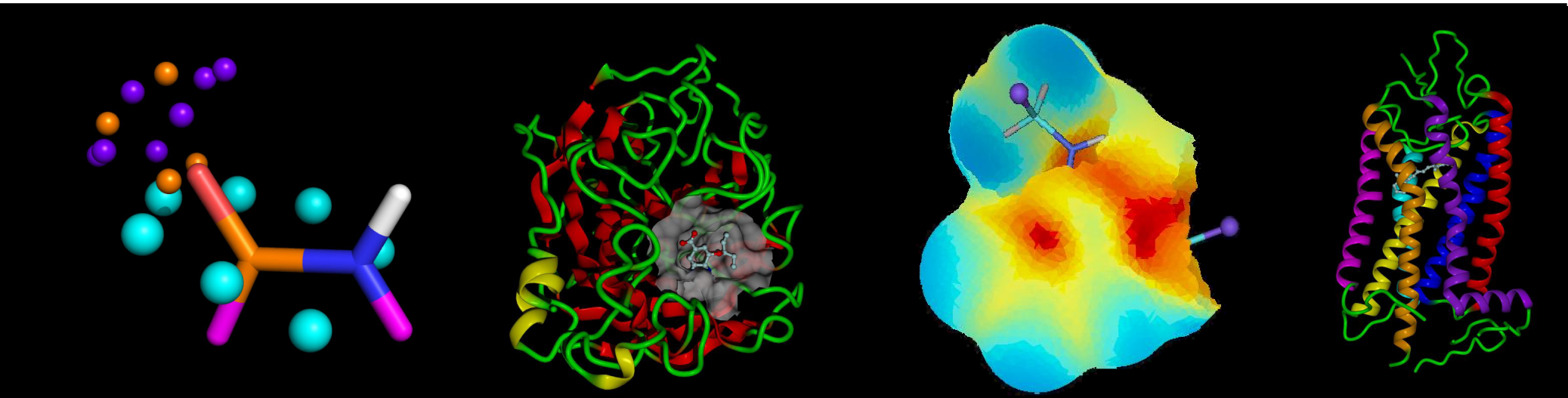
ParaFrag
A New Tool for Bioisoster Searching

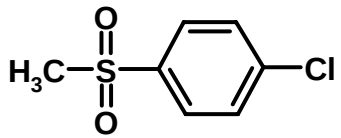
Harald Mauser



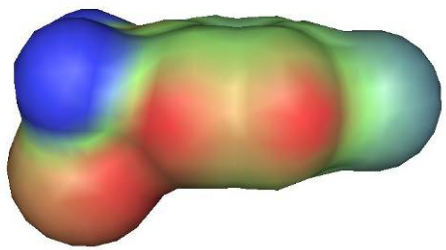
Local Properties

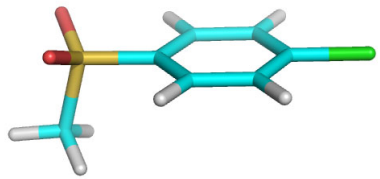
Molecular properties are not isotropic

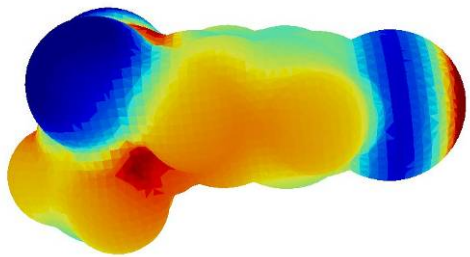
Classical MEP

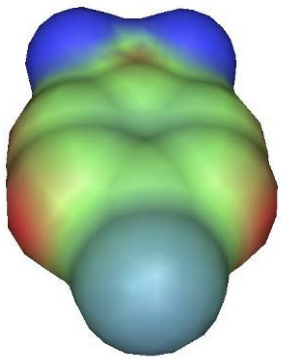


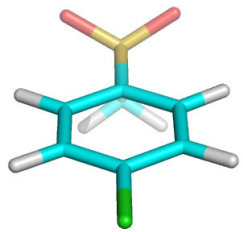
Quantum mechanical MEP

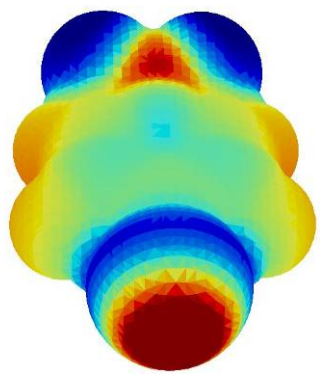










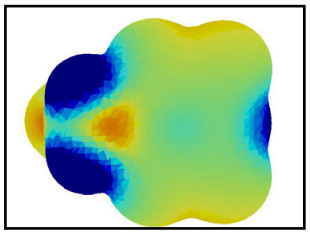


Implemented in most pharmacophore search and docking algorithms

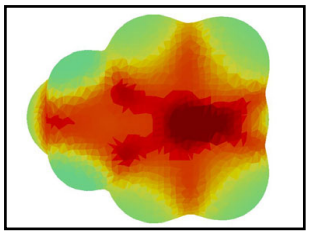
see work on σ-hole bonding by Clark and Politzer (eg J Mol Model 2007)

The Four Local Properties

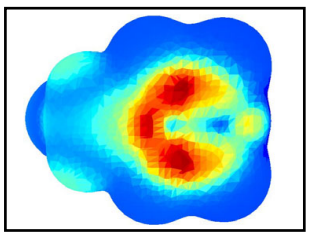
*Derived from quantum-mechanical calculations**



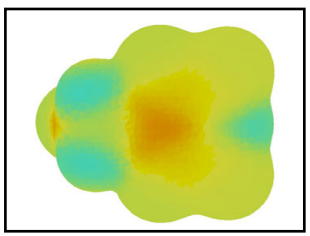
Molecular Electrostatic Potential (MEP):
Electrostatic Interactions



Local Ionization Energy (IE_L)
Lewis Donor Properties → electrophilic processes:



Local Electron Affinity (EA_L)
Lewis Acceptor Properties → nucleophilic processes

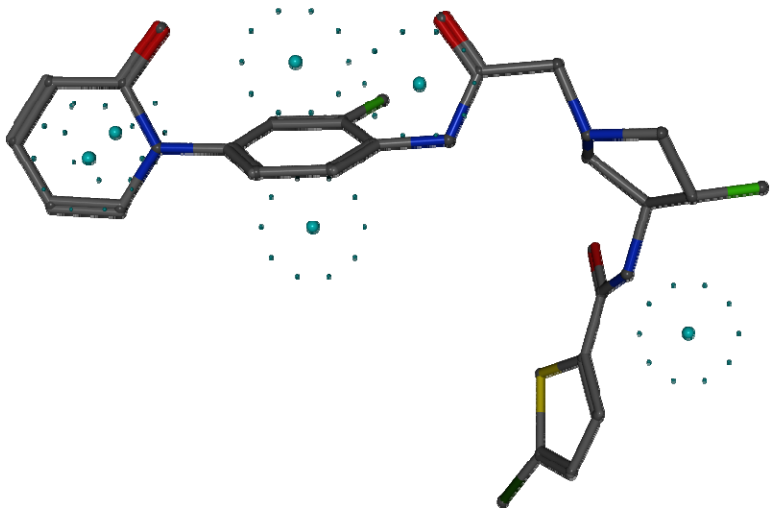


Local Polarizability (α_L)
Dispersion Interactions → London forces

(*) ParaSurf, Cepos InSilico Ltd, Ryde, UK (http://www.ceposinsilico.com)

