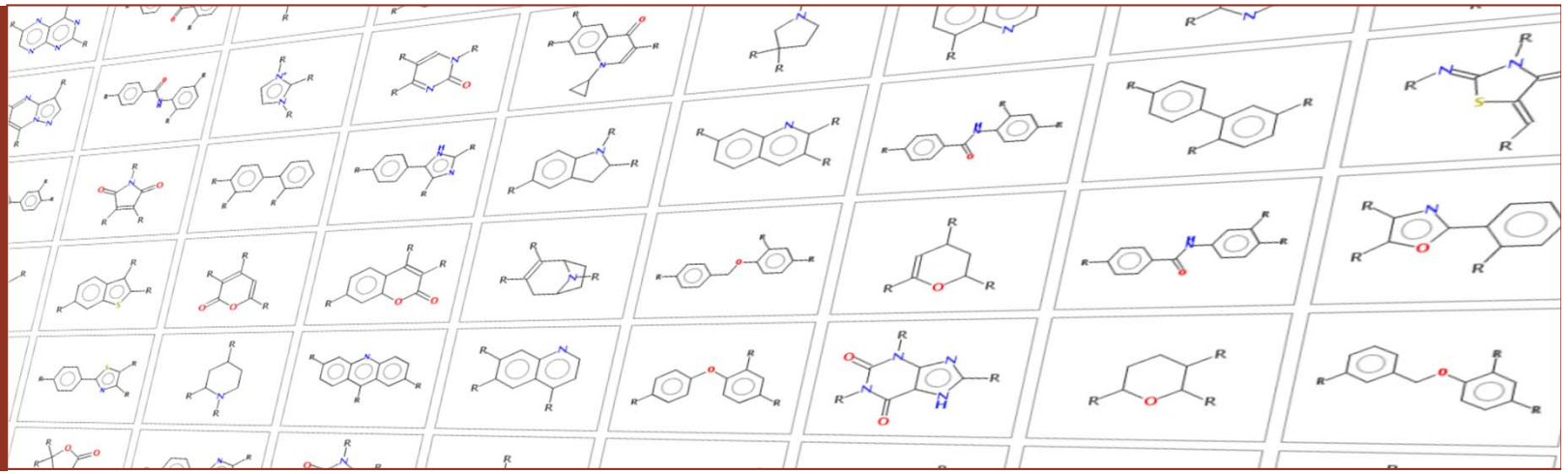

In silico identification of bioisosteric substituents, linkers and scaffolds for medicinal chemists

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September 2014

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Bioisosteric replacements

The everyday medicinal chemistry challenge:

Molecule has good potency, but has a liability (high clearance, not sufficient solubility, bad selectivity, poor permeability, phototox ...)

Solution:

One has to identify part of the molecule responsible for the liability (what is not easy, sometimes a trial and error procedure is required) and then to replace it by another compatible part that would keep potency but fix the liability.

The big question

How to identify the optimal bioisosteric group?

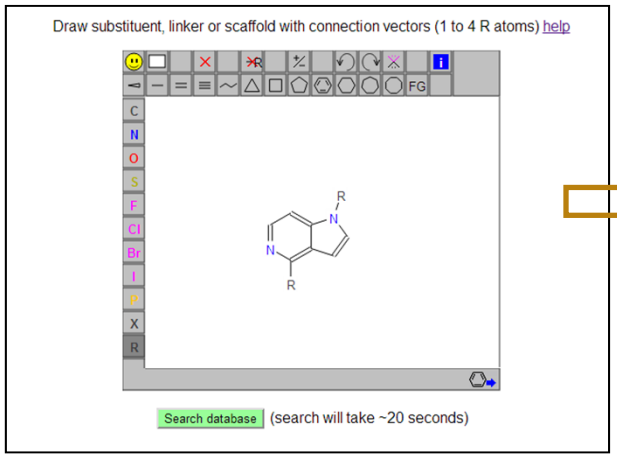
1. medicinal chemistry experience
   - validated by numerous examples
   - subjective, limited in scope

