The magic rings: Navigation in the ring chemical space guided by the bioactive rings

Peter Ertl

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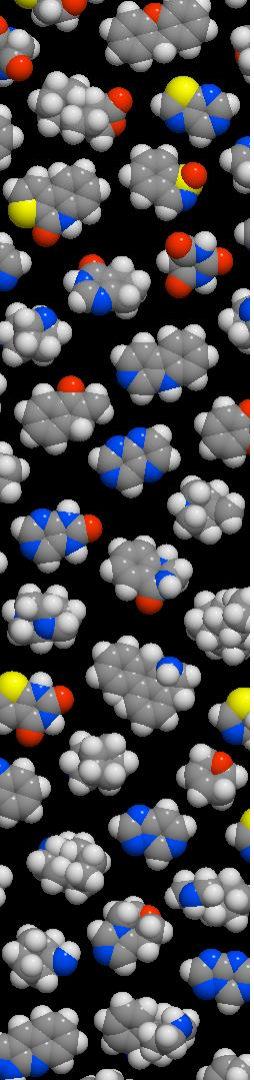
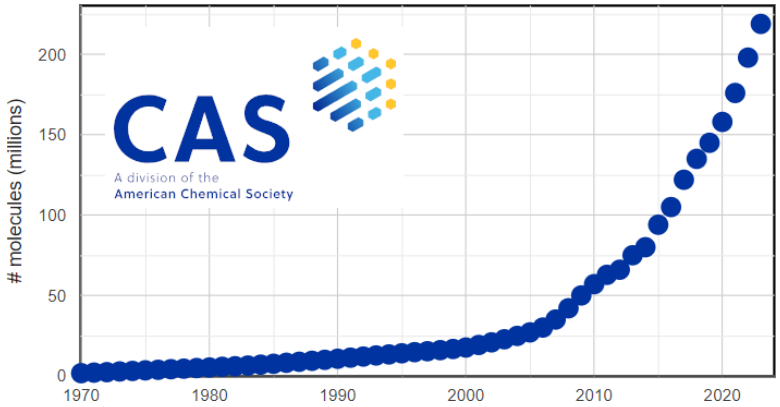


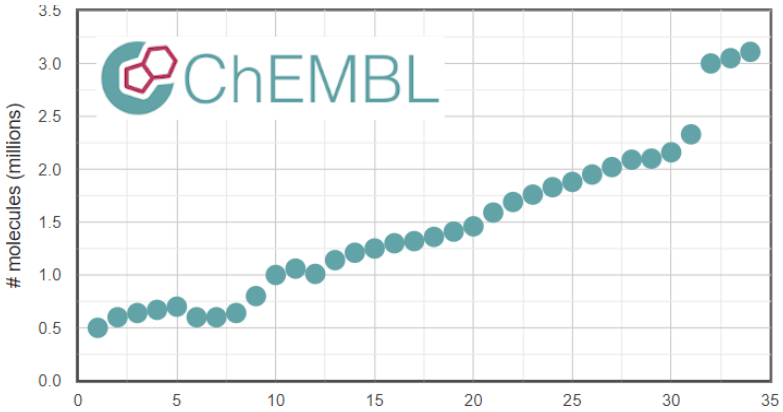
Magic Rings

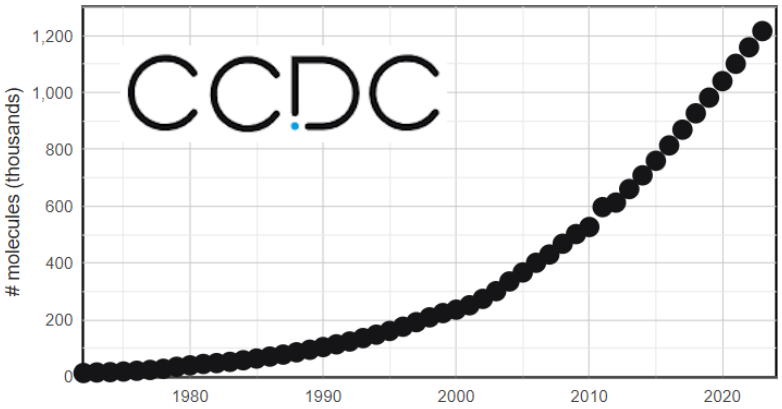
Navigation in Chemical Space Guided by the Bioactive Rings

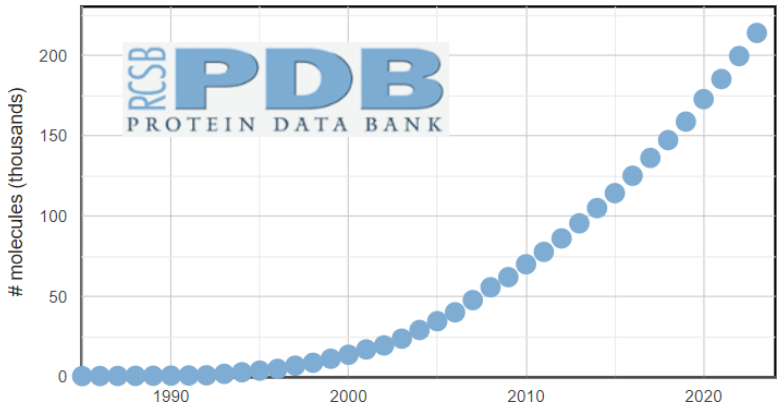
Peter Ertl
https://ertlmolecular.com
ChemTalks, Basel, September 2024

Chemical space is growing exponentially









ChEMBL database of medchem molecules

ChEMBL v.34 (April 2024)

