Property-Based Design Methodology II: Assessing Elementary Substituents

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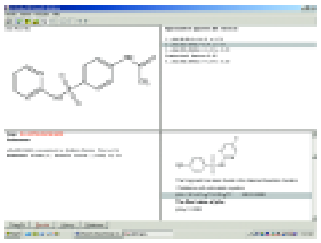
Abstract

Given the following working hypotheses for improving solubility within a medicinal chemistry series: increase ionization and reduce lipophilicity, one would like to ask the question: how can I change my compound to accomplish this? Specifically, how can I decrease the log*D* value at a specific pH? In this case study, we focus on design principals and software techniques that enable the chemist to design compounds with lower log*D*.

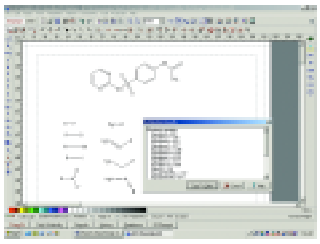
This series of posters develops an approach for addressing these questions using the drug acetyl sulfadiazine as an example. We illustrate the principles in action by considering a set of elementary substituents.

Step I: Understand the Structural Basis of pK_a



We begin by reviewing the calculation protocol for the pK_a as computed by ACD/pK_a DB. In this instance, you can see that the pK_a of the sulfonamide nitrogen is computed as 6.30, and that for this specific compound, a measured value of 6.34 has been reported in the literature. Furthermore, one can see that the acidity of such protons (with respect to substitution at the 3-position) is described by a Hammett Equation based on the inductive and resonant sigma constants, each with large negative coefficients. Therefore, we seek to identify substituents with large positive sigma constants for both inductive and resonant electron withdrawal. Recalling the relationship between intrinsic solubility and log*P*, we seek such electron withdrawing substituents that also do not significantly increase the lipophilicity of the compound.

Step 2: Review the Electronic Properties of Substituents



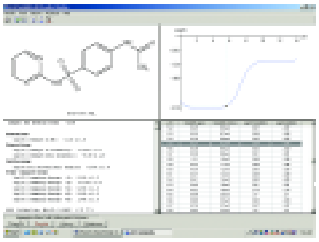
This figure shows a listing of potential substituents which are relatively simple. There are a variety of electron donating and withdrawing functional groups, also with a varying degree of lipophilicity. There are two ways in which to proceed with the selection of substituents: 1) by evaluating the appropriate sigma constants of each (as shown above for the methoxy substituent, or 2) by substituting the appropriate substituent on to the parent compound and evaluating pK_a, log*P*, and solubility.

R	σI	σR	π	Log*P*	pK_a
CH2N	0.12	-0.7	0.48	1.29	7.6
dioxolo				1.18	6.69
CH3CH2	-0.01	-0.14	0.99	1.4	6.7
CH3	-0.01	-0.16	0.46	0.87	6.76
CH3O	0.3	-0.58	-0.09	0.95	6.47
H	**0**	**0**	**0**	**0.41**	**6.3**
CF3	0.4	0.11	0.57	1.38	4.19
Cl	0.47	-0.25	0.59	1.23	4.83
I	0.4	-0.16	1.03	1.67	4.91
NO2	0.67	0.1	-0.27	0.74	3.01
Br	0.47	-0.25	0.77	1.41	4.83
F	0.54	-0.48	0.05	0.69	5.13

Here we look at the sigma and Pi properties of each substituent, as measures of the electron withdrawal and lipophilicity tendencies. From these values, we can see that aliphatic carbon chains provide no electron withdrawal and serve to increase the lipophilicity. Thus, in these compounds, such transformations will likely reduce the solubility. The halogen substituents, on the other hand, provide strong inductive electron withdrawal and a less intense resonant donation of electrons. Recall that the Hammett equation for this particular ionization centre depends more strongly on inductive mechanism (the coefficient was -4.5 vs. -2.2 for inductive sigma constants), and so these substituents achieve the goal of lowering the pK_a. However, the larger the substituent, the more lipophilicity it adds to the parent molecule. For this reason, in this particular situation, the fluorine substituent is the most favoured halogen substituent.

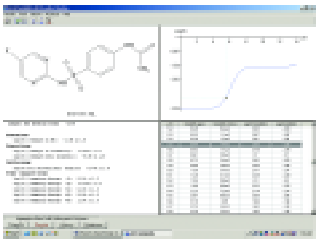
The nitro substituent has been included to illustrate an ideal physicochemical profile. In this case, both sigma parameters are positive, and the lipophilicity is marginal. Thus, despite concerns over potential toxicity due to the inclusion of a nitro-aromatic in the compound, it is likely to have the most favourable solubility.