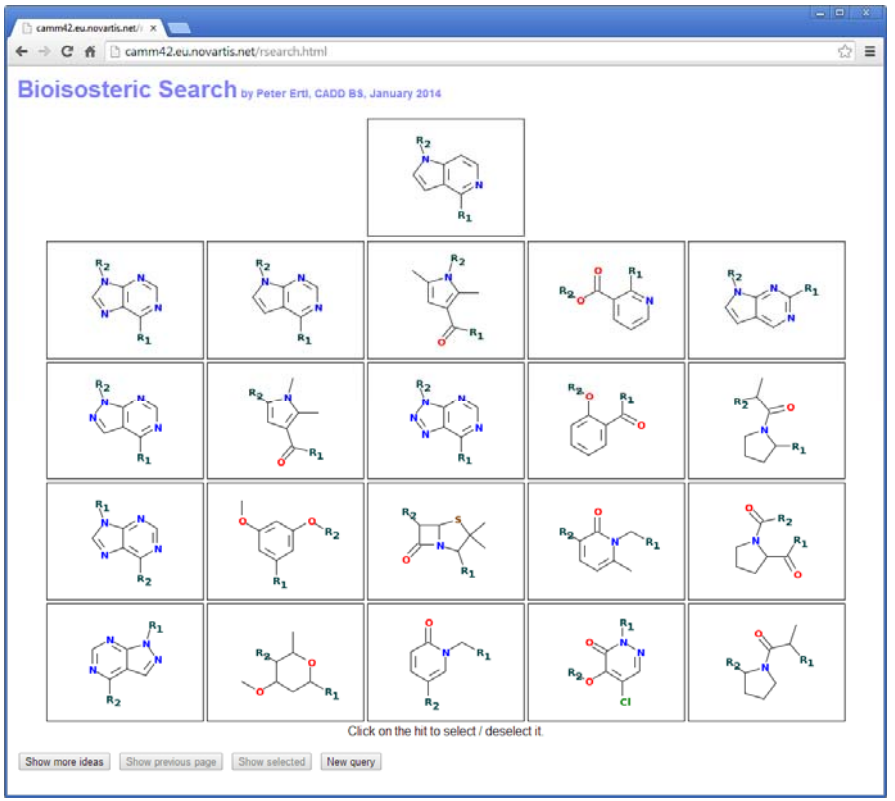
2. examples from literature ("matched molecular pairs")
   - broader coverage, validated by experiment
   - limited only to published examples; "my scaffold" often missing

3. similarity based on calculated group properties
   - allows to find also novel bioisosteres; practically unlimited scope
   - not experimentally validated

Interactive web tool for medicinal chemists

Easy to use web tool developed at Novartis allows medicinal chemists to identify bioisosteric groups (substituents, linkers, scaffolds) based on similarity in their properties:





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A look under the hood

How does the bioisosteric search tool work

1. creation of the fragment database - extraction of fragments (substituents, linkers, scaffolds) from known bioactive molecules

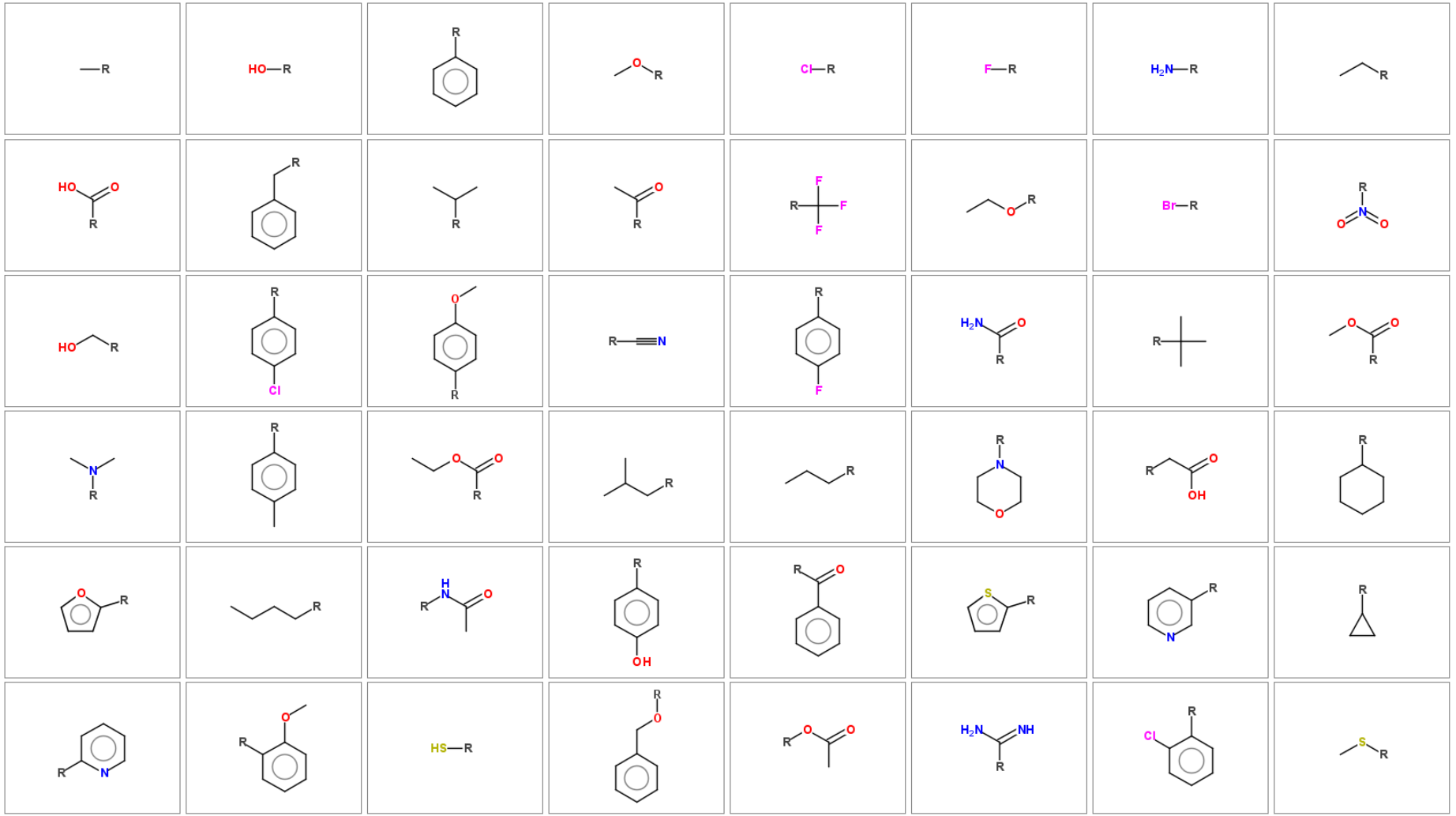
2. characterization of fragments by medicinal chemistry relevant calculated properties

