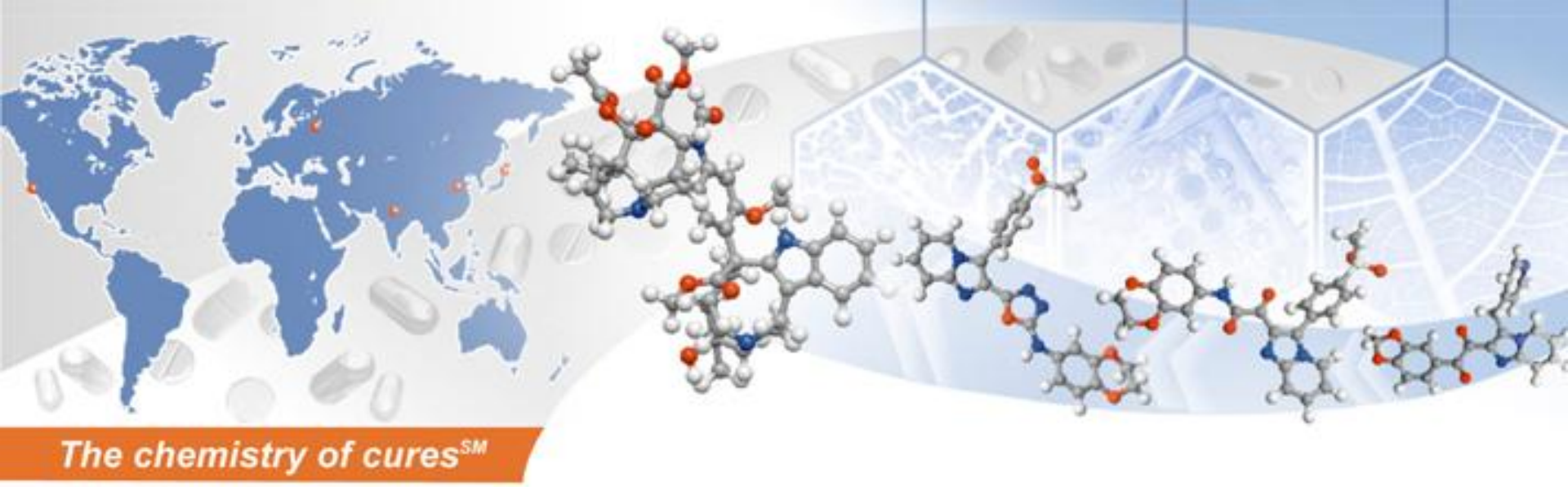


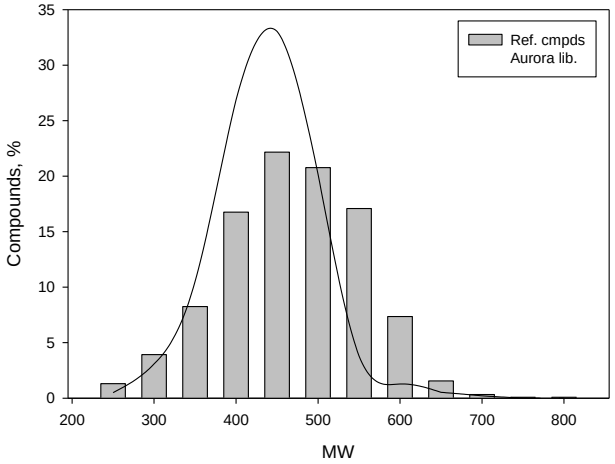
Aurora A-B kinase

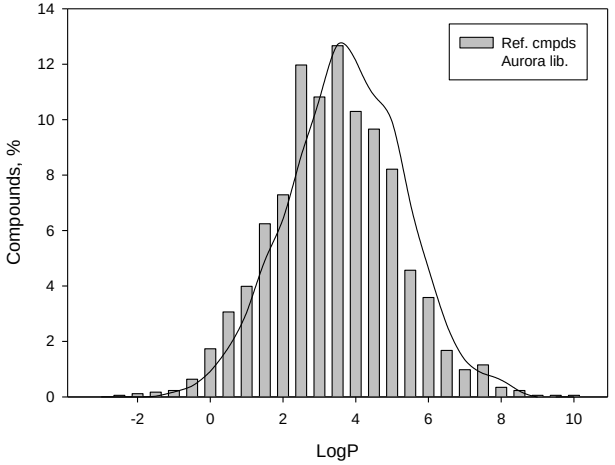
targeted library

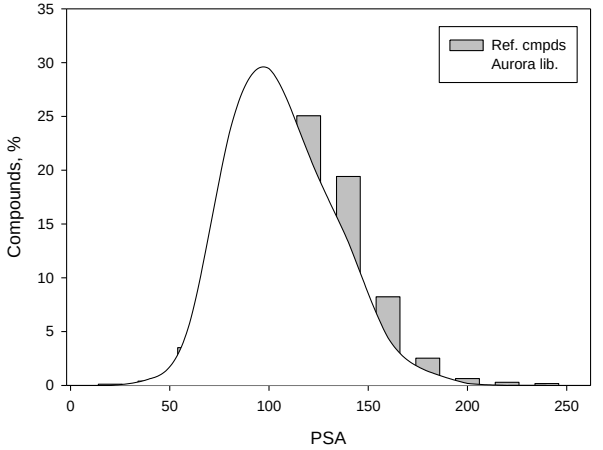
2014

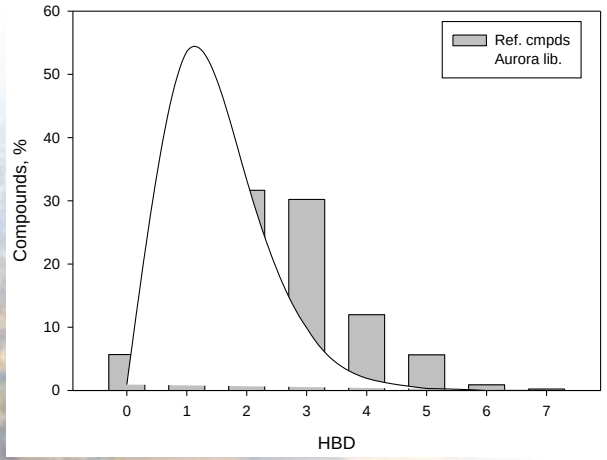
A brief insight into the property space of the reported Aurora kinase inhibitors and compounds from the Lib

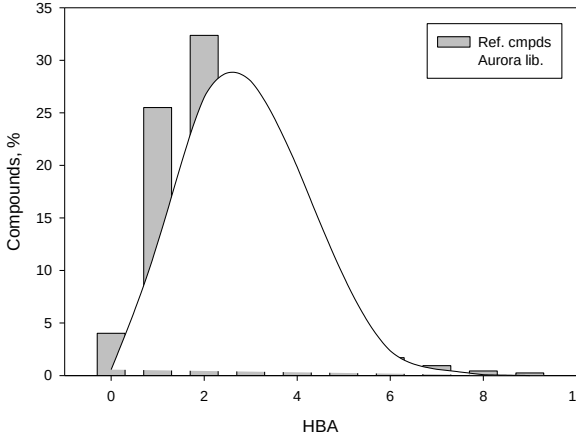
- more than **1700** small-molecule Aurora kinase inhibitors (MW<800) have been reported

