

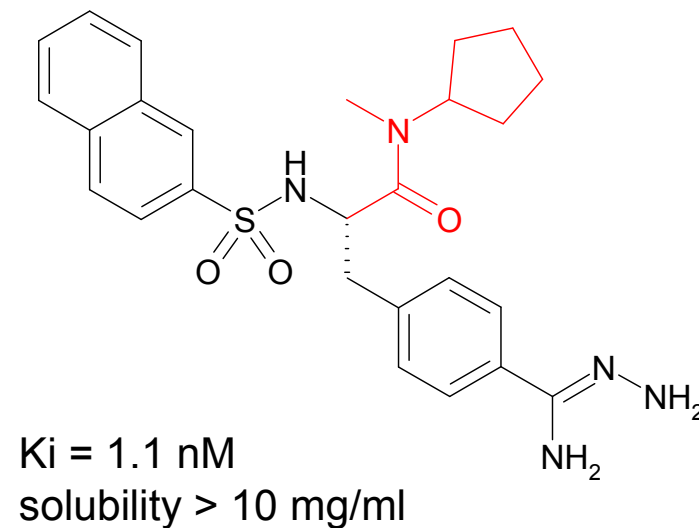
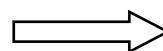
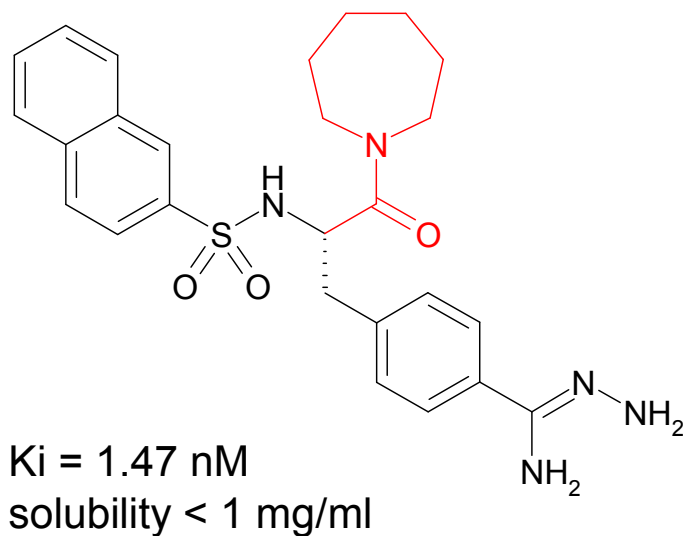
The Quest for Bioisosteric Replacements

M. Wagener, J. Lommerse

NV Organon, The Netherlands



Bioisosterism



YS Oh et al *Bioorg. Med. Chem. Lett.* **1998**, 8, 631.

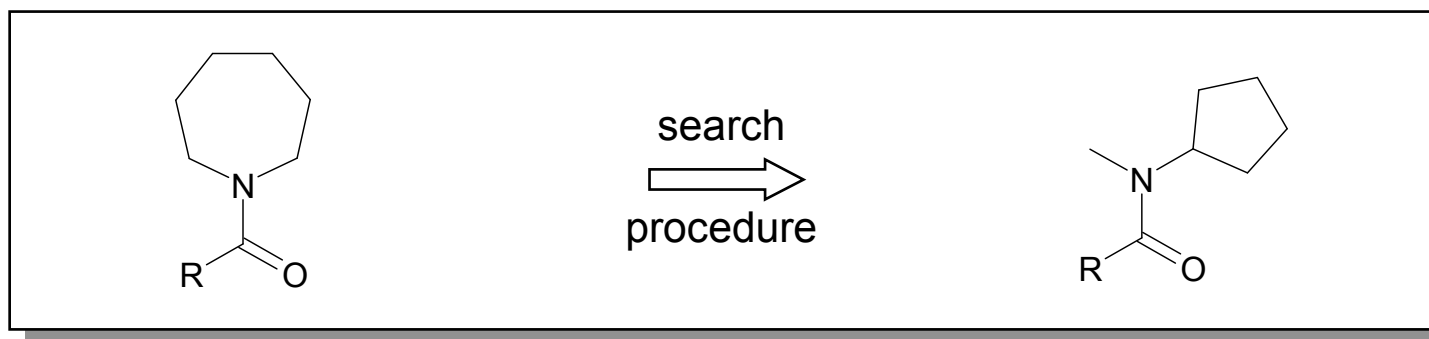
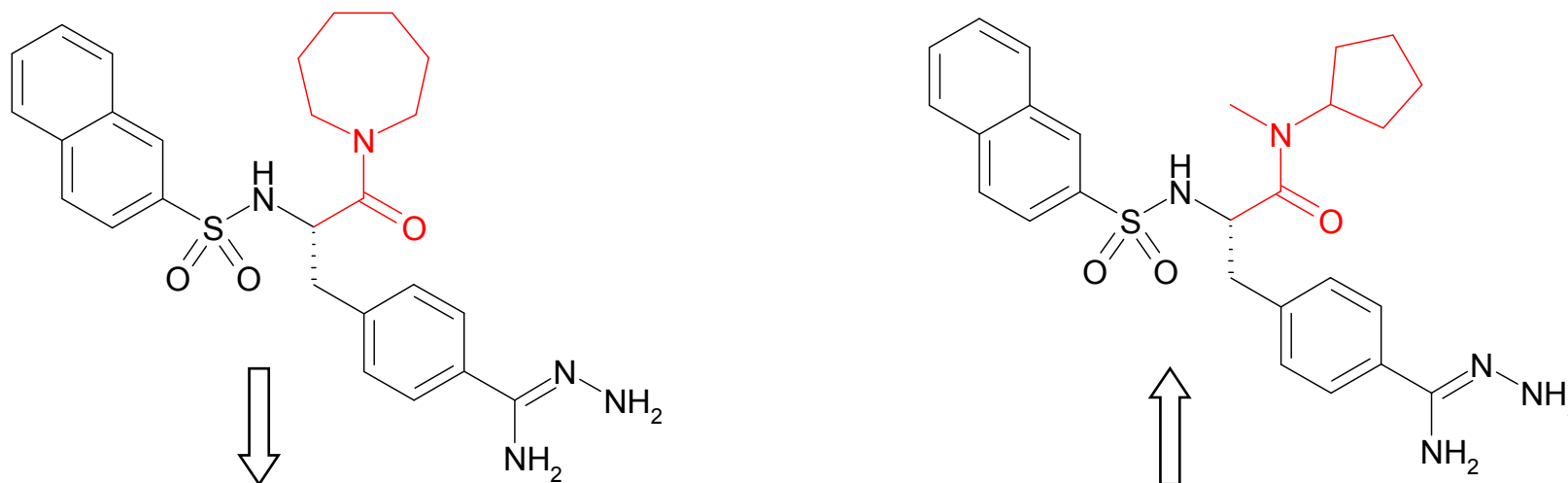
Friedman (1951) / Burger (1991): Structurally related compounds with similar biological activity

