A Software-Aided Approach to Reducing the Synthetic Burdens of Lead Structure Optimization

Sanjivanjit K. Bhal, Karim Kassam, and Ed Kolovanov

ACD/Labs, Toronto, ON, Canada

Toll Free: 1-800-304-3988
Email: info@acdlabs.com
www.acdlabs.com

Advanced Chemistry Development

INTRODUCTION

The biological activity of a drug depends, among other factors, on its ability to reach the intended site of action. In many cases this occurs via passive transport that is modulated by the physicochemical properties of a compound: pK_a, log*P*, and solubility. These properties also have a direct influence on ADME (absorption, distribution, metabolism, elimination) characteristics, such as permeability and distribution.

Following the identification of a lead compound that displays activity and selectivity towards a target, the usual next step is optimization of that lead via slight structural modifications to improve or retain potency while simultaneously minimizing liabilities (ADME, toxicity). Achieving this "magic" balance of required properties for a compound to become a drug is a significant challenge. While not claiming to be a complete solution to the lead optimization process, ACD/Structure Design Suite is a software tool that significantly helps the medicinal chemist rapidly identify structural modifications to lead compounds (from a database of 30,000 substituents), that are expected to produce analogs with improved selected physicochemical properties. The chemist applies their knowledge of the pharmacaphore and physicochemical/ADME liabilities to quickly generate a manageable group of analogs with an improved pharmacokinetic profile, for synthesis.

To illustrate the software-aided optimization process, poor solubility, which is a ubiquitous problem encountered by scientists in drug discovery and development, will be used. Solubility issues can be complex, and often lead to excessive expenditure of money and scientific resources at the discovery and development stage, ultimately impacting the commercial viability of the drug.

Most drug substances are ionizable and their solubility profiles change according to the pH environment.[1]

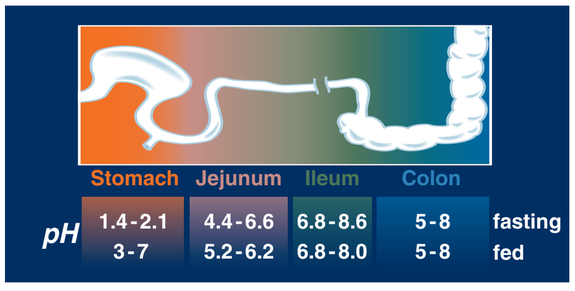


Figure 1 - pH profile of the human gastrointestinal (GI) tract.

Solubility is a function of two important physicochemical properties: pK_a and log*P*. The pK_a is a measure of the tendency of a substance to ionize, and log*P* a measure of its lipophilicity. Log*P* is of particular significance for substances without ionizable sites, or where dissociation is not relevant at the pH of interest. Due to the acid/base nature of most drugs, it is important that solubility be modified appropriately for the most relevant pH. Solubility of drugs intended for oral administration (preferred due to convenience and economics) should be optimized at a pH which is relevant to the site in the GI tract where the substance will absorb into the bloodstream; parenteral administration, however, requires attention to the pH of blood plasma (7.4). By aligning structural modification with enhancement of the appropriate physical properties at the relevant pH, it is possible to improve solubility of drug candidates in lead optimization.

1) Improving Solubility by Simultaneously Optimizing pK_a and Log*P*

In cases where an ionizable site exists, one can optimize solubility by simultaneously considering both lipophilicity (log*P*) and ionization (pK_a).

We can approach this challenge by making slight structural modifications to the lead compound via substituent addition or heterocyclic replacement. In this example, we will illustrate the latter. We will make the assumption that the pharmacaphore of the molecule has been identified and it does not include the pyrimidine ring. In order to retain the overall topology of the molecule, we will consider only replacement of the pyrimidine ring with structurally similar heterocycles.

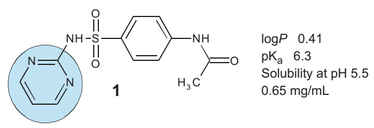


Figure 2 - Select physical properties of acetyl sulfadiazine.