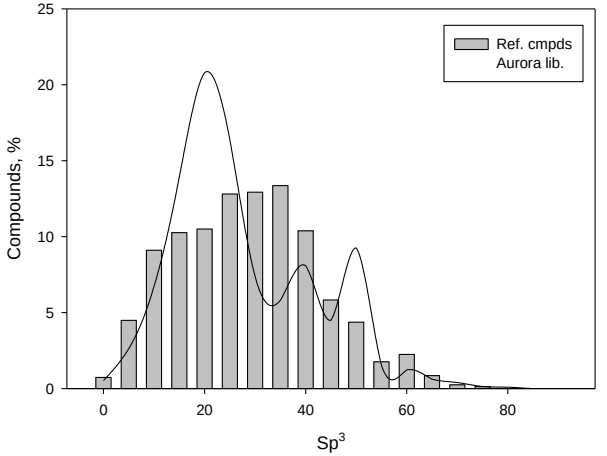












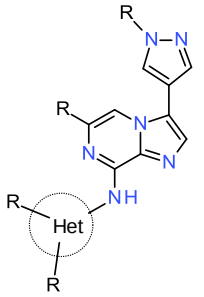
ChemDiv Aurora kinase library

- good **MW** cover (>85%)
- optimal **LogP** values (peak 3-5) / Lipinski rule matched
- good **PSA** for a sufficient solubility (peak 90-100A)

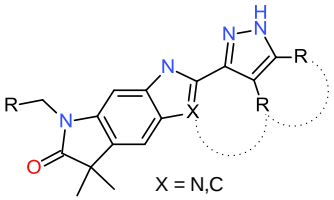
Clustering of reference chemical space / scaffold survey

▶ cmpds, of total: **1738** ▶ clusters, total amount: **104** ▶ similarity threshold: **0.6** per cluster (*Tanimoto*)
▶ singeltones: **883** ▶ minimal cluster size: **5**