3. identification of proper search metrics – scaling of properties, fine tuning of property contributions for different user cases

Development of fragment database

- The ChEMBL database contains about 1.7 million structures extracted from medchem literature together with their bioactivities
- about 500,000 of these molecules are reported to be “active” (activity < 10 μm)
- all substituents, linkers and scaffolds with up to 4 connections were extracted from these bioactive molecules and top 10,000 from each class stored in the database

The most common organic substituents



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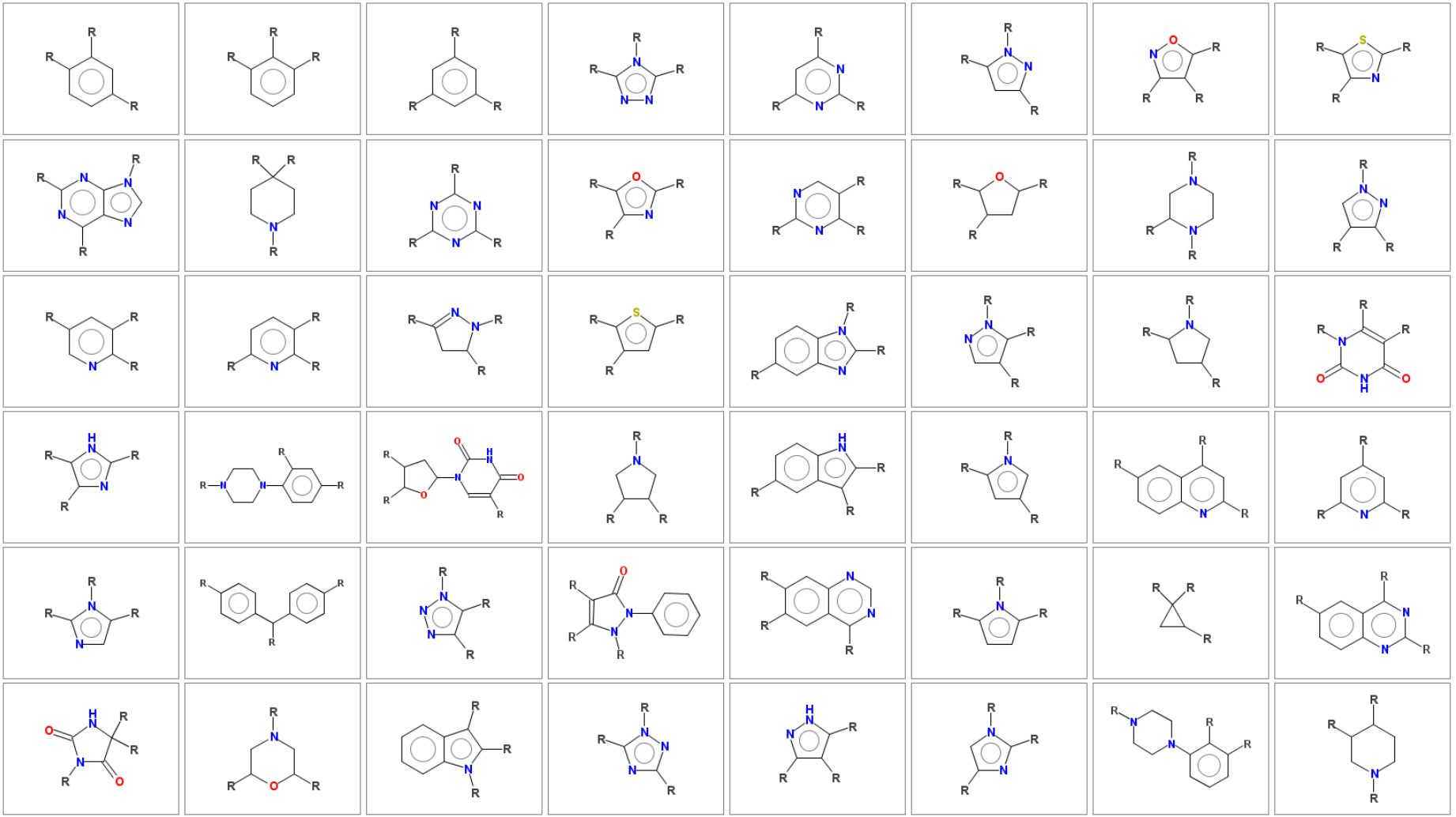
The most common scaffolds with 3 connections