Bioisosteric Replacements

Can be used to address compound related issues:

- phys. chem. parameters
- potency and/or selectivity
- metabolic stability
- patent position

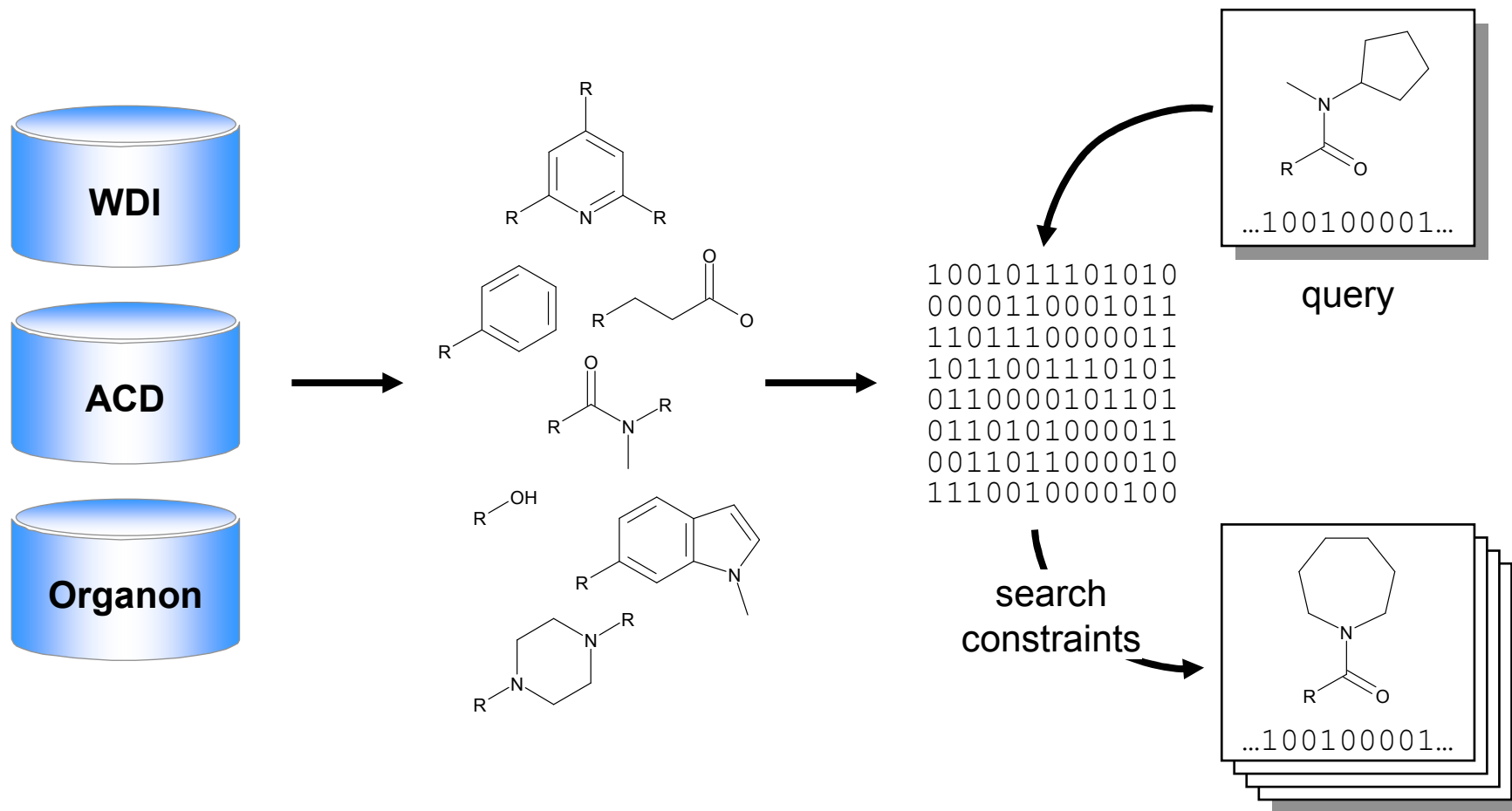
Search for Bioisosteric Replacements



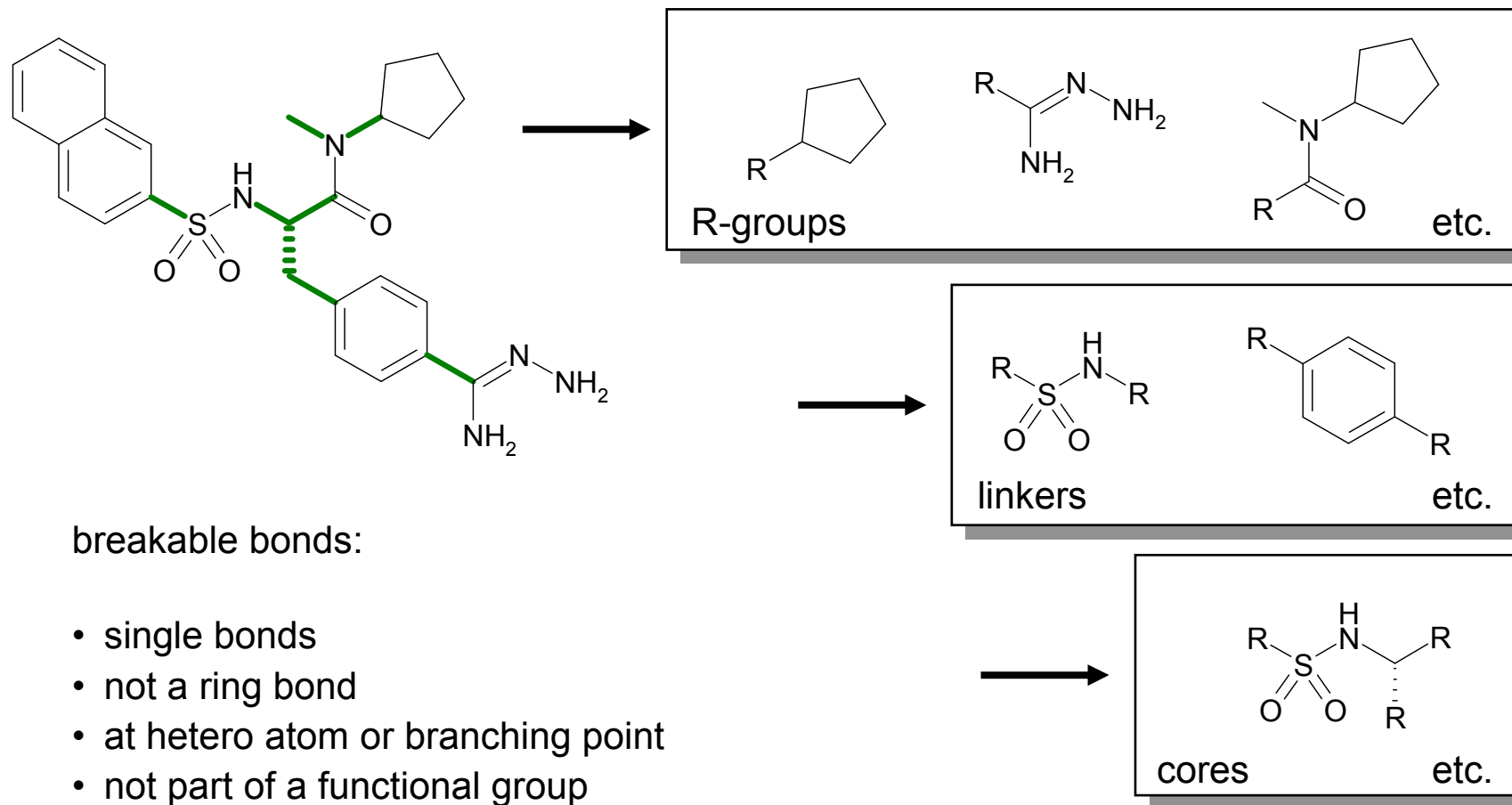
Overview

- generation of a fragment database
- atom pair descriptors
- processing of bioisosters from literature
- selection and validation of descriptors
- applications
- conclusions

Search for Bioisosteric Replacements



