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EDITORIAL

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Is there enough focus on lipophilicity in drug discovery?

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1. Introduction

Drug discovery is an expensive and prolonged process with a new drug molecule requiring approximately 12–15 years of development and an estimated $2.6 billion to reach the market as an effective therapeutic agent [1]. In part, increases in out-of-pocket expenses and higher attrition rates for drugs tested in humans have accounted for the rising drug development costs with seven out of eight compounds that enter clinical testing failing in development [1]. Efficacy and toxicity have become major contributors to the overall compound related attrition. As a result, many companies are focusing on compound properties early in preclinical development as a way to mitigate more expensive clinical failures at a later stage.

The idea that greater *in vitro* potency will lead to a more effective therapeutic is often embedded in early drug discovery schemes; however, to be a successful drug candidate careful attention to physicochemical properties can improve the likelihood for efficient delivery and therapeutic success [2]. Lipophilicity, expressed as the logarithm of *n*-octanol partition coefficient (log P), has long been recognized as a predictor of a drug's successful passage through clinical development to the marketplace. Lipophilicity contributes to the ADMET (absorption, distribution, metabolism, excretion, and toxicity) characteristics of drugs by influencing their pharmacokinetic, pharmacodynamic, and toxicological profiles. Increasing evidence suggests that monitoring lipophilicity may contribute significantly to the overall quality of candidate drugs at different stages of discovery and to reduced attrition; thus, a greater focus on lipophilicity, controlled within a defined optimal range, is warranted.

2. Lipophilicity and drug development

Lipophilicity reflects the affinity of a molecule for an aqueous or lipophilic environment and can be used to predict the ability of molecules to cross cell membranes and bind to proteins, which are mostly hydrophobic in nature. Lipophilicity is measured using log *P*, which is defined as the logarithm of solute concentration in octanol over unionized solute concentration in water, or log *D*, the distribution coefficient in octanol-water at a specific pH. In practice, the calculated log *P* (clog *P*) is often used instead of the measured log *P* as an assessment of lipophilicity, with measured partition coefficients obtained on key compounds through a project's progression. Since clog *P* values used for screening virtual libraries are often inaccurate, this can lead to imprecise results that cause promising compounds to be abandoned and/or flawed compounds to move forward [3,4]. Comparisons made between marketed oral drugs and compounds in earlier stages of development indicate that log P values beyond Lipinksi's rule-of-five criteria (>5) are associated with undesired drug features, such as rapid metabolic turnover, poor aqueous solubility, high plasma protein binding, and tissue accumulation. There is also an increased likelihood of *in vitro* receptor promiscuity and *in vivo* toxicity if lipophilicity is too high; while a drug will generally display poor ADMET properties if lipophilicity is too low [5].

Despite the fact that there has been low variance of lipophilicity for approved oral drugs in the last 30 years, there continues to be a noted trend that lipophilicity is increasing along optimization paths [6,7]. This undesired shift is a major factor for the well documented inflation of physicochemical properties of drugs in most medicinal programs and is attributed to the intrinsic biology of the target, considerations of risk/benefit, and varied drug discovery practices [5]. In a study that compared the physicochemical profiles of marketed drugs, clinical candidates, and compounds disclosed in the patent literature from 2001 to 2007, Leeson and Springthorpe demonstrated that the physicochemical properties of molecules in pharmaceutical patents were diverging from those of successful drugs and tended to be larger and more lipophilic than marketed drugs (median MW of 450 Da and clog *P* of 4.1) [8]. A similar trend was observed for compounds appearing in the *Journal of Medicinal Chemistry* between 1959 and 2009, which Walters et al. noted had become larger and more lipophilic than marketed drugs over time [7]. In a study by Gleeson that analyzed ADMET and physicochemical data from a diverse set of GSK compounds, MW and clog *P* were identified as key drivers for predicting potential ADMET problems; thus, he concluded that compounds with log $P < 4$ (and a MW < 400) stand a much higher chance of success against a comprehensive set of ADMET parameters [9]. Indeed, the lowest risk for adverse toxicity outcomes and optimal ADME properties are expected if a compound's lipophilicity at pH = 7.4 lies in a log *D* range between ~1 and 3 [10] or a log *P* between 2 and 4 [11].

The idea that control of physicochemical properties like lipophilicity during compound optimization is beneficial has

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been reaffirmed in a recent study by Waring et al. Combined data from four major pharmaceutical companies between 2000 and 2010 were compiled to identify the causes of attrition of drug candidates and assess potential links to their physicochemical properties [12]. Overall, the four companies identified a total of 812 oral development compounds, of which 422 had not progressed into clinical studies, 231 were in Phase I, 145 had progressed to Phase II, 8 to Phase III, and 2 to Phase IV. Non-clinical toxicology was the highest cause of attrition among the 605 terminated compounds, accounting for 40% of the failures and most often occurring in the preclinical phase. Clinical safety failures were prominent in Phase I as well as Phase II, suggesting that it remains a key area for improvement. With regard to physicochemical descriptors, the compounds had a mean molecular mass of 443 Da and a mean clog *P* of 3.2, falling within the expected and desirable ranges for these properties. However, when these compounds were compared to marketed drugs and to those compounds published in patent applications by the four pharmaceutical companies during a similar period [5], the mean molecular mass of marketed drugs was significantly lower (396 Da); further, clog *P* showed significant downward trends from compounds in patent applications to drug candidates to launched drugs (clog *P* = 3.6, 3.2, 2