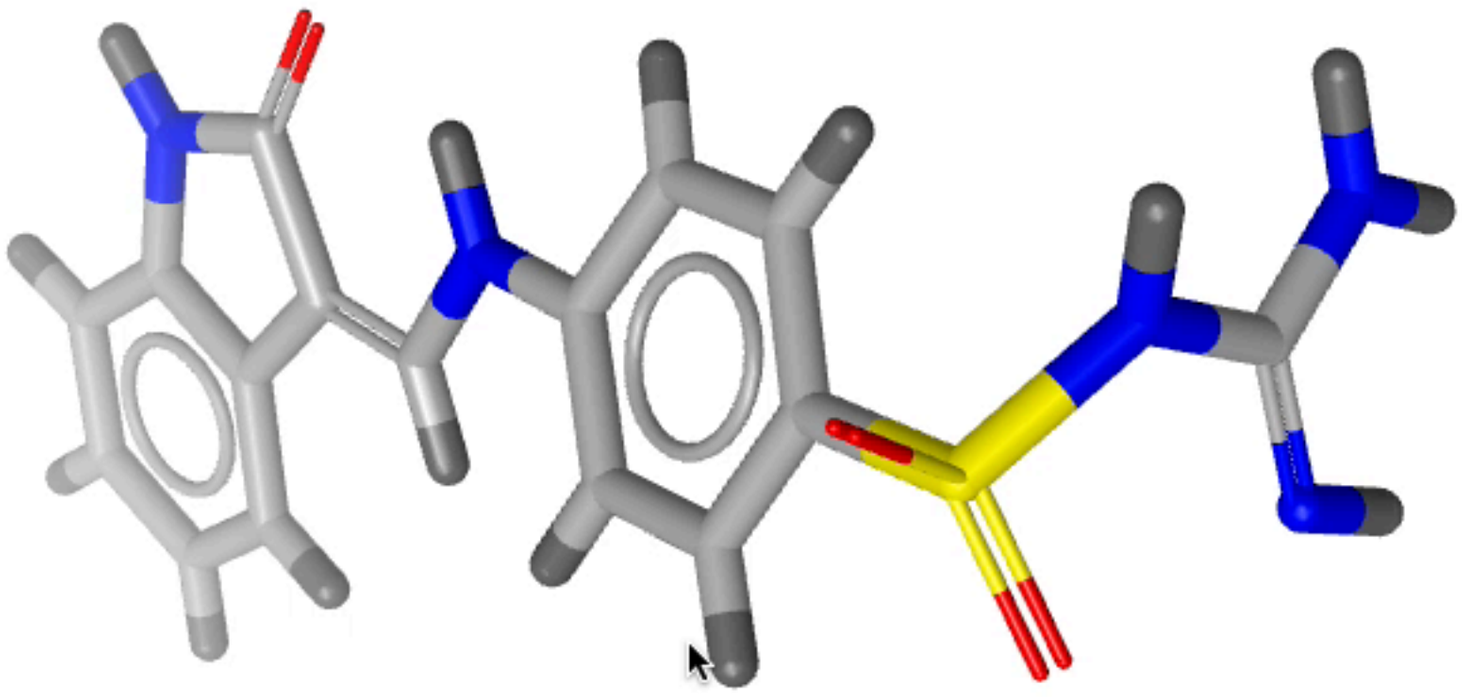

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We Need Speed & Accuracy

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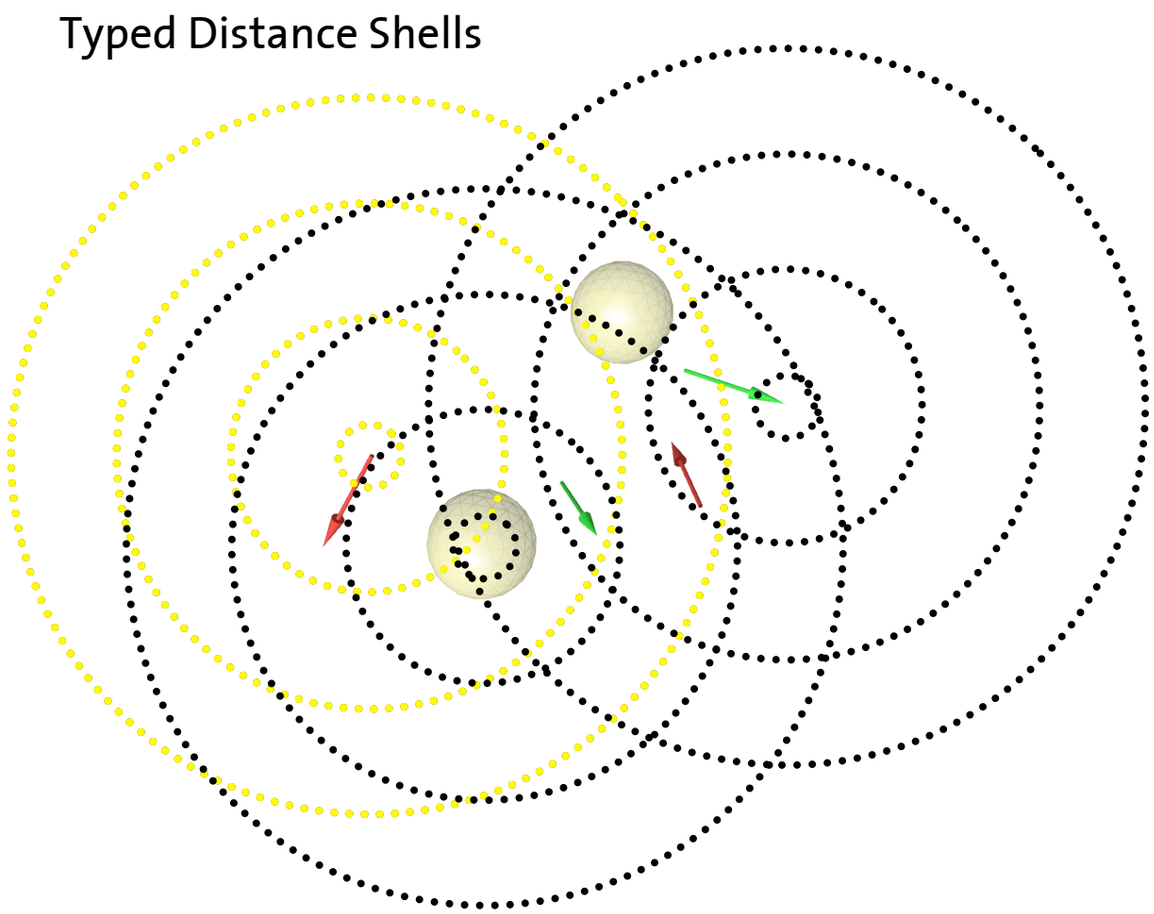
- Redesign the alignment algorithm
- Avoid computationally inefficient graph matching
- Create a pattern recognition based approach



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LigandScout Design Platform

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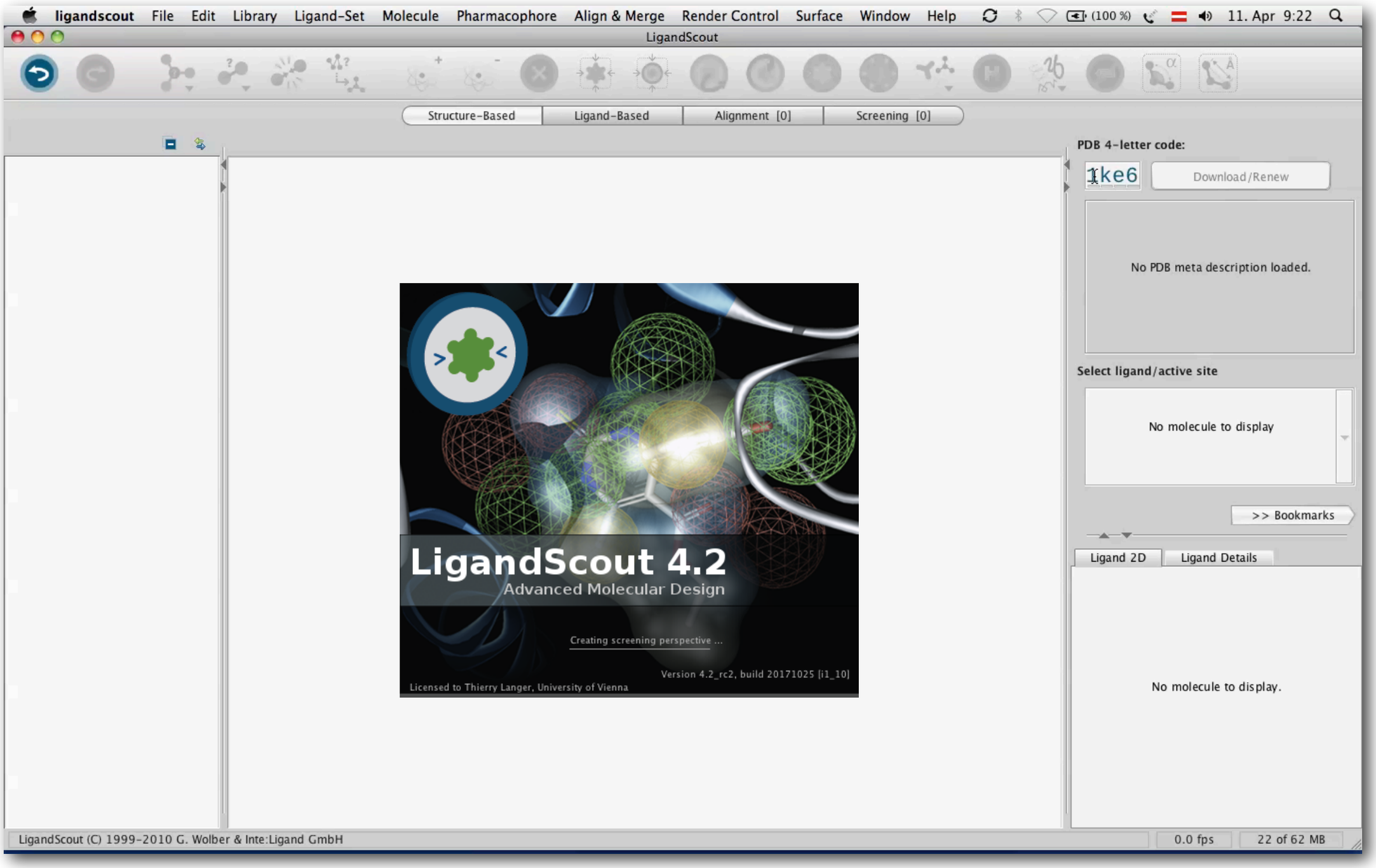

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LigandScout Scientific Articles