The ParaFrag Pharmacophore

Local properties & surfaces



1. 3D structure

↓

IE_L surface

↓

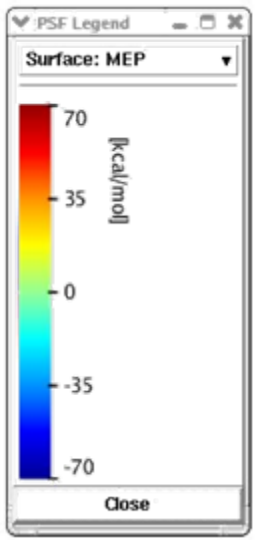
IE_L extremes

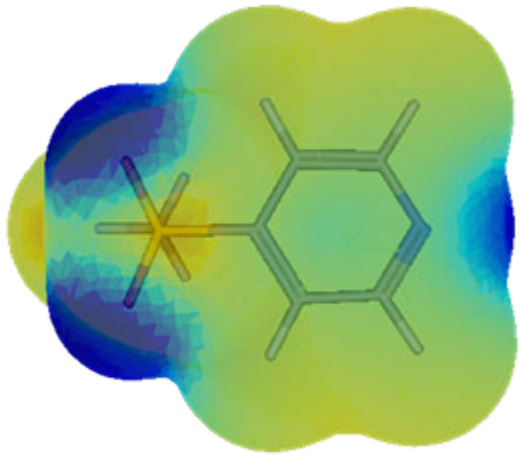
Factor-Xa inhibitor taken from X-Ray structure 2vwo (K. Zbinden et al. *Eur J Med Chem.* **2009**, *44*, 2787)

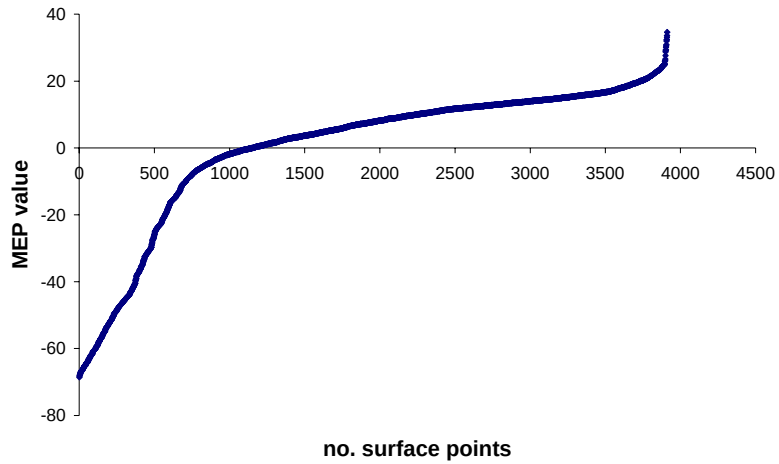
Calculation of the ParaFrag Pharmacophore

