Optimising the Physicochemical Properties of Lead Compounds

A software tool has been developed to assist medicinal chemists in addressing the challenging task of optimising their lead compounds by relating structural modification to changes in physical properties.

By Sanjivanjit Bhal and Michel R.J. Hachey at Advanced Chemistry Development, Inc

Lead optimisation is a defining point in a drug discovery project. To this point, time and resources have been dedicated to virtual and in vitro screening to identify a chemical space that fits predefined project requirements. Requirements include affinity towards the target at dose responsive concentrations in the low (M range); freedom from intellectual property; chemical tractability; reasonable solubility in water (>100 µM); absence of acute cytotoxicity; and compliance with drug-likeness filters such as Lipinski’s ‘Rule of 5’ (1). While these help focus the project from millions of compounds to a manageable handful of well-characterised molecules, there is generally still room for improvement. The ultimate objective of lead optimisation is to make slightly modified analogues – using the same underlying criteria used in early lead discovery – that will ultimately provide drug candidates with more realistic chances of completing development (see Figure 1).

In lead optimisation, scientists strive to simultaneously improve potency and drug-like properties of a lead compound while minimising liabilities. Off-target activity is curtailed to avoid side effects, and the physicochemical and metabolic properties are driven toward reasonable in vivo pharmacokinetics (PK), pharmacodynamics (PD), and absorption, distribution, metabolism and excretion (ADME) values. Optimisation is carried out through empirical (trial-and-error) modification of the structure, and/or using structure-based design when sufficient information is available. Usually, improvement efforts are focused on one parameter at a time. It is important, however, that the comprehensive suitability of a compound as a drug be respected. This can be trickier for purely trial-and-error approaches, where structure-activity relationships are more easily explored one parameter at a time, leading to many syntheses to investigate each individual concern.

Focusing on Physicochemical Properties

Traditionally, the primary area of focus for lead optimisation was for achieving the best efficacy and selectivity. The remainder – toxicological and ADME parameters – were generally considered later in discovery, sometimes not until early development. But with approximately 50% of drug candidates being rejected due to poor physicochemical properties, and 30% of this occurring during development, the expense of late attrition is unacceptable. To prevent this, criteria that were studied later are now considered in parallel with potency optimisation. Figure 2 illustrates the main acceptability criteria classes.

A particularly important prerequisite for the effectiveness of therapeutic agents is that they must reach the target site. A compound with excellent efficacy and selectivity in a test tube is worthless as a drug if it offers no viable mechanisms to deliver itself to the site of action in a patient. Fortunately, designing a compound to be amenable to passive transport is achievable because in vivo behaviour is guided – in large part – by predicted and measured biological testing.

Physical properties

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physicochemical properties such as logP, logD, pK, and solubility. These properties play a critical role toward attaining other favourable PK/PD and ADME characteristics. For example, pK influences metabolite formation, lipophilicity (logP, logD) is a key factor in blood brain barrier penetration and solubility contributes significantly to bioavailability.

We need not look far into the past to discover an example where property optimisation was used to overcome therapeutic problems. In the late 1990s, Pfizer introduced the first COX-2 inhibitor, Celebrex – a non-steroidal anti-inflammatory drug (NSAID). This drug showed moderate bioavailability and non-linear pharmacokinetics due largely to poor aqueous solubility. It therefore became the focus of continued lead optimisation efforts. Bextra, a second generation NSAID that showed an improved physicochemical profile compared with Celebrex, was the result of this effort. Figure 3 shows a limited physical property profile of the two drugs (2). Subsequent unrelated side-effects of Bextra, although unfortunate, do not detract from the science behind producing a better therapeutic (by physicochemical improvements) with a patient-friendly dosing regime.

LIMITATIONS OF CONVENTIONAL STRATEGIES

The synthetic work undertaken by medicinal chemists is guided in part by the assistance of a broader team of biochemists and discovery support workers, such as computational chemists and PK/PD groups. These experts work with the medicinal chemist to help design suitable analogues, test for activity and selectivity using in vitro assays, measure physicochemical properties, and quantify liabilities and overall improvements. While this team is capable of determining which properties and liabilities should be optimised, they can rarely provide information about how to achieve the desired optimised properties.

Computational chemists utilise modelling tools – such as docking and pharmacophores – to optimise potency, and do not necessarily consider the impact of these modifications on the physicochemical property profile. Experts specialised in the prediction of toxicity and metabolites may provide specific suggestions as to what to avoid, but generally leave the chemists to their own devices as to what modification is appropriate toward maintaining drug-likeness. Computational and physical property experts use sophisticated property prediction software to learn about permeability, distribution and bioavailability of compounds, but these are generally employed in screening and do not suggest viable modifications. In other words, while all these support groups provide invaluable expertise, translating this information into specific structural modifications can still be challenging.

Within the confines of available PK/PD information, medicinal chemists must still rely on their experience and knowledge to determine optimum structural modifications, especially since synthetic feasibility is a significant limiting factor. Overall, the chemist receives either predicted or measured property values from experts, along with a list of pre-set criteria that must be met by the next generation of compounds. Because the relationship between the number and structural elements of the analogue are often unclear, two problems occur: the extent to which a proposed modification will change a property is not always what the chemist anticipates; and modifications that are made to improve a particular liability, like efficacy, often create an imbalance elsewhere. In order to avoid shifting from one problem area to the next, it is necessary to conform to a broad set of criteria at once.

