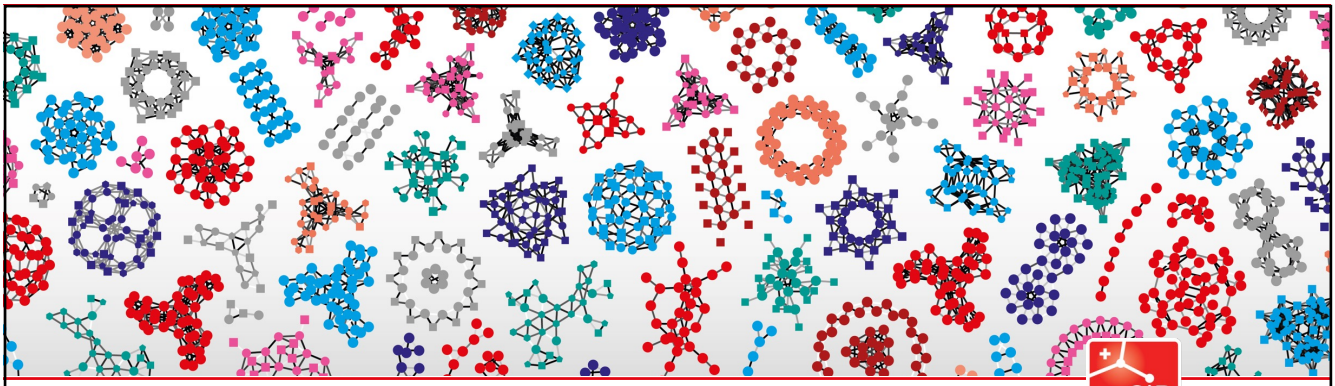

SIB
Swiss Institute of Bioinformatics

Computer-Aided Drug Design

Session 6. Bioisosteric Design

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Lectures & Practices Agenda

Session	Lecture	Practice
1	Prologue: molecular representation	
	Introduction to (computer-aided) drug design	
	Origin of 3D structures	
	Molecular recognition	Use of UCSF chimera to analyze protein-ligand complexes
2	Binding free energy estimation	
	Introduction to molecular docking	Ligand-protein docking with AutoDock Vina
3	Introduction to molecular (virtual) screening	Ligand-based virtual screening with **SwissSimilarity**
4	Short introduction on target prediction of small molecules	Use of **SwissTargetPrediction** to perform reverse screening.
5	Introduction to ADME, pharmacokinetics, druglikeness	Estimate physicochemical, pharmacokinetic, druglike and related properties with **SwissADME**
6	Short introduction to bioisosterism	Use of **SwissBioisostere** to perform bioisosteric design

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Old simple principles are still valid for modern drug design

- With the aim of discovering, designing or optimizing molecules to make potent and secure drugs
- Strategies, techniques and methodologies are very diverse, but the ancient **similarity principle** was (and is still today) surely one of the most used:

> ”Similar molecules are prone to have similar effects”

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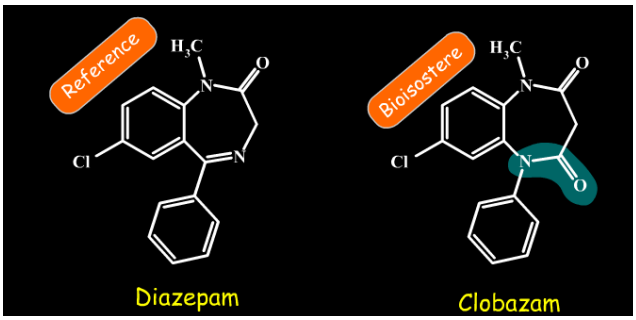
Molecular mimicry and biosiosterism

- The most common information to design a bioactive molecule is another **reference molecule** (« template »).
- So, it is possible to make a **copy** this molecule (« mimicry »).

- The property to copy is the biological effect of the drug:
  - Primarily, one tries to mimic **pharmacodynamic** properties (effect at the biotarget, eg. agonism to a receptor, inhibition of an enzyme, …)
  - but also the **pharmacokinetic** properties (access to the biotarget, eg. GI absorption, metabolic route, bioavailability, ...).