1.1) Experimental Details

Structure Design Suite leverages the capabilities of our industry-standard physicochemical predictors for aqueous solubility, log*P*, log*D*, pK_a, and sigma (σ), as well as a database of 29,520 drug-like substituents. For this study, Structure Design Suite version 9.5 was used.

To prevent large structural modifications that may have detrimental effects on activity, the database was initially limited to six-membered rings that were within the molecular weight range 60-100 Daltons. Acetyl sulfadiazine was drawn and the pyrimidine ring selected for optimization of both pK_a (at pH 5.5) and log*P*.

This search resulted in 11 hits, from which the two candidates exhibiting dramatic solubility improvements were removed to avoid potential permeability problems, leaving 9 analogs to consider.

1.2) Results & Discussion

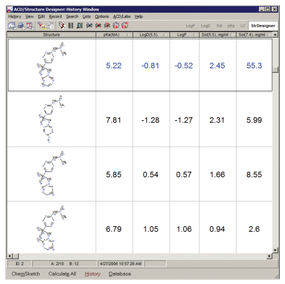


Figure 3 - Select analogs with predicted physicochemical properties—pK_a, log*D* (pH 5.5), log*P*, solubility in mg/mL(pH 5.5).

The (see Figure 3) results show how enhancement of solubility is a fine balance of the ability of a compound to ionize, and its lipophilicity.

The subtle change of one carbon atom in acetyl sulfadiazine (1) to nitrogen (replacement of pyrimidine with triazine) is enough to significantly increase solubility at pH 5.5 (hence improve bioavailability). There is a greater than three-fold increase, from 0.64 mg/mL to 2.45 mg/mL. This heterocycle replacement also retains the aromatic character and basicity of the substituent in the lead. Evaluation of the analogs for changes in other relevant physicochemical properties and ease of synthesis will focus synthetic efforts for the optimization of **1**.

It is important to note that log*D* values are key to this study. As acetyl sulfadiazine (and proposed analogs) dissociate, the composition of species in aqueous media changes according to pH. Log*D* at pH 5.5, therefore, is more relevant than log*P* of the neutral compound when analyzing the overall effect of modifying pK_a and lipophilicity for ionizable compounds.

2) Improving Solubility Using Only Log*P* Optimization

In therapeutic substances with no ionizable sites, solubility can only be optimized by adjusting lipophilicity (log*P*). This is demonstrated in the following example.

In the late 1990s, Pfizer brought Celebrex onto the market as a non-steroidal anti-inflammatory drug (NSAID). Limitations of this drug became the focus of continued lead optimization efforts, resulting in the introduction of Bextra.

The drawbacks of Celebrex, relating to its physicochemical properties, were that it was only moderately bioavailable, and had a non-linear pharmacokinetic profile due largely to poor aqueous solubility.[2] In Table 1, we see a direct correlation between the modification of log*P* and an improvement in solubility (and consequently bioavailability).

Table 2 - Select pharmacokinetic parameters of Celebrex and Bextra—calculated using ACD/Structure Design Suite (v9.0).

NSAID	Log*P*[a]	Solubility[a] (μg/mL)	Bioavailability (%)[2]
Celebrex	4.2	9	40
Bextra	1.7	76	83

Inspection of the structure of numerous Cox-2 inhibitors, including Celebrex, Bextra, and Vioxx indicates that all but the central 5-membered ring structure of should be conserved, and that the spatial arrangement of the two benzyl substituents should be preserved. For this reason, we began with Celebrex, and used ACD/Structure Design Suite to select alternative five-membered heterocycles that would preserve the overall architecture and provide improved solubility values.

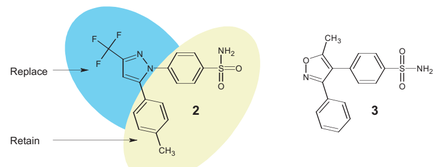


Figure 4 - Computational design approach for optimizing the physicochemical and pharmacokinetic properties of Celebrex (**2**), and structure of Bextra (**3**).

Since Celebrex does not have any ionizable sites, modifications are guided by log*P* only.