2,431,025 unique compounds

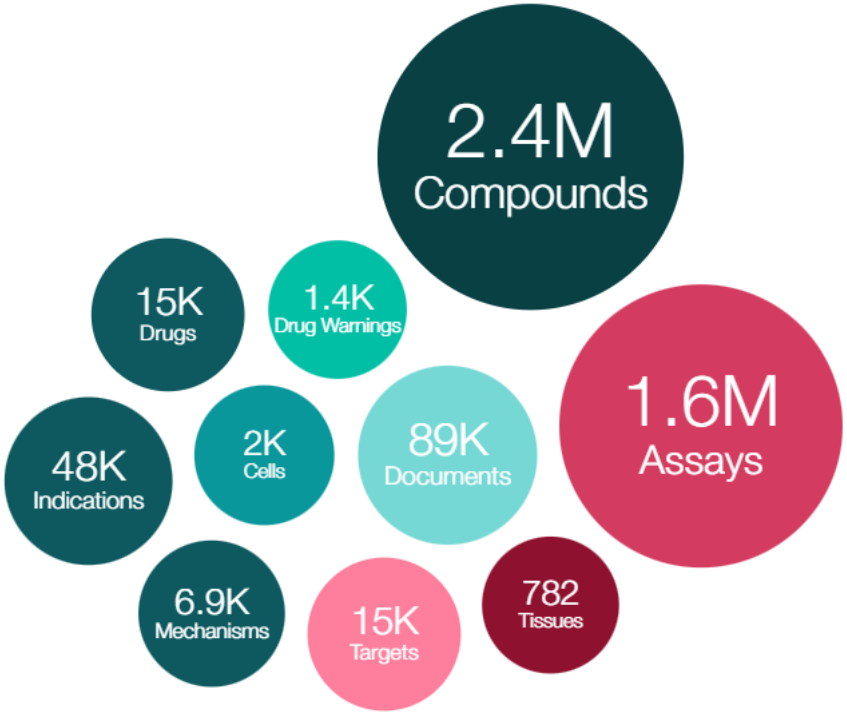
~800,000 bioactive molecules

20,772,701 activities

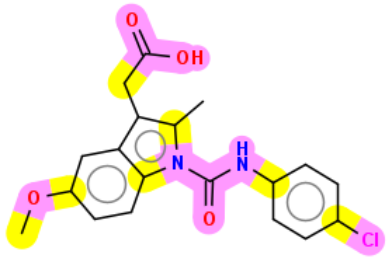
1,644,390 assays

15,598 targets

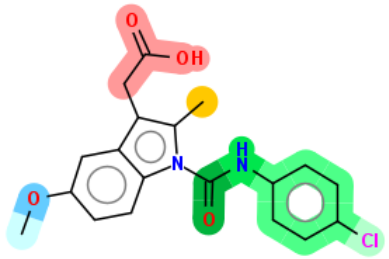
89,892 documents



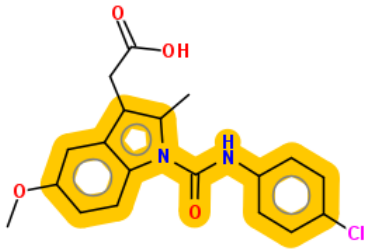
Substructure analysis



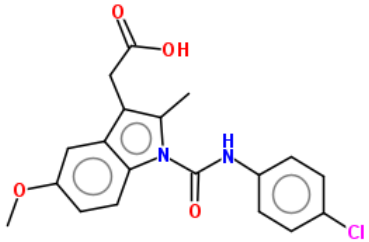
functional groups with carbon environment



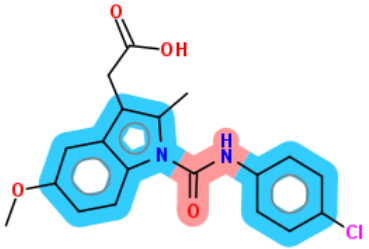
substituents



scaffold

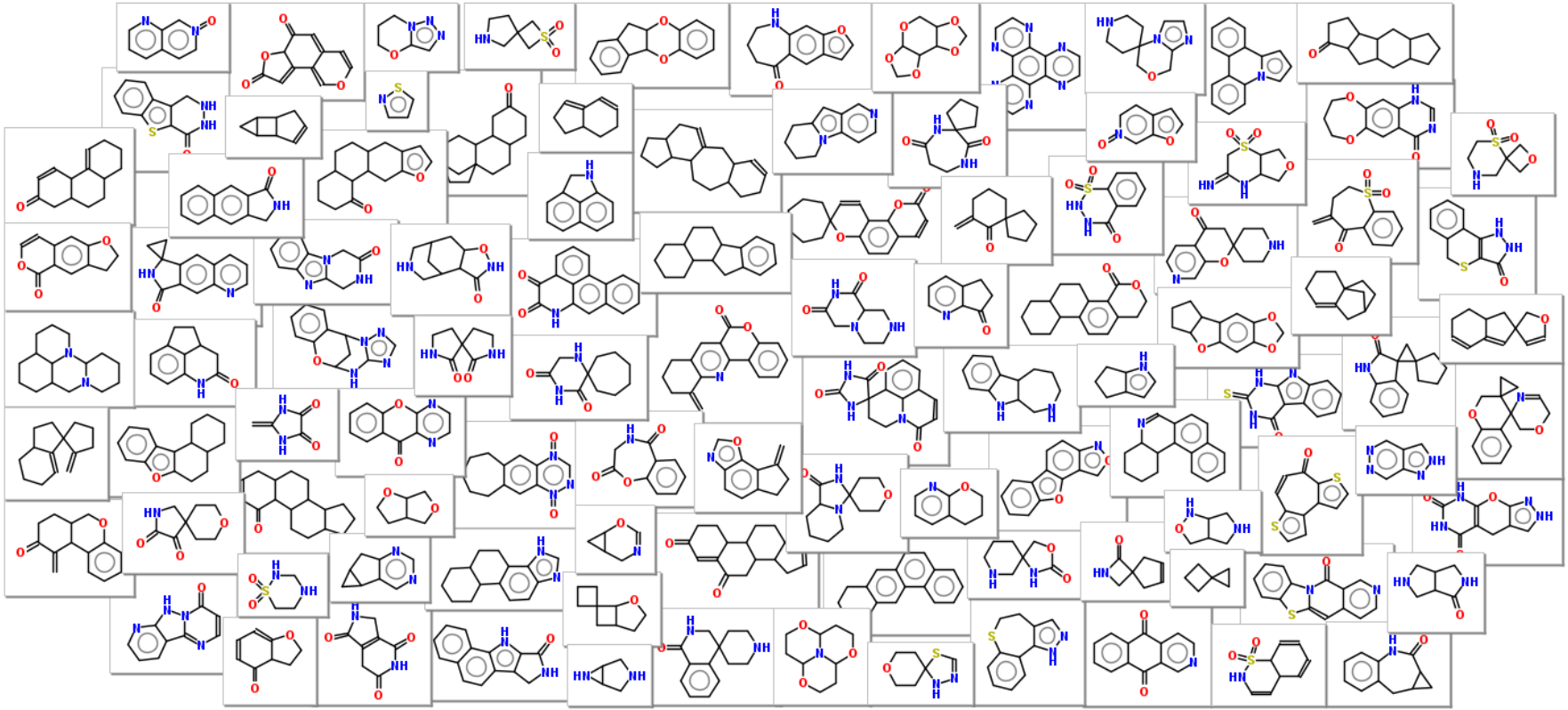


analyzed molecule



2 ring systems and a linker

Examples of rings from bioactive molecules



Rings in Bioactive molecules

Rings are the most important part of bioactive molecules:

they give molecules their shape, determine flexibility / rigidity

keep substituents in their proper 3D positions

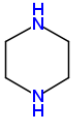
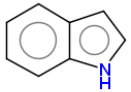
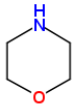
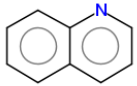
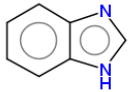
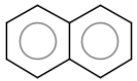
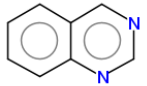
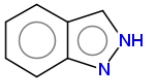
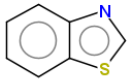
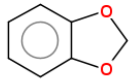
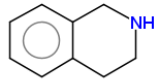
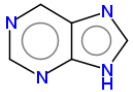
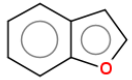
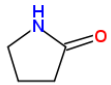
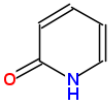
influence global molecular properties like hydrophobicity and polarity

in many cases the rings directly interacts with the protein target and directly determine the bioactivity of their parent molecules

~99.5 % of bioactive molecules contain at least 1 ring

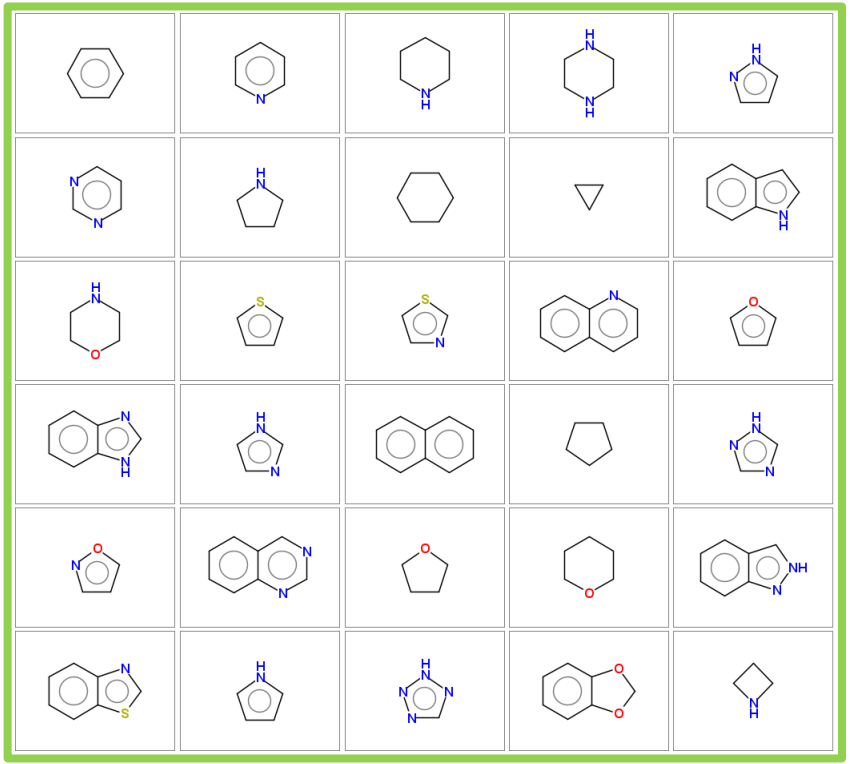
Rings play important role in several medicinal chemistry techniques including scaffold hopping, combinatorial chemistry, DEL libraries, IP analysis ...

The most common rings in ChEMBL

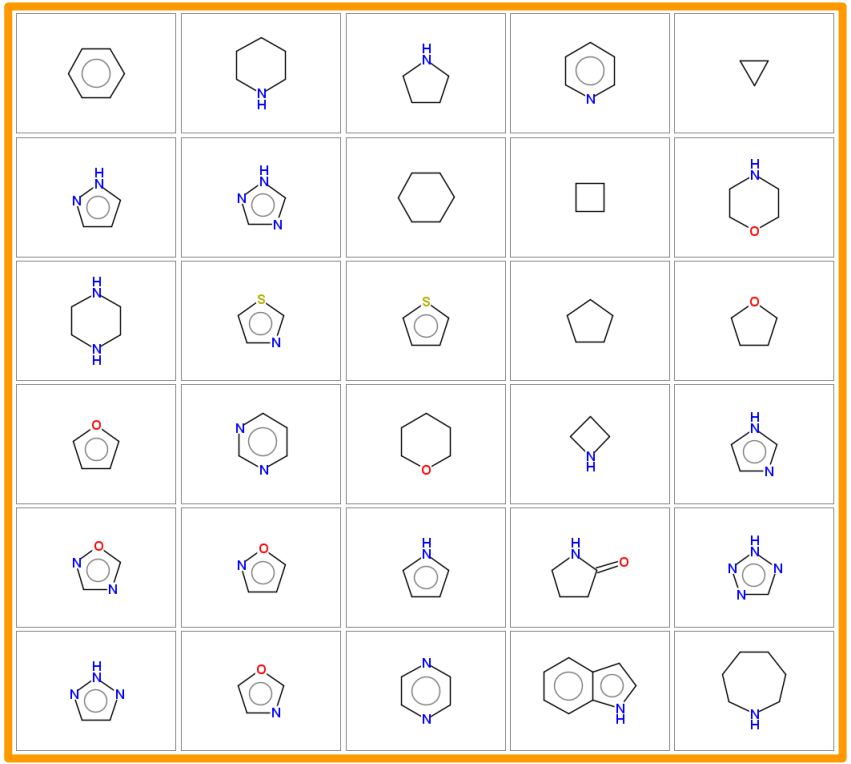
 557575	 102585	 73852	 55947	 40215	 40074	 36346	 31984
 31304	 30202	 26752	 24903	 22474	 22389	 21829	 18877
 18433	 16532	 12364	 12162	 11449	 11071	 9669	 9245
 9115	 9078	 8678	 8673	 7924	 7797	 7761	 7161
 7073	 7062	 6746	 6515	 5946	 5872	 5821	 5743

