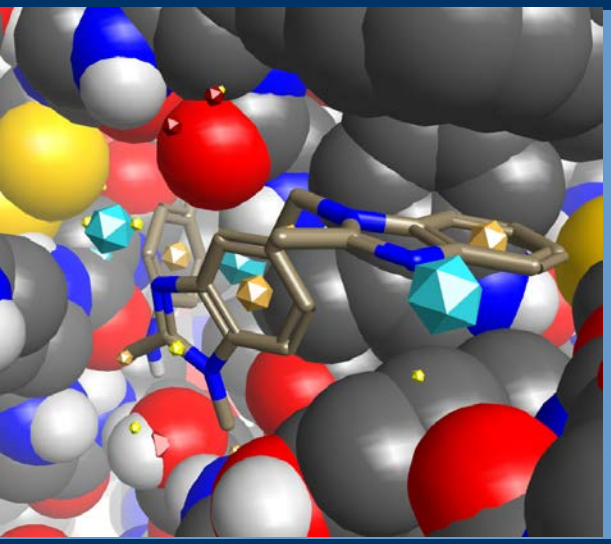


From FieldScreen to Activity Miner:

One Decade of Cresset Software at Boehringer Ingelheim Pharma GmbH & Co.KG

Dr. Bernd Beck

Cresset User Group Meeting

June 16th, 2016

Boehringer Ingelheim

Insilico Drug Discovery

Boehringer Ingelheim

Outline

Boehringer Ingelheim

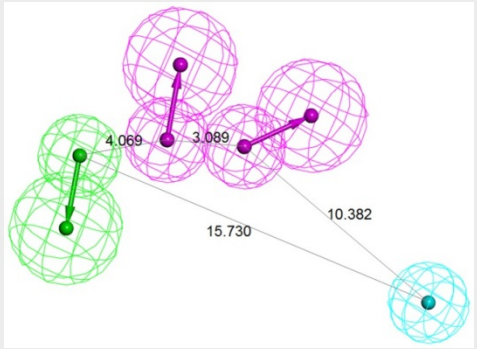
- Introduction
  - History of pharmacophore software at BI Germany
  - Decision for Cresset FieldScreen
- Cresset Tools @BI
  - BI Germany
  - Other Sites
- Examples
- Summary

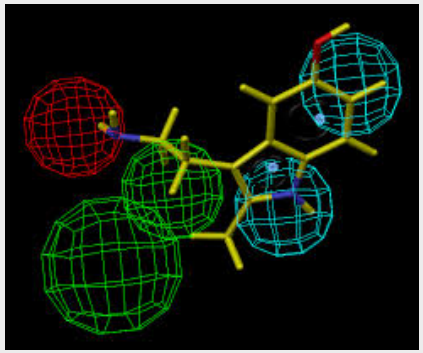
INTRODUCTION

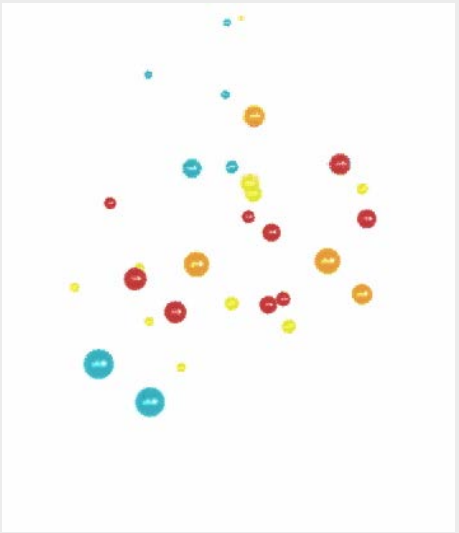
Pharmacophore

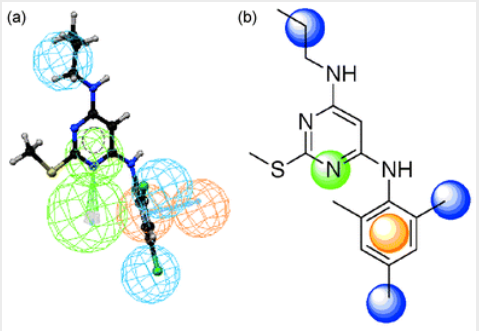
- **1909 Paul Ehrlich**
  " a molecular framework that carries (phoros) the essential features responsible for a drug's (pharmacon) biological activity"