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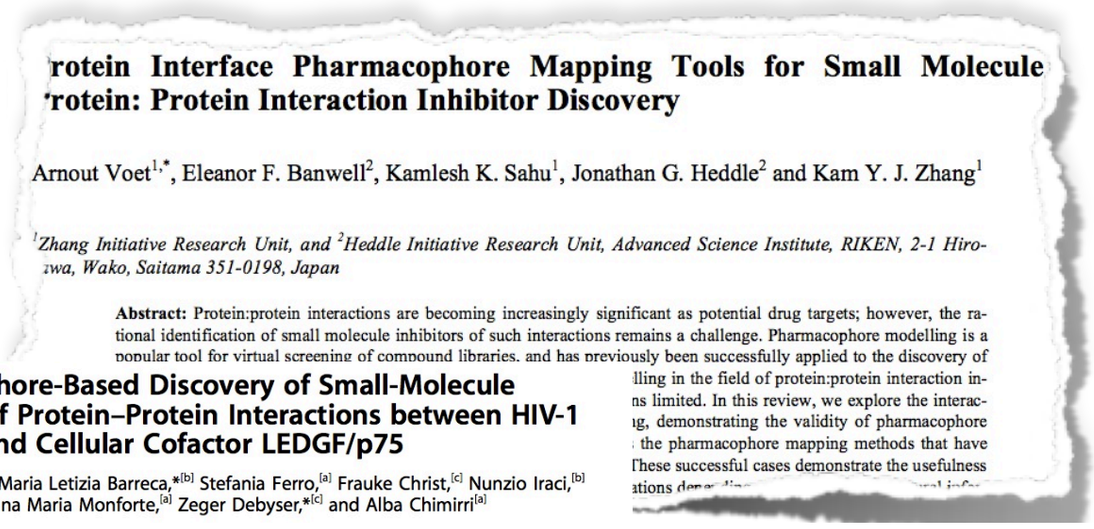
- More than 1500 papers*
  - structure-based modeling
  - ligand-based modeling
  - virtual screening
- Hit identification
- Fragment-based design
- Lead structure optimization
- Protein-Protein Interactions
- Drug repurposing
- Profiling (side-effects)



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 epitheliun 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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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 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, March 2018

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Drug Repurposing

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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.*

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

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LigandScout Model of ABCG2-I

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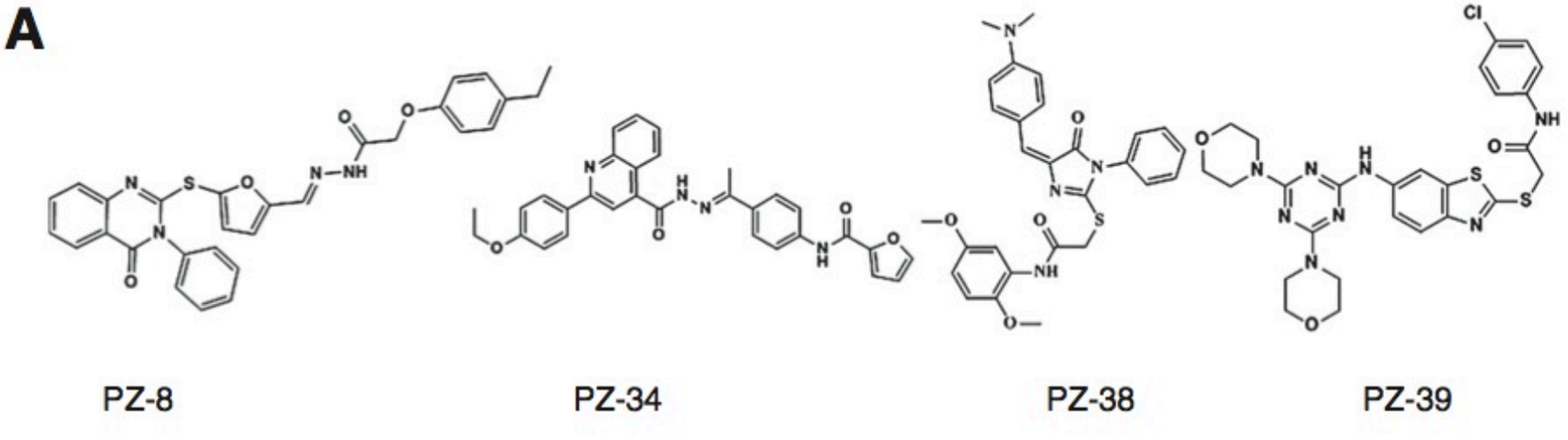

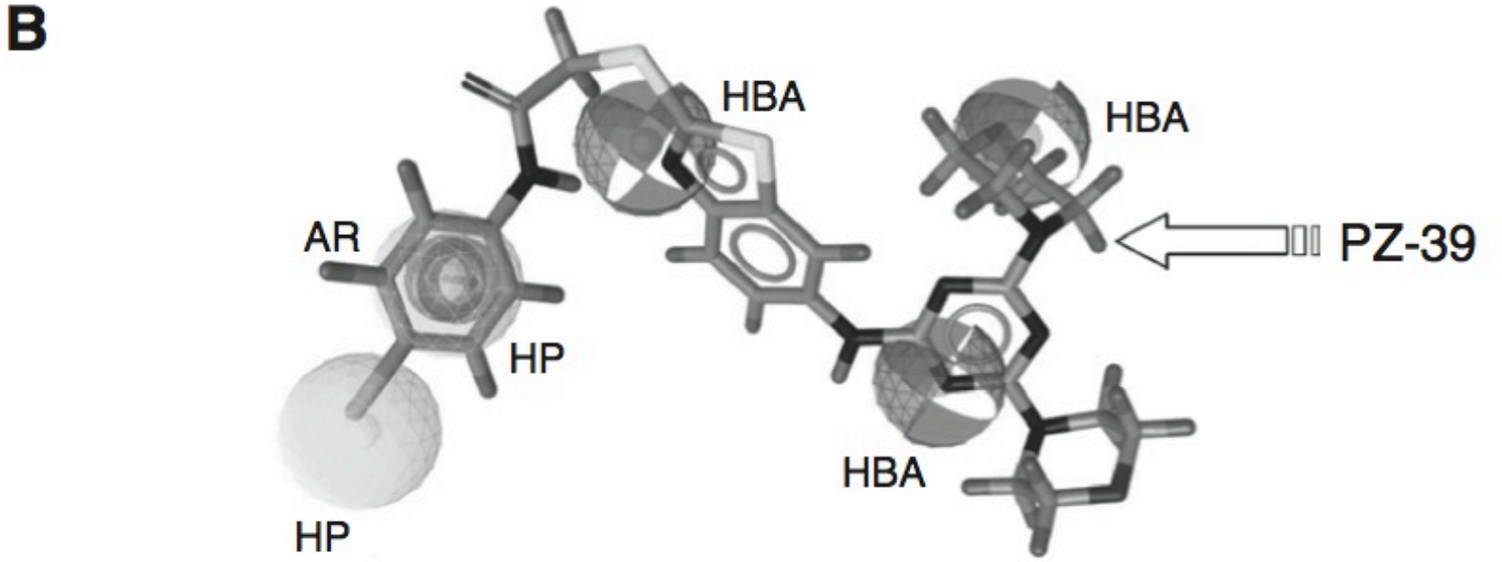

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Yinxiang Wei et al., Mol Cancer Ther 2012, 11, 1693-1702.

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Inhibiting ABCG2 With Sorafenib

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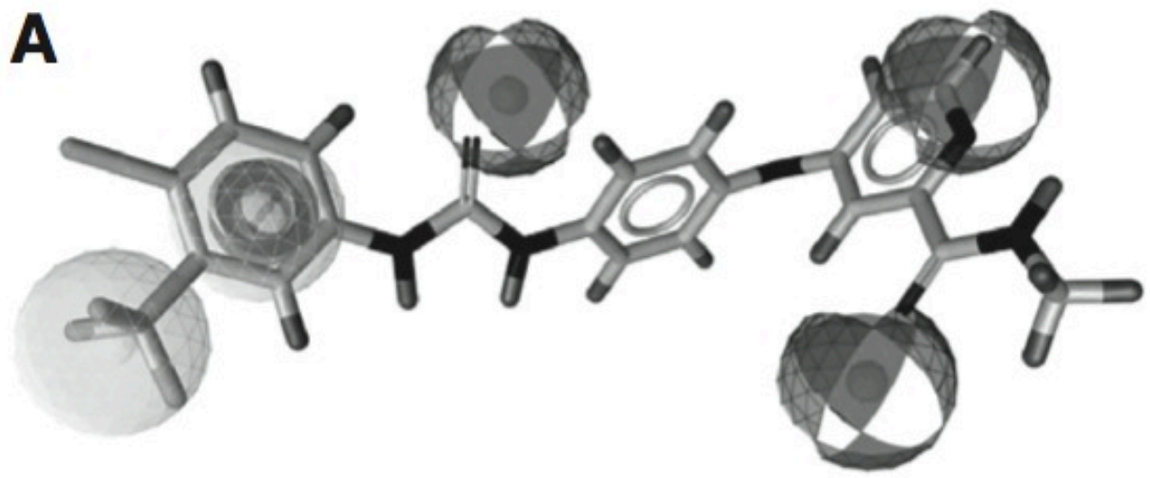

... at a concentration up to 2,5µM/L

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 ...

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

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One Step Further - Ligand Profiling

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Usual Virtual Screening Protocols

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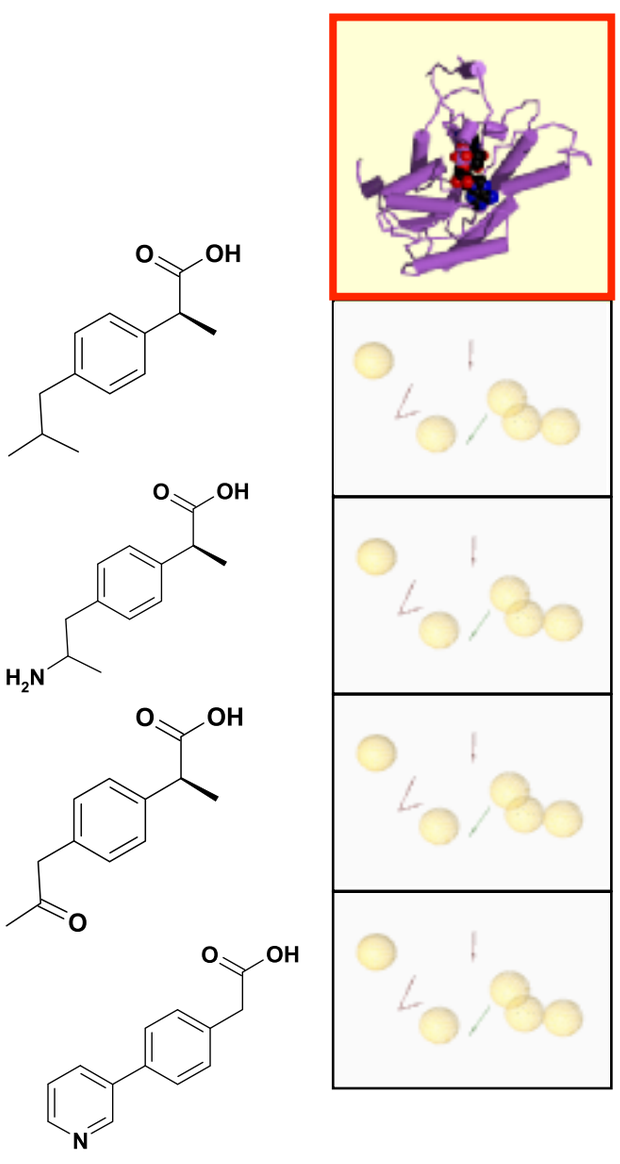