For example, poor solubility is a ubiquitous problem in drug discovery. Solubility can be modified by increasing the ionisability of the compound (by adding groups that ionise, or modifying them to maximise ionisation at a relevant pH), and/or decreasing lipophilicity. Herein lies the conflict – lipophilicity and solubility must be delicately balanced to achieve an optimal property profile. On the one hand, poor solubility compromises the bioavailability and distribution of a compound. If an adequate concentration cannot be maintained in blood, the drug cannot be effective, or extremely large doses must be used leading to possible side effects. On the other hand, increasing aqueous solubility reduces lipophilicity. This can lead to difficulties in penetrating biological barriers and poor permeability. Predictive software that could suggest modifications to improve solubility in a measured way in the context of the full property profile would allow chemists to pick from a list those targets that are synthetically feasible. With feedback about how a structural modification relates to other physicochemical properties, chemists are less likely to run experiments that produce imbalance.

TOOLS FOR MEDICINAL CHEMISTS

While a handful of software companies have provided some solutions specifically for medicinal chemists, the majority do not address property-based lead optimisation directly. Having spent 10 years developing and refining property prediction algorithms for computational experts and physical chemists, ACD/Labs has collaboratively developed an application for synthetic/medicinal chemists. The
ACD/Structure Design Suite (SDS) (3) extends physicochemical property prediction software from the realm of the expert to make it accessible to medicinal chemists. It combines predictors with a database of substituents and a helpful wizard-driven interface. Using literature expertise of common modifications made by chemists, and applying pre-defined rules linking physicochemical properties with structural elements, the system quickly proposes analogues that are rationally designed to improve physicochemical properties (logP, logD, pKa, and solubility). The proposed structural modifications give the medicinal chemist guidance towards promising analogues within a broader chemical space than individual experience may allow. Computational experts can improve the accuracy of property predictors to better reflect experimental data collected in-house on proprietary compounds. SDS allows the medicinal chemistry team to prioritise and plan their synthetic efforts based on physical properties without the pre-requisite of expertise in statistics, quantum theory, and complex computational tools.

By allowing optimisation of the target physical property, SDS software provides the full physicochemical profile for the generated analogues (polar surface area, Lipinski’s Rule of 5 violations, molecular weight, logP/logD, solubility, and so on). Additionally, graphing tools are provided that allow results to be plotted versus the full array of molecular physical properties. This allows analogues with extreme and unbalanced profiles to be removed. While the true impact of such software can only be gauged in the research environment, we can assess its effectiveness to a point through analysis of previous research.

**REDUCING UNWANTED CNS ACTIVITY**

A historical case study of the optimisation of logP to reduce central nervous system (CNS)-related side effects in a lead compound is well documented in the discovery of Sulmazole – a cardiotonic drug used in the treatment of congestive heart failure.

In the original study, 2-(2-dimethoxyphenyl)-1H-imidazo[4,5-b]pyridine made it through discovery and development to clinical trials in humans. It was then found that although the compound was effective as a cardiotonic agent, some patients reported seeing bright flashes. This is a side effect indicative of CNS activity caused by an agent, some patients reported seeing bright flashes. This is a side effect indicative of CNS activity caused by the compound, and retained the desired cardiotonic activity.

Using the Structure Design Suite software, we targeted the 4-methoxy substituent of 2-(2-dimethoxyphenyl)-1H-imidazo[4,5-b]pyridine for replacement by a fragment (of similar molecular weight 50-70g/mol) that would yield a decrease in logP. The software returned 25 analogues predicted to have logP < 2. Although the therapeutic significance of these cannot be evaluated without synthesis and biological evaluation, we are confident that the results are worthy of consideration. Firstly, Sulmazole (the drug developed as a result of the research of Kutter and Austel) is among the suggestions. Secondly, observed accuracy of physicochemical predictions is sufficiently good to give a high degree of confidence that the predicted lowering of logP would indeed be observed experimentally. This investigative work to find alternative analogues to the lead compound was completed in less than an hour. In a high pressure research environment, this leaves more time for synthesis and evaluation of results.

**CONCLUSION**

The uncertain climate of today’s pharmaceutical industry demands that scientists become more efficient and increase productivity to remain competitive and minimise the costs associated with developing a drug. Empirical lead optimisation – where there is deep focus on a single criterion and a handful of compounds – can be disastrous, leading to late stage failures. Since many of these failures are attributed to poor physicochemical properties, it is desirable to consider these at the earliest possible stage in the lead optimisation process. ACD/Structure Design Suite has been developed specifically to assist medicinal chemists in evaluating these complex properties and helping to directly relate structural modification with property values that define the in vivo behaviour of compounds. An added advantage of this approach is that fewer syntheses should be required to achieve one’s objectives. Greater efficiency at reaching the drug candidate in which potency and physical parameters have been simultaneously optimised will also reduce some of the problems encountered in development.

The authors can be contacted at michel@acdlabs.com and sanji.bhal@acdlabs.com

**References**