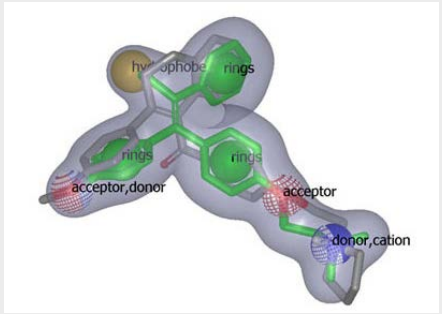
- **1977 Peter Gund**
  " a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity"











History of pharmacophore software at BI Germany

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- End of 2001 virtual screening campaigns in BI were based on fingerprint searches (e.g. Daylight fingerprints) or docking tools
- In 2003 a first overview of available pharmacophore software was generated and possible evaluation scenarios were discussed.
- In 2004 the Computational Chemistry group in Biberach started to evaluate different software for the usage in virtual screening campaigns
  - Fingerprint approaches like Daylight FP, feature trees and BCUTs
  - Docking software like FlexX, Fred and Glide
  - Pharmacophore tools including THINK, ROCS (shape similarity), Catalyst, MOE, FLAP and FieldScreen (Blaze)
- In 2005 the tests with all pharmacophore tools were concluded

Decision for Cresset FieldScreen/Blaze

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- All pharmacophore tools were tested in 4 different research projects
- As criteria for the decision we focused on
  - Interface/usability
  - Run-time
  - Quality of the results
- One measurement of the quality of the obtained results we used was the number of hits (<10 µM) found in the first 100000 hits (2 million compounds screened). Here are 2 examples (between 6 and 8 different search structures per project; best results selected)

Project 1: 1438 active compounds

Cresset Ranking	#Hits <10 µM
100000	1366 (95,0 %)
50000	1349 (93,8 %)
25000	1323 (89,2 %)
10000	1283 (56,0 %)
5000	1217 (84,6 %)
1000	774 (53,8 %)
100	45 (3,0 %)

Project 2: 3776 active compounds

Cresset Ranking	# Hits <10 µM
100000	1996 (52,9 %)
50000	1651 (43,7 %)
25000	1436 (38,0 %)
10000	1202 (31,8 %)
5000	1068 (28,3%)
1000	538 (14,2 %)
100	85 (2,3 %)

Decision for Cresset FieldScreen/Blaze

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Cons

- Technical problems during the implementation
- Initial performance

Pros

- Quality of the results compared to other tools
- Usability
- Fieldpoint concept

=> Decision end of 2005 to use Blaze as an alternative to ROCS and MOE

=> FieldAlign and other Cresset Tools (now Forge)

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CRESSET TOOLS @ BI

Usage at BI Germany

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- Original we start to use Cresset software as a pure virtual screening tool
- Between 2005 and 2010 this was the main application field
- Still used from time to time but not on a regular basis
- Since 2015 we use KNIME workflows to update our compound collections in Blaze

- FieldAlign and FieldTemplater functionality more and more used since 2010
- In the last 3 to 4 years we more often use the 3D QSAR functionality (LO project support)
- Since last year more and more colleagues in CompChem also use the activity miner functionality

- Spark is use for several years now
- BI's BICLAIM approach as internal generated database for spark available
- Idea generator
- Support of LO activities

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USAGE AT OTHER BI SITES

Usage at other BI sites

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- **Vienna**
  - **Blaze** is used on a regular basis for ligand based virtual screening
    - used together with ROCS
  - **Spark** is used quite often for core replacement/virtual screening and also as support in the compound design process
  - **Torch** – rollout to the MedChem community beginning of this year
  - **Forge** – just started
- **Ridgefield**
  - **Forge** – Alignment - very often used
  - **Forge** – Templater - used from time to time
  - **Forge** - Usage of the 3D-QSAR since last year
  - **Spark** – Main tool for scaffold hopping with external and internal (BICALIM)DBs
  - **Blaze** – rarely used