Fragment Generation



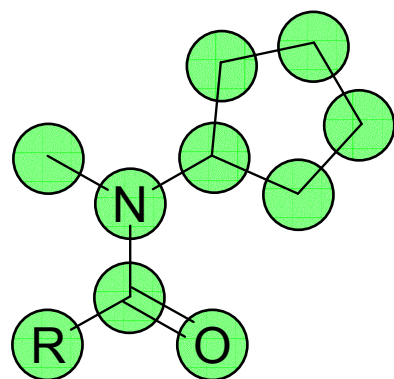
Databases

- derived from several source databases:
 - ACD, Organon in-house, WDI
- comprehensive set of unique fragments:
 - 162000 R-groups (one attachment point)
 - 294000 Linkers (two attachment points)
 - 322000 Cores (three attachment points)
- between 1 and 12 non-hydrogen atoms
- precalculated properties (pKa, logP, #rings, alerts, ...)

Overview

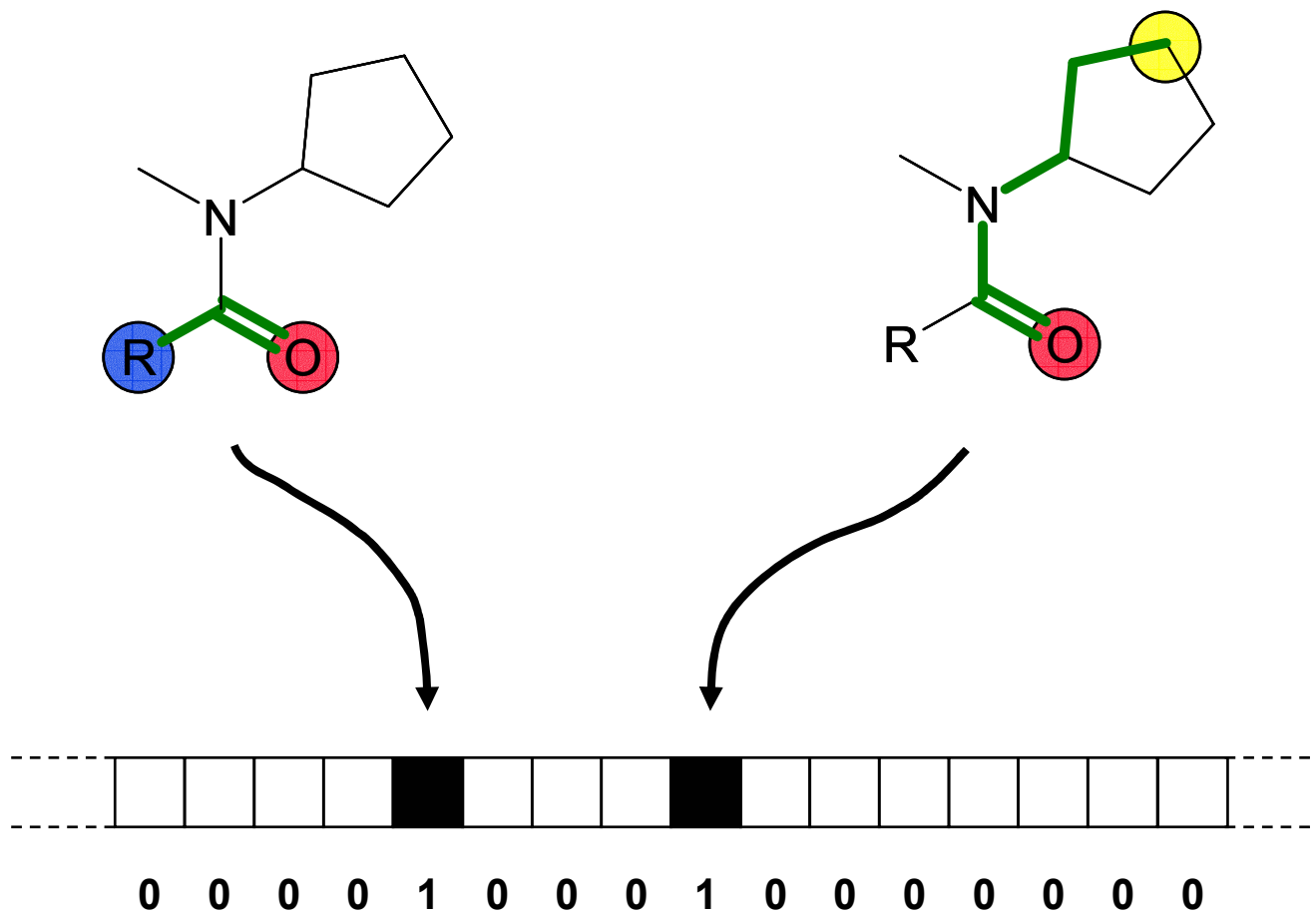
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Pharmacophore Atom Types