	Valium® Roche 1963	**Urbanyl®** Roussel 1975
Anxiolysis	++	+++
IIary effect	+++	+
$t_{1/2}$	+++	+

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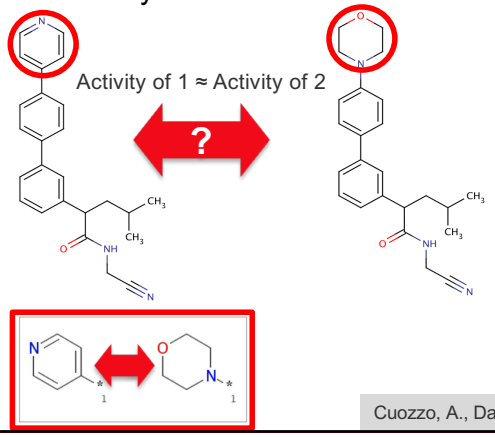
Bioisosteric design

Molecular replacements can aim at:
- enhancing affinity for target
- correcting an ADME problem
- preventing toxicity
- circumventing an IP issue
- ... many other deficiencies.

Hope to generate a **bioisostere**: a molecule with similar properties to the template molecule.
Q: Where does this replacement fragment come from?
A: Chemist experience!



But no extensive, freely accessible data resource available

➔ **SwissBioisostere: database** of more than **25'000'000** fragments, based on ChEMBL data:

free, user-friendly web-based access.

Cuozzo, A., Daina, A., Perez, M. A. S., Michielin, O. & Zoete, V. *Nucleic Acids Res* **50**, D1382–D1390 (2022).

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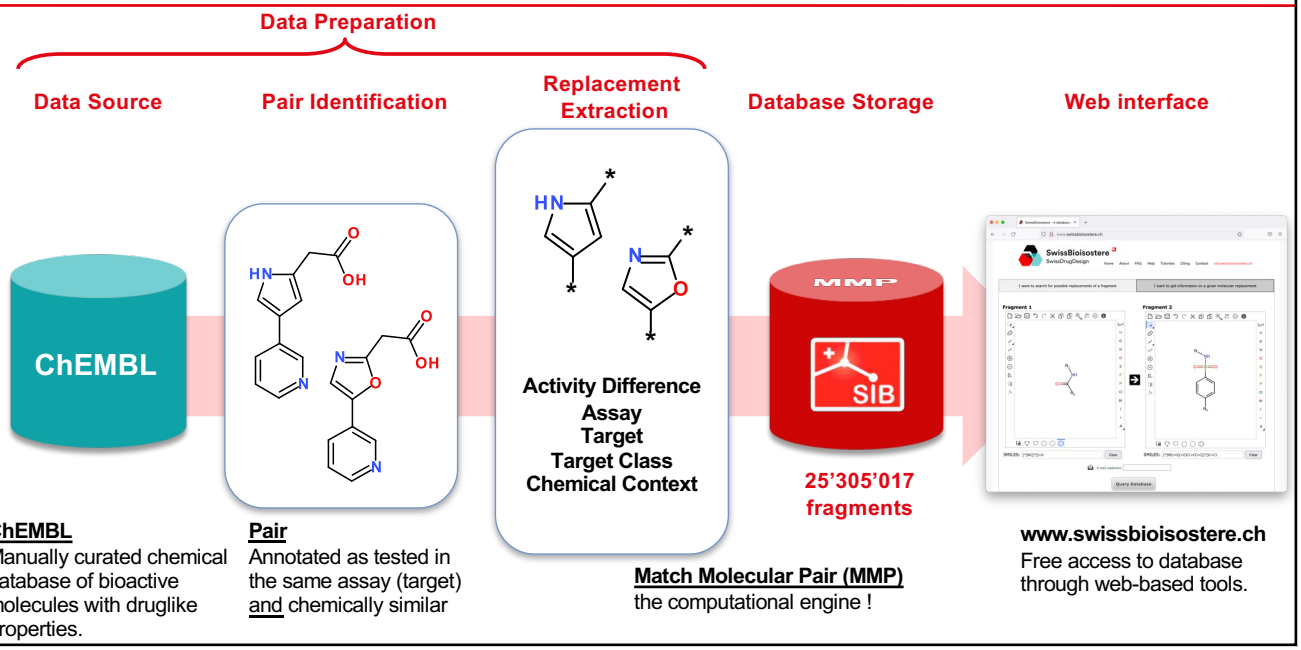
SwissBioisostere.ch



ChEMBL
Manually curated chemical database of bioactive molecules with druglike properties.

Pair
Annotated as tested in the same assay (target) and chemically similar

Match Molecular Pair (MMP)
the computational engine !

www.swissbioisostere.ch
Free access to database through web-based tools.