Symmetry needs to be considered



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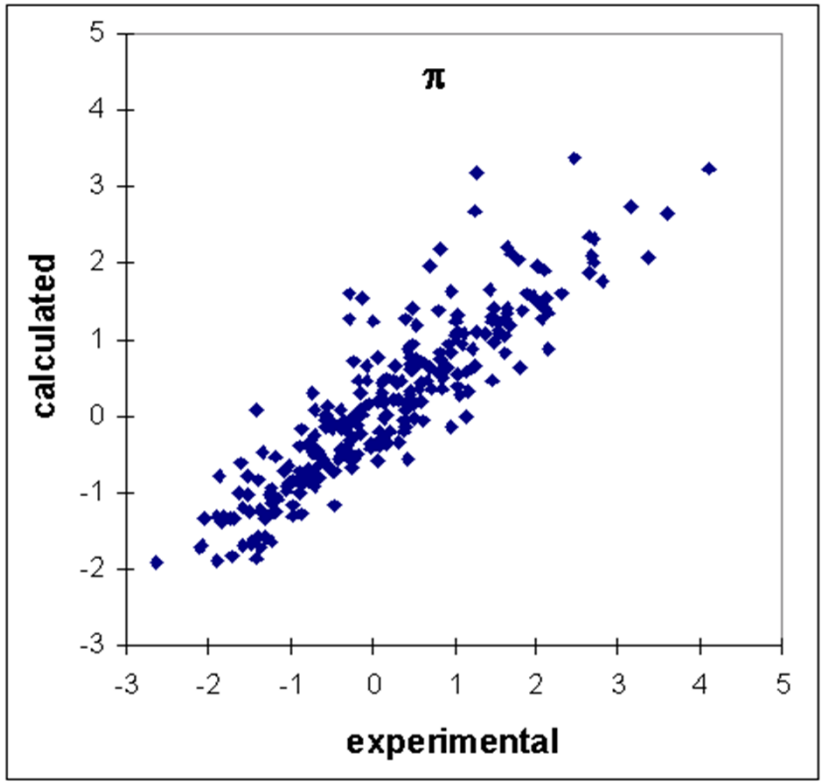
Descriptors relevant to medicinal chemistry

Descriptors used in search should cover all properties playing a role in ligand receptor interactions:

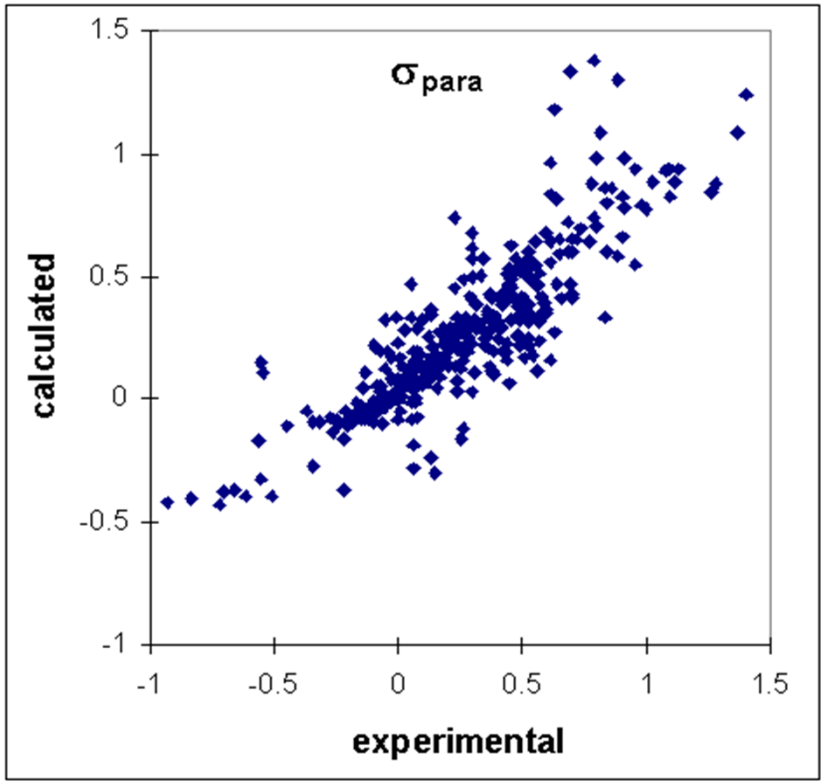
- hydrophobicity
- polarity; electron accepting- / donating-strength
- pharmacophore features
- size and shape

Hydrophobic and electronic substituent properties

Hydrophobicity (π constant)



Hammett σ parameter



Calculated vs experimental substituent properties
for 300 common substituents

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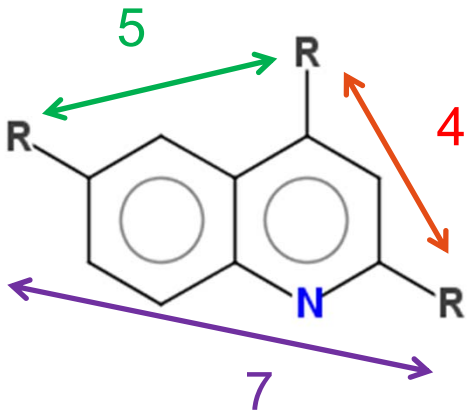
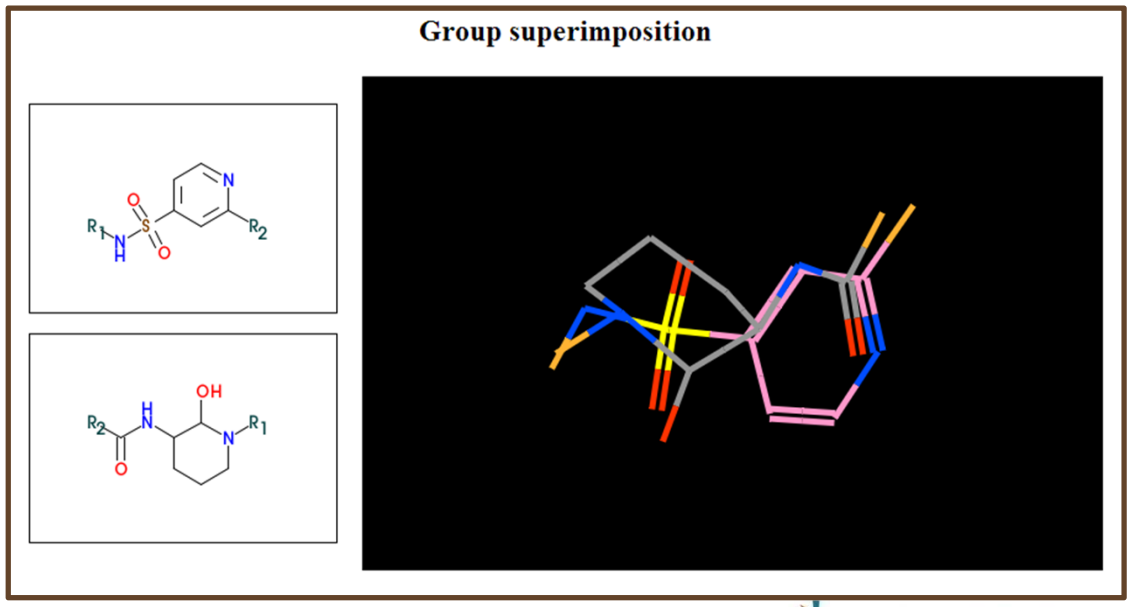
Size and shape properties