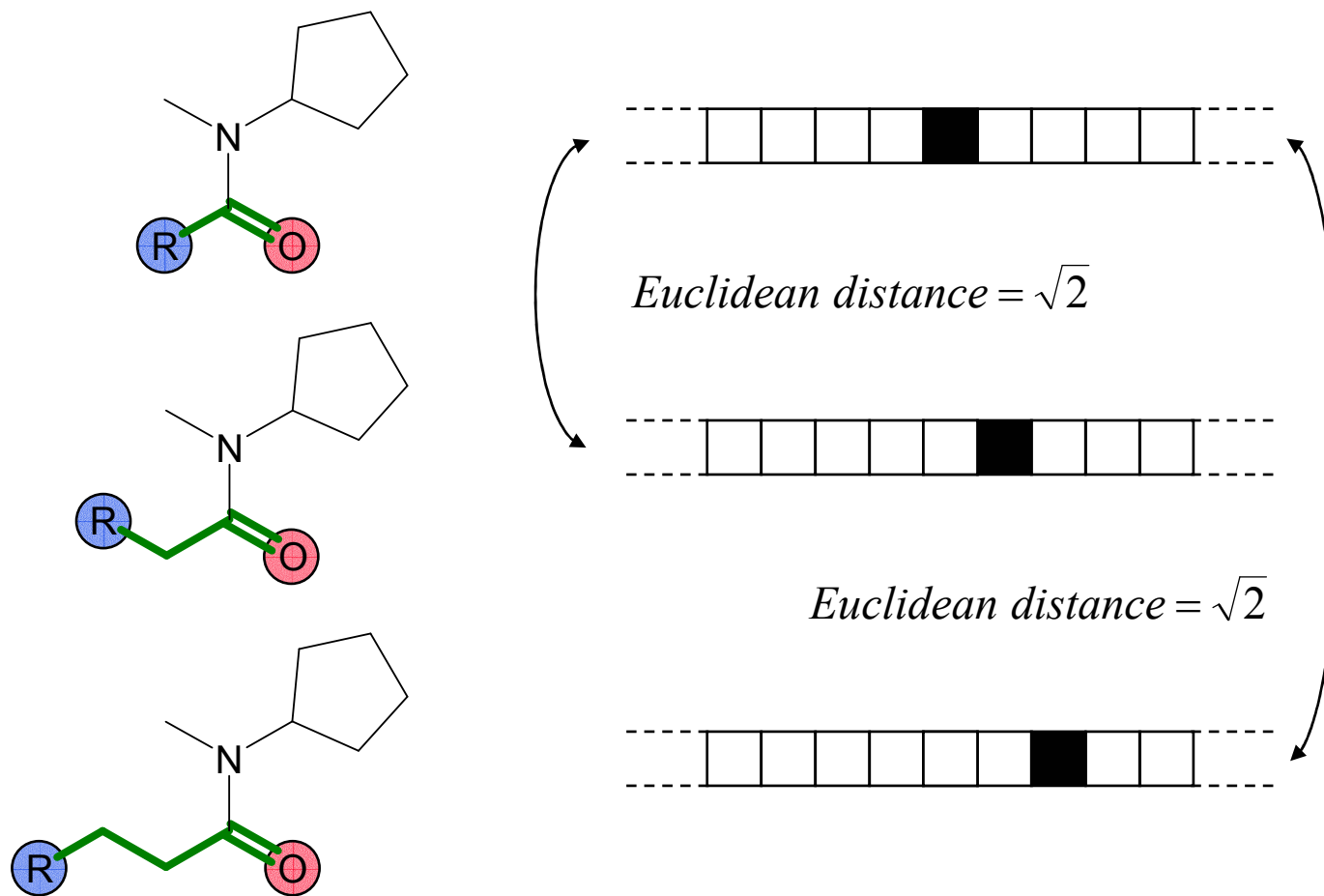


- Acceptor
- Donor
- Attachment
- Hydrophobe
- Conjugated Atom
- Heavy Atom

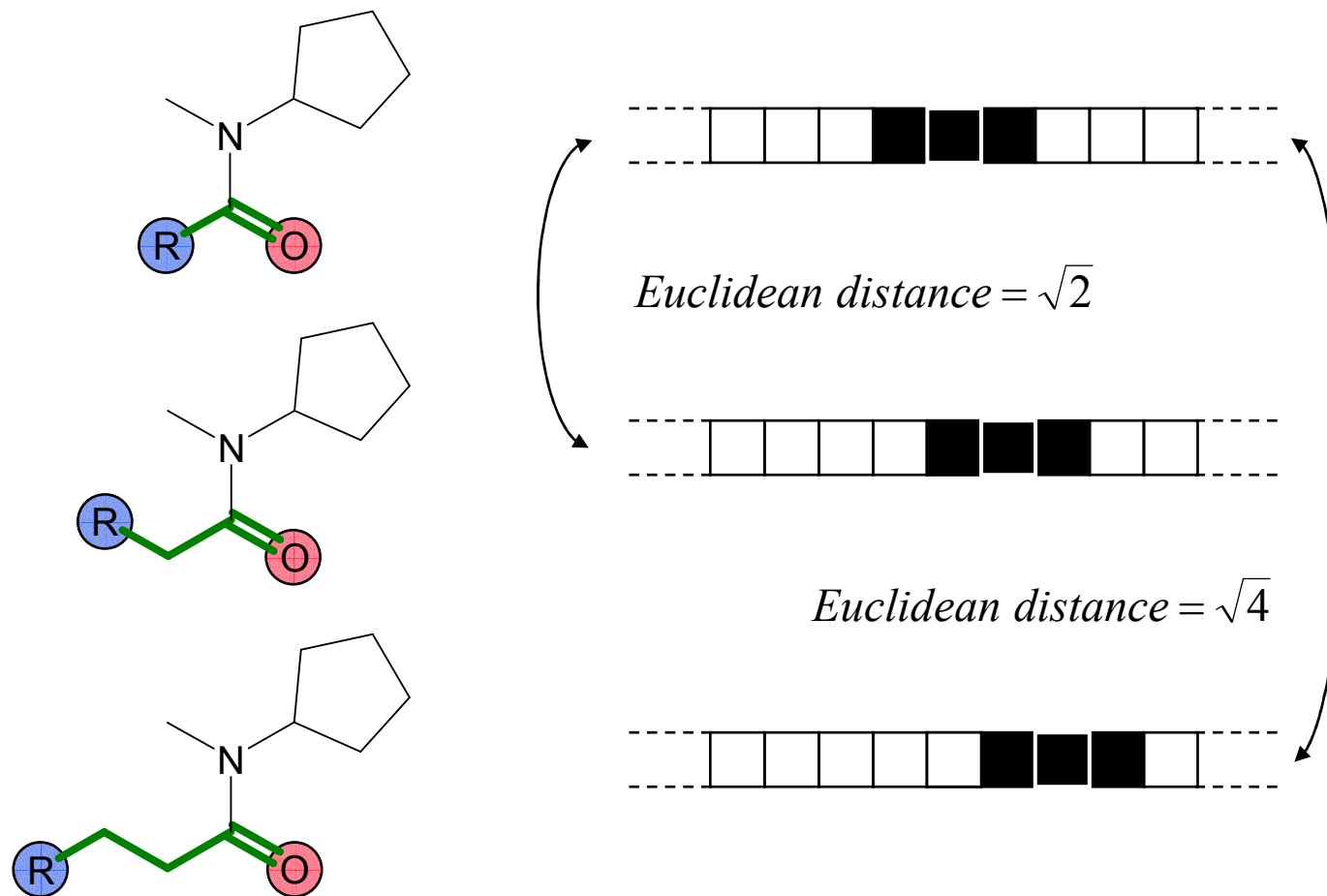
2D Pharmacophore Fingerprints



Fingerprint Distances



Fuzzified Fingerprints

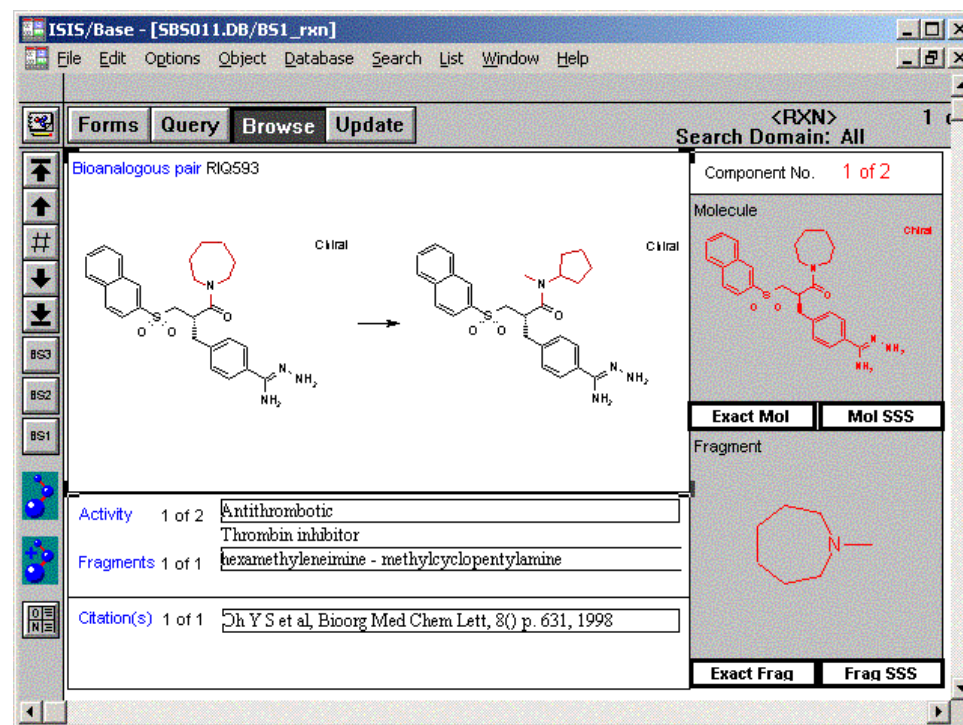


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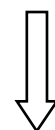
