



ChemSABRE and Bioisosterism

Bioisosteres are functional groups or groups of atoms, with similar physicochemical properties. The expectation is that replacement of a functional group in a bioactive molecule with another of similar physicochemical properties will result in maintaining an observed biological activity. The concept of bioisosterism is one of the oldest in theoretical medicinal chemistry that can be traced to the Langmuir definition of isosteres. Isosteres are atoms or groups of atoms of similar size, bioisosteres are generalization that encompasses other physicochemical properties beyond steric similarity.

Note that bioisosteres mean fragments or chemotypes and not whole molecules. Consequently databases of bioisosteric replacements do not refer in our view to pairs of molecules with similar biological activity, but to molecular fragments that have been observed to substitute for each other without affecting the biological activity. A library of bioisosteres can be explored through **ChemSABRE**.

Our database contains a compilation of bioisosteres from the literature. For them to be included they have to be explicitly claimed as such in the article. The articles from where the information was obtained can be reviews or articles that report bioisosterism. If the observation is for a particular target or family of targets, we provide that information as well, with appropriate annotations. Over 150 fragments have been compiled in that way, resulting in over 60 groups. We are continuing to expand this part of the database.

Since bioisosterism reflects similarity in physicochemical properties it is possible to extend the database by computing similarity among chemical fragments. Thus, the database is populated with small molecular weight fragments that are commonly used in medicinal chemistry. Because fragments are not complete molecules, they have to be capped to be able to compute properties. That is we attach a fragment such as methyl systematically to all the fragments under study. For each molecule that results from capping a fragment, we compute its properties, using semiempirical quantum mechanical methods when needed. We group properties as steric, entropic and electronic.

- ✓ *Steric properties* relate to shape and size and include MW, Sterimol parameters, number of atoms, rings and globularity.
- ✓ *Entropic properties* include polar surface area, logP, and number of hydrogen bond donors and acceptor.
- ✓ *Electronic properties* comprise Mulliken charges, in particular those at the capped atom, which would be the point of attachment of the fragment to the scaffold, dipole moment, magnitude and direction relative to its attachment direction and average polarizability.

The properties are descriptors of the fragments used to determine similarity among the groups. The closer the values of the properties the more similar the fragments are. The Euclidean distance provides is used in **ChemSABRE** to determine similarity. We chose to keep a separate score for each property class. The reason is that in some cases maintaining biological activity may depend more on having similar size and shape, while in other cases retaining lipophilic character or the correct magnitude and direction of the molecular dipole may be what is critical.

The similarity among fragments results from the steric, entropic and electronic contributions each can be weighted by the user according to what is known about the problem at hand. The default is equal weight for each of the three components of the similarity. We have computed properties for over 1200 low molecular weight substituents and are contained in the **ChemSABRE** database.

USEFUL REFERENCES

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