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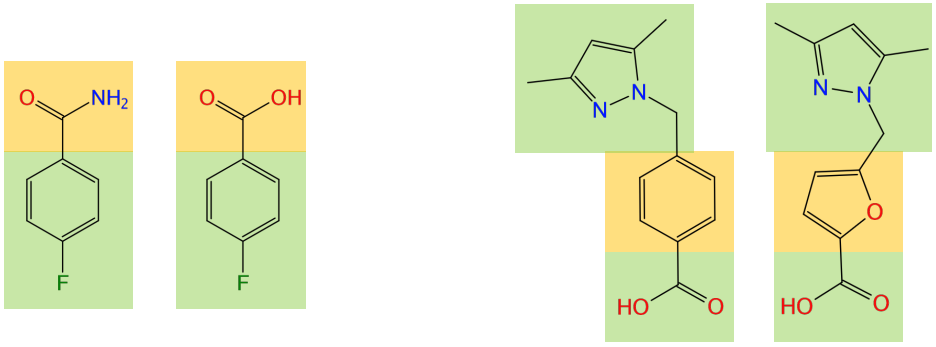
SwissBioisostere: Engine
Match Molecular Pair, MMP (1)

Pairs of compounds with a small structural exchange



Used to understand the impact of structural replacements on a given property (or parameter)

Hussain et al., *JCIM*, 2010, *50*, 339-348

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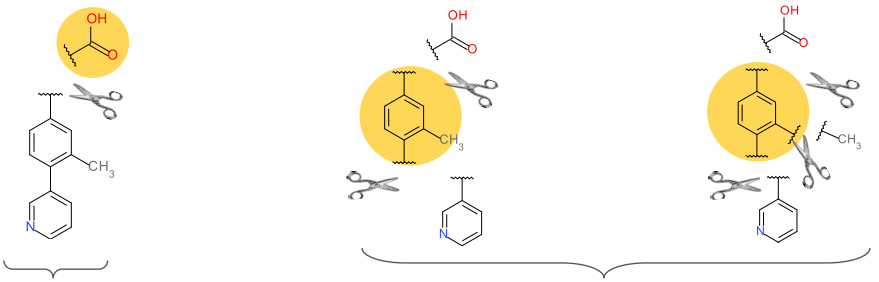
SwissBioisostere: Engine
Match Molecular Pair, MMP (2)

- Cutting rules: 1. cut single bonds / not part of functional group nor ring
2. cut additionally exocyclic double bonds

Single Cut | **Double Cut** | **Triple Cut**



sidechain replacement
➔ DESIGN IN **OPTIMIZATION**

scaffold replacement
➔ DESIGN IN **HIT FINDING** ("scaffold hopping")

- Stereochemistry treatment
chiral centers neglected in fragments, included in molecules

Hussain et al., *JCIM*, 2010, *50*, 339-348

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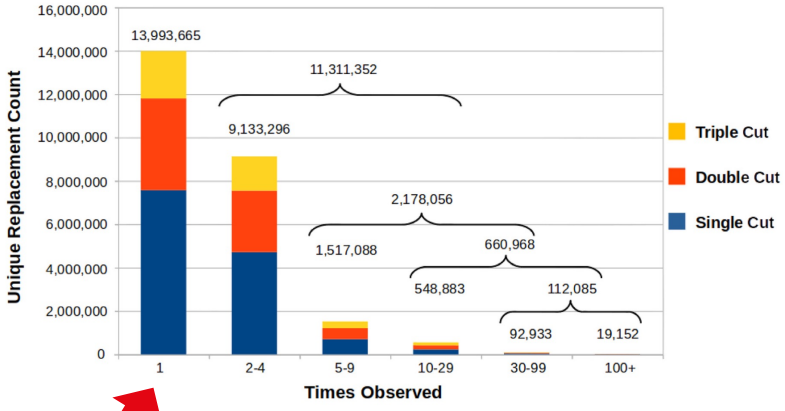
SwissBioisostere: What's in the database?