Which descriptors are used in search depends on the search scope

Topological size and shape properties + distances between connection points (R atoms)



3D shape match and exact superimposition of exit vectors



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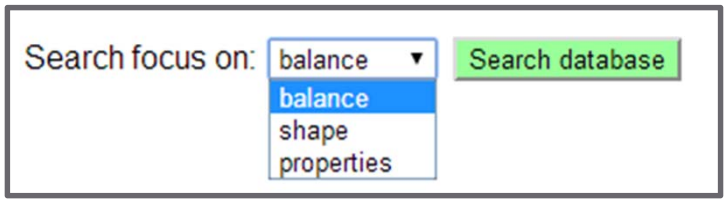
Fine-tuning of the search procedure

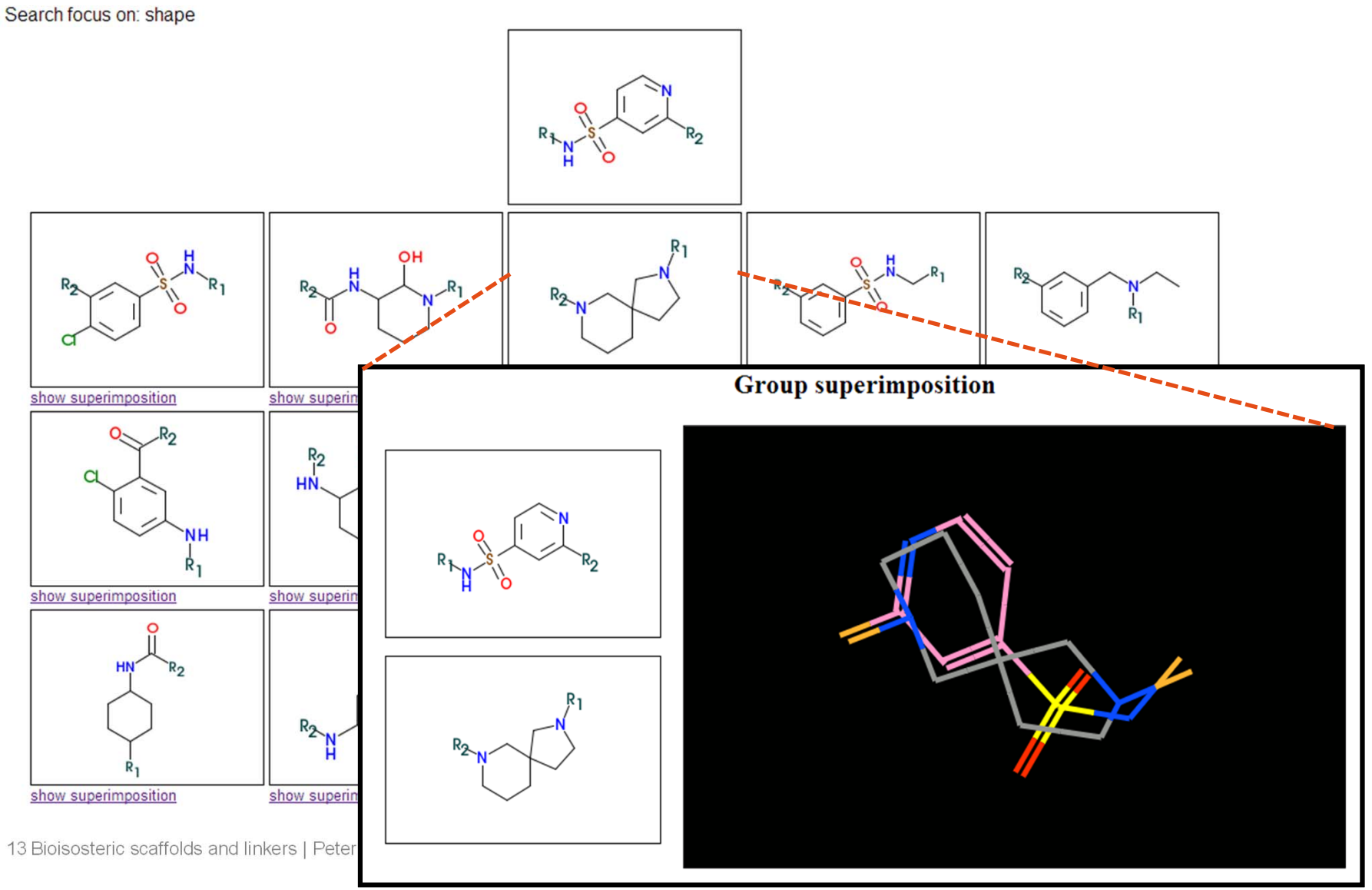
Different users have different requirements on the bioisosteric replacements - selection of proper search scope is important.