10^x molecules against one target

Hypothesis Data Spreadsheet: ACE-hypogen 20 Compounds Pag

Row	Name	Activ	Uncert	Color	Estimate	Error	MolWt	Principal	MaxOmitFeat
1	ala-gly	2.5e+06	3.0				146.146		
2	ala-his	9e+06	3.0				226.235		
3	ala-leu	1.6e+06	3.0				202.253		
4	ala-pro	270000	3.0				186.21		
5	ala-val	300000	3.0				188.226		
6	arg-ala-pro	16000	3.0				342.397		
7	glu-ala-pro	360000	3.0				315.326		
8	gly-asp	9.2e+06	3.0				190.155		
9	gly-glu	5.4e+06	3.0				204.182		
10	gly-lys	5.4e+06	3.0				203.241		
11	gly-phe	450000	3.0				222.243		
12	ile-pro	150000	3.0				228.291		
13	ile-tyr	3700	3.0				294.35		
14	leu-ala-pro	2300	3.0				299.369		
15	nleu-ala-pro	700	3.0				299.369		
16	phe-ala-pro	4200	3.0				333.387		
17	phe-pro-pro	78000	3.0				359.424		
18	pro-pro	7.5e+06	3.0				212.248		
19	val-pro	420000	3.0				214.264		
20	val-trp	1700	3.0				303.36		

results in a hit list

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Pharmacophores for Profiling

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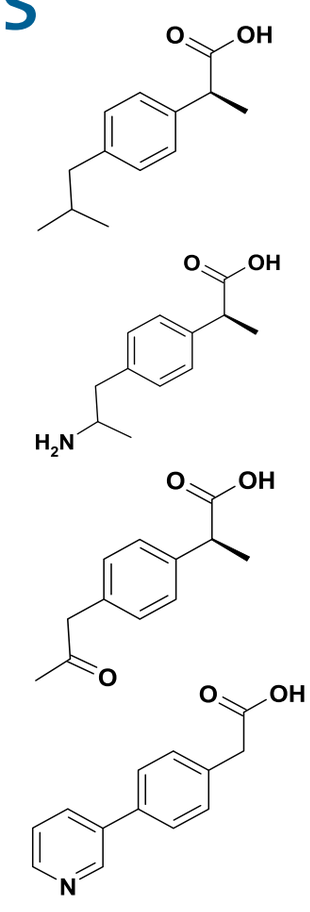
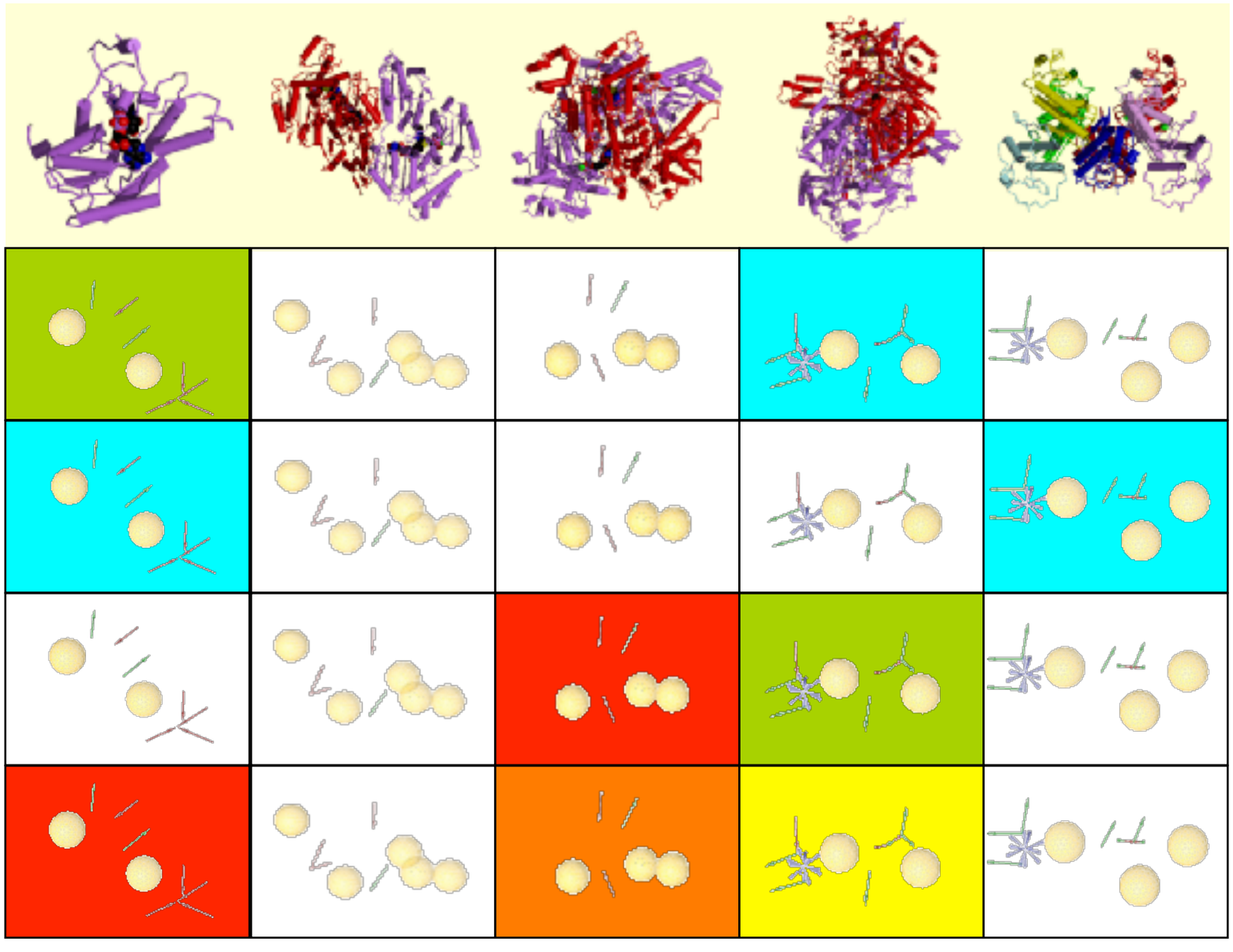
10^x molecules

against

10^x targets





… needs a large number of models !

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Multitarget Activity Profiling

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- Make easy-to-use technology available for parallel screening
- Create multitude of interaction models for interesting targets
- Our solution: The KNIME Workflow Environment

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http://www.knime.org

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KNIME Analytics Platform - /Users/thierrylanger/knime-workspace

100%

Quick Access

KNIME Explorer

EXAMPLES (knime-guest@htt

LOCAL (Local Workspace)

Node Repository

LigandScout

LigandScout
- Alignment
  - Pharmacophore/Molecule
- Clustering
  - Diversity Picker
  - Fingerprint Clustering
  - Pharmacophore/Molecule
- Conformer Generation
  - ICon
- Data Manipulation
  - Active Site Ligand Extract
  - 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

*0: IL Pharm...

0: T2 Build ...

2: T8 Advanc...

3: T5 Perfor...

LDB

drag & drop

Node Description

Console

KNIME Console

```
WARN  Database List          0:14      Loading model settings failed: /Users/thierrylanger/Desktop/Meclofe
WARN  LoadWorkflowRunnable             Warnings during load: Status: Warning: IL PharmDB Profiling Ono 1.4
WARN  LoadWorkflowRunnable               Status: Warning: IL PharmDB Profiling Ono 1.4.3 0
WARN  LoadWorkflowRunnable                 Status: Warning: Database List 0:14
WARN  LoadWorkflowRunnable                   Status: Warning: Loading model settings failed: /Users/thierr
WARN  Meta-data              0:13      No CSV meta-data file specified.
```

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KNIME Analytics Platform - /Users/thierrylanger/knime-workspace

100%

Quick Access

KNIME Explorer

EXAMPLES (knime-guest@htt

LOCAL (Local Workspace)

Node Repository

LigandScout

LigandScout
Alignment
Pharmacophore/Molecule
Clustering
Diversity Picker
Fingerprint Clustering
Pharmacophore/Molecule
Conformer Generation
ICon
Data Manipulation
Active Site Ligand Extract
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

*0: IL Pharm...

0: T2 Build ...

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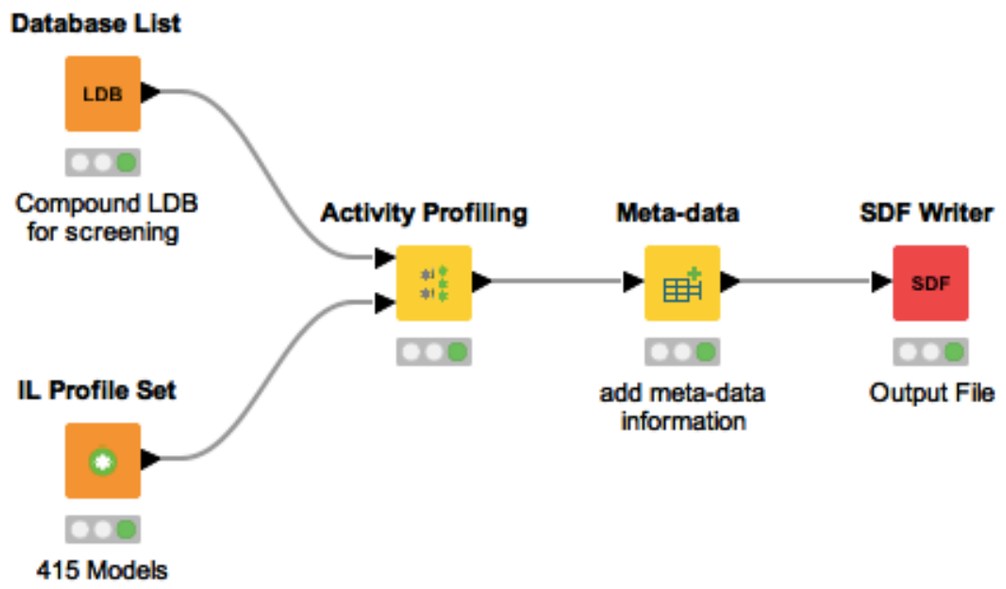
3: T5 Perfor...