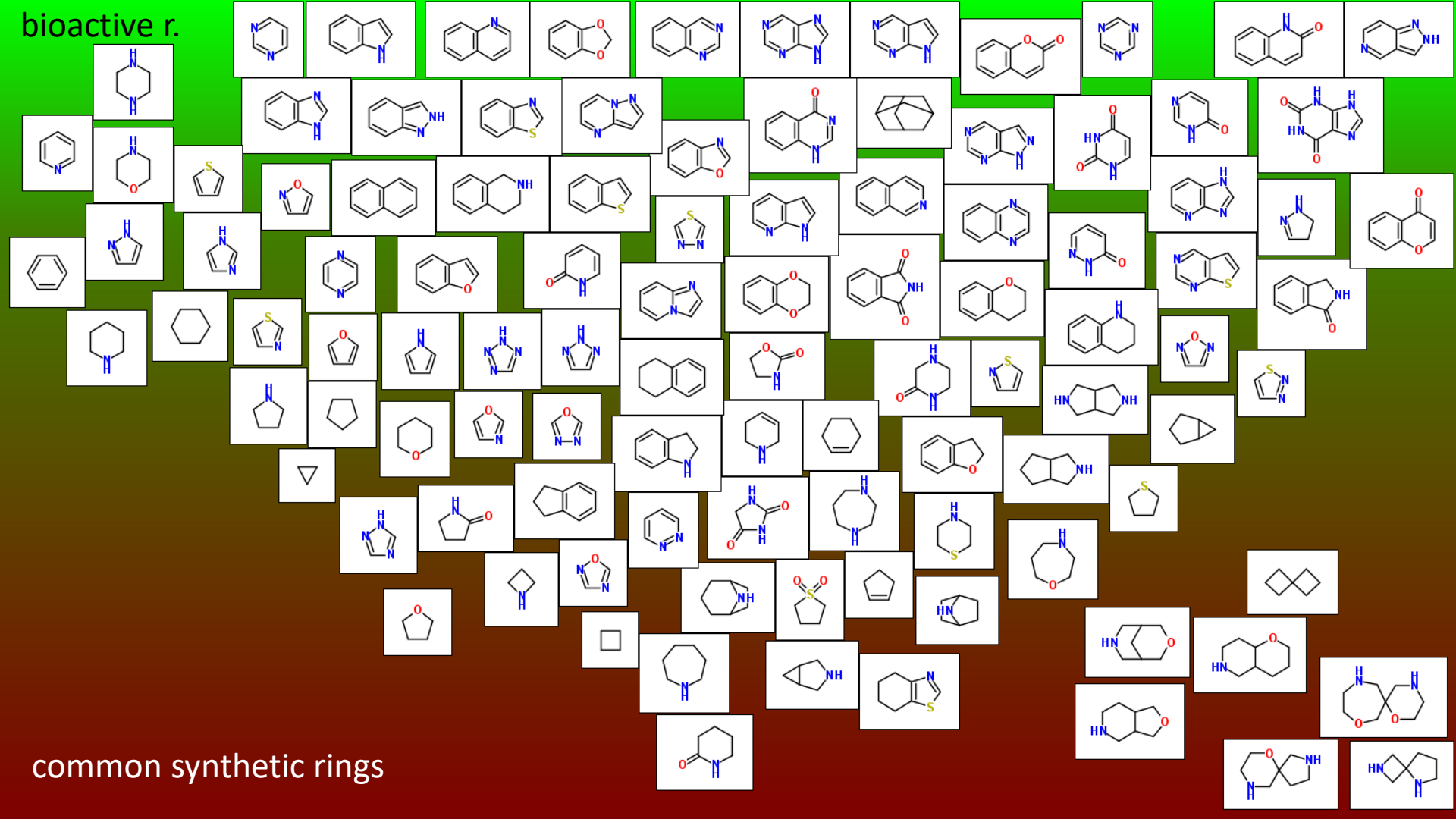
Bioactive rings *vs* common rings

bioactive molecules (ChEMBL)