Fast statistical approach

1. Property distribution (Example MEP)



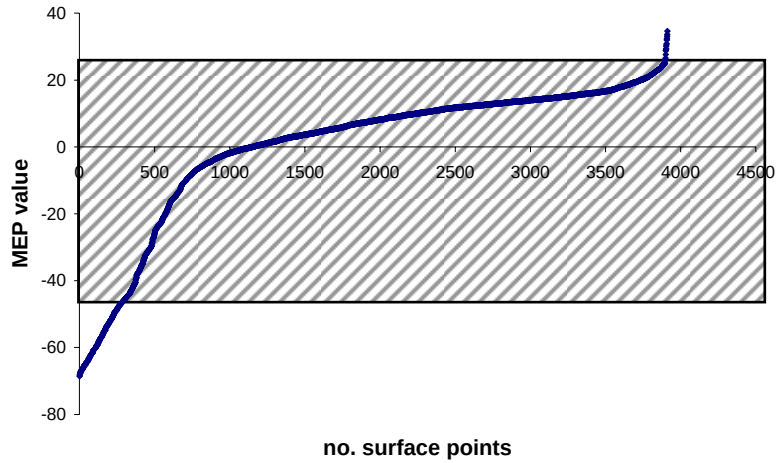


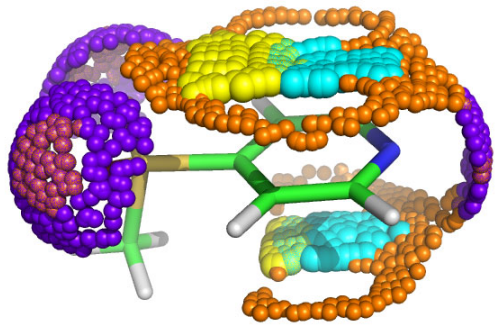


Calculation of the ParaFrag Pharmacophore

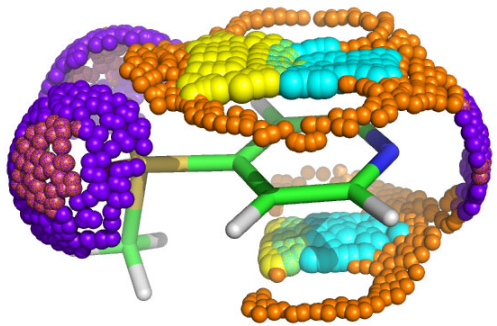
Fast statistical approach

2. Consider extremes above (robust Median + 2*MAD) or below (robust Median – 2*MAD)



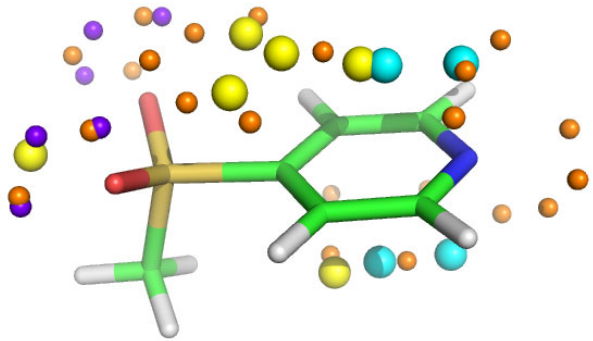


3. Identify representative centroids



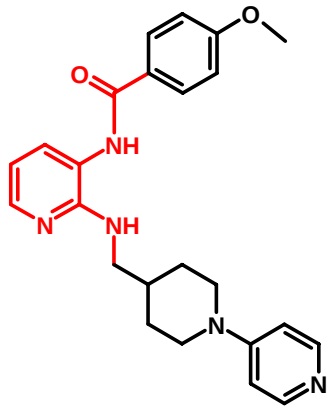
keep only

- one representative per cluster
- top 6 extremes per property

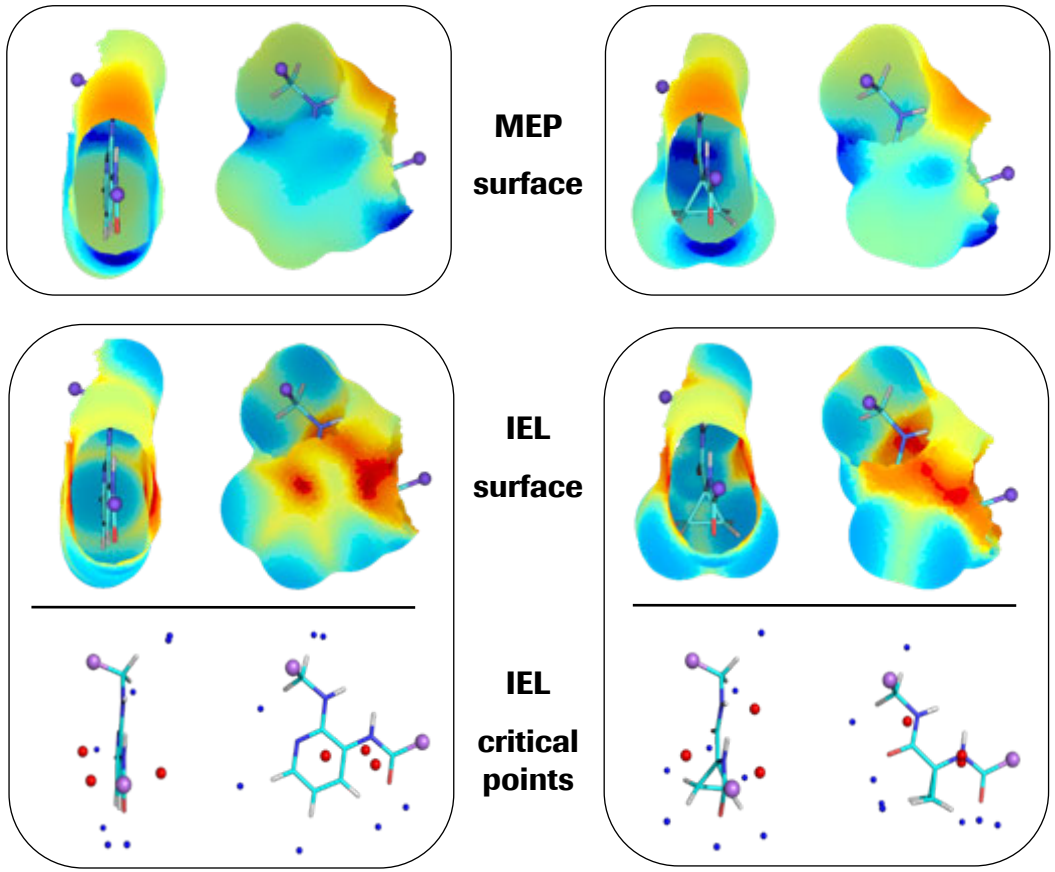


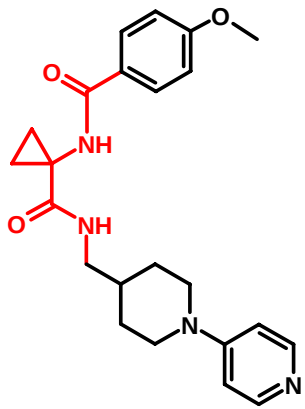
A First Application: Scaffold Hopping

*Retrospective Analysis of FactorXa Inhibitors**



QUERY





TARGET

Pharmacophore match = 0.59

(**0.47** automated exit vector matching on conformer library)

(*) Jakobi, A.-J.; Mauser, H.; Clark T. *J. Mol. Model*. **2008**, *14*, 547–558.

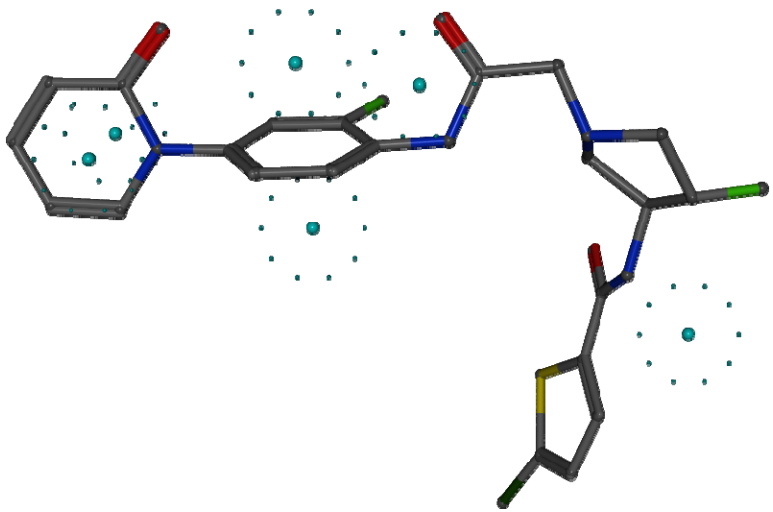
ParaFrag: Training on In-house Dataset

Outline

- In house data with activity and structural information
- Activity sensitive to electronic properties
- Dataset biased to active compounds
- Challenging as in-actives show high similarity to actives
- ***Training for***:
  - Separation of actives and inactives (full molecule similarity comparison)
  - Bioisosteres
  - Comparison of molecular fragments across different series