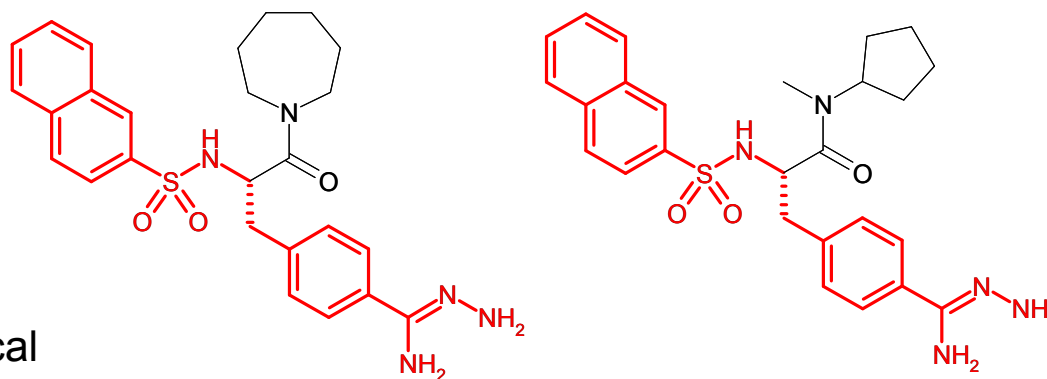
Experimental Data

- Bioster Database from Accelrys
- More than 9000 pairs of bioisosteric drugs or agrochemicals from literature
- Abstracted by Dr. I. Ujvary, The Plant Protection Institute, Hungarian Academy of Sciences

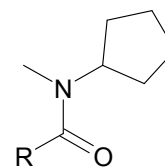
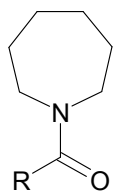