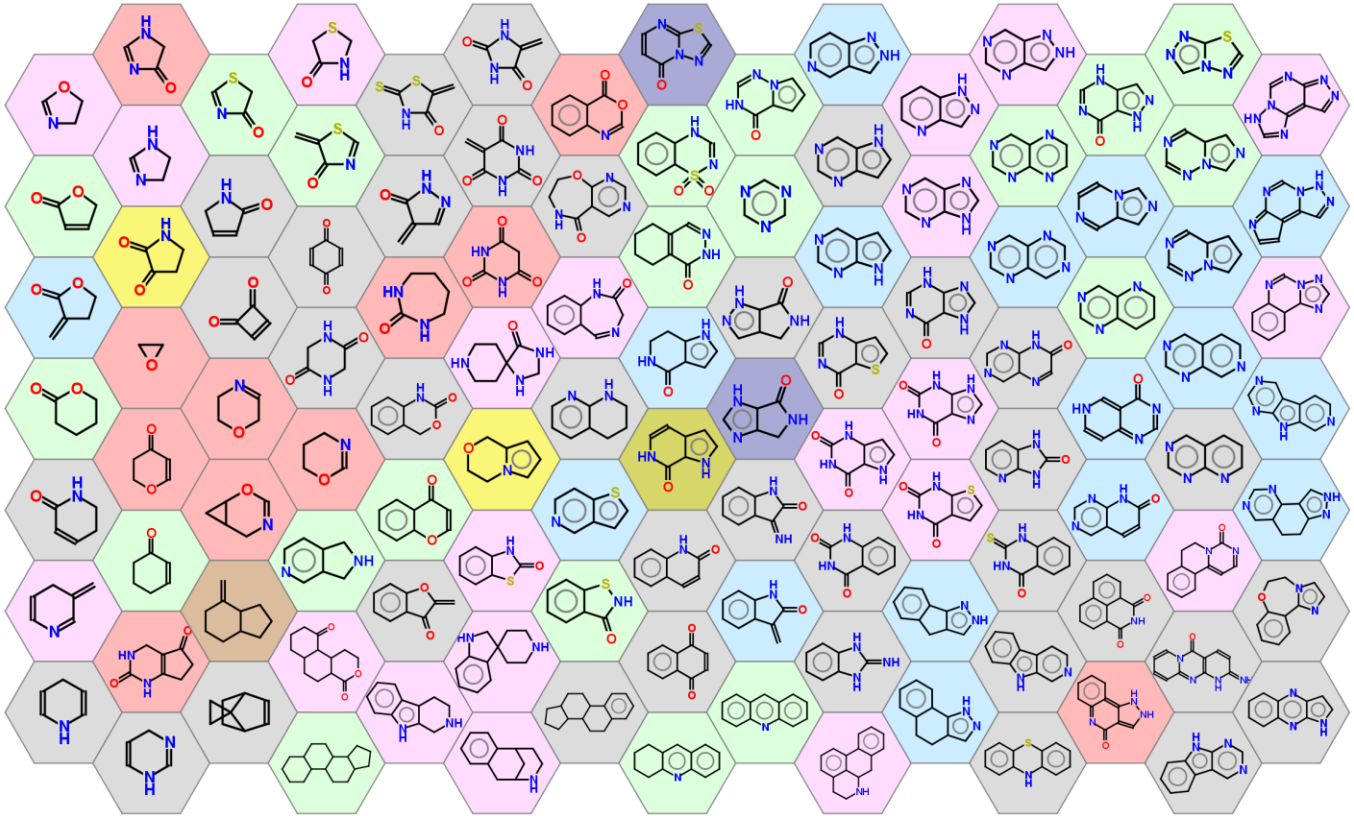


common molecules (ZINC)




bioactive r.
common synthetic rings

Target preferences for common rings



Target classes:

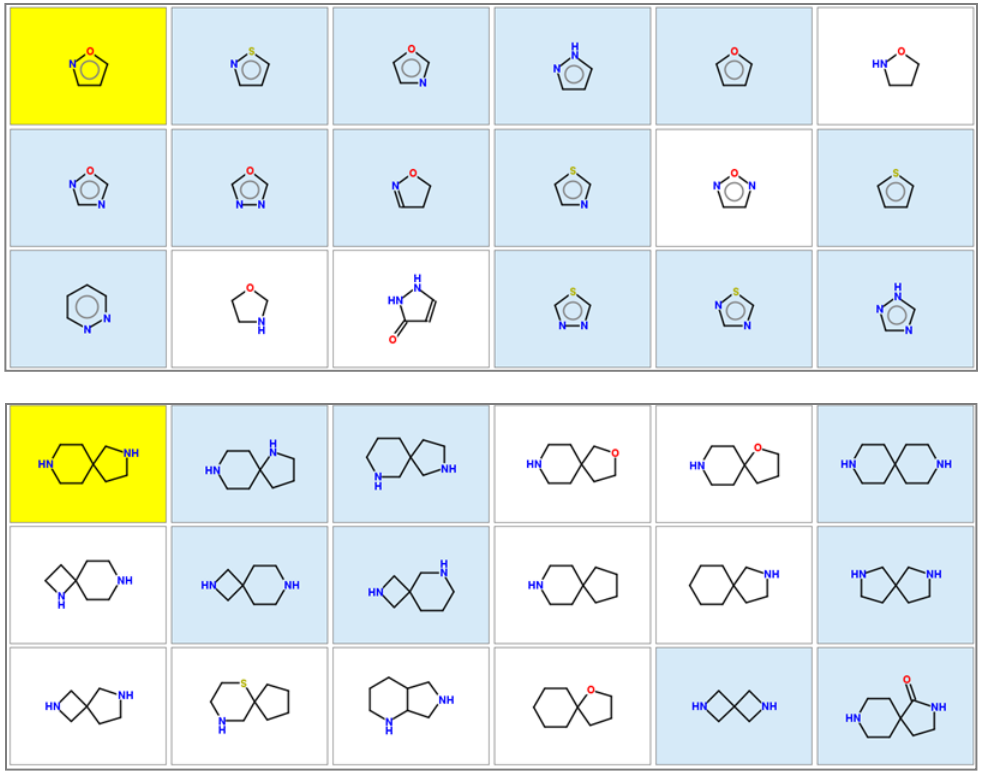
GPCRs
kinases
proteases
other enzymes
nuclear receptors
ion channels
epigenetic
another target
multiple targets

Scaffold Keys – tailored ring descriptors

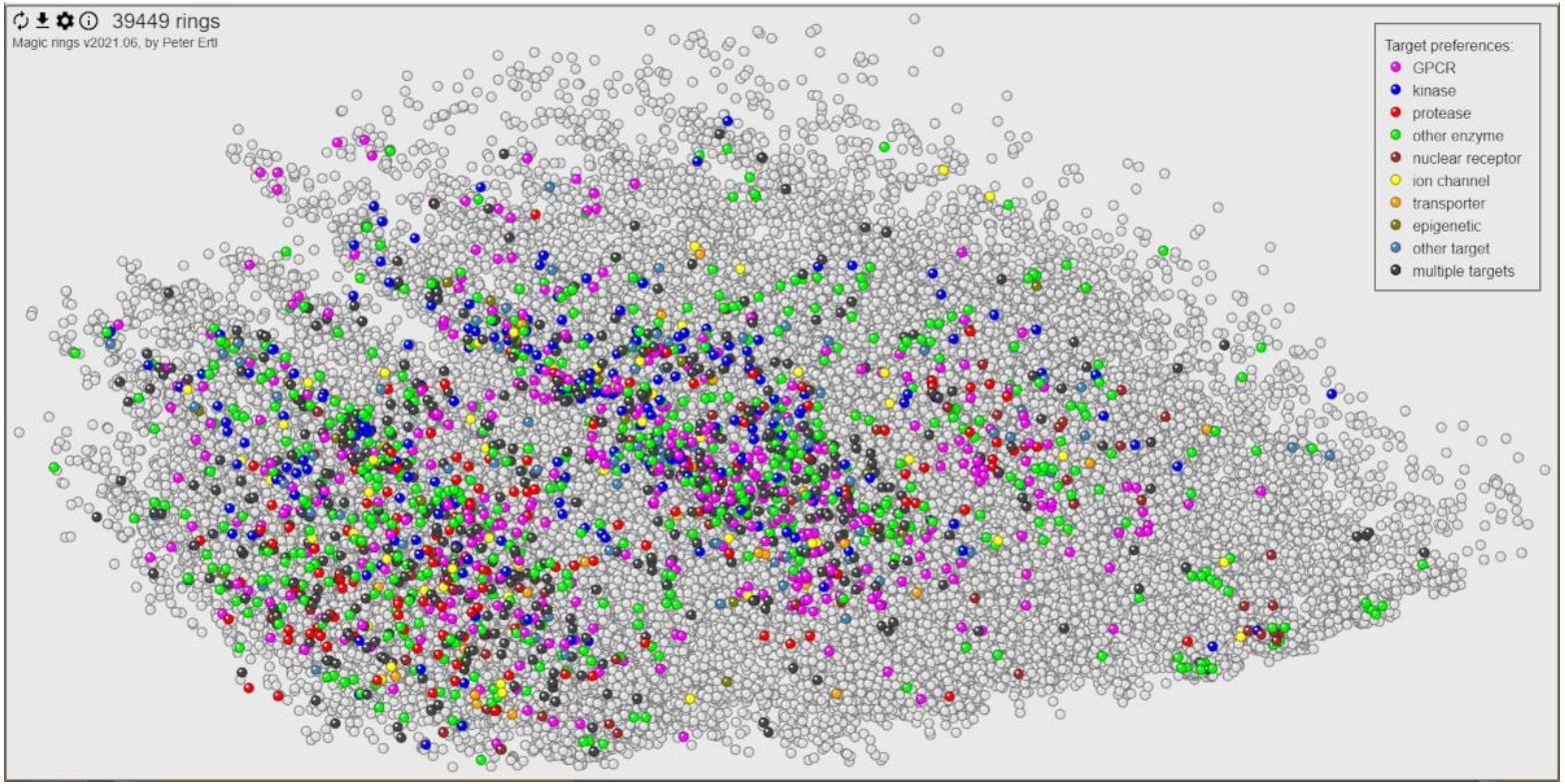
Set of 42 simple topological descriptors characterizing:

- number of atoms and bonds of certain types
- number of ring atoms, exocyclic and spiro atoms
- properties of subrings (number of aliphatic, aromatic rings, ring size, fusion ...)

The optimal set of Keys was selected to provide optimal recovery of bioisosteric scaffold replacements described in the medicinal chemistry literature.
doi:10.26434/chemrxiv.13525457.v2

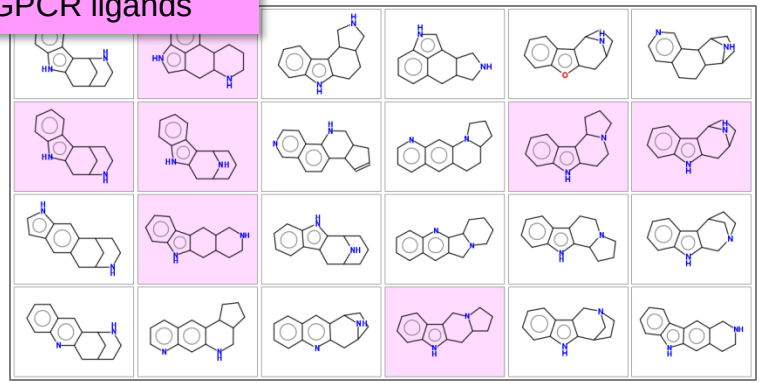


Chemical space of 40,000 rings

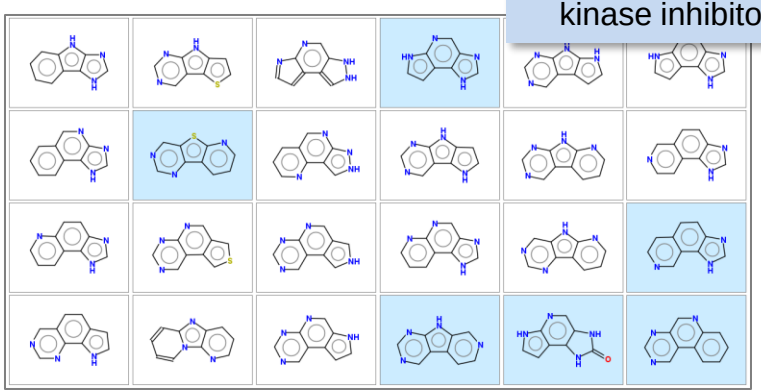


Bioactive clusters – bioisosteric design

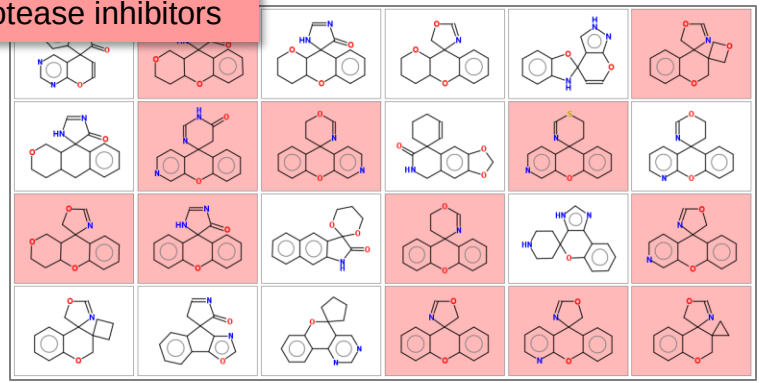
GPCR ligands



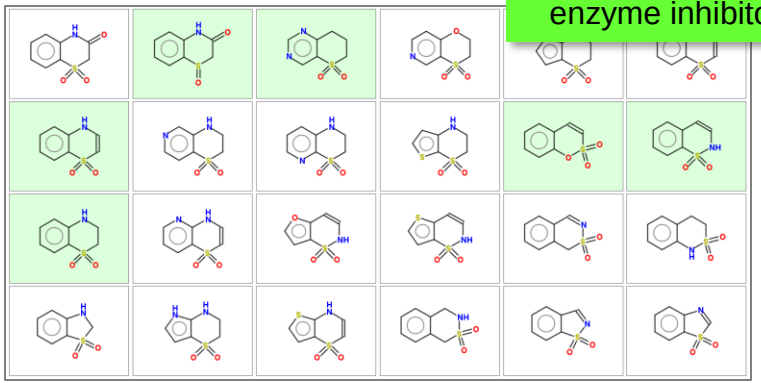