Node Description

Console

KNIME Console

```
WARN  Database List          0:14      Loading model settings failed: /Users/thierrylanger/Desktop/Meclofe
WARN  LoadWorkflowRunnable             Warnings during load: Status: Warning: IL PharmDB Profiling Ono 1.4
WARN  LoadWorkflowRunnable               Status: Warning: IL PharmDB Profiling Ono 1.4.3 0
WARN  LoadWorkflowRunnable                 Status: Warning: Database List 0:14
WARN  LoadWorkflowRunnable                   Status: Warning: Loading model settings failed: /Users/thierr
WARN  Meta-data              0:13      No CSV meta-data file specified.
```

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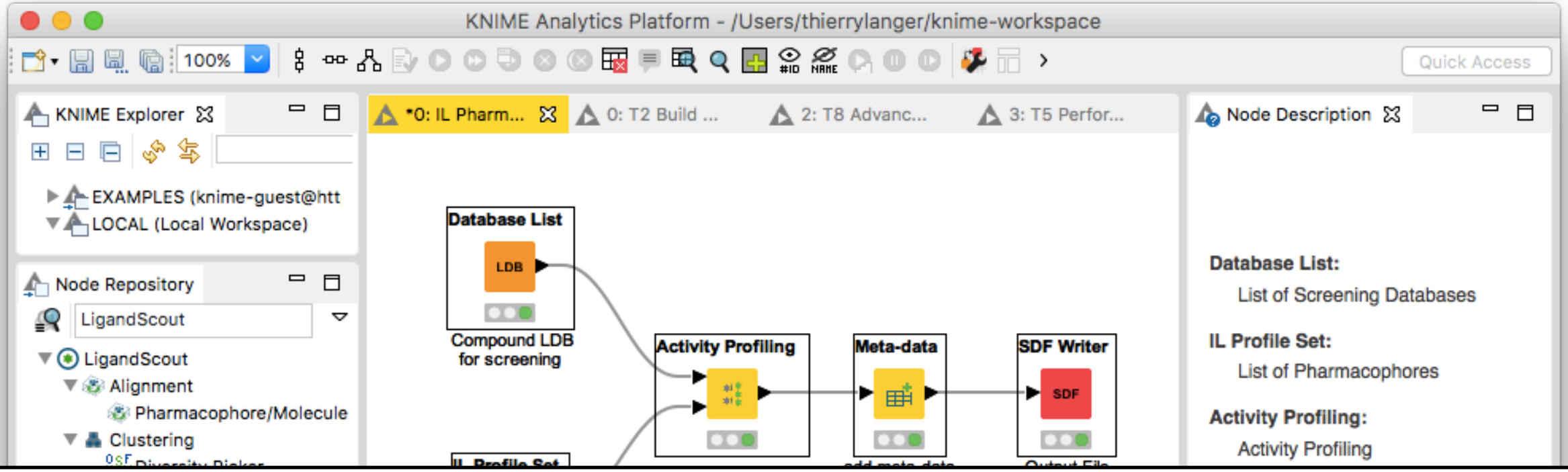

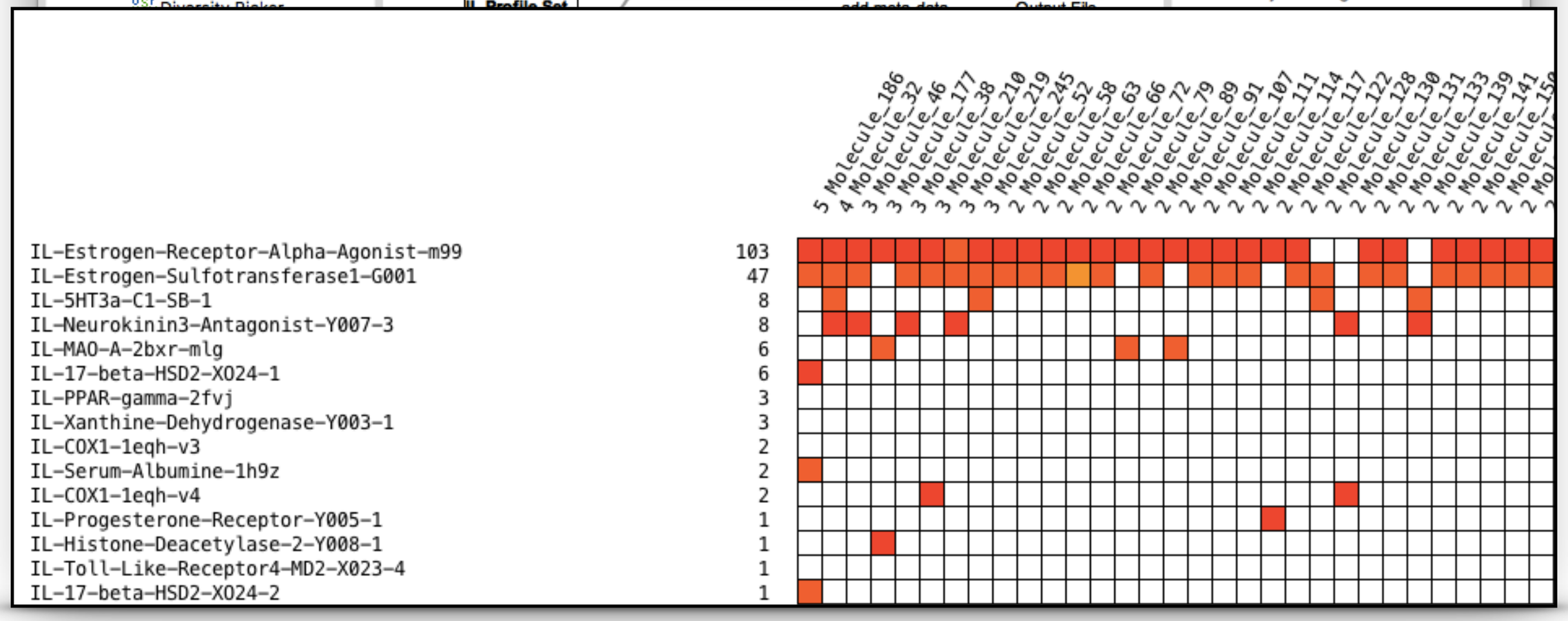

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Toxicity Assessment Models

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7 year collaborative EC Project on Toxicity Prediction

Executive Committee

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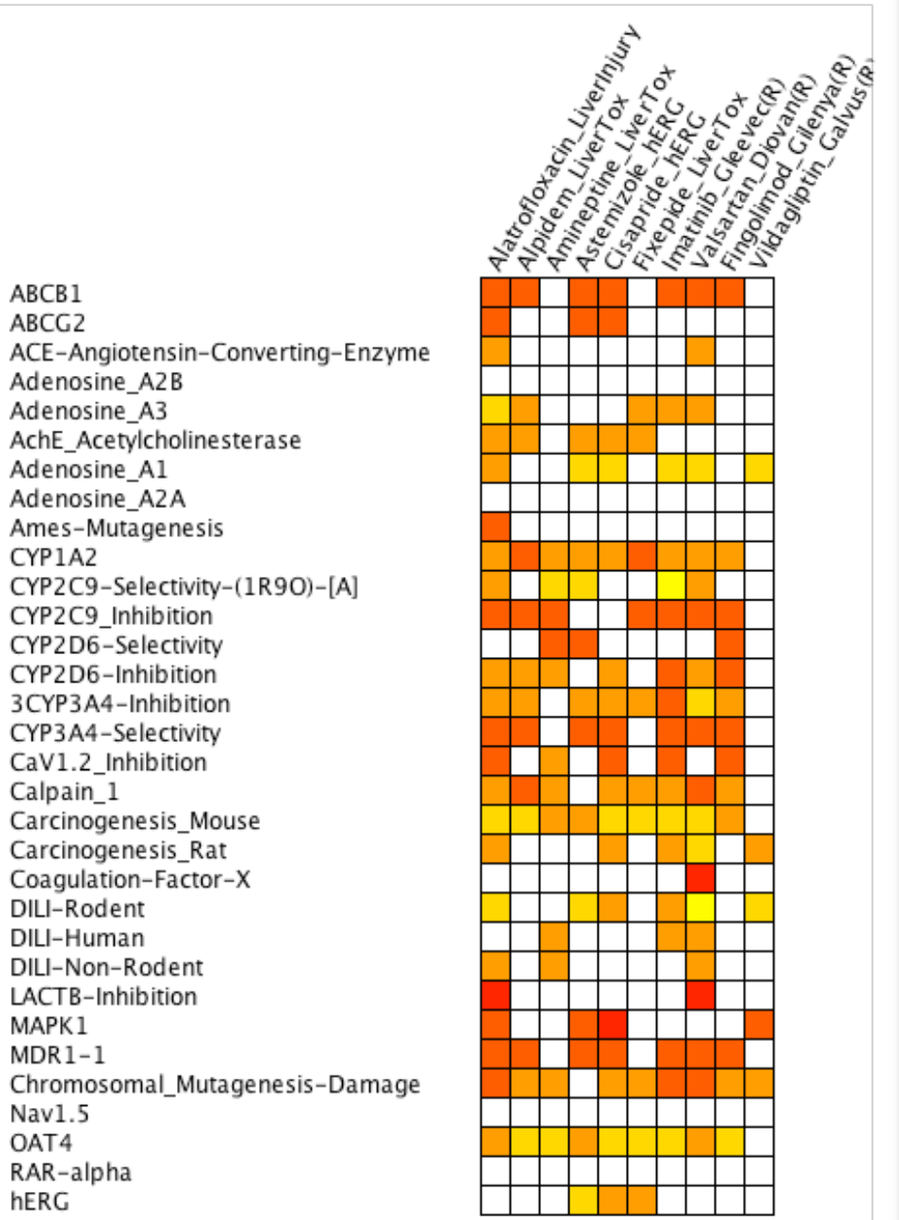
Chemotargets · inte:ligand · LMD Lead Molecular Design s.l. · Lhasa Limited · Molecular Networks Inspiring Chemical Discovery



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KNIME Workflow Tutorials

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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 2

Create Ligand Based Pharmacophore Models

Experience level: intermediat

Time needed: 15 minutes

Node Repository	Sequence
○ I/O - PDB Reader ○ **Pharmacophore** - Ligand-based Pharmacophore Creator	○ Read a SMILES file by using "SMI ○ Connect the output of "SMILES F Conformer Generator" node ○ Configure "Icon Conformer Gene ○ Connect the first port of "Icon C with the second input port of " Clustering" node and execute it ○ Connect the second output por "Pharmacophore/Molecule Clust port of "Ligand-based Pharmaco ○ 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 dov
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 dra
node (black triangle) with the input port of the "Icon
node and configure it. In the pop-up window, click or
(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 t
second output port of "Pharmacophore/Molecule Clus
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 Pro

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 ard 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)

drop down menu in the LigandScout section to see all the Input/Output nodes. Look for
to 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 and a filtering row will appear. Configure the row by choosing "MolWt" in the
tton[2] until "<" symbol appears. Write then in the editable text box a value to use for
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]

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Advanced controls (opt.)
○ Change Ligand parameters: - Configure "SDF Reader" node to extract name from a different column - Change "Icon Conformer Generator" settings (e.g. Apply BEST settings) Modify parameters for "iScreen" node: - Change the scoring function - Shift to fragment screening mode - Choose different retrieval modes - Configure the node in order to not check the exclusion volumes repare batch mode processing: Configure "Pharmacophore Reader" node to read multiple files at the same time Explore Boolean expression with "iScreen" node [e.g.: (1 and 2) not 3. Numbers are referred to the pharmacophores ranking in the "Pharmacophore Reader" node]

Scout section into the workspace. Configure the
drag and drop the "Icon Conformer Generator"
t the output port of the "SDF Reader" node
er Generator" node. In the pop-up window,
From the "I/O" drop down menu ,select the
put of the "Icon Conformer Generator" node
to save the LDB file.[3] Execute and then
"Screening" drop down menu. Add the
8 to the pharmacophore model you want to
ode with the second input port of the
r choosing the name for the output file.
ed the hit molecules as a sdf file.