Bioisosteric Fragment Pairs

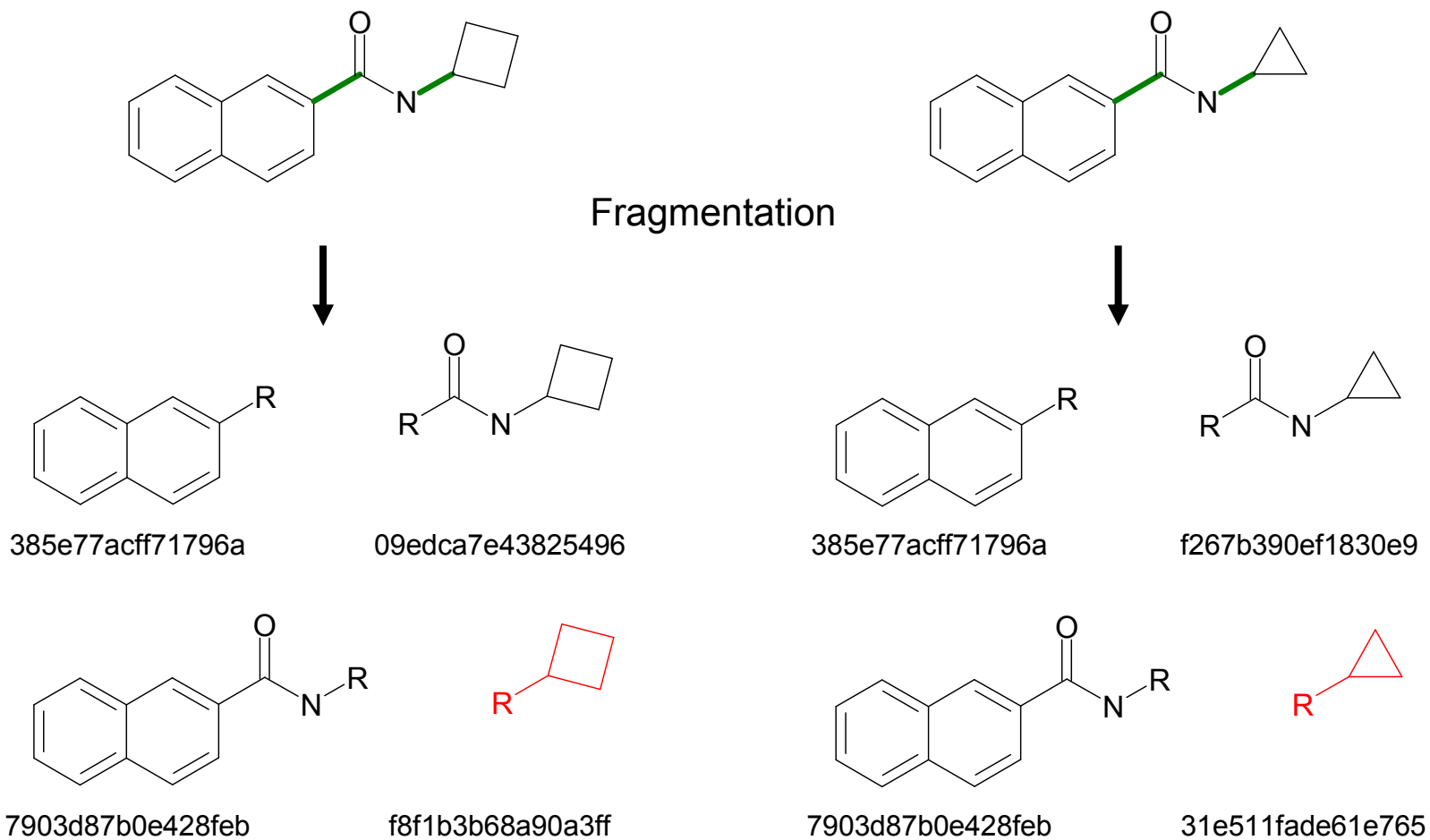
search for identical substructures



extract remaining part as bioisosteric groups



Identification of Fragment Pairs



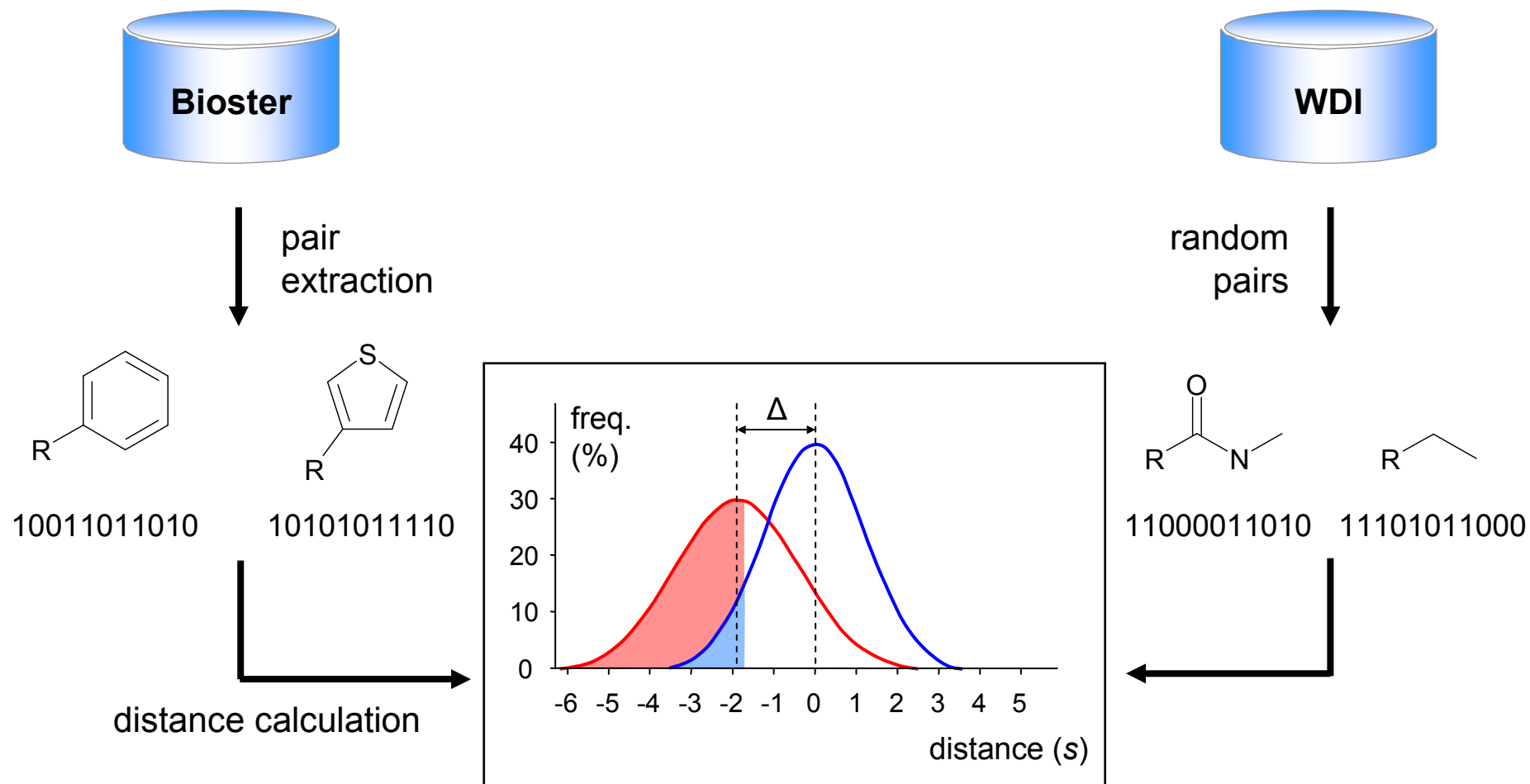
Results Pair Identification

fragment	attachment points	bioisosteric pairs	unique fragments
R-group	1	1042	1208
linker	2	940	1140
core	3	299	434