kinase inhibitors



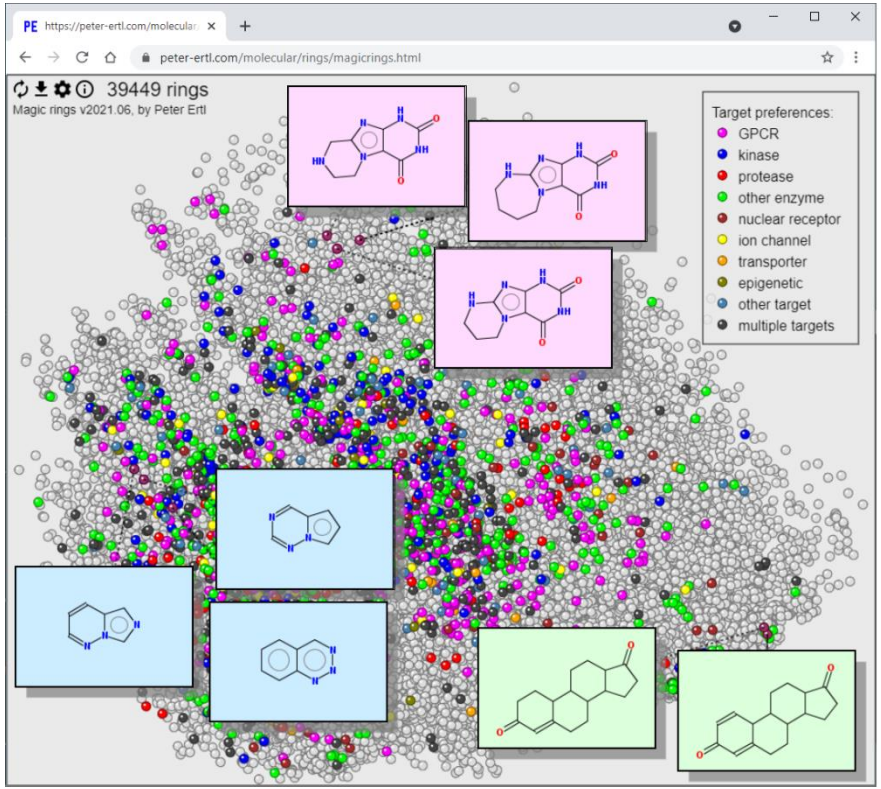
protease inhibitors

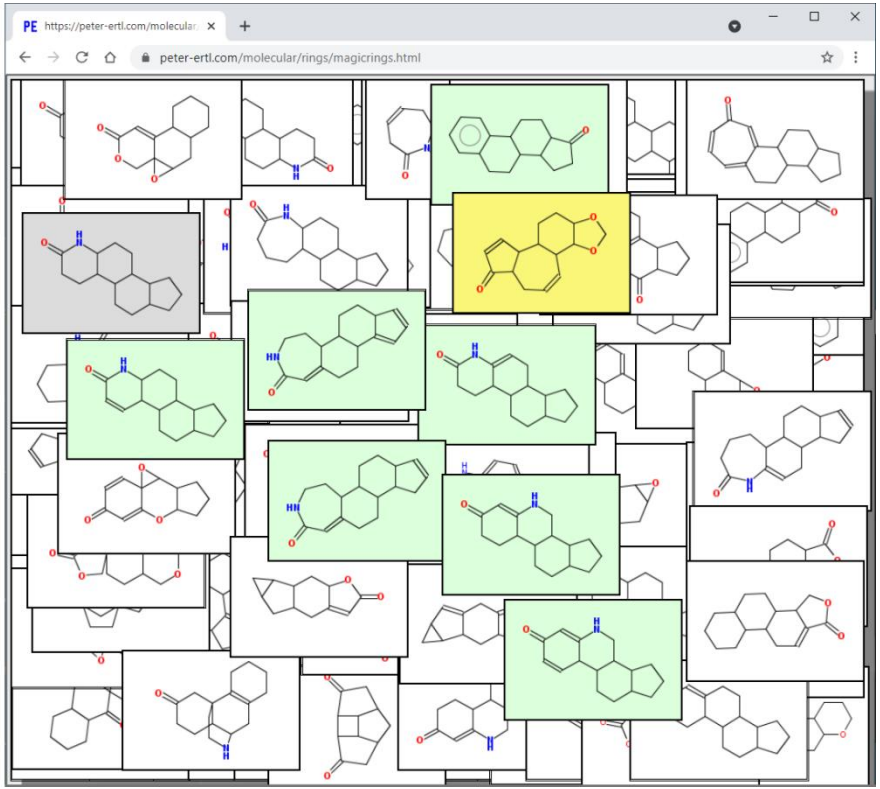


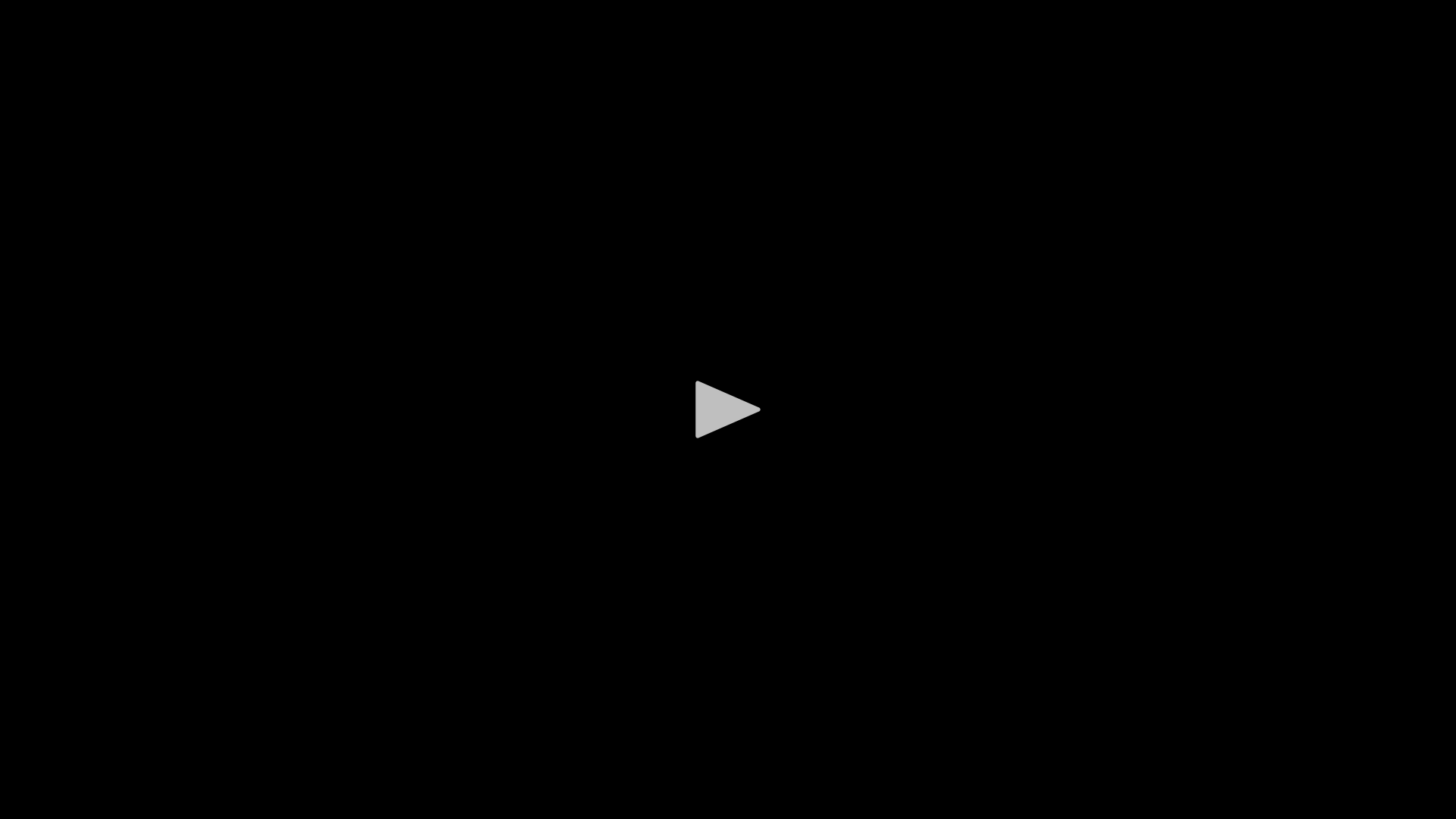
enzyme inhibitors



Magic Rings web tool https://ertlmolecular.com







Magic Rings - Summary

- cheminformatics analysis of large data sets extracted from medicinal chemistry literature can provide very useful information for the design of novel bioactive molecules
- we can use this information to visualize and navigate ring chemical space, to identify ring bioisosteres and to identify ring replacements providing good chance of improving bioactivity