483'927	extracted bioactive compounds
21,293,355	fragment
1'216'118	unique replacements
61'199	assays
2'036	protein targets
35	target classes



55% are singletons
(observed only once)

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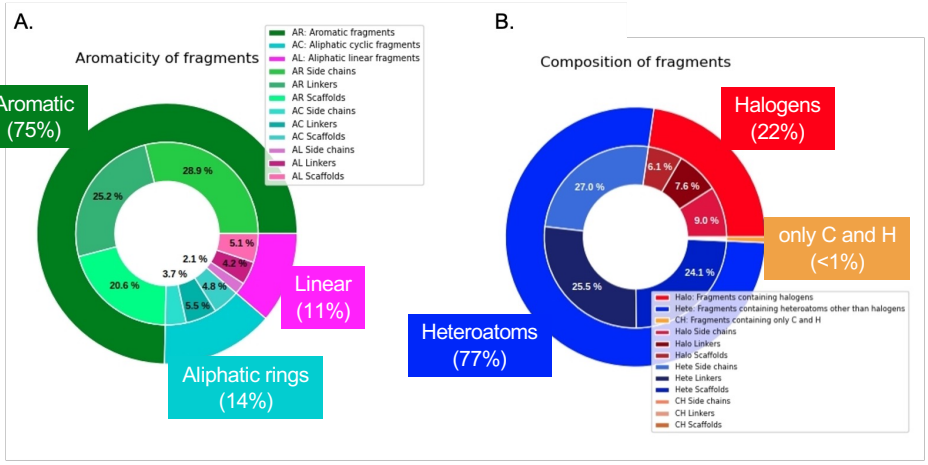
SwissBioisostere content analysis 1. Chemical nature of fragments



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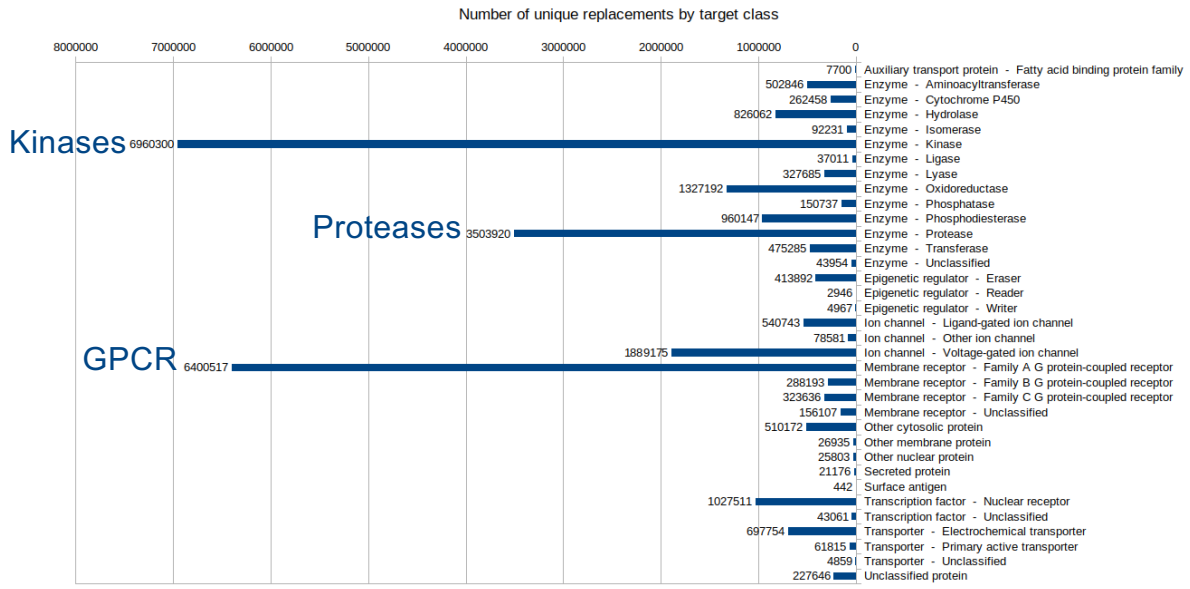
SwissBioisostere content analysis 2. biological space



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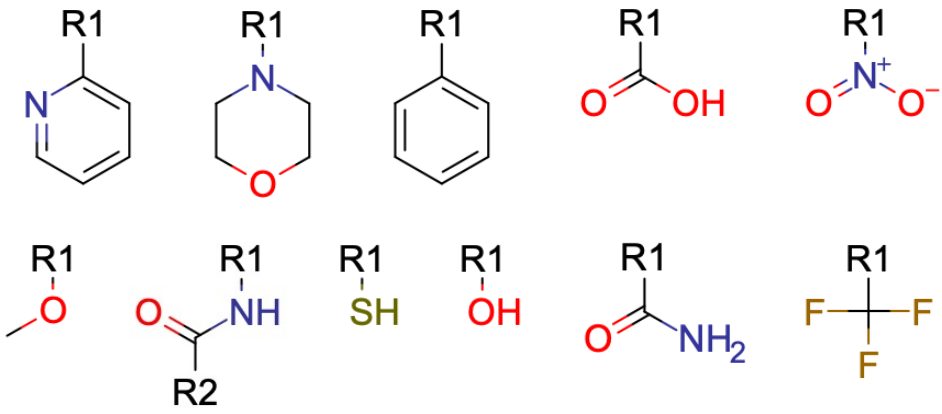
Most frequent inputs by users on www.swissbioisostere.ch