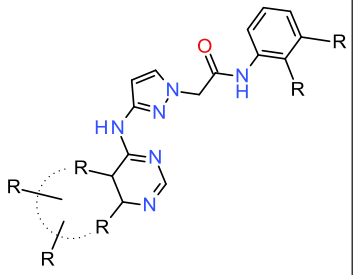
30 cmpds



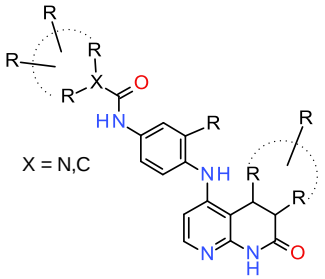
26 cmpds



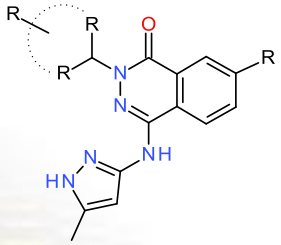
23 cmpds



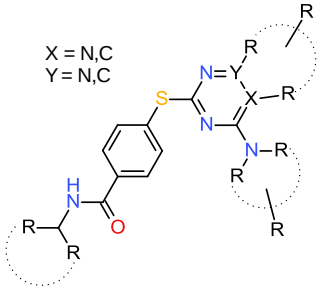
19 cmpds



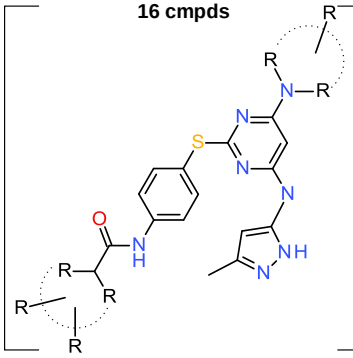
17 cmpds



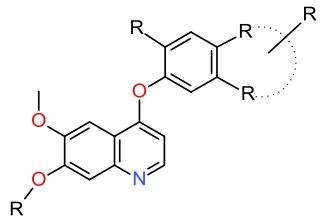
16 cmpds



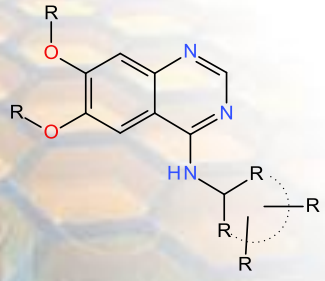
16 cmpds



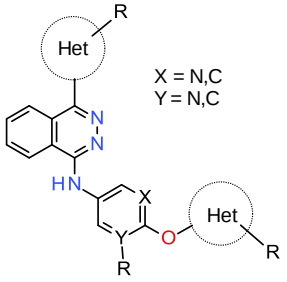
14 cmpds



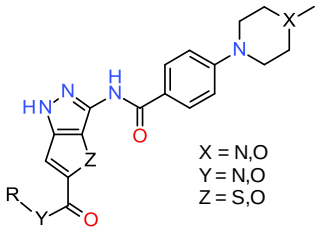
13 cmpds



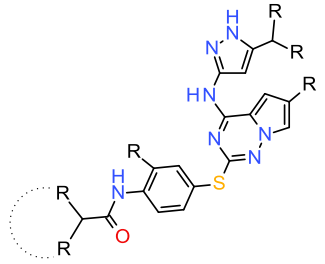
12 cmpds



12 cmpds



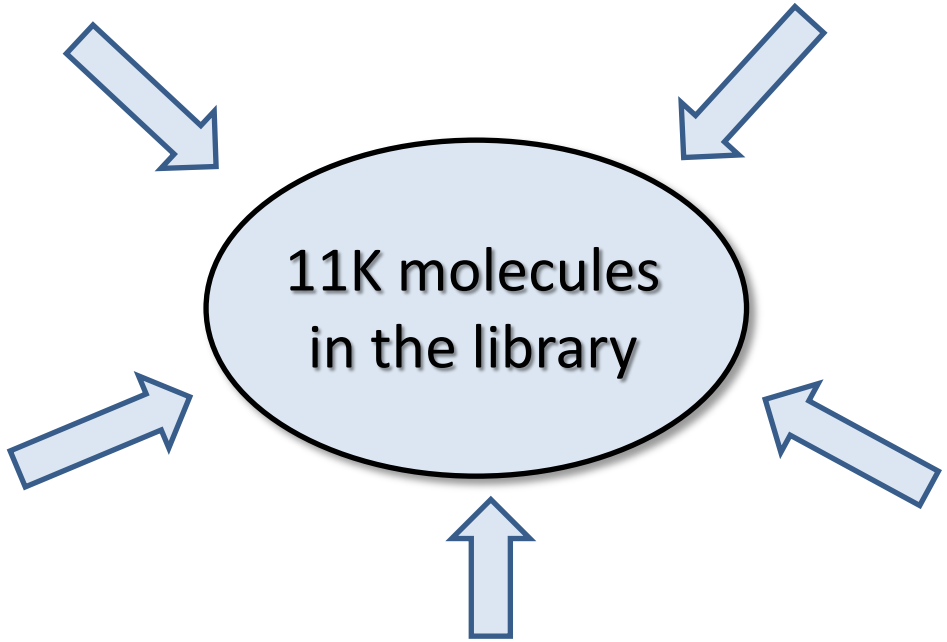
12 cmpds



The common approach to design of Aurora kinase targeted library