The ParaFrag Pharmacophore

Local properties & surfaces



1. 3D structure

↓

IE_L surface

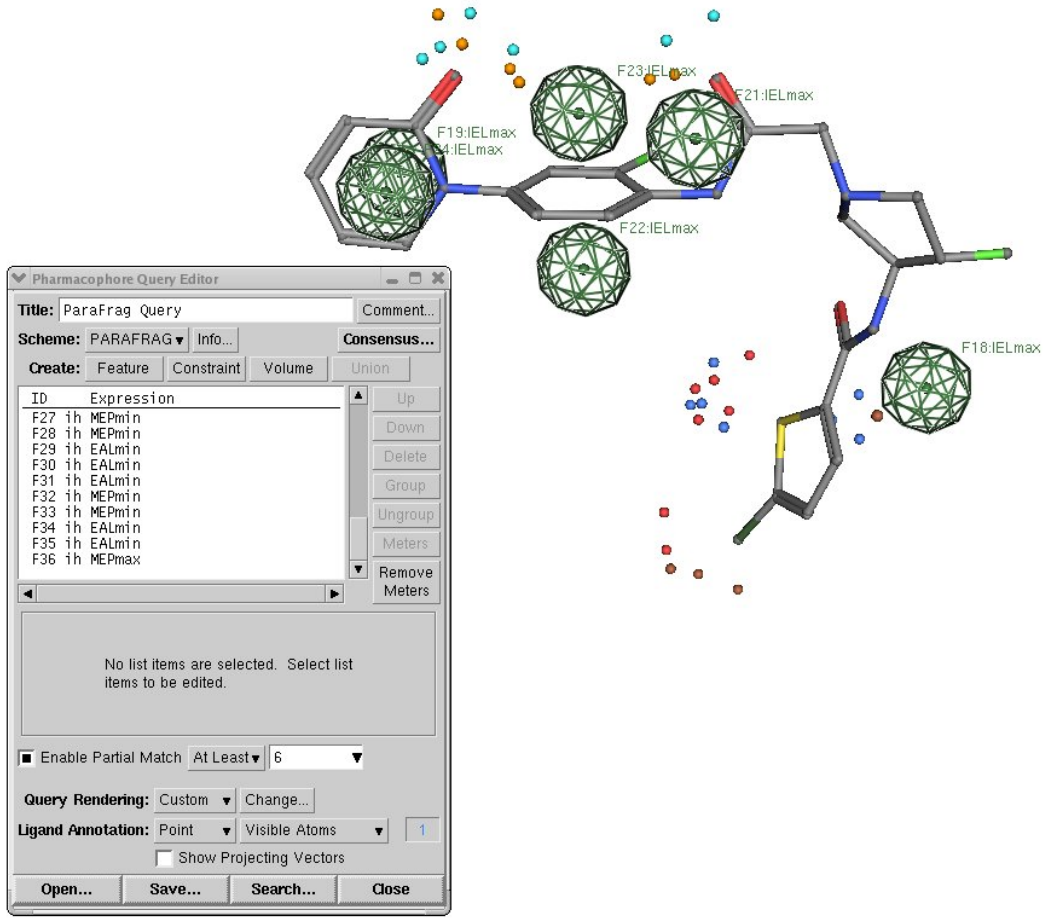
↓

IE_L extremes

Factor-Xa inhibitor taken from X-Ray structure 2vwo (K. Zbinden et al. *Eur J Med Chem.* **2009**, *44*, 2787)