EXAMPLES

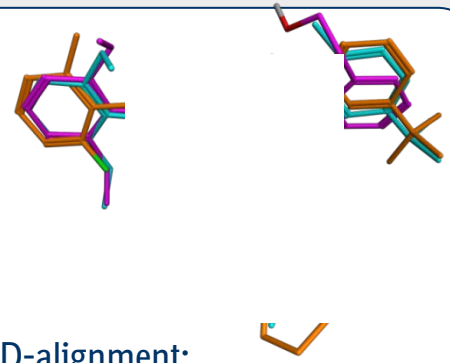
3D-QSAR to identify bioactive conformation

Patent & Literature analysis

- Data set with activity data extracted
- Generated conformations for the most interesting compound (not very flexible)
- Generate 3D QSAR models for every conformer
- Use conformer of the best model to search the BICLAIM space

Starting Point:

Sample Code	Structure	MW TPSA cLogP PCS40 Solid BC	Assay 1
Compound1	Chiral	540.7 88 3.6 5 tubes 405.2 mg	8.4 29/29



3D-alignment:
Bioactive conformation hypothesis derived from 3D QSAR

Search BICLAIM space:
17 cores explored

~1400 cpds

Examples of the two new BICLAIM chemotypes*

Sample Code	Structure	MW TPSA cLogP PCS40 Solid BC	Assay 1 nM	Hill LE	LILO Assay 2	Hill LE	Assay 3	%max Hill	Assay 4
Compound2	Chiral	579.7 83 5 2 tubes 25.9 mg	91.6 1/1	2.04 -1.26 .229	341.9 1/1	-6.9 -0.81 .211		n.a. n.a.	43.9 6/6
Compound3		540.7 96 5.8 1 tubes 5.6 mg	464.0	1.26 -1.41 .217	>30000.0	65.1 n.a. .155	532.6	5.7 -0.67	1339.0