2D Structural Similarity
searching (*Tanimito coef. ≥ 0.65*), **20%** of cmpds

2D Topological Pharmacophore
searching, **35%** of cmpds



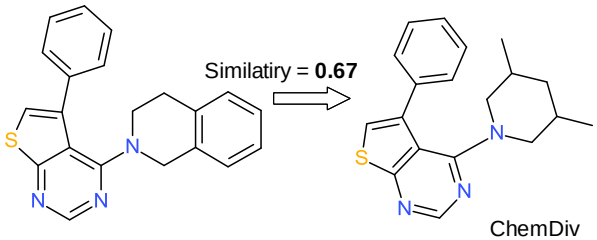
Expert Opinion
10% of cmpds

2D "Hot Spots"
15% of cmpds

Isosteric and Bioisosteric morphing
20% of cmpds

Examples

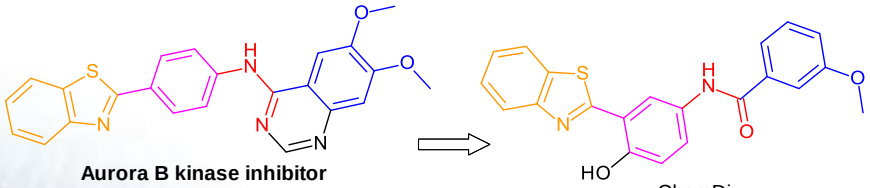
2D Structural Similarity



Aurora B kinase inhibitor
IC_{50} = 0.141 μM

ChemDiv
K841-0168

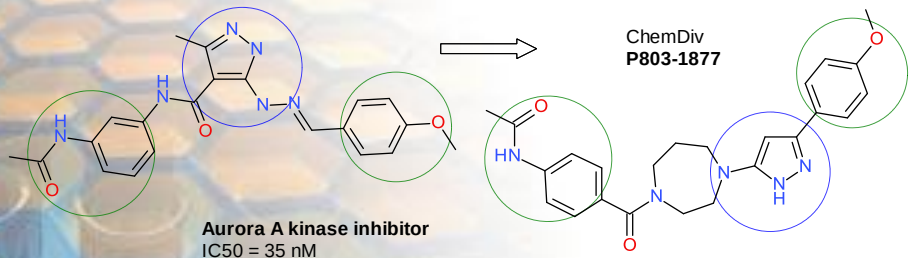
2D Topological Pharmacophore



Aurora B kinase inhibitor
IC_{50} = 0.134 μM

ChemDiv
3205-1856

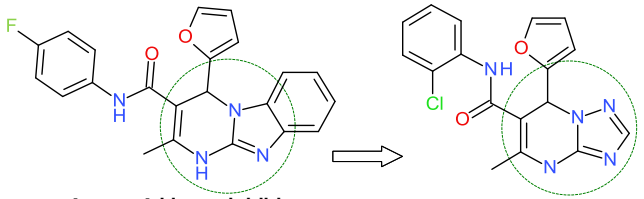
2D "Hot Spots"