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Validation: Overview

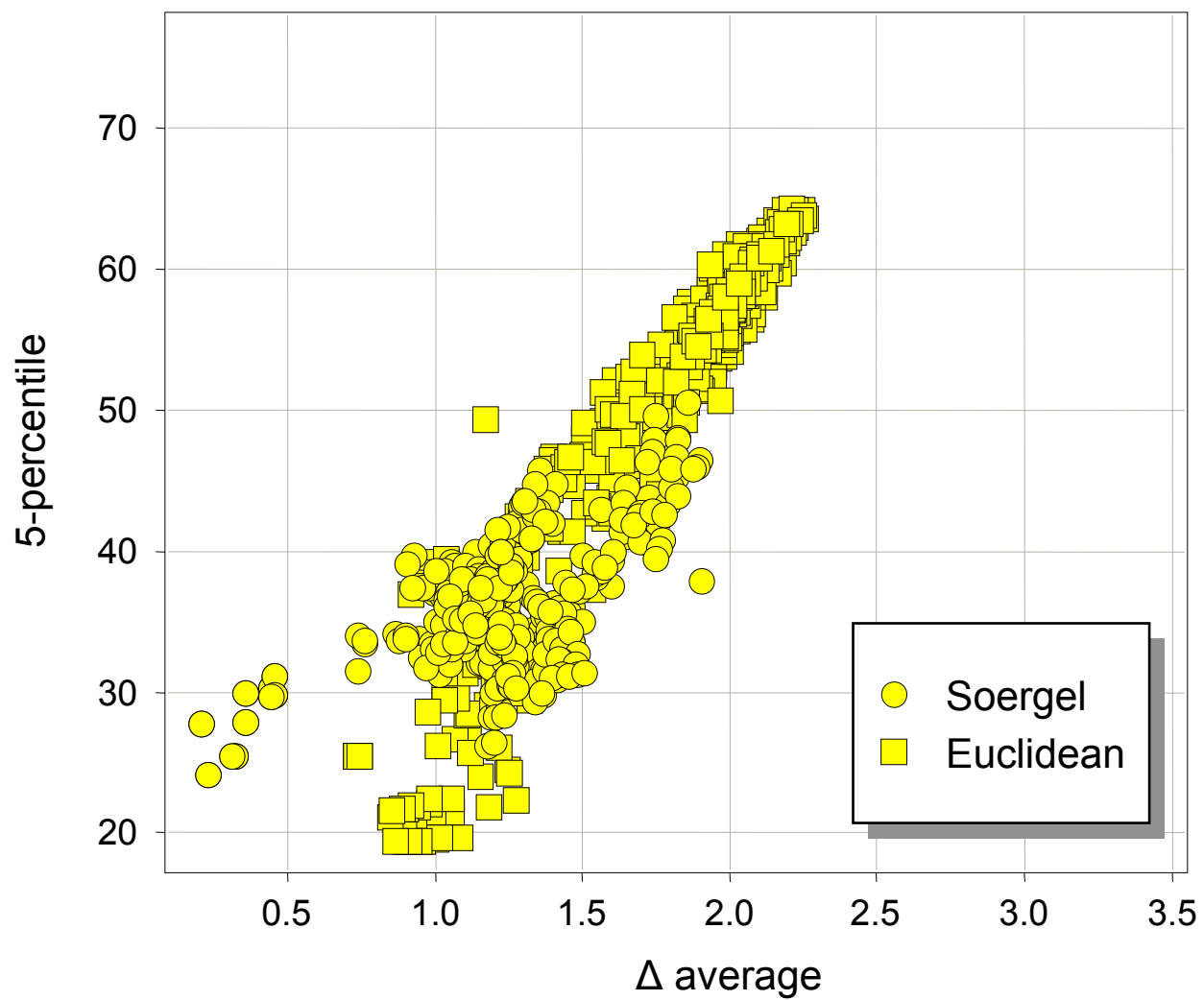


Descriptor Optimization

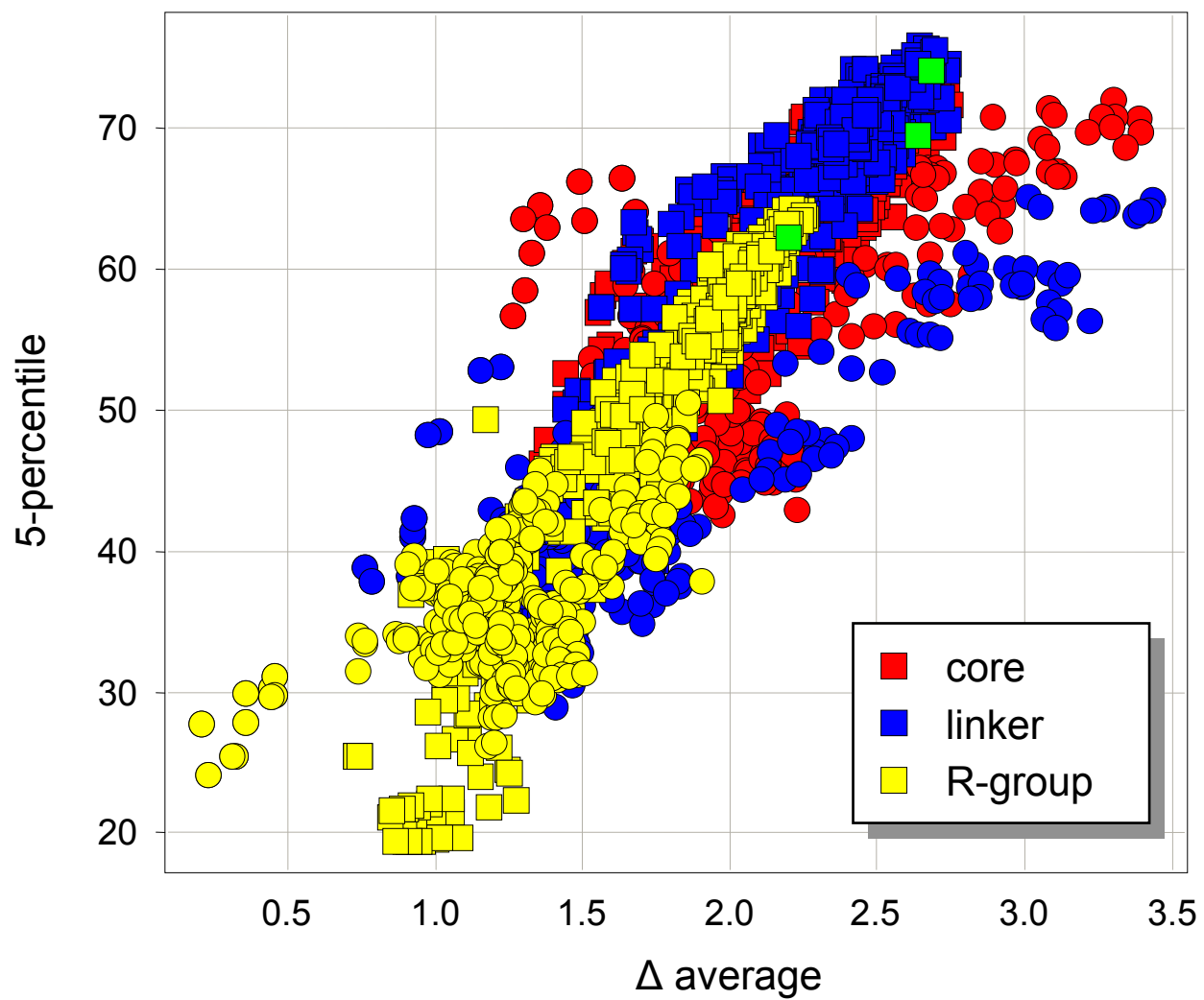
- pharmacophore properties and relative weight of pharmacophore properties (23 combinations)
- normal / fuzzified fingerprints
- Euclidean / Soergel distance
- charged / uncharged
- frequency of atom pairs (1, 2, 3, 4, 7)