Synthesis prioritization:
- 3D superposition
- CCFW solubility predictions

3D QSAR → improvement of MicStab and solubility

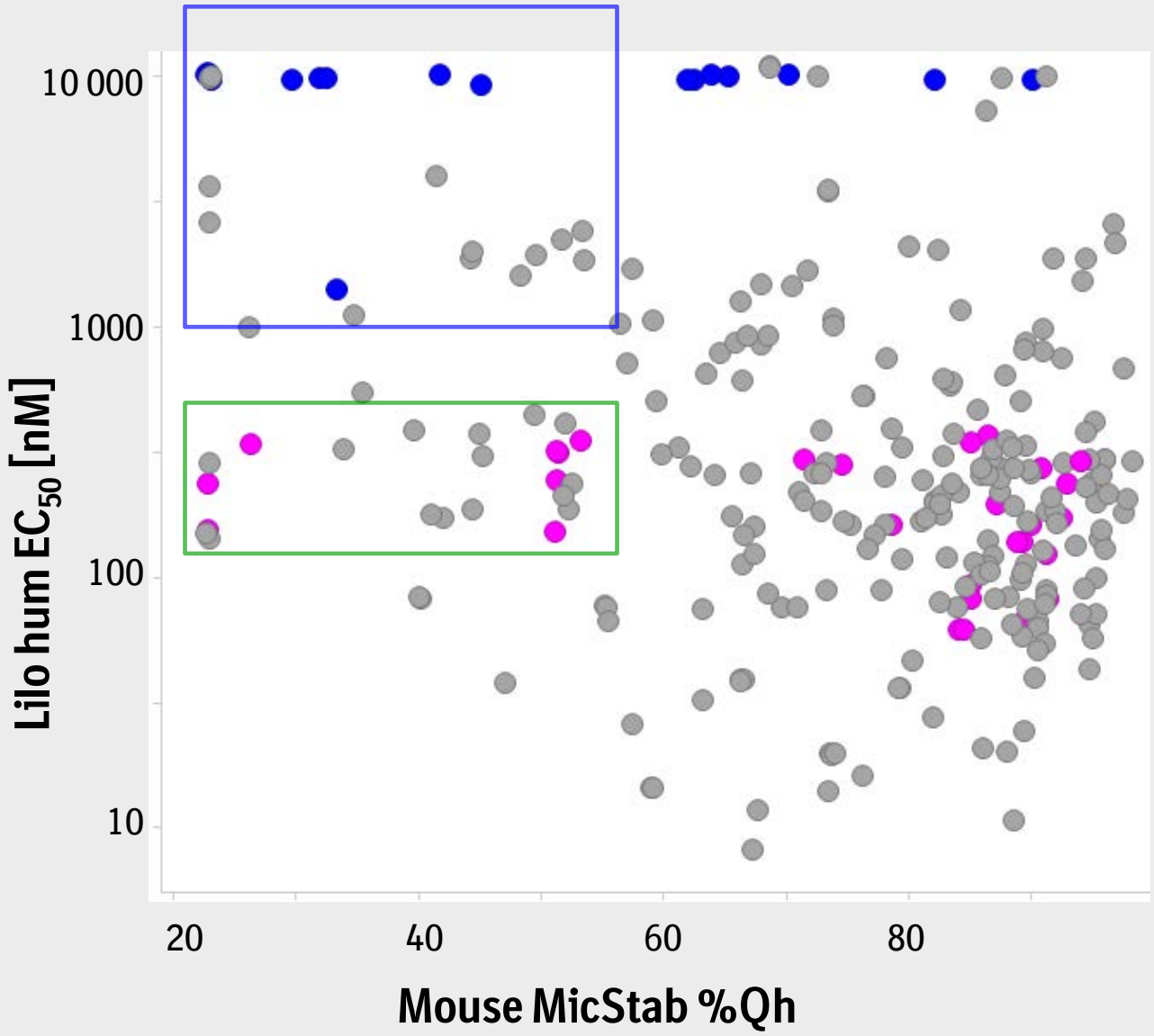
2 planning campaigns:

- 1st campaign: proof of concept: optimization of MicStab + Solubility
  Aim: check if stable compounds can be found and in silico predictions work
  → results: stable, soluble compounds BUT potency was (more or less) gone

- 2nd campaign: optimization of MicStab + solubility and retain potency
  → some stable and soluble compounds with quite good potency designed
  → starting points for new MedChem explorations

Methods:
- CompChem in-silico models for mouse MicStab and HTSol
- Model building framework (Potency predictions)
- Forge (3D-QSAR) approach for potency