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

P. Ertl, Magic Rings – Navigation in the Ring Chemical Space Guided by the Bioactive Rings, *J. Chem. Inf. Model.* 62, 2164 (2022)

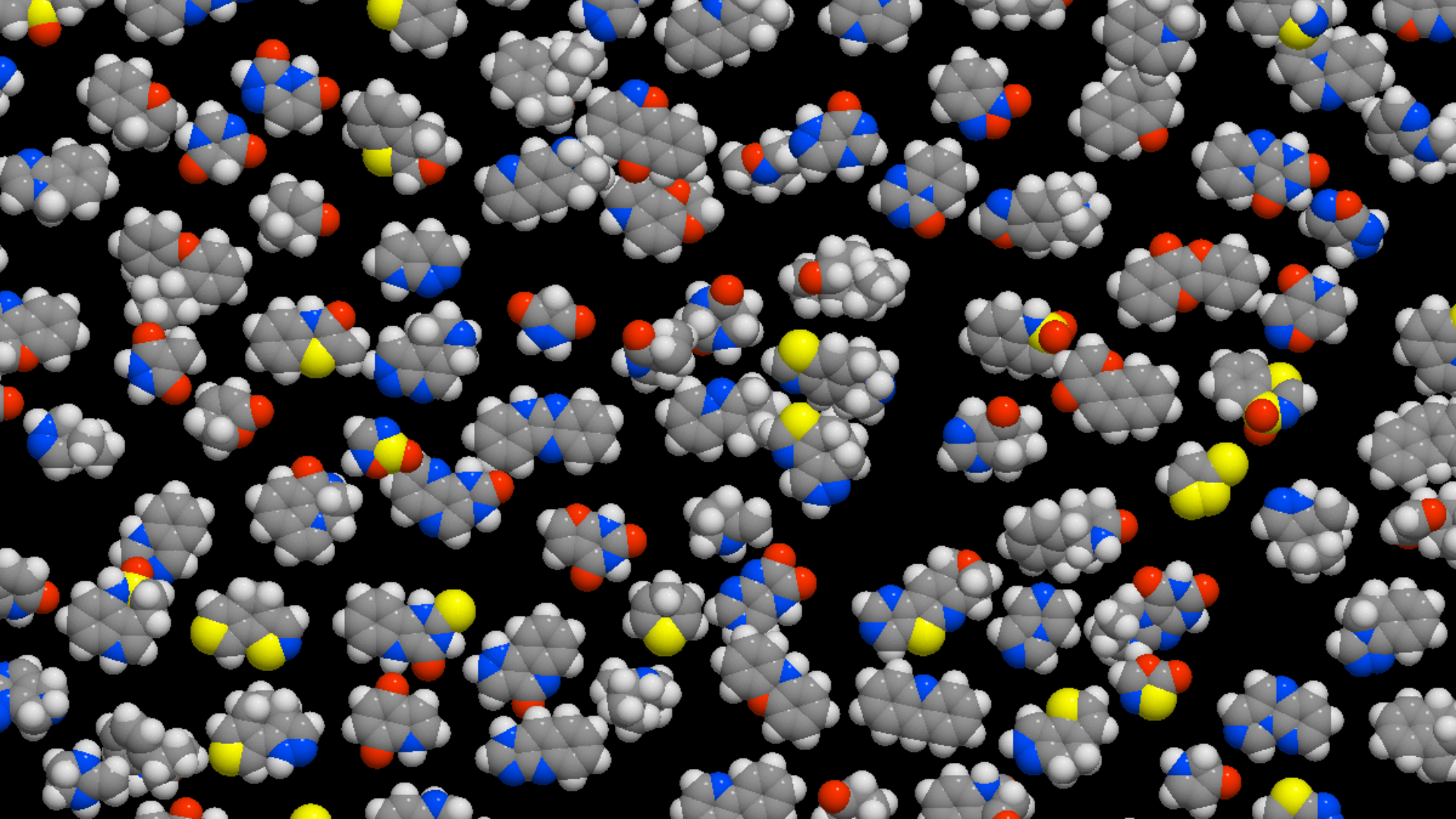
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY

P. Ertl, E. Altmann, S. Racine, R. Lewis, Ring Replacement Recommender, *Eur. J. Med. Chem. 238*, 114483 (2022)

Journal of Medicinal Chemistry

P. Ertl, The Most Common Functional Groups in Bioactive Molecules, *J. Med. Chem. 63,* 8408 (2020)

The web tools are available at: https://ertlmolecular.com



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