$$23 * 5 * 2 * 2 * = 920 \text{ combinations}$$

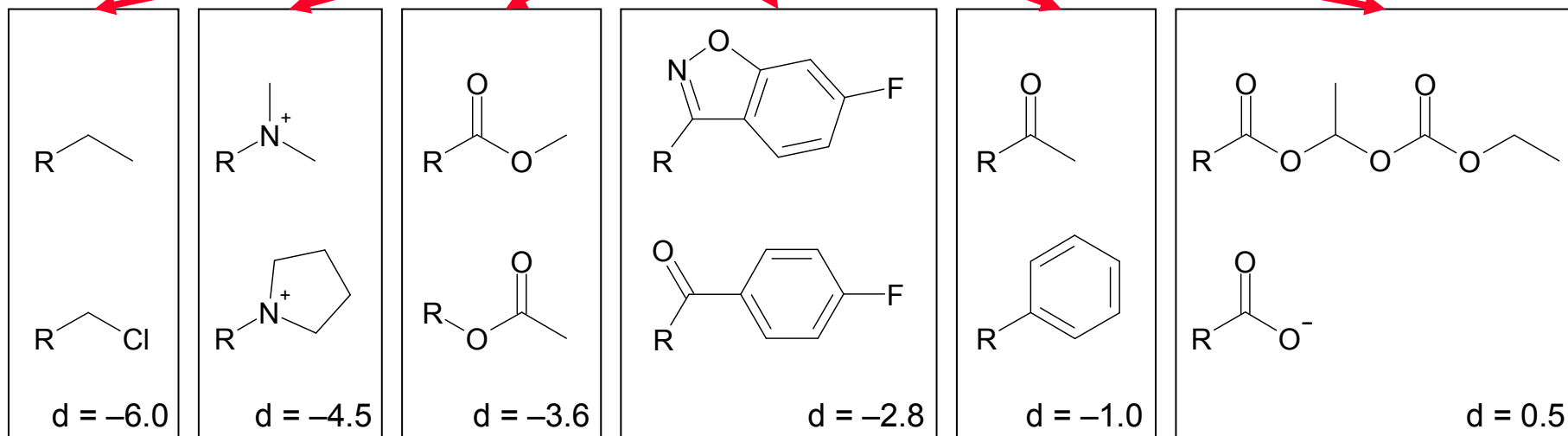
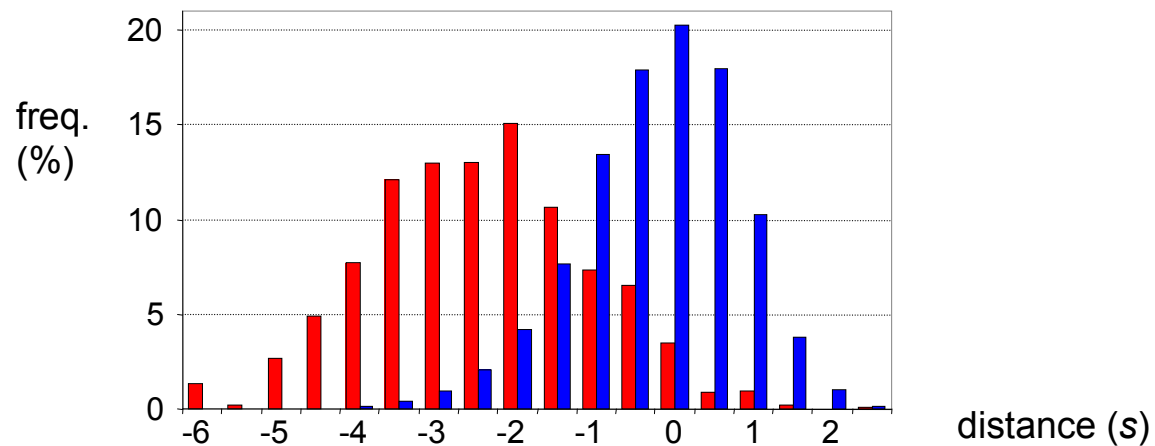
Descriptor Optimization



Descriptor Validation



Validation Examples



IBIS Applications

The screenshot displays a Microsoft Internet Explorer browser window titled "Chemoinformatics Webpages - Microsoft Internet Explorer". The address bar shows "http://cheminf/". The website header includes the "Chemoinformatics" logo and navigation buttons for "Home", "Misc.", "Search", "Contact", and "Help".

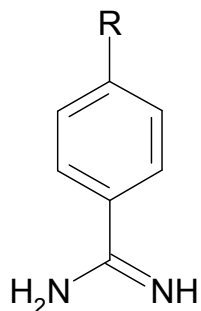
On the left side, there is a vertical menu titled "Access to tools and databases" with buttons for "All", "Databases", "ADME/Tox", "Drugs", "Modelling", "Bibliographic", and "General".

The main content area features a teal header for "Ibis v1.1" with a help icon. Below this, there are three tabs: "Structure Input" (selected), "Ibis Options", and "Output Options". Under the "Structure Input" tab, there are sub-tabs for "Ibis Options", "Ibis Constraints", and "Output Options".

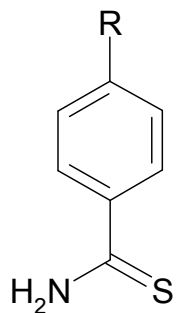
The "Structure Input" section includes a "Draw" area with a chemical structure of a cyclopentane ring attached to a nitrogen atom, which is further attached to a carbonyl group (C=O). The text next to the structure lists options: "R-Group or R-Linker-R or R-Core-R" and "R". Below this, it says "(Double Click):".

At the bottom of the "Structure Input" area, there are two buttons: "Reset All" and "Search Biososters".

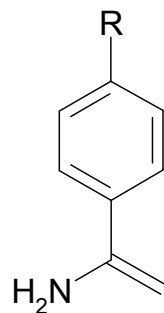
IBIS Results: Benzamidine



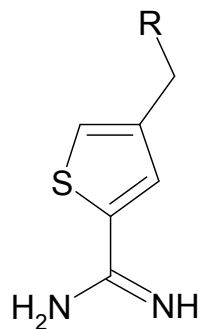
$\text{pK}_a = 10.5$



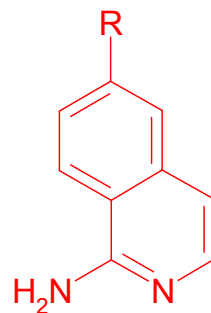
$\text{pK}_a = 1.4$
 $d = -3.8$



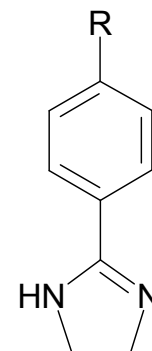
$\text{pK}_a = 7.5$
 $d = -3.7$



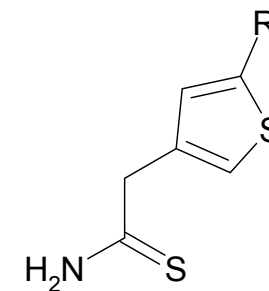
$\text{pK}_a = 10.2$
 $d = -3.5$



$\text{pK}_a = 7.9$
 $d = -3.2$



$\text{pK}_a = 10.1$
 $d = -3.2$



$\text{pK}_a = 1.4$
 $d = -3.2$

Conclusions

- Intranet application to search for bioisosteric replacements
- Based on 2D pharmacophore description of structures
- Optimized and validated using 2200 literature bioisosteric pairs
- Constraints (logP, pKa, etc) allow for focused search