Aurora A kinase inhibitor
IC50 = 35 nM

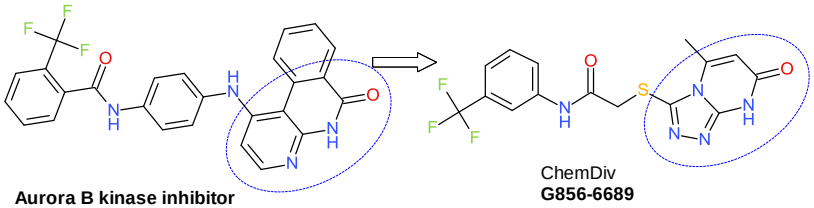
ChemDiv
P803-1877

Isosteric and Bioisosteric morphing



Aurora A kinase inhibitor
IC_{50} = 6.15 μM

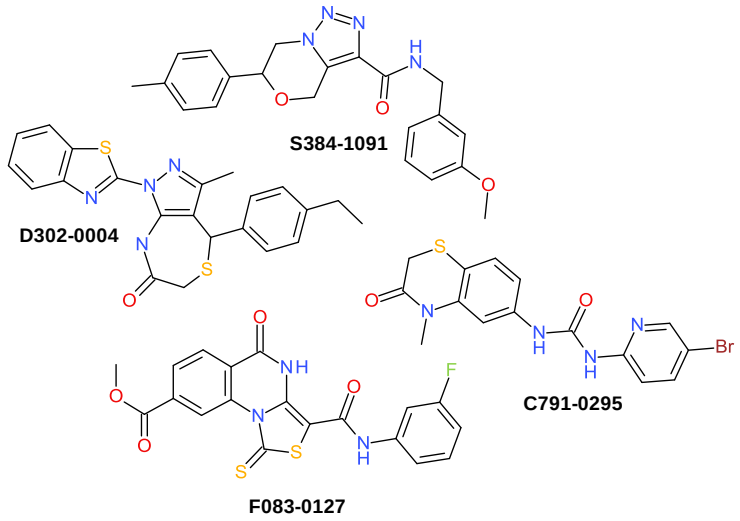
ChemDiv
G628-0549



Aurora B kinase inhibitor
IC_{50} = 1 nM

ChemDiv
G856-6689

Expert Opinion



S384-1091

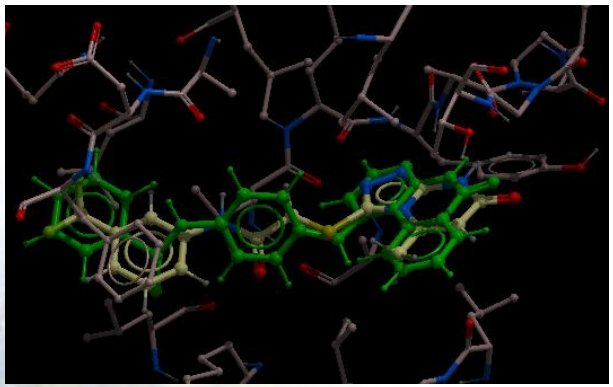
D302-0004

C791-0295

F083-0127

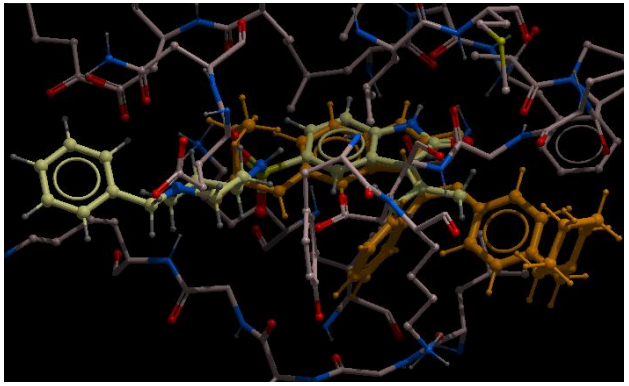
3D molecular docking

Currently, more than 100 crystallographic complexes obtained for various small-molecule Aurora kinase inhibitors are available within PDB databank. **3D model** of the Aurora kinase active site was *re*-constructed based on the selected X-Ray data (PDB: 4JAI and 2BFY). The reference compounds and molecules from the library were then docked into the constructed model starting form 2D structures without any stereo assignment. The obtained results are well correlated with the RSA data used (av. RMSD=0.3). Representative compounds from ChemDiv library have demonstrated similar binding mode compared to reported Aurora kinase inhibitors.



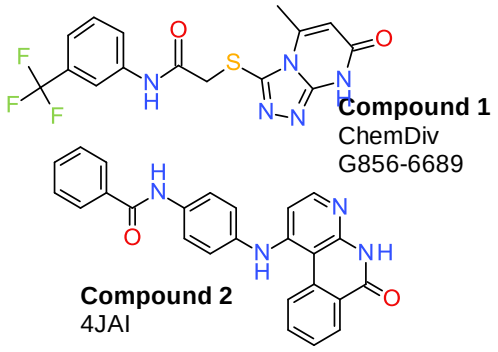
overlapping of compound **1** (*yellow*) and **2** (*green*) in the active site of Aurora Kinase A(*RSA data*)

PDB: 4JAI



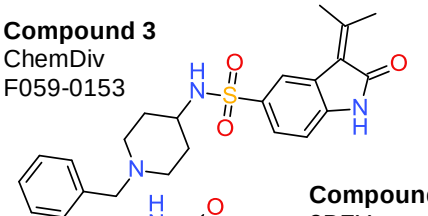
overlapping of compound **3** (*yellow*) and **4** (*orange*) in the active site of Aurora Kinase B (*RSA data*)