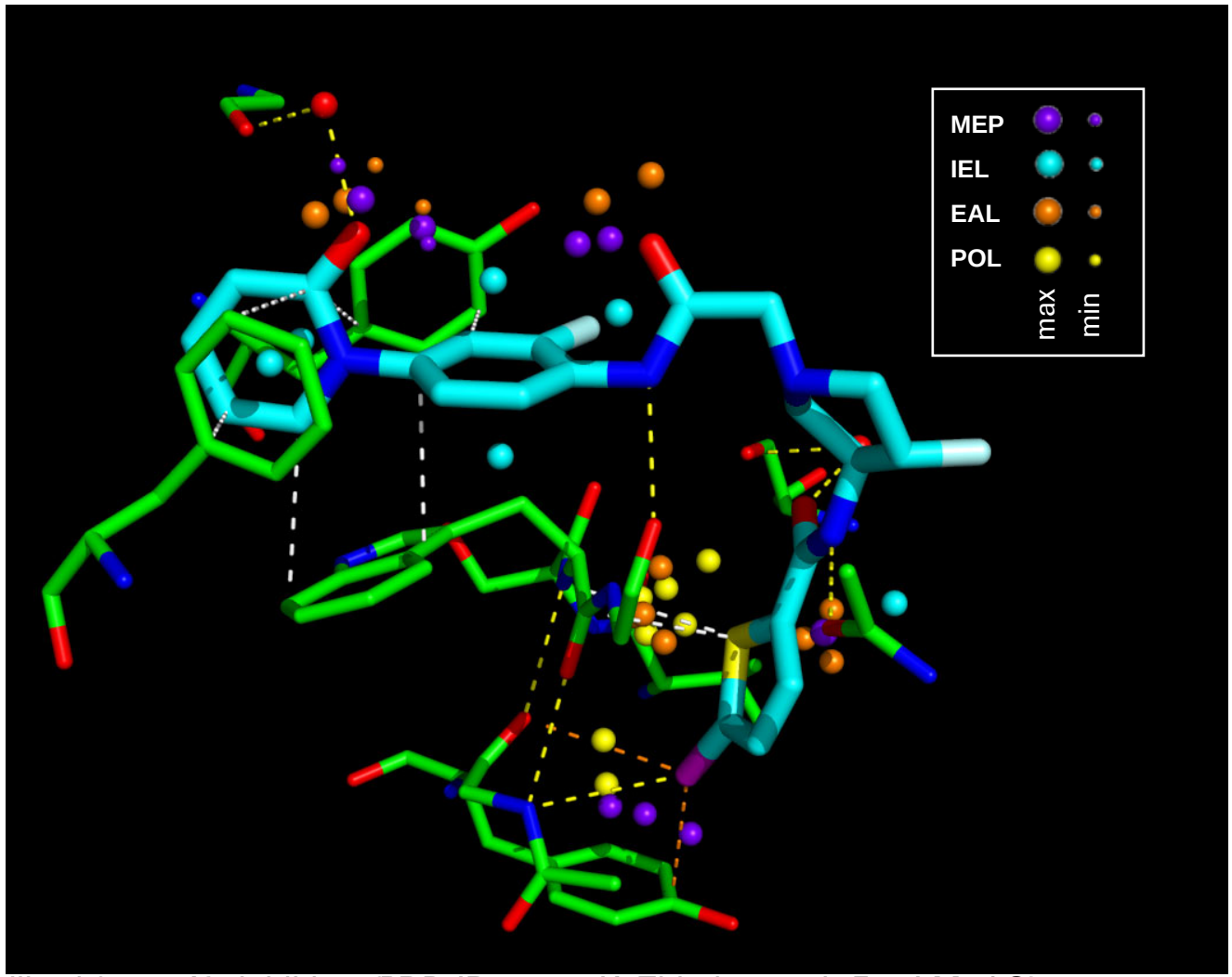
The ParaFrag Pharmacophore in MOE

Extension of the MOE Pharmacophore Schemes



Key interactions coded by local surface properties

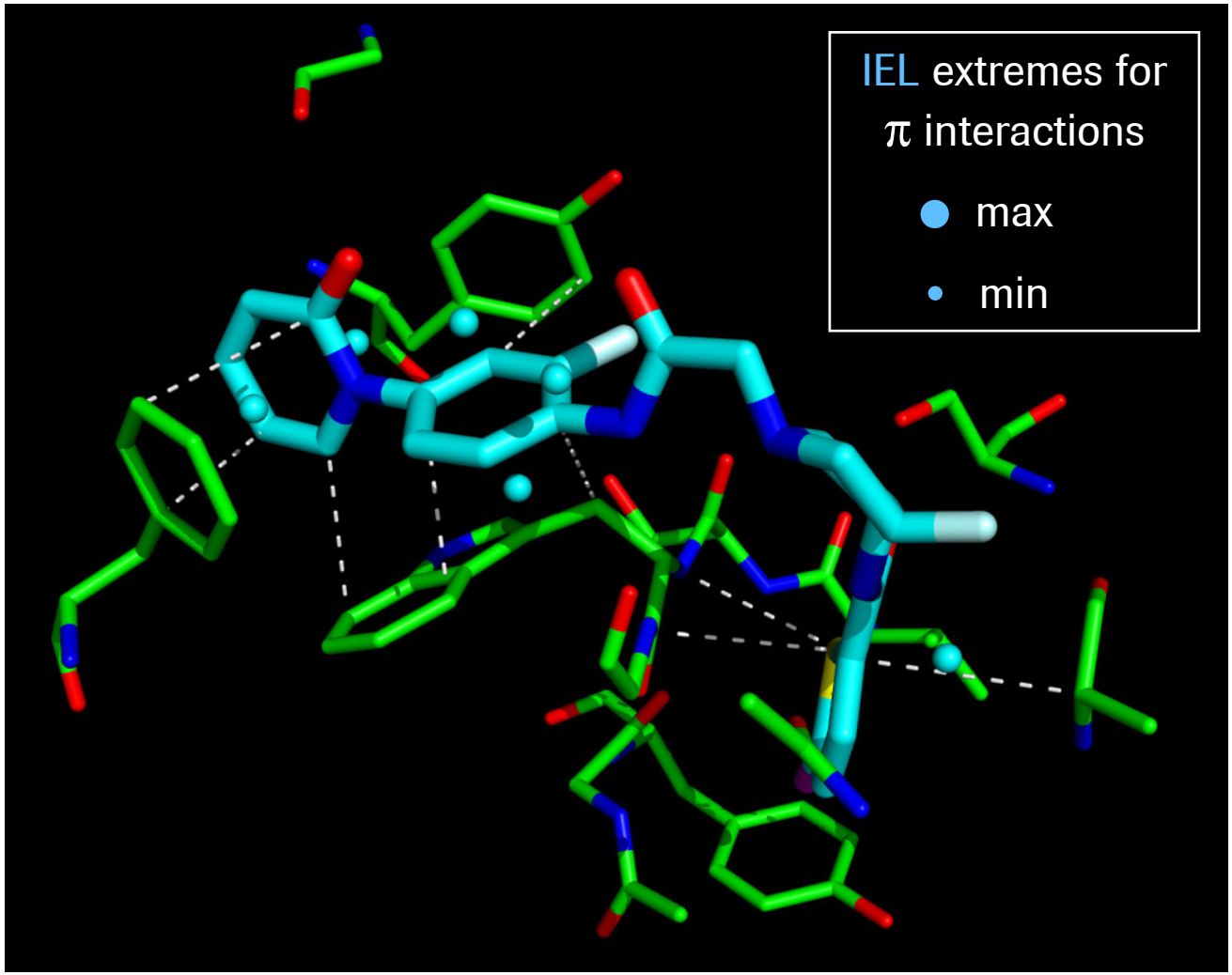
Extremes & Interactions



Co-crystallized factor-Xa inhibitor (PDB-ID: 2vwo; K. Zbinden et al. *Eur J Med Chem.* **2009**, *44*, 2787)