2.1) Experimental Details

A substructure search was initially carried out for a ring system similar to pyrazole, while allowing for other heteroatoms to replace nitrogen. This generated 217 hits. Celebrex was loaded into ACD/ChemSketch from ACD/Dictionary and the terminal methyl benzene ring was removed. From the remaining partial structure, pyrazole was selected as the fragment for optimization of solubility at pH 5.5. The software automatically recognized that the substructure did not have any ionizable sites and suggested log*P* as the only parameter that could be modified for this optimization, and set up the appropriate search query.

The original hit list of 92 suggested substituents was refined by limiting molecular weight (30-70 Daltons), which resulted in the generation of 6 analogs. Finally, the methyl-benzene fragment was reattached to the bicyclic substructure and the resulting analogs were analyzed.

2.2) Results & Discussion

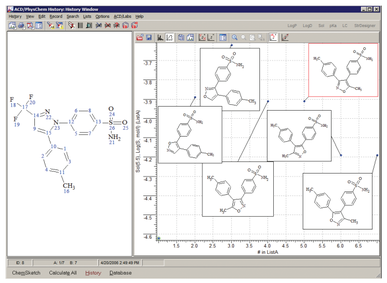


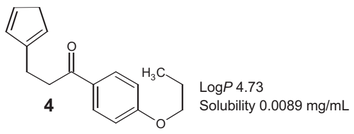
Figure 5 - Regression plot showing analogs of Celebrex (**2**) with improved solubility.

The six analogs proposed replaced pyrazole with an isoxazole ring system.

The structure outlined in red (Figure 5) is only one methyl group removed from Bextra, the drug presently on the market and the result of conventional lead optimization carried out on Celebrex. Again, evaluation of the proposed analogs for additional liabilities and synthetic feasibility, followed by synthesis and biological evaluation, would allow assessment of their therapeutic value.

3) Increasing Solubility by Optimizing pK_a

In the previous examples we showed how Structure Design Suite could be used to suggest heterocyclic replacements to improve solubility via optimization of lipophilicity. In cases where the lipophilicity cannot be adequately reduced, and when the pharmacaphore can tolerate additional substitution, solubility can be increased by addition of a substituent that contains an ionizable group. This approach will be highlighted in the following example. In a case such as the hypothetical lead compound 3-cyclopenta-1,4-dien-1-yl-1-(4-propoxyphenyl)propan-1-one (**4**), assumed to be delivered to the site of action via passive diffusion and administered by injection, we need improved solubility at pH 7.4 (the pH of blood).



3.1) Experimental Details

In this example, we make the assumption that the pharmacaphore has been identified and that its binding can tolerate substitution at the specific position. As in the last example, in order to avoid significant structural changes, the size of the suggested fragments was limited by molecular weight.

3.2) Results and Discussion

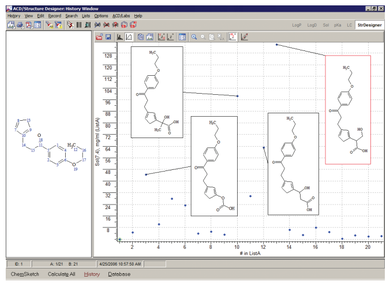


Figure 6 - Regression plot illustrating analogs of **4** with improved solubility.

20 fragments were identified, and analogs generated that are predicted to have improved aqueous solubility at pH 7.4 compared with the lead compound (**4**). 3-Hydroxy-2-{3-[3-oxo-3-(4propoxyphenyl)propyl]cyclopenta-1,3-dien-1-yl}propanoic acid (highlighted in Figure 6) shows a marked improvement with >100-fold increase in solubility (133.86 mg/mL).

CONCLUSION

Conventional structure-based design, biased to only improving efficacy, can be detrimental to physicochemical properties that influence ADME characteristics of a drug substance. Structure Design Suite permits a chemist to quickly design a diverse array of potential analogs, focused on improving critical physicochemical properties such as solubility. With options of further elaboration, heterocyclic replacement, or simple adaptation of existing substituents, the software allows for both subtle and drastic structural modification while preserving the identified pharmacaphore.

REFERENCES

1. B. A. Hendrickson et al., *AAPS Pharm. Sci.*, **2003**, 5.
2. *C&E News*, **2004**, vol. 82.
3. R. DeWitte, personal communication.