- to find an alternative to the existing solubilizing group
- modification of a group affecting electronic properties (charge) on a neighboring atoms
- find an alternative to the central heterocyclic system
- replacement of the linker connecting two parts in the exactly same angle



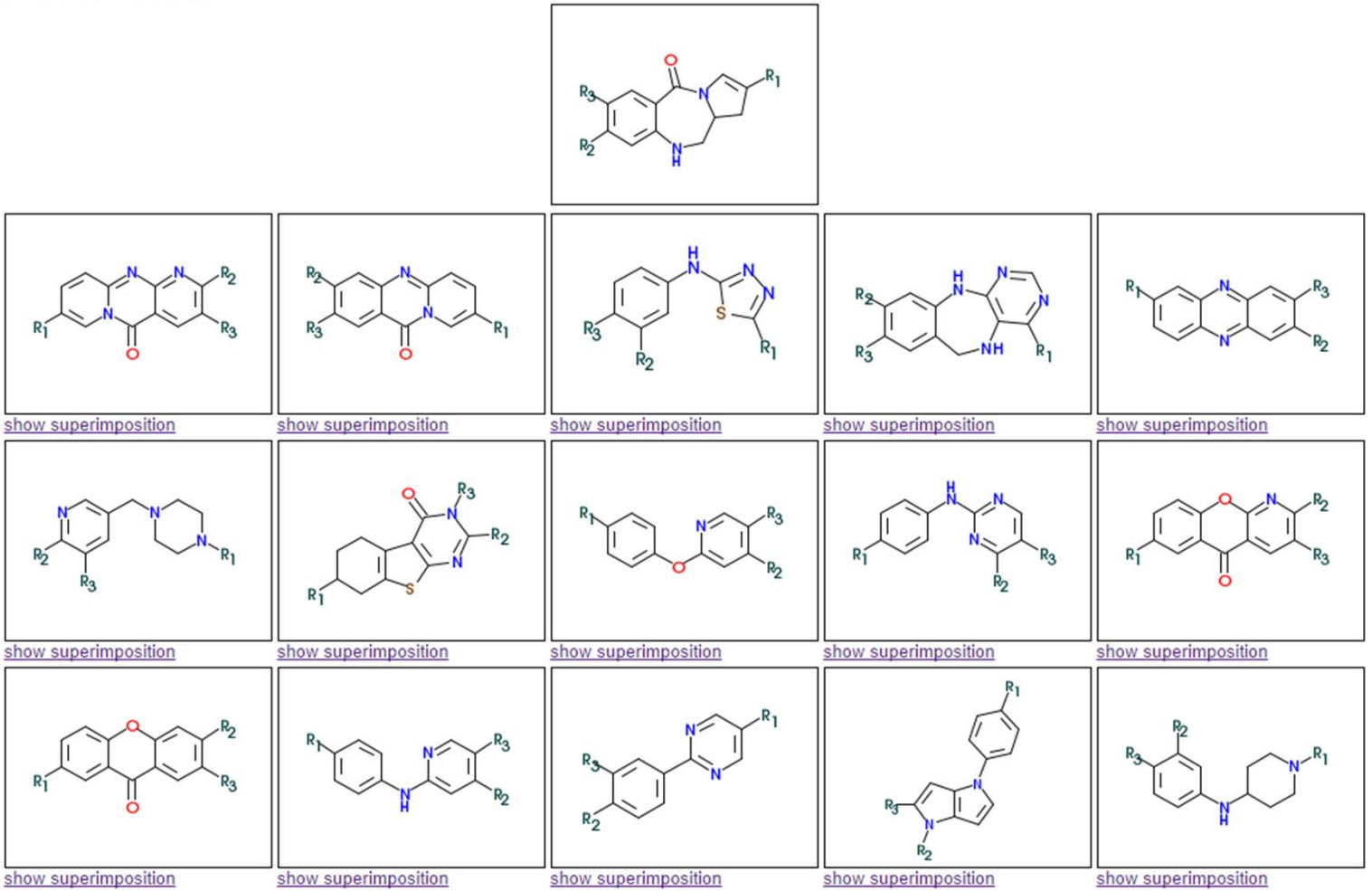
Menu with 3 search options offered

Shape match search



Central ring system replacement

Search focus on: balance



Click on the hit to select / deselect it.