Key interactions coded by local surface properties

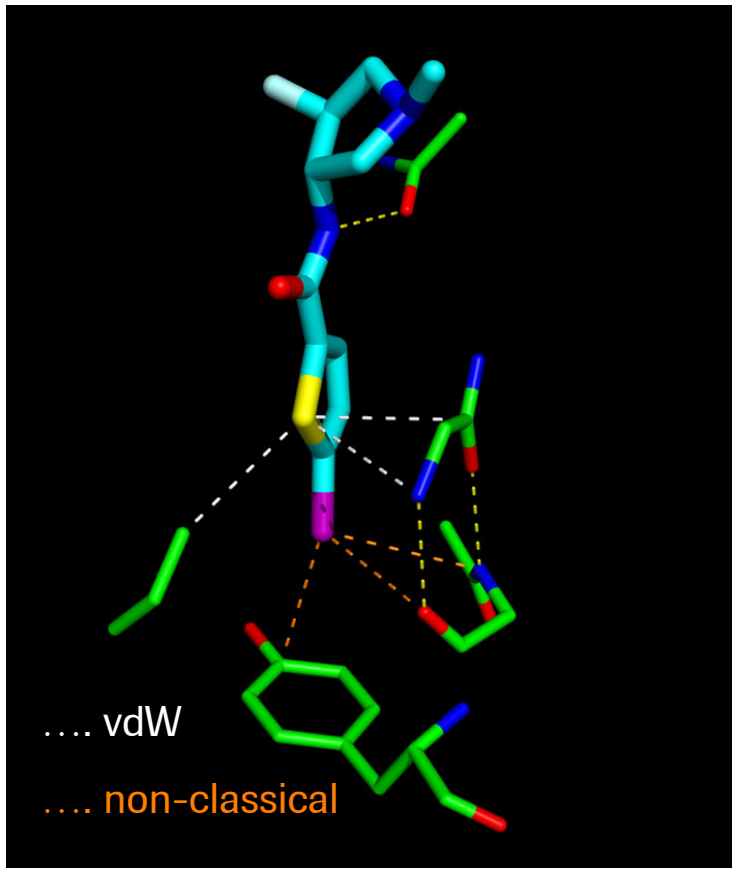
Example: π-stacking

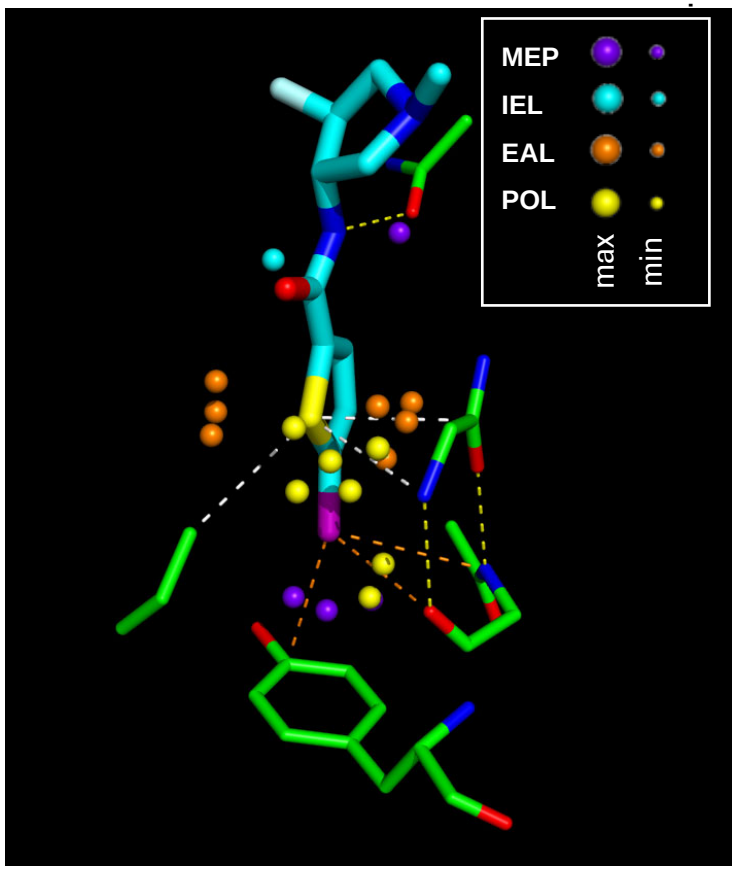


Co-crystallized factor-Xa inhibitor (PDB-ID: 2vwo; K. Zbinden et al. *Eur J Med Chem.* **2009**, *44*, 2787)

Key interactions coded by local surface properties

Example: non-classical interactions





ParaFrag: Training on In-house Dataset

Learnings

- Definition of defaults for ParaFrag pharmacophores
  - Feature radius*:* 1.0 Å (all properties)
  - Partial matches min. six features
  - *Shape filter (optional)*: *3.0 Å exterior volume*
  - Exit vector alignment (bioisosteres): 0.2 Å tolerance (EV1 & EV2)

- Revision of statistical identification of extremes
  - correct representation of local symmetries
  - correlation with observed interaction patterns (visual control)

ParaFrag – Final Validation with Full molecules

In-house validation sets for virtual screening

Kinase

9600 decoys, 96 actives

after stereoisomer enumeration 18062 : 114

Enzyme A

10000 decoys, 100 actives

after stereoisomer enumeration 22026 : 140

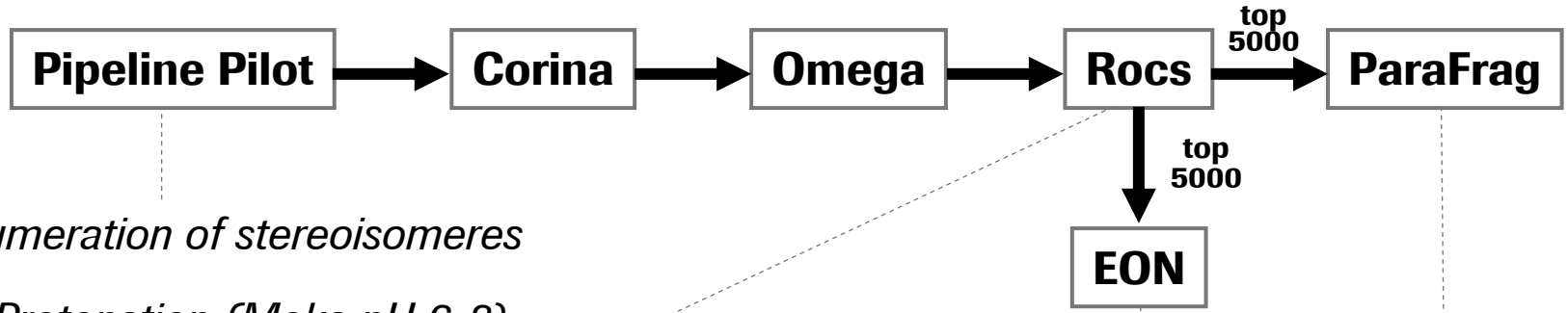
Serin Protease

6500 decoys, 66 actives

after stereoisomer enumeration 12400 : 94

ParaFrag – Final Validation with Full molecules

Workflow



Enumeration of stereoisomeres

& Protonation (Moka pH 6-8)

*Selecting single conformers by **shape,***

***Aligning** (needed by ParaFrag)*

& Scoring by ShapeTanimoto

(additional: ComboScore)