Forge: 3D 3D QSAR → improvement of MicStab and solubility



First planning campaign

Second planning campaign

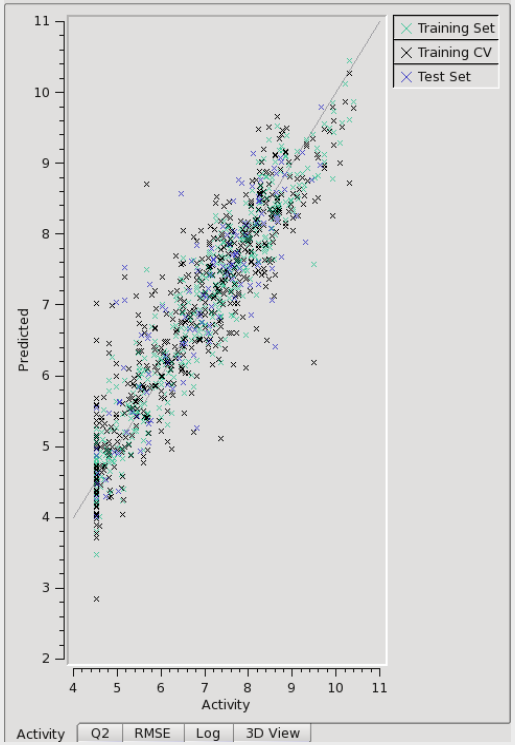
Other compounds in that class

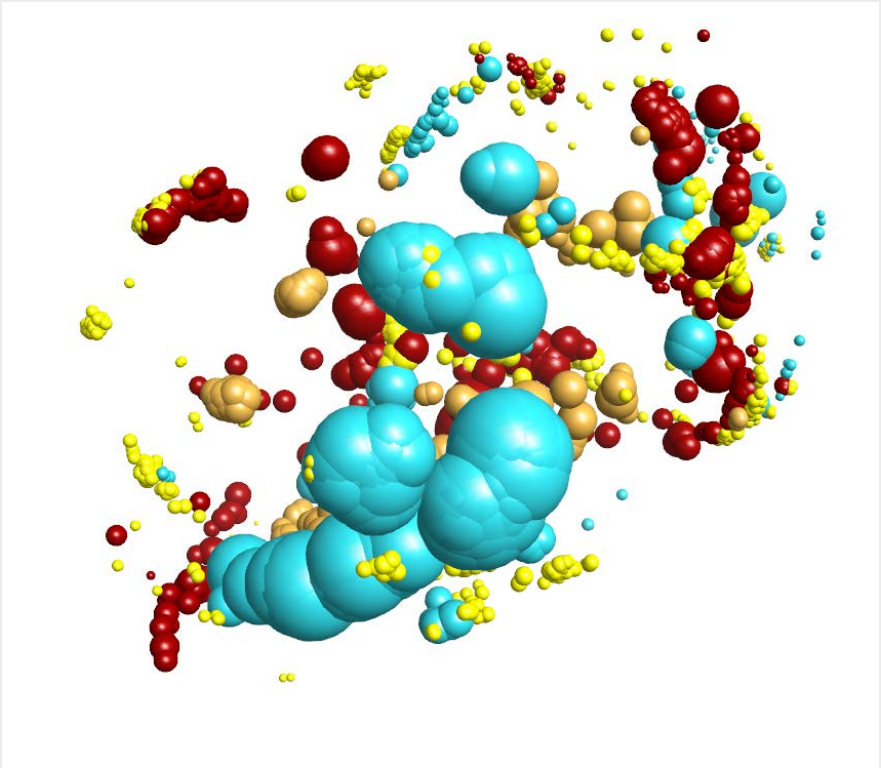
1st campaign yielded many stable but mostly inactive compounds

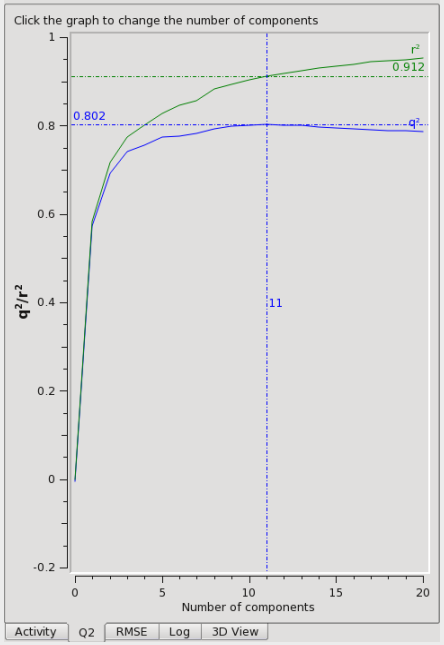
2nd campaign yielded some stable compounds with good activity

Forge: 3D QSAR - Example 2

- Pre-alignment decisive for model quality
- Automatic alignment do not work neither with Forge nor with ROCS
- Final models for Target 1 and Target 2 with manual curation of automatic ROCS alignment



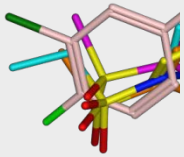




Applied to prioritize RHS and LHS variations
Disadvantage: manual alignments

Field Templater

Project A:
Alignment of competitor compounds
Bioactive conformation hypothesis used during the whole project:



Project B:
Trial to generate a bioactive conformation hypothesis for interesting hit classes failed due to strange conformations of the sulfonamide part.
We were not able to reproduce this in the current version of Forge.

