Property-Based Design Methodology III: Identifying Creative Substituents

Robert DeWitte ACD/Labs, Toronto, ON, Canada

Fedor Gorohov, Eduard Kolovanov ACD/Labs, Moscow, Russian Federation

Abstract

With the overall goal of selecting substituents that influence molecular properties in order to reduce the molecular log*D* at a specific pH (in this case 5.5, since we are focused on aqueous solubility), it would be advantageous to be able to consult a database of substituents indexed with their physicochemical properties. This poster illustrates the application of such a database in a case study to improve the aqueous solubility of acetyl sulfadiazine at pH 5.5.

ACD/MedChem Advisor

As described in poster I in this series, an alternative to considering elementary substitutions would be to consult a database of substituents which includes the pertinent σ parameters. A set of such databases is available as part of ACD/MedChem Advisor, which allows sorting, filtering by data ranges, and chemical structure queries. Further, substituents are divided into four categories:

- Acids
- Bases
- Neutrals
- Heterocycles

which allows the user to preserve the general acid/base characteristics of the compound while optimizing the pH profile of log*D* through modification/introduction of the strength of a specific ionization centre. Note that the database of heterocycles can double as a source of substituent ideas as well as an index of possible ring substitution. Note that each heterocycle is reported multiple times, each with a separate point of attachment, which will dramatically influence its electron withdrawal strength, and therefore the electronic impact of the ring system on the balance of the compound.

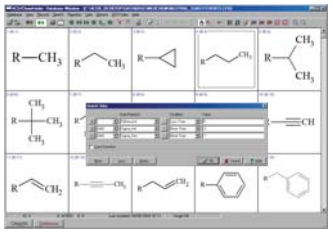
Each record in these databases is annotated with critical molecular design parameters:

- Molecular Weight
- Molar Volume
- Hansch π values (so that you can anticipate the affect of each substituent on the log*P* of your compound)
- A complete set of σ parameters (so that you can anticipate the affect of each substituent on the pK_as in the parent molecule)
- An indication of drug-likeness—essentially equivalent to having a USAN or INN name—so that you can limit your creativity to substituents that have appeared in other clinically developed compounds.

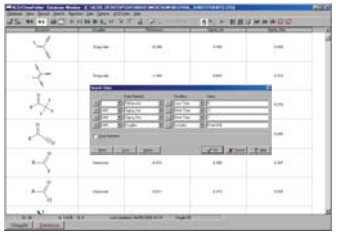
ACD/MedChem Advisor—a bundle of ACD/ChemFolder, ACD/Log*D* Sol Suite, and this set of databases—provides the medicinal chemist with a design studio that equips him or her with the ability to rapidly identify and assess chemically relevant modifications in terms of their ability to aid in the optimization of molecular physical properties.

Returning to our active case study, let's use the substituents database to identify two novel ways to improve the aqueous solubility of Acetyl Sulfadiazine: i) selection of more creative substituents; and ii) heterocycle replacement.

Step I: Finding Substituents with Suitable Physical Properties



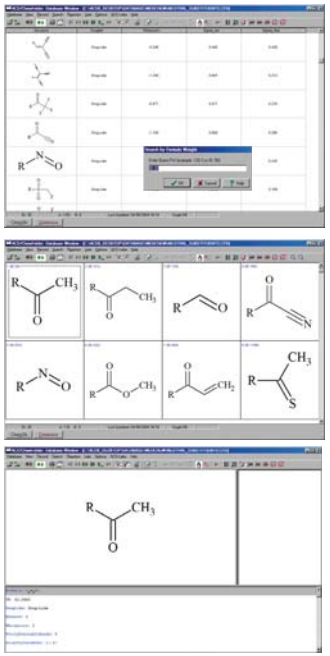
We begin by opening the "Neutral Substituents.CFD" database and querying for all records with strong electron withdrawal strength through both inductive and resonant mechanisms, with the additional constraint that these will likely reduce the overall log*P* of the compound.



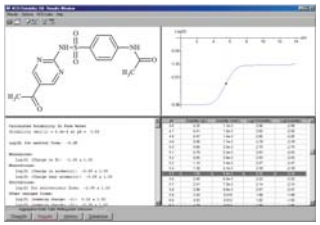
This query returns 434 candidate substituents, but several of them are large and/or look rather exotic (from the point of view of synthetic feasibility and drug-likeness).

We can refine this list by including the drug-likeness criterion (next figure) and limiting the molecular weight to be less than 60 (subsequent figure).

Step II: Refine for Drug-likeness and Size



The result of these additional filters is that eight substituents are recommended. The acetate substituent seems like a reasonable modification to investigate. Not only does it carry high inductive and resonant sigma constants, but also has a reasonably negative Pi constant.



Application of this acetyl substituent to the parent compound gives an excellent expected solubility at pH 5.5 (1.66 mg/mL).

Conclusions and Next Steps

In this example, we have seen the utility in having access to a precompiled listing of molecular substituents to aid in the conceptualization of molecular substitutions and additions that will improve the physicochemical properties of a compound of interest. Particularly compelling attributes are the ability to select substituents based on electron withdrawal simultaneously with their inherent lipophilicity. Furthermore, the annotation indicating whether a certain substituent has appeared in a clinical compound in the past gives added confidence that the resulting molecule will be drug-like.

Advanced Chemistry Development

90 Adelaide St. W., Suite 600
Toronto, Canada M5H 3V9

Tel: (416) 368-3435
Fax: (416) 368-5596
Toll Free: 1-800-304-3988

Email: info@acdlabs.com
www.acdlabs.com