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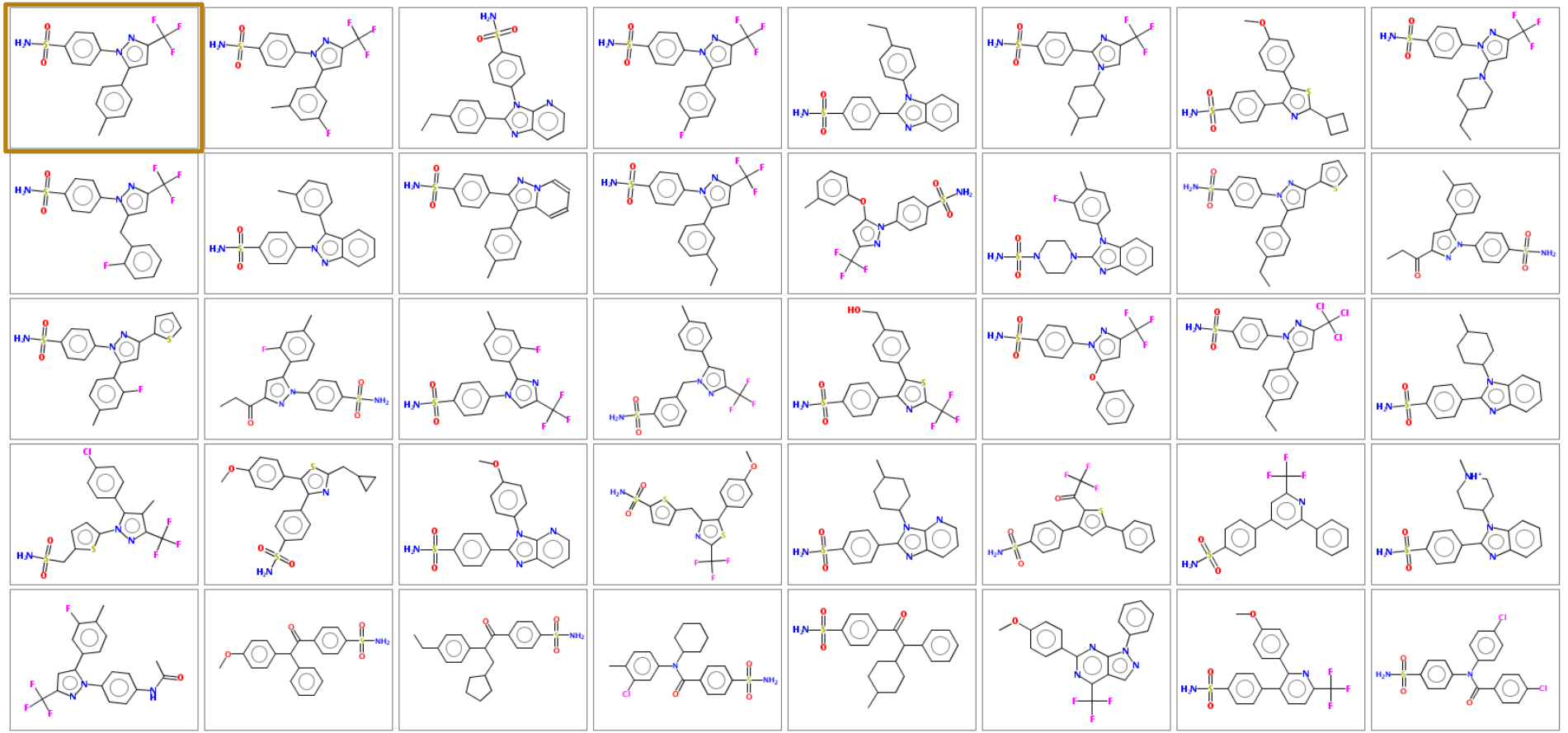
Exploration of novel chemical space

Automatic analog generator (with Celecoxib as an example)

This concept may be extended to the whole molecules. The template has to be dissected into pieces, analogs for every piece found and combinatorially combined. The generated molecules may be ranked according to desired criteria.



Additional technology details

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IADE: a system for intelligent automatic design of bioisosteric analogs
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Quantitative Structure-Activity Relationships 16, 377-382 (1997)