Activity Miner Example

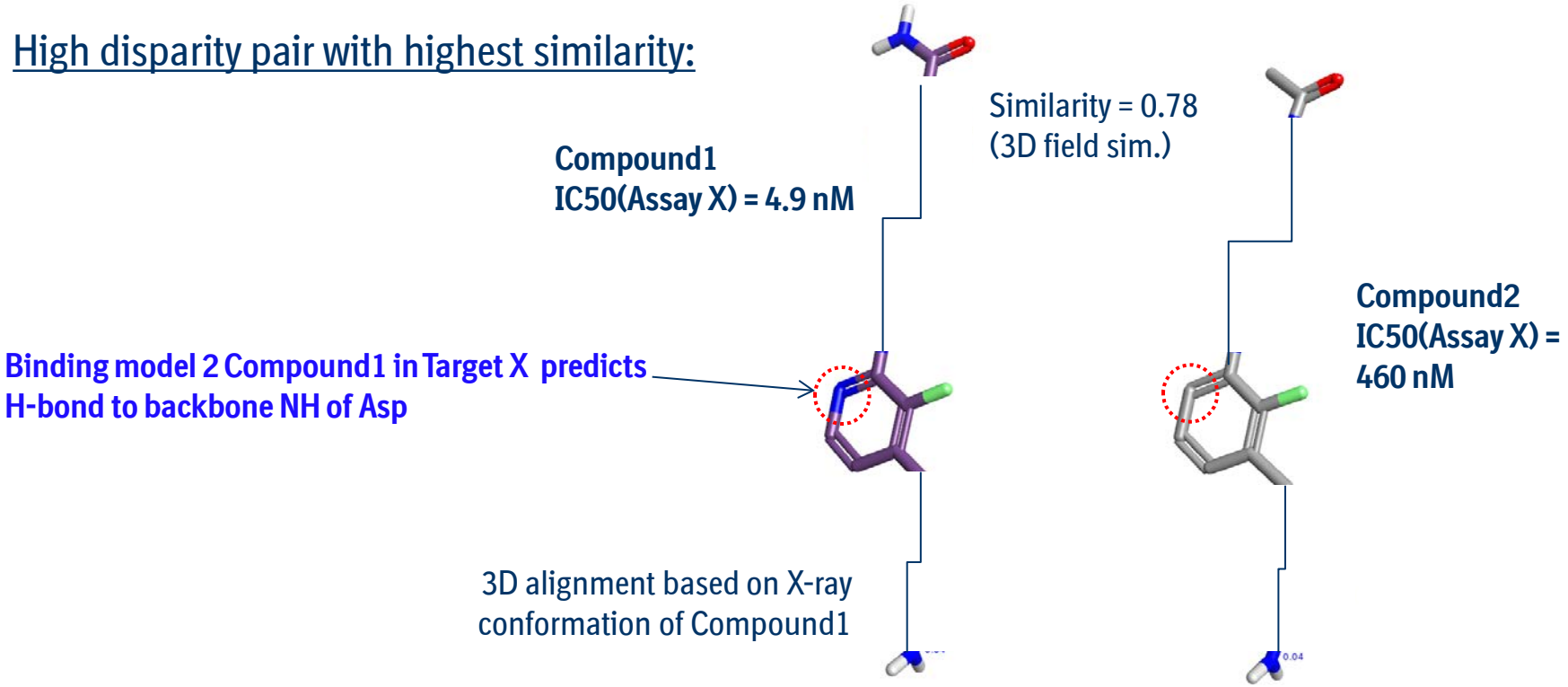
Identify compounds with a better selectivity

$$\text{Disparity} = \frac{\Delta\ \textbf{Activity}}{\textbf{(1 - similarity)}}$$

High disparity: Similar molecules with highly different activity („activity cliff“)