Step 3: Review the Predicted Solubility Profile

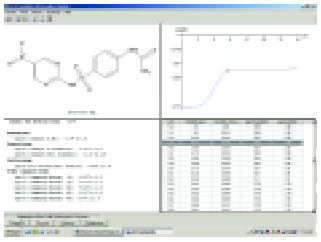


This figure shows the predicted solubility profile of the parent compound. In this example, we have designated the compound as a solid with an unspecified melting point. The experimental solubility at pH 5.5 was given as 263 μg/mL, and is reported by the prediction software as 260 μg/mL. Note that the solubility at pH 7.4 is much higher than at pH 5.5, due to the affect of ionization (the pK_a of the sulfonamide in this compound is 6.3).

Step 4: Assess the Predicted Impact of Substituents on Solubility



Here is the predicted pH profile of solubility for the fluoro-substituted compound. Note that the solubility is predicted to be increased to 440 μg/mL at pH 5.5. The graph makes it clear that this system begins to exploit the advantage of ionization in order to achieve improvements in solubility. Certainly at pH 7.4, the compound is nearly completely ionized and the solubility is much higher still.



The nitro substituted compound, with much lower pK_a, shows a solubility at pH 5.5, tenfold higher than the fluorine substituent, because of the strong affect it has on the pK_a. In this case, the compound is nearly completely ionized at pH 5.5.

R	Log*P*	pK_a	Sol(7.4)	Fion(7.4)	Sol(5.5)	Fion(5.5)
CH2N	1.29	7.6	95	39%	59	1%
dioxolo	1.18	6.69	380	84%	70	6%
CH3CH2	1.4	6.7	440	83%	81	6%
CH3	0.87	6.76	720	81%	150	5%
CH3O	0.95	6.47	1190	89%	150	10%
H	**0.41**	**6.3**	**2790**	**93%**	**270**	**14%**
CF3	1.38	4.19	3720	100%	700	95%
Cl	1.23	4.83	3870	100%	260	82%
I	1.67	4.91	5100	100%	320	80%
NO2	*0.74*	*3.01*	*5680*	*100%*	*4330*	*100%*
Br	1.41	4.83	6610	100%	450	82%
F	*0.69*	*5.13*	*8800*	*99%*	*440*	*70%*

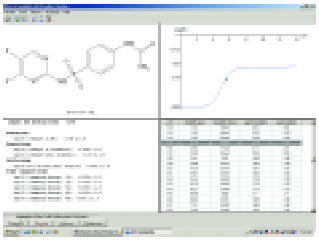
A summary of the predicted solubilities of the various compounds reported at two pHs and together with the log*P* and pK_a data. At pH 7.4, the most favoured substituent is fluorine, because it contributes the least lipophilicity among the compounds with near complete ionization at pH 7.4. At pH 5.5, however, it is only 70% ionized, and thus the solubility is inferior to the more electron withdrawing substituents CF_3 and NO_2.

Step 5: Consider Di-substitution

We only reviewed one point of substitution, though there are three open sites for attachment. Difluoro substitution will further reduce the pK_a, and add only marginal lipophilicity.

R	Log*P*	pK_a	Sol(7.4)	Fion(7.4)	Sol(5.5)	Fion(5.5)
H	0.41	6.3	2790	93%	270	14%
F	0.69	5.13	8800	99%	440	70%
di-F	0.86	3.99	8300	100%	2160	97%
NO2	0.74	3.01	5680	100%	4330	100%

In this di-substituted form of the compound, we have succeeded in nearly completely ionizing the compound at pH 5.5 without the introduction of the nitro-aromatic toxicophore. This compound is nearly an order of magnitude more soluble than the parent compound at pH 5.5, and about three-fold more soluble at pH 7.4.



Conclusion and Next Steps

We have been able to identify several substituents that are predicted to improve the aqueous solubility of the drug acetyl sulfadiazine. However, the nitro substitution may not be desirable, and so the chemist would like to be able to consult a listing of suitable substituents for his or her purpose. Additionally, the constraints of SAR on this compound may be such that substitutions are not feasible at this site. In this case, it would be best to limit the structural changes to replacement of the pyrimidine heterocycle with a more advantageous ring system.

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