PDB: 2BFY

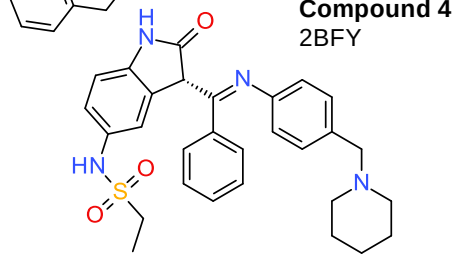


Compound 1
ChemDiv
G856-6689

Compound 2
4JAI



Compound 3
ChemDiv
F059-0153



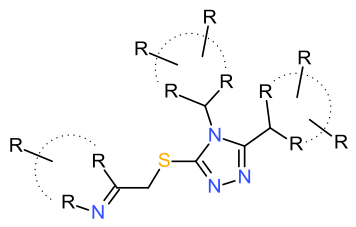
Compound 4
2BFY

Key Properties

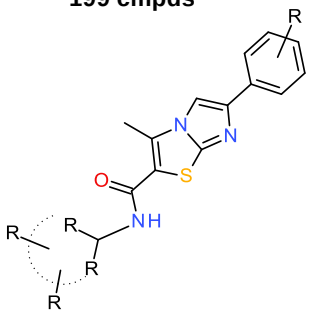
Examples of key clusters within the library

▶ cmpds, of total: **10947** ▶ clusters, total amount: **317** ▶ similarity threshold: **0.6** per cluster (*Tanimoto*) ▶ singeltones: **262** ▶ minimal cluster size: **5** ▶ Diversity: **0.80** ▶ Screens: **4100** ▶ Number of unique heterocycles: **213**

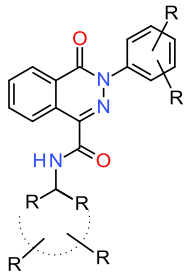
213 cmpds



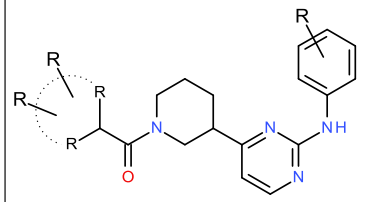
199 cmpds



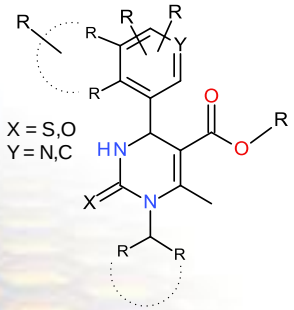
178 cmpds



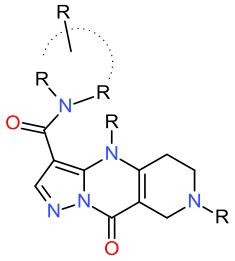
168 cmpds



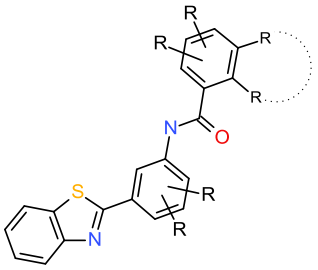
166 cmpds



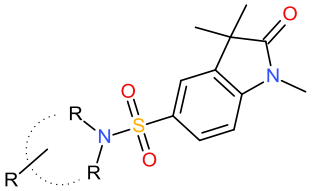
149 cmpds



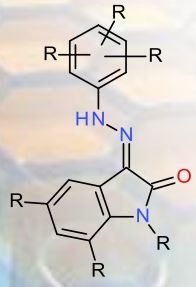
145 cmpds



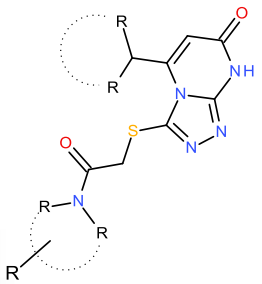
131 cmpds



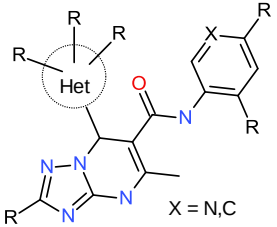
120 cmpds



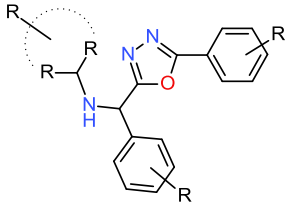
116 cmpds



104 cmpds



104 cmpds



Representative examples