- 11 highest ranked pairs: Change from core with meta nitrogen to core without

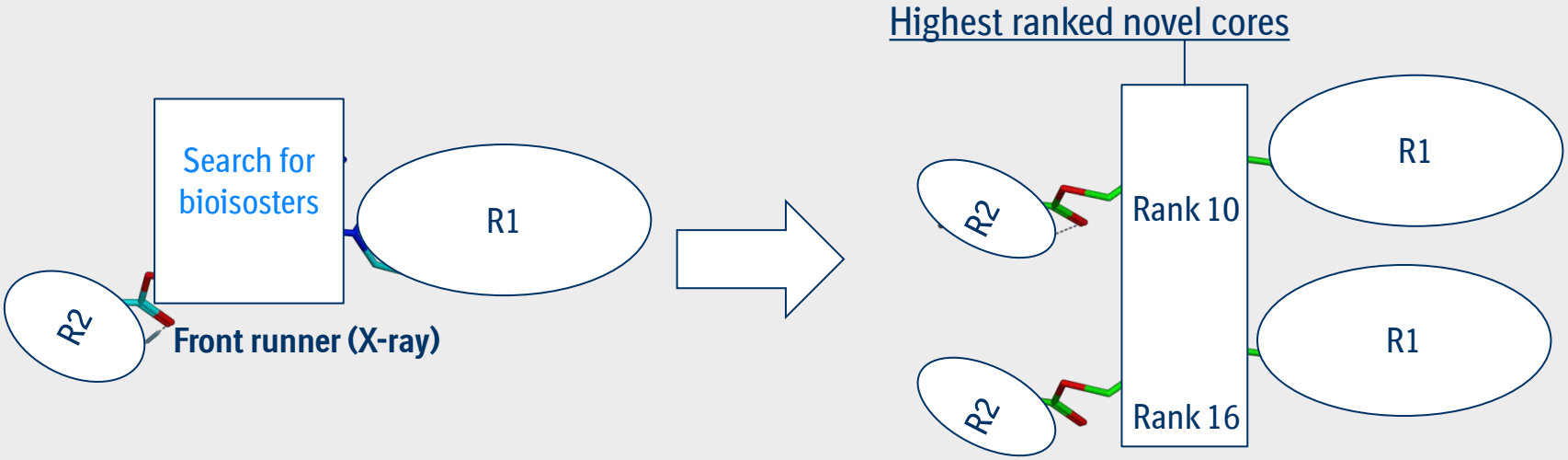
High disparity pair with highest similarity:



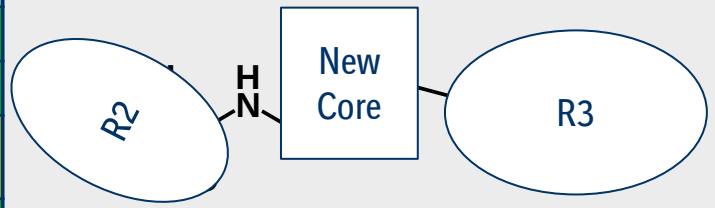
Virtual screens for core modifications inspired synthesis of new chemotype

Starting from the X-ray structure of our front runner:

- Search for bioisosteric core replacements
  - Software: Spark – match of shape and electrostatic field
  - Protein considered as exclusion volume



Sample Code	Compound2		
Assay X: IC_{50} h/r [nM]	3.0	6.3	
Assay Y: IC_{50} h/r [nM]	11	7.2	
HT-Sol [µg/ml] @ pH 2.2/4.5/6.8	90	78	73
CaCO2 [10^{-6} cm/s]/Efflux	6.3	3.1	
HLM / RLM [%Q_H]	<23	<22	
HHEP/RHEP [%Q_H]	7.4		



Compound 2

SUMMARY

Summary

- Cresset Blaze (FieldScreen) convinced us with very good virtual screening results
- After initial technical issues the software runs very stable over years
- Very good user interface for the different tools
- Over the years the focus in the usage of Cresset tools changed. Less virtual screening in early projects and more support (3D QSAR, Activity miner or focused virtual screening in Spark) for lead optimization projects
- At the moment we observe an increasing usage of the tools

- Very good support and good relationship to Cresset
- Cresset is open for new ideas

- Currently internal discussions are ongoing if and how medicinal chemists should have access to the Cresset tools
- Most of the comp. chemist use the tools from time to time, 3 to 4 on a regular basis

Acknowledgements

- All colleagues from the BI CompChem group
- Mark & Tim for the very good support and the very good relationship in the last 10 years

Thank You