(Re-)Scoring by ET_Combo

Pharmacophore matching

& (Re-)Scoring by

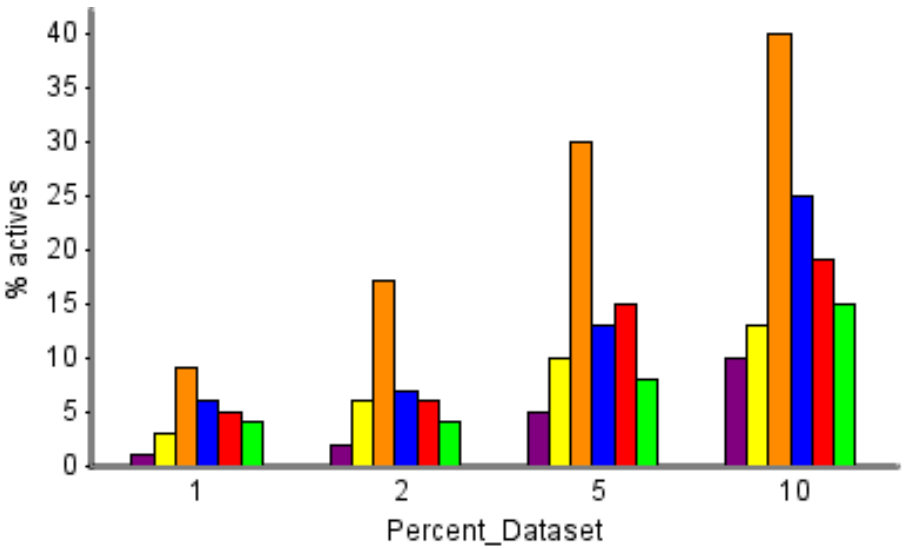
*ParaFrag-Score**

(*) ParaFrag-Score = No. Matched Features/ No. Features Query Molecule

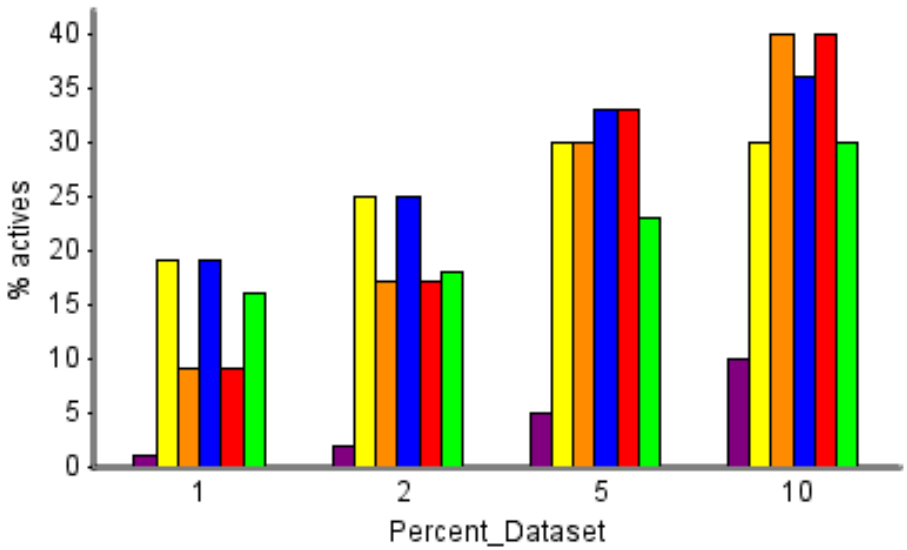
ParaFrag – Final Validation with Full molecules

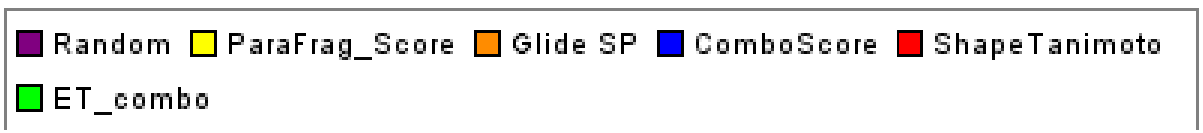
Enrichment – Enzyme A

Query structure 1:



Query structure 2:

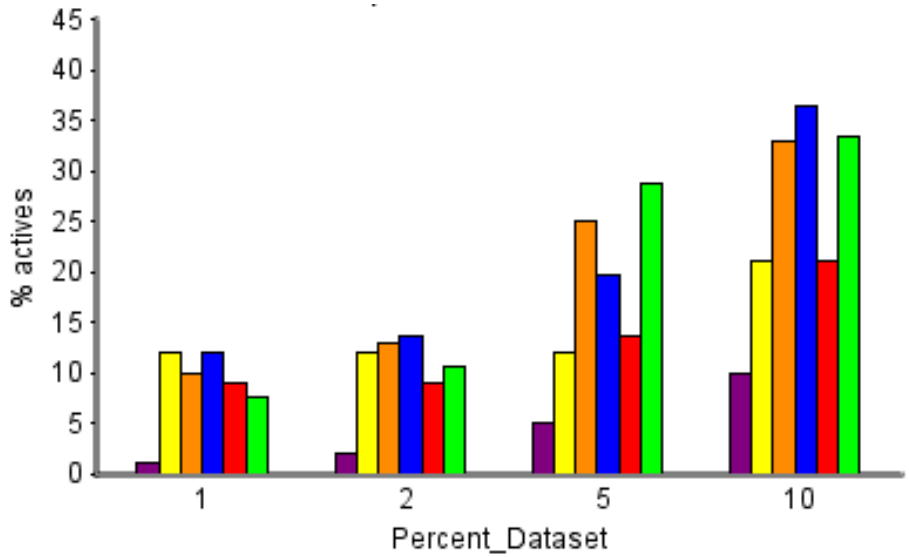




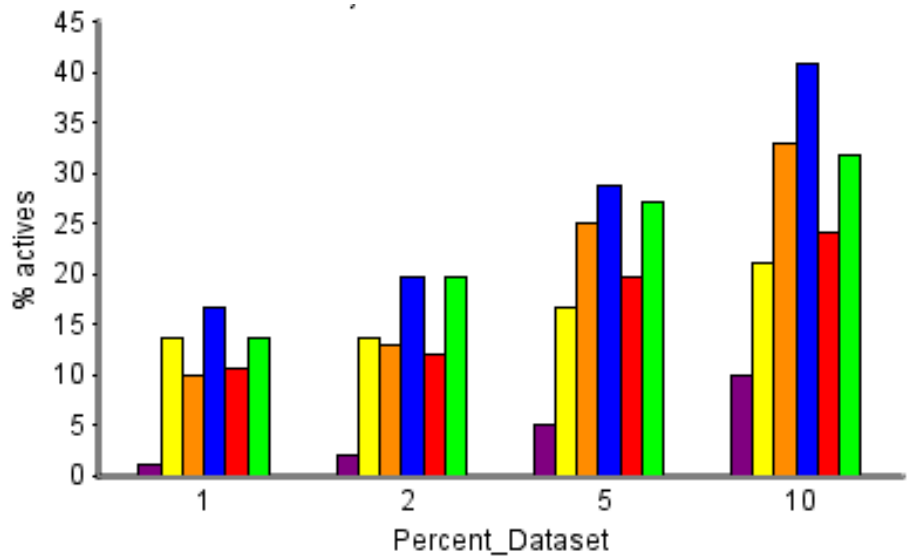
ParaFrag – Final Validation with Full molecules

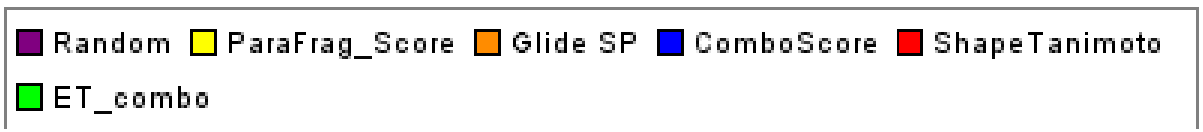
Enrichment – Serine Protease

Query structure 1:



Query structure 2:





ParaFrag – Final Validation with Full Molecules

Conclusions

- ParaFrag performs comparable to established virtual screening (VS) tools
- Recognition of surface extremes reliable for structurally diverse molecules
- Defaults from in-house training set proved to be robust across different targets

➢ Now we are ready for Bioisosters

ParaFrag – Final Validation

Bioisoster Searching

- Scope:
  - Transfer knowledge from virtual screening
  - Reproduce results known from literature
  - Identify novel, putative bioisosters (visual inspection)
- Dataset:
  - Static Bioisoster database
- Query Fragments:
  - Carboxylic acid ester
  - Aniline
  - Pyridine