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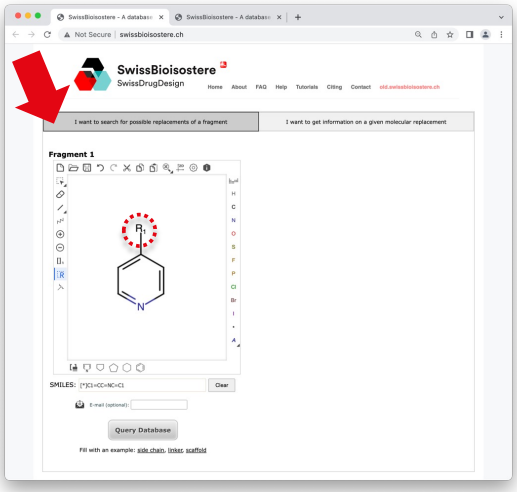
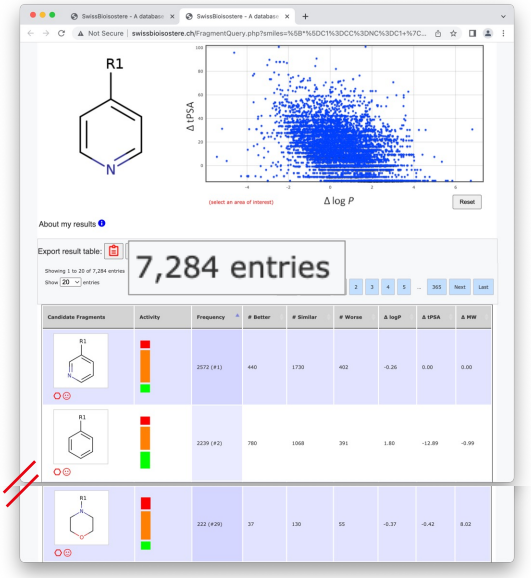
Web interface: search for possible replacements





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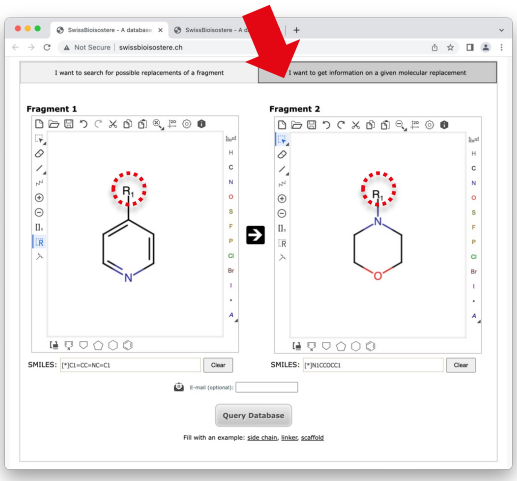
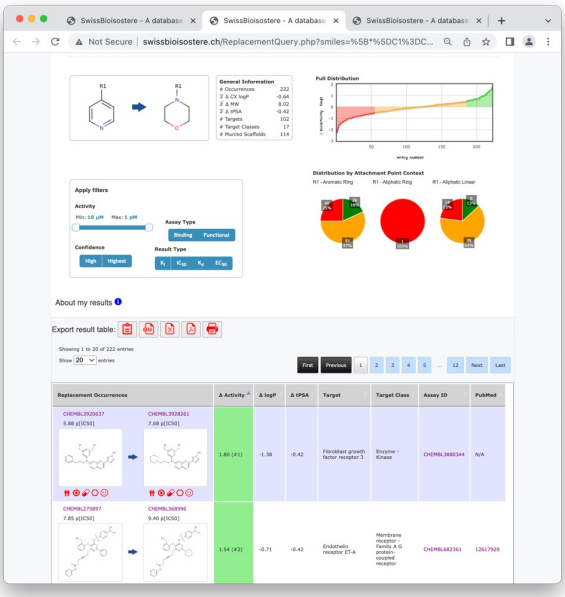
Web interface: search for in-depth info on a given replacement





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