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Another Success Story

- Collaboration with Domain Therapeutics (F)
  - Target: mGluR4 positive allosteric modulators
  - Disease area: Parkinson, Schizophrenia
- Project Setup
  - 3 years, 2.5 FTEs at Prestwick for med. chem. (hit to lead & and lead optimization)
- Result
  - Optimized lead family, in vivo proof of concept
  - Patent filed by October 2009

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mGluR4 PAMs

DOMAIN THERAPEUTICS

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C07D 405/14 (2006.01) *A61P 25/28* (2006.01)
C07D 471/04 (2006.01) *A61P 25/22* (2006.01)
C07D 487/04 (2006.01) *A61P 25/14* (2006.01)
C07D 495/04 (2006.01) *A61P 25/16* (2006.01)
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

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mGluR4 PAMs Project

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- Starting point: (-)-PHCCC

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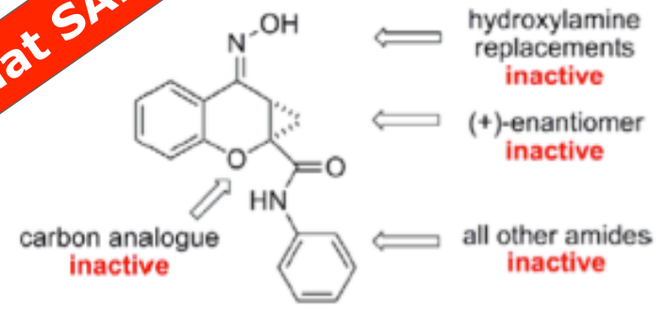
(−)-PHCCC, a positive allosteric modulator of mGluR4: characterization, mechanism of action, and neuroprotection

M. Maj [a,1], V. Bruno [b,1], Z. Dragic [a], R. Yamamoto [a], G. Battaglia [b], W. Inderbitzin [a], N. Stoehr [a], T. Stein [a], F. Gasparini [a], I. Vranesic [a], R. Kuhn [a], F. Nicoletti [b,c], P.J. Flor [a,*]

[a] *Novartis Institutes for BioMedical Research, Neuroscience Disease Area, WKL-125.6.08, Basel CH-4002, Switzerland*
[b] *Istituto Neurologico Mediterraneo, Neuromed, Pozzilli, Italy*
[c] *Department of Human Physiology and Pharmacology, University of Rome, Rome, Italy*

Received 25 February 2003; received in revised form 27 May 2003; accepted 23 June 2003

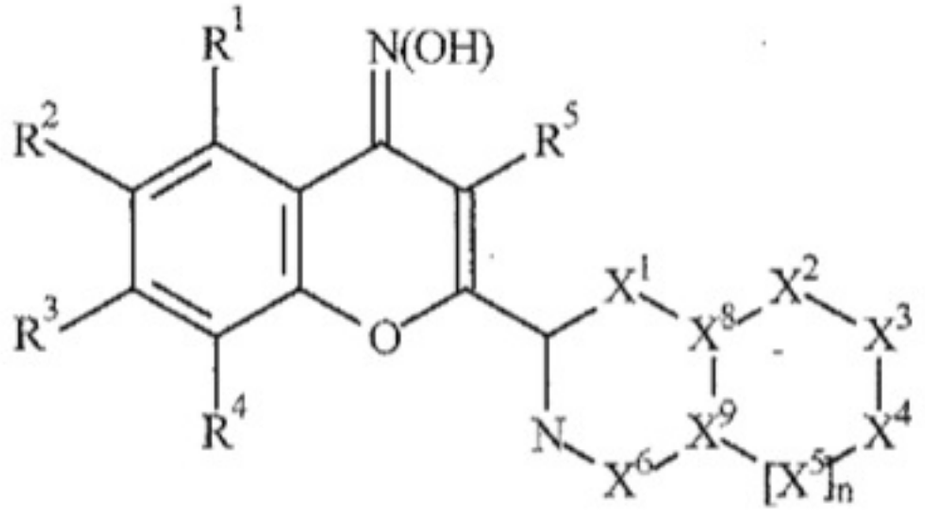
Flat SAR



(-)-PHCCC, **3**

Figure 2. Chemical modifications and the resulting 'flat' SAR for (−)-PHCCC.

- The result:



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mGluR4 PAMs Patent

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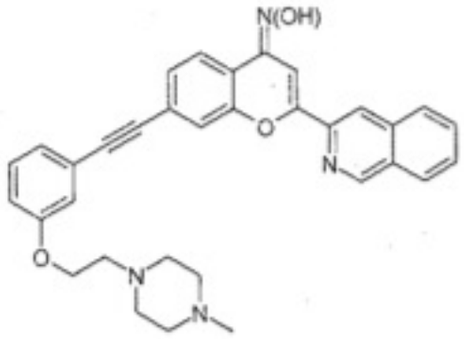

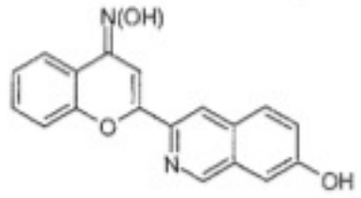

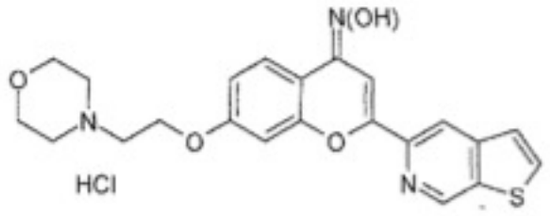

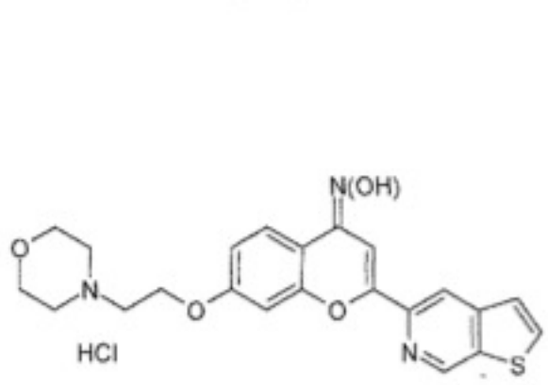

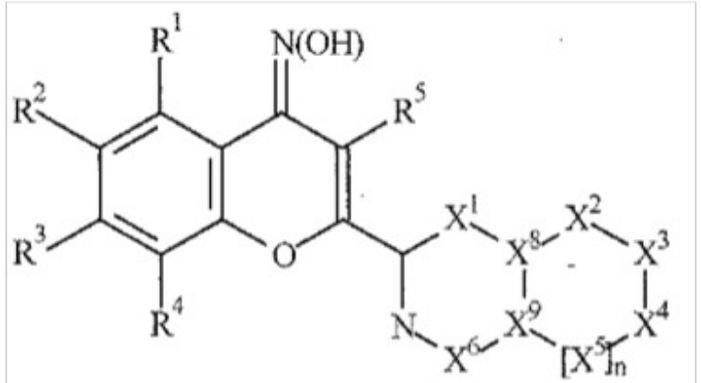

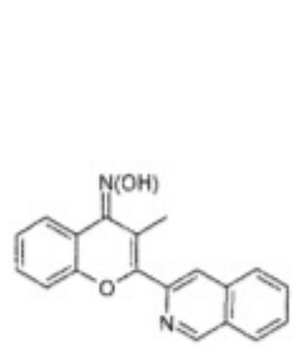

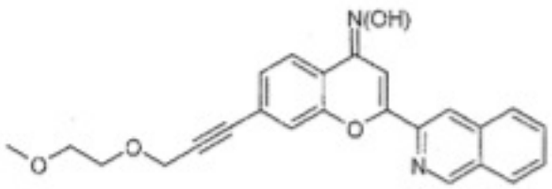

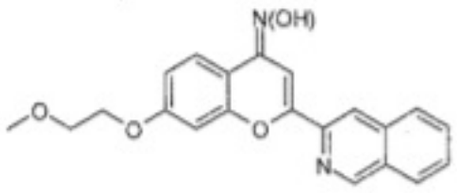

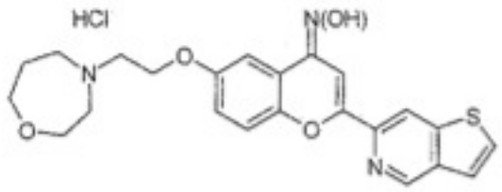

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mGluR4 PAMs Patent

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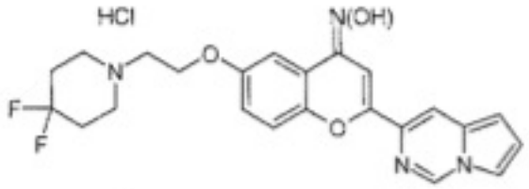