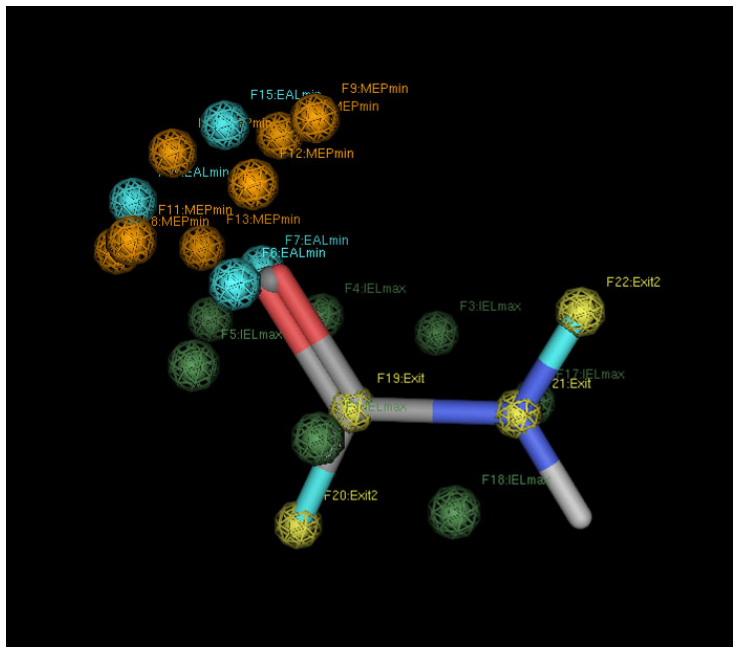
The ParaFrag Pharmacophore

Bioisoster Search

Static Bioisoster database:

- fragments derived from CSD using Recore*
- experimental conformations
- filter for small fragments (MW $\leq$ 150)
- max. 3 exit vectors (EV)
- approx. 70,000 template fragments in total
- link-atoms saturated with methyl for QM calculation (automated process)
- – surface extremes for fragments stored in MOE db

Molecular fragment with surface extremes

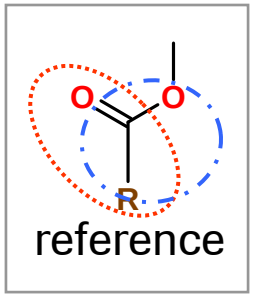


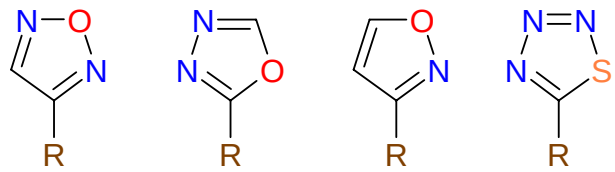
high number of extremes to account for directionality of interactions

(*) Maass, P.; Schulz-Gasch, T.; Stahl, M.; Rarey, M. *J. Chem. Inf. Model.* **2007**, *47*, 390 -399.

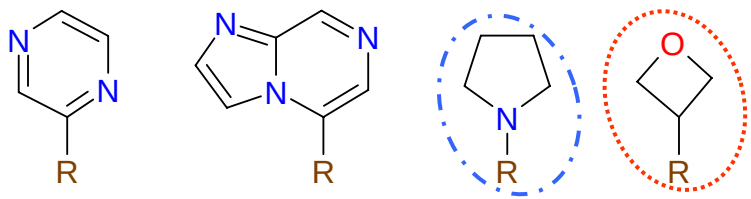
Example Bioisoster Searching

Ester





known

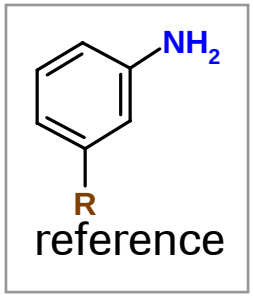


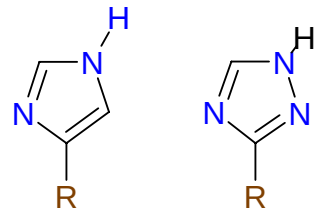
new

partial matches!

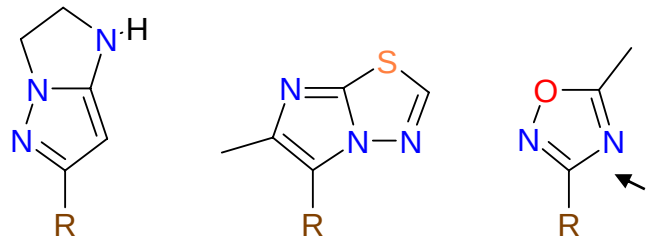
Example Bioisoster Searching

Simple Aniline





known

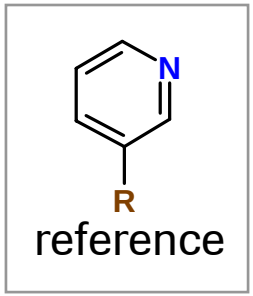


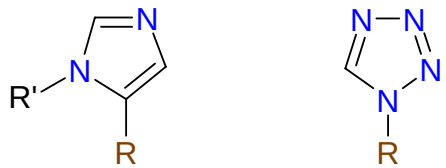
partial match
(electron-rich π-system)

new

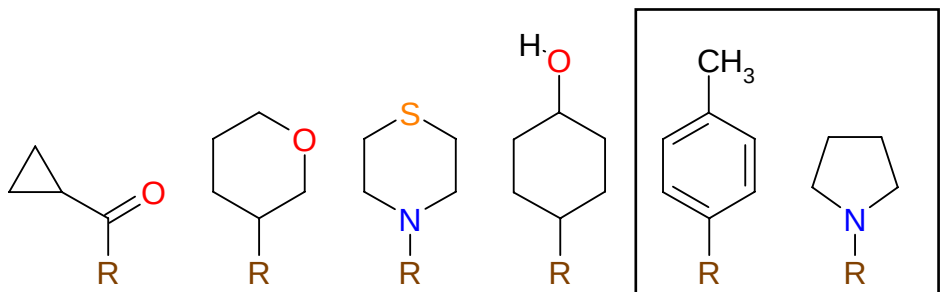
Example Bioisoster Searching

Simple Pyridine





known



new

↖ partial match
(π-system)

Critical Considerations

- Recognition of the local symmetry of surface properties is challenging
  - ➢ use spherical harmonics for detailed analysis (CPU-intensive)
- Instabilities in accessing the compute-server
  - ➢ employ new MOE WSDL/SOAP technology
- Long response time for MOE pharmacophore searches
  - ➢ code not yet optimized for speed

Conclusions

- ParaFrag is an innovative approach for bioisoster searching
- Could be valuable for rescoring in specific cases
  - comparable performance to established VS tools over all targets investigated
- Easy to use graphical interface for interaction hot spot analysis
- Robust defaults for different search strategies established
- User has full access to all parameters
  - refinement of pharmacophores
  - shape filtering

Acknowledgements

Students

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Wolfgang Guba

Jérôme Hert

Bernd Kuhn

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Tanja Schulz-Gasch

Daniel Stoffler

Chemical Computing Group

Guido Kirsten (MOE Interface)

Wolfram Altenhofen

Alex Clark (WSDL/SOAP)

Computer-Chemie-Centrum, University Erlangen-Nürnberg

Tim Clark

Cepos InSilico

We Innovate Healthcare