Property-Based Design Methodology IV: Heterocycle Replacement

Robert DeWitte ACD/Labs, Toronto, ON, Canada

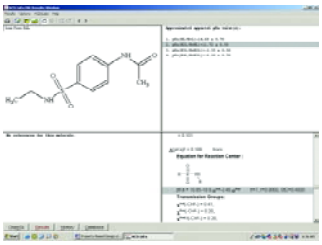
Fedor Gorohov, Eduard Kolovanov ACD/Labs, Moscow, Russian Federation

Abstract

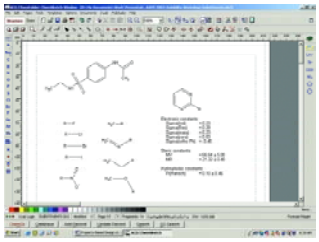
Often, such gross chemical modification as addition or replacement of a substituent is incompatible with SAR of a compound, due to the fact that specific shape or electrostatic complementarity has been well captured in the parent compound. In such a case, it is often difficult to design modifications to the chemical structure to reduce the log*D* of the compound at a specific pH. In this poster, we explore a methodology for identifying heterocycles, which, when used in the place of ring systems in the parent compound, will give compounds predicted to have improved physicochemical properties. The drug acetyl sulfadiazine is used as an example.

Step I: Review the Properties of the Parent Heterocycle

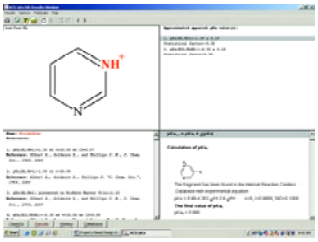
It is not always possible to change the overall shape of a compound, in which case one is limited to alterations within the molecular topology of the parent compound. If we review the acidity of the sulfonamide group in Acetyl Sulfadizine, with a view to replace the pyrimidine with another suitable heterocycle, we must first understand how the acid pK_a depends on the electronics of direct substitution. To do this, we draw an illustrative replacement of the pyrimidine group (ethyl in this case) that reveals a Hammett equation for the direct substitution adjacent to the Sulfonamide group:



From this we learn that Sigma inductive is the critical parameter and that substitutions with large positives values of this parameter will increase the acidity of the parent compound.
Next we explore the Sigma and Hansch parameters of the pyrimidine substituent ***using the same point of attachment as exploited in the parent compound.***

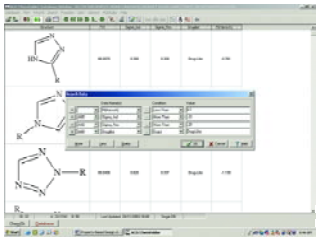


HWe will focus our search in the heterocycles database to identify ring systems with Sigma inductive > 0.23, Sigma Resonant > 0.29, and Pi < 0.1. Before this step, however, we should (for completion sake) compute the pK_as of the pyrimidine group.

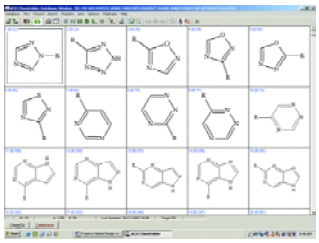


This confirms our intuition that pyrimidine is a very weak base, and therefore acts essentially as a neutral ring system throughout the GI tract.
We should limit our consideration of heterocycles to those that are also expected to remain neutral throughout the GI tract. (This can be done by reviewing and/or querying on the pK_a values included in the Heterocycles.CFD database.)

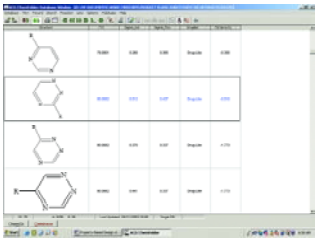
Step II: Identify Heterocycles with Suitable Properties



The database is queried for heterocycles with lower lipophilicity and higher electron withdrawal than pyrimidine, limiting the query to those that have been found in clinical compounds.

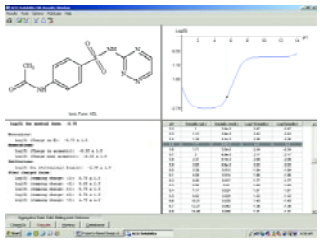


56 heterocycles fit the criteria. Note that four of them are also six member rings (this was identified by sorting on molecular weight).

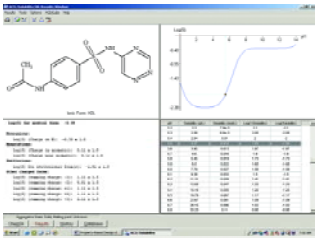


Among these, the 3-substituted 1,2,4-triazine has the optimal properties (recall the large negative coefficient for sigma inductive in the sulfonamide Hammett Equation). Note that triazine is also a very weak base, and therefore has the same acid/base properties as pyrimidine. The alternative attachment points of the triazine system are also worth consideration, however, though they are less electron withdrawing, they have much lower Pi constants, and are therefore expected to have a significantly lower log*P*.

Step III: Assess the Favoured Heterocycles



And here we see that a simple heterocycle substitution (amounting to the change of one atom from carbon to nitrogen) has been sufficient to increase the solubility at pH 5.5 six-fold from the parent compound. Note that the pK_a of this compound is not as low as we would like, and one can now consider further substitution of the new heterocycle with electron withdrawing substituents in order to further increase the solubility. Alternatively, one could abandon the pH-dependence, and use an alternative attachment point for the triazine in order to exploit its extremely low Pi constant.



IHere we see that the selection of the alternative point of attachment for the triazine heterocycle yields a solubility at pH 5.5 of 3.37 μg/mL, a factor of ten above the parent compound, and comparable to the original nitro substitution.

Conclusions

By considering the relationship between pK_a and the solubility at a certain pH, we were able to focus our attention on the choice of chemical modifications that would increase the fraction of compound ionized at pH 5.5. We examined an approach to heterocycle substitution that rapidly identified two alternative points of attachment on a 1,2,4-triazine system. Both were shown to be very effective at improving the solubility of the parent system with minimal impact on the overall topology of the compound. In fact, one of the points of attachment led to a much lower log*P* for the compound and resulted in ten-fold solubility increase (at pH 5.5) over the parent compound.

Through a combination of prediction, data, and calculation protocols, we were able to come to a working hypothesis for improving the aqueous solubility within a series of compounds related to acetyl sulfadiazine.

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