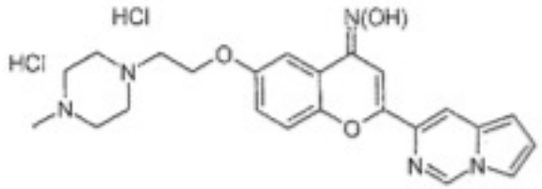

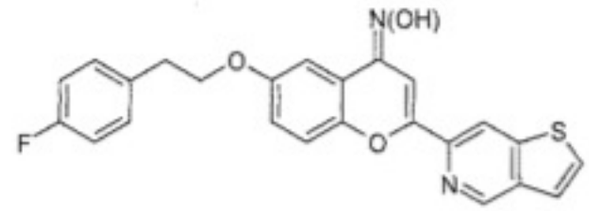

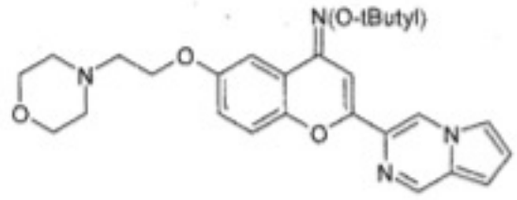

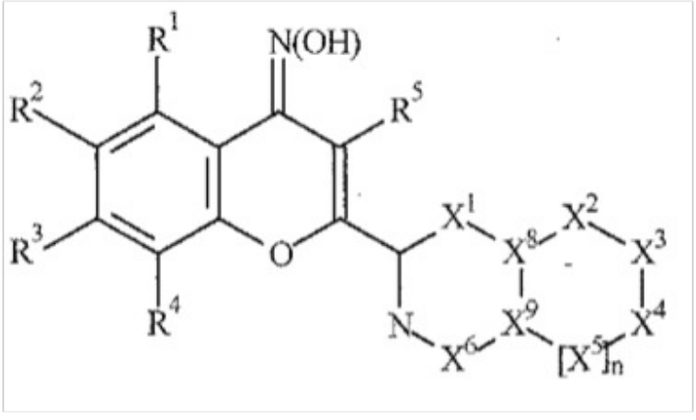

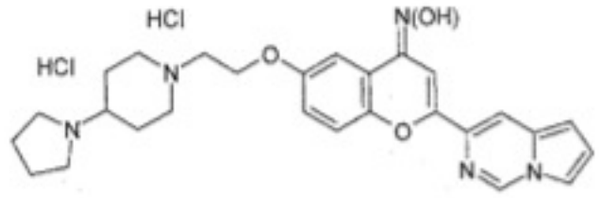

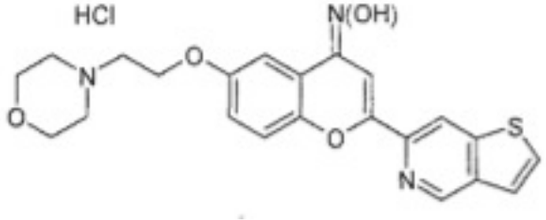

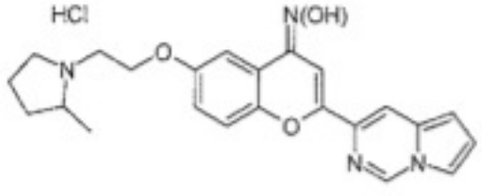

in total:
124 examples
described

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Pharmacophore Modeling

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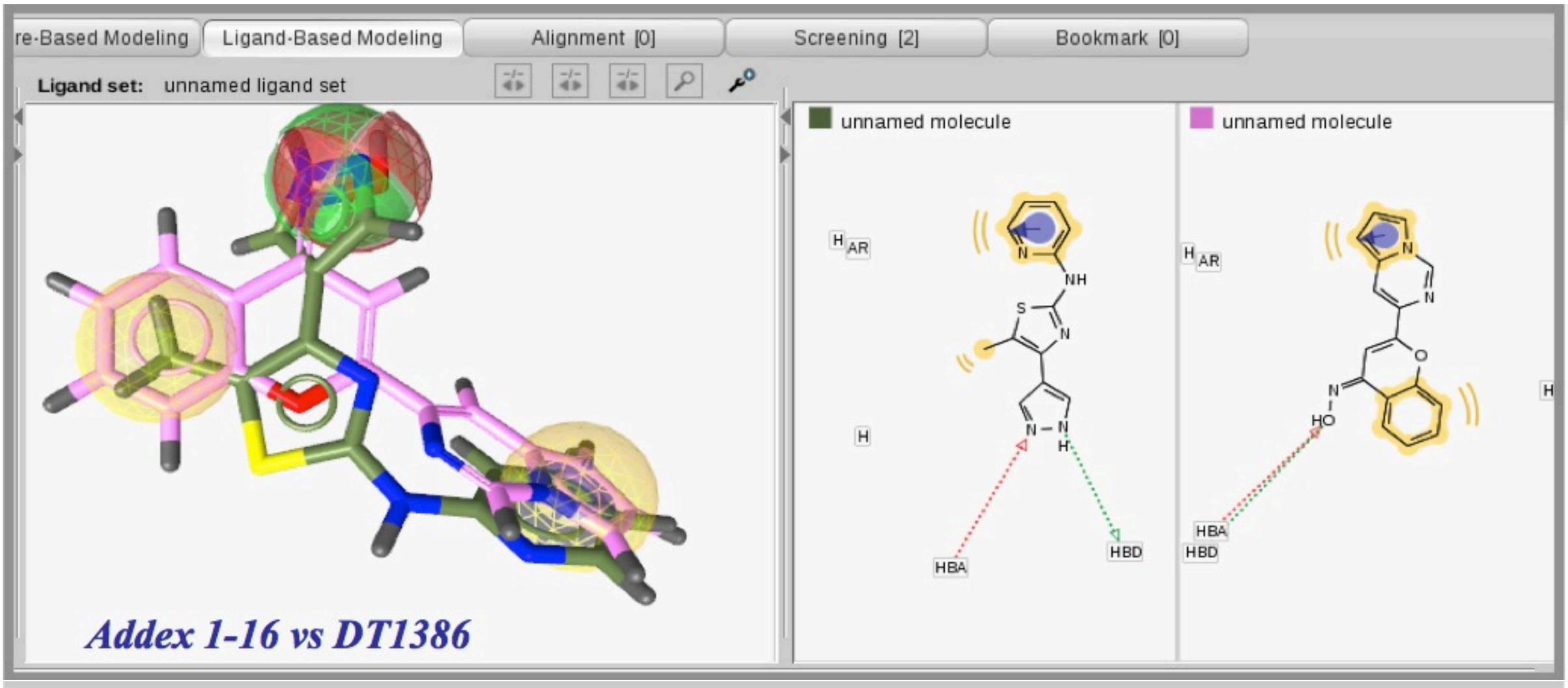
For benchmarking against Addex compounds …



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In silico Profiling

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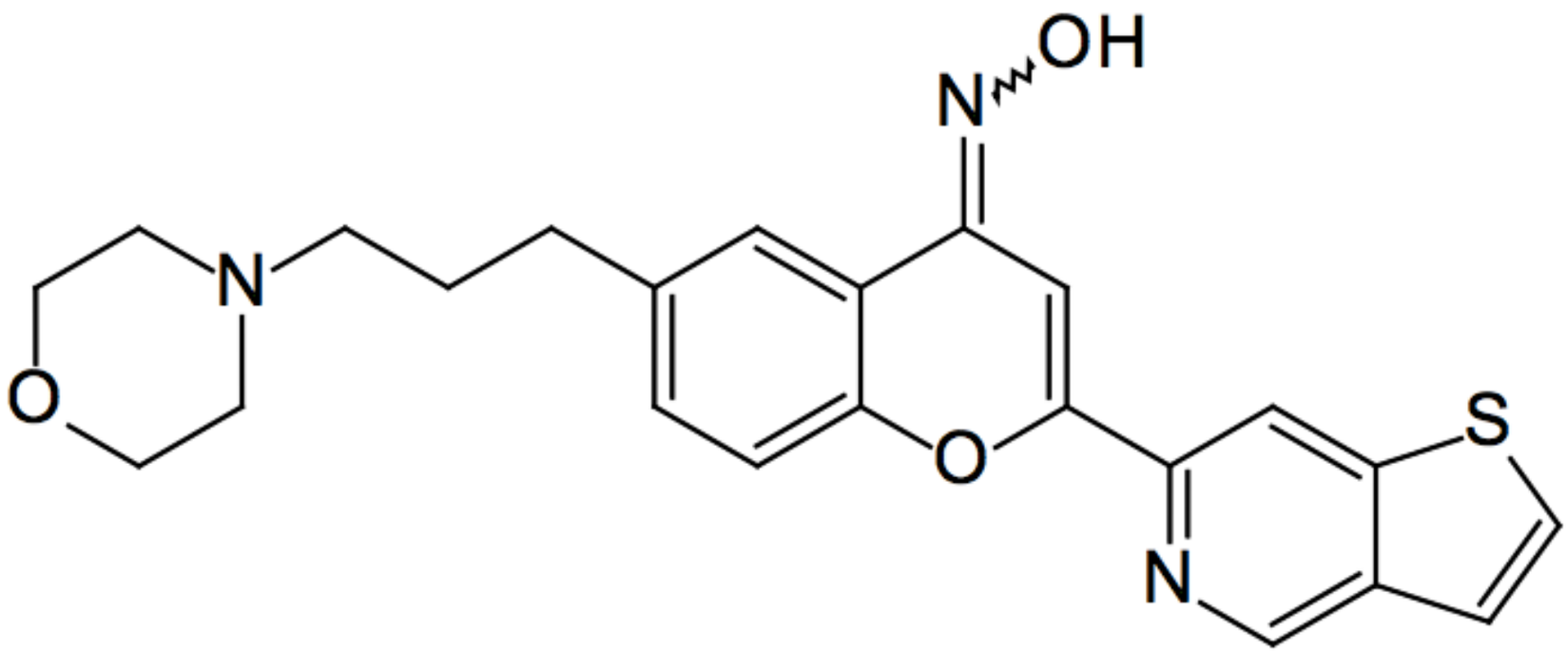
Another Success Story

- Collaboration with Domain Therapeutics (F)
  - Target: mGluR-4 positive allosteric modulators
  - Disease area: Parkinson, Schizophrenia
- Project Setup
  - 3 Years, 2.5 FTEs at Prestwick for med chem (hit to lead & and lead optimization)
- Result
  - Optimized lead family, in vivo proof of concept
  - License agreement signed in Q4 2010



Foliglurax

How did the story continue ?

- Merck Serono closed their site in Geneva in 2012 and gave up all their neuroscience projects
- An ex-Merck team started Prexton Therapeutics and acquired the mGluR4 PAM project
- Foliglurax was selected as candidate and was developed into the clinics up to Phase II
- March 2018: Lundbeck acquired Prexton Therapeutics (total deal volume 1.12 billion USD)

Lundbeck to acquire Prexton Therapeutics adding foliglurax in clinical phase II to its pipeline of innovative treatments for patients suffering from Parkinson's disease

- *Lundbeck will make an upfront payment of EUR 100 million and the deal terms also include up to EUR 805 million in development, regulatory and sales milestones*
- *Foliglurax is a first-in-class treatment which entered clinical phase II testing in Parkinson's disease in July 2017*
- *There remains a large unmet need for effective treatments for Parkinson's patients to sustain the utility of dopaminergic therapies*

Valby, Denmark, Oss, The Netherlands, 16 March 2018 - H. Lundbeck A/S (Lundbeck) and Prexton Therapeutics BV (Prexton) today announced signing of a definitive agreement in which Lundbeck will acquire Prexton. Under terms of the agreement, Lundbeck will pay EUR 100 million (approximately DKK 750 million) upfront and is furthermore required to later pay up to EUR 805 million (approximately DKK 6 billion) in development and sales milestones to the group of current owners.

By acquiring Prexton, Lundbeck will obtain global rights of an attractive compound (foliglurax) which currently is in clinical phase II testing for symptomatic treatment of *OFF*-time reduction in Parkinson's disease and dyskinesia including Levodopa Induced Dyskinesia (LID). First data from the ongoing clinical phase II programme is expected to be available during the first half of 2019.

Natural Product Target Fishing

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Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Leoligin, the major lignan from Edelweiss, activates cholesteryl ester transfer protein

Kristina Duwensee[a], Stefan Schwaiger[b], Ivan Tancevski[a], Kathrin Eller[c], Miranda van Eck[d], Patrick Markt[e], Tobias Linder[e], Ursula Stanzl[a], Andreas Ritsch[a], Josef R. Patsch[a], Daniela Schuster[e], Hermann Stuppner[b], David Bernhard[f], Philipp Eller[g,*]

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ABSTRACT

Objective: Cholesteryl ester transfer protein (CETP) plays a central role in the metabolism of high-density lipoprotein particles. Therefore, we searched for new drugs that bind to CETP and modulate its activity.
Methods: A preliminary pharmacophore-based parallel screening approach indicated that leoligin, a major lignan of Edelweiss (*Leontopodium alpinum* Cass.), might bind to CETP. Therefore we incubated leoligin *ex vivo* at different concentrations with human ($n = 20$) and rabbit plasma ($n = 3$), and quantified the CETP activity by fluorimeter. Probucol served as positive control. Furthermore, we dosed CETP transgenic mice with leoligin and vehicle control by oral gavage for 7 days and measured subsequently the *in vivo* modulation of CETP activity ($n = 5$ for each treatment group).
Results: In vitro, leoligin significantly activated CETP in human plasma at 100 pM ($p = 0.023$) and 1 nM ($p = 0.042$), respectively, whereas leoligin concentrations of 1 mM inhibited CETP activity ($p = 0.012$). The observed CETP activation was not species specific, as it was similar in magnitude for rabbit CETP. *In vivo*, there was also a higher CETP activity after oral dosage of CETP transgenic mice with leoligin ($p = 0.015$). There was no short-term toxicity apparent in mice treated with leoligin.
Conclusion: CETP agonism by leoligin appears to be safe and effective, and may prove to be a useful modality to alter high-density lipoprotein metabolism.

PRESTWICK CHEMICAL

K. Duwensee, et al., Atherosclerosis (2011) 219, 109-115

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Leoligin: Pharmacophore Profiling

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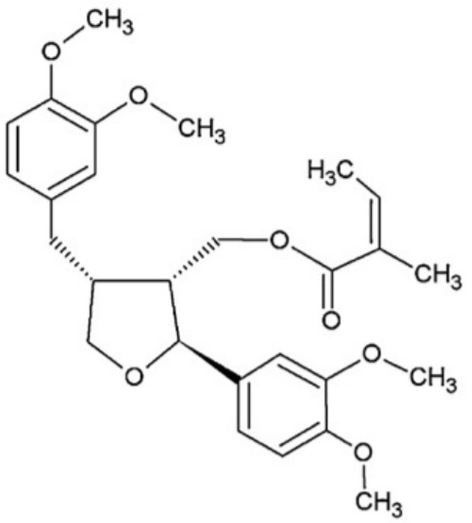

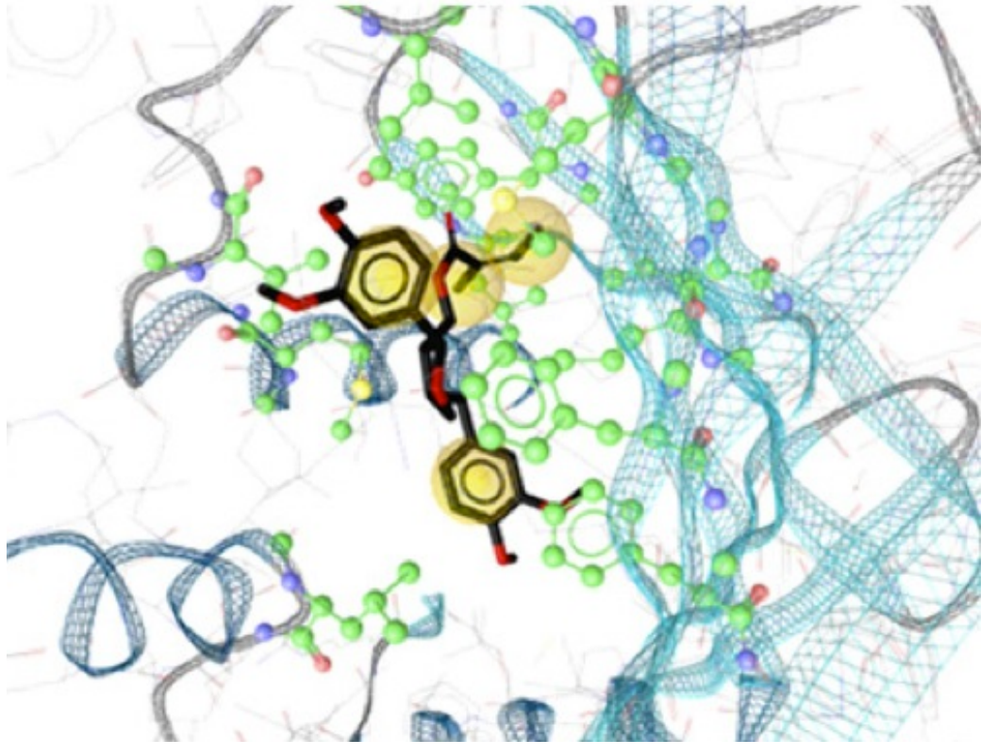

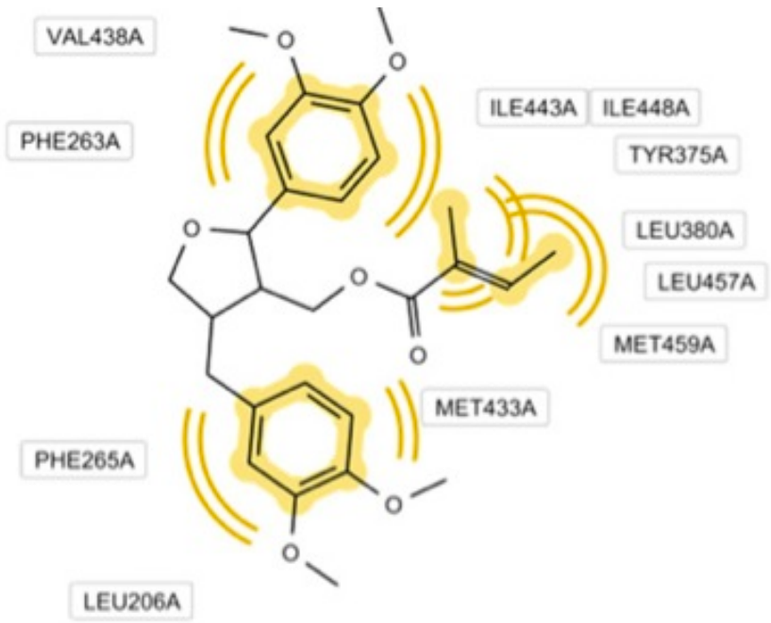

Leoligin matches the pharmacophore model encoding for the interaction site of cholesteryl ester transfer protein (CETP)

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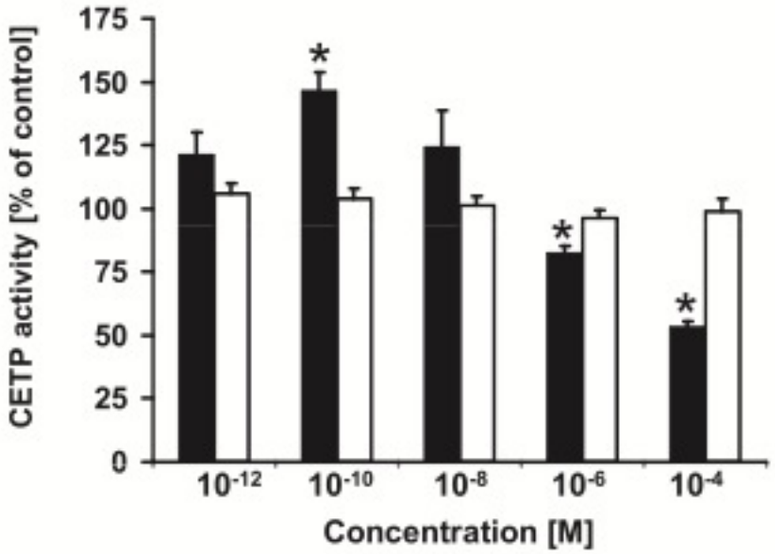
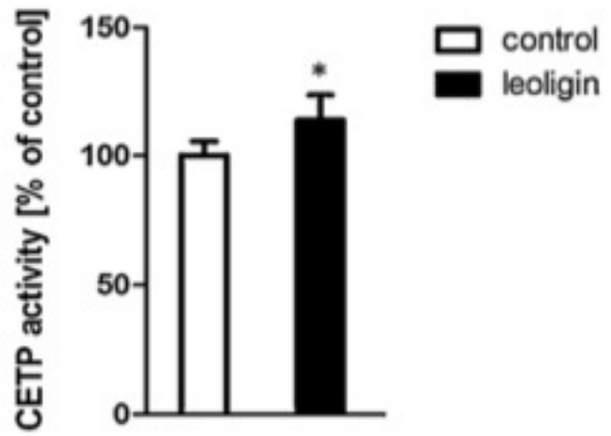
Biological Testing



Leoligin enhances the activity of human and rabbit CETP in vitro when applied in **subnanomolar concentration** (control Probucol)



Leoligin activates CETP in vivo (7 days test with CETP transgenic mice, leoligin dosed orally)

K. Duwensee, et al., Atherosclerosis (2011) 219, 109-115

Further Analysis: New Target ?

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Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Leoligin, the major lignan from Edelweiss, inhibits 3-hydroxy-3-methyl-glutaryl-CoA reductase and reduces cholesterol levels in ApoE −/− mice

Bernhard Scharinger [a], Barbara Messner [a], Adrian Türkcan [a], Daniela Schuster [b], Anna Vuorinen [b], Florian Pitterl [c], Katharina Heinz [d], Kathrin Arnhard [c], Günther Laufer [e], Michael Grimm [d], Hermann Stuppner [f], Herbert Oberacher [c], Philipp Eller [g], Andreas Ritsch [h], David Bernhard [d,*]

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[g] *Department of Internal Medicine, Intensive Care Unit, Medical University of Graz, Graz, Austria*
[h] *Department of Internal Medicine I, Medical University of Innsbruck, Innsbruck, Austria*

Further Analysis: New Target ?

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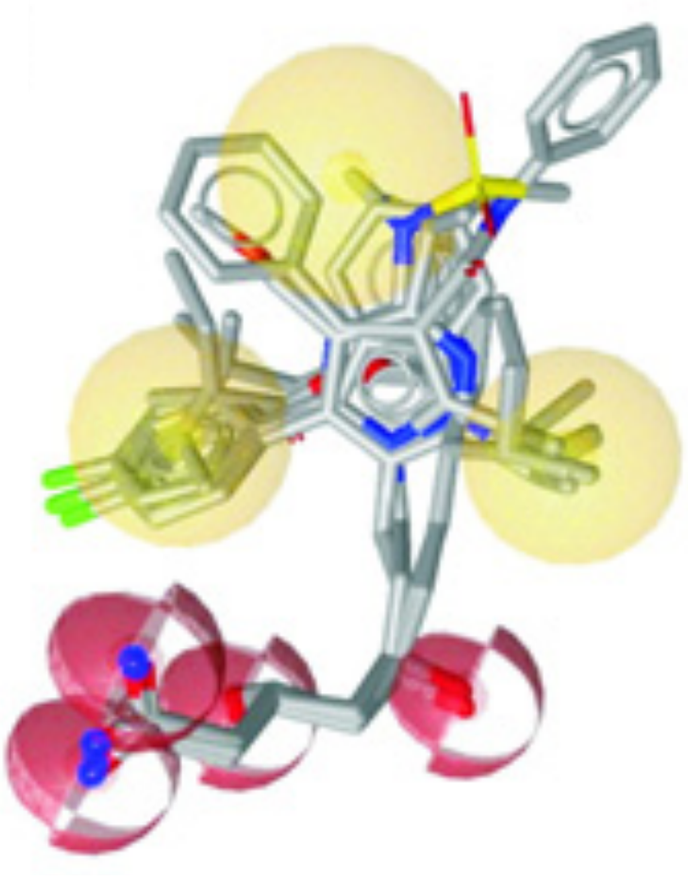
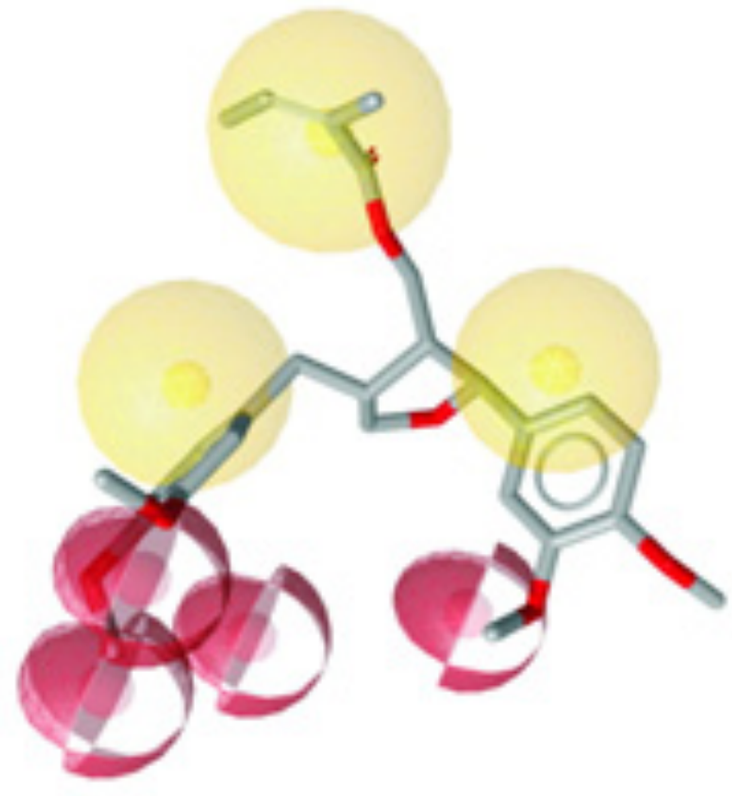
- Pharmacophore model suggests that leoligin is able to form similar protein-ligand interactions with HMGCR as statins do



statins derived model



Leoligin fit onto model

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B. Scharinger, et al., J Mol Cell Cardiol (2016) 99, 35-46

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New Target Confirmed (1)

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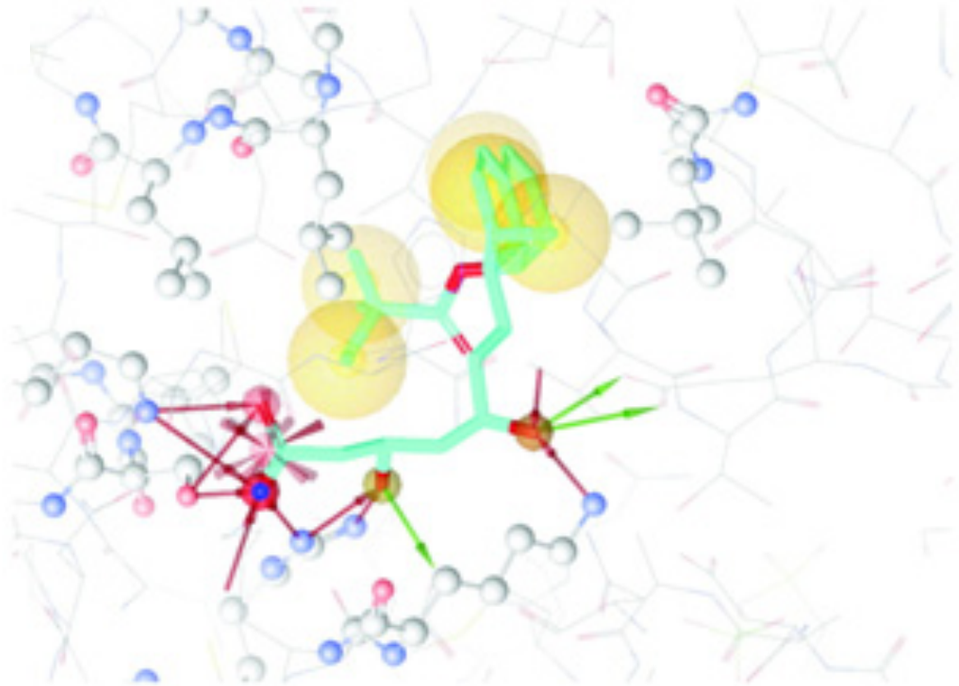
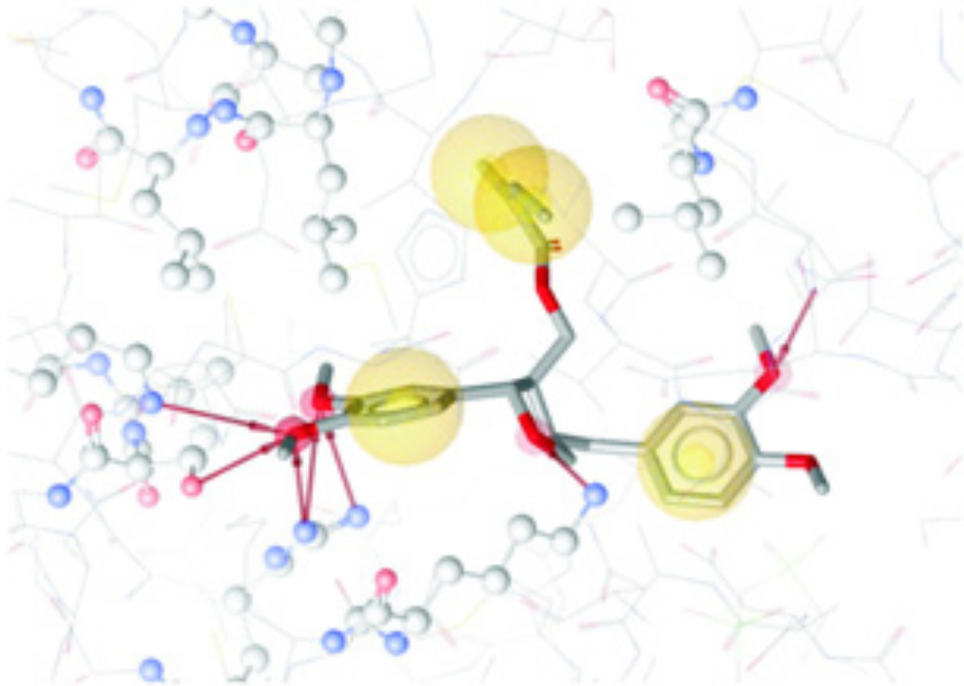
- Leoligin is able to form similar protein-ligand interactions with HMGCR as statins do: confirmed by docking



Simvastatin in HMGCR



Leoligin docked into HMGCR

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New Target Confirmed (2)

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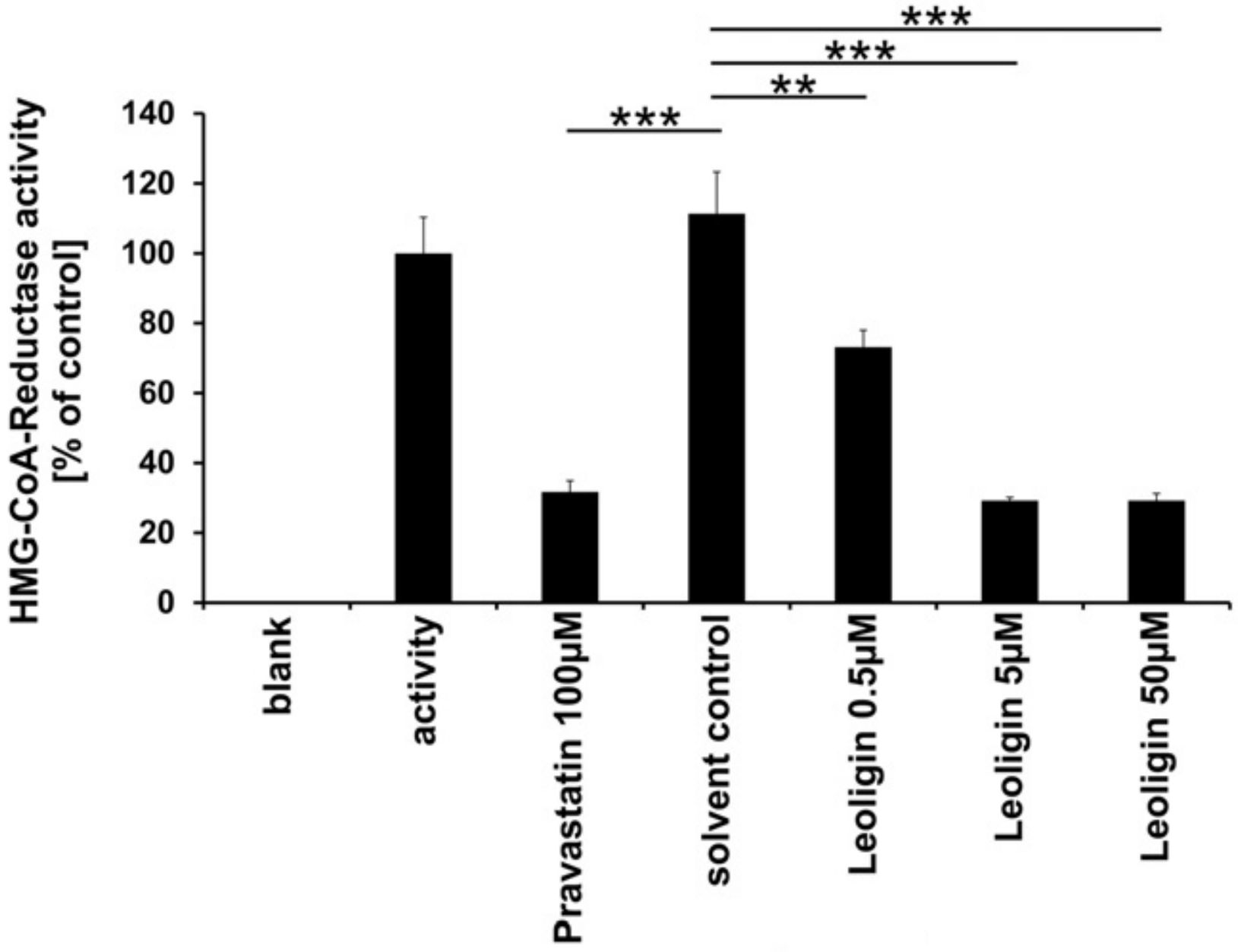
- Biological evaluation

Effect of leoligin on HMGCR activity is comparable to that of pravastatin, however, at 20-fold lower concentration !



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B. Scharinger, et al., J Mol Cell Cardiol (2016) 99, 35-46

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LigandScout Profiling Advantages

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- Speed and Accuracy
  - Due to pattern recognition based alignment, LigandScout virtual screening is amendable for ligand profiling:
    - no speed limitation by the number of features
    - 10000 models can be aligned per minute (standard CPU)
  - Due to its advanced pharmacophore technology, the technique is much more accurate than traditional pharmacophore approaches
    - no limits for the number of features
    - several features on one atom possible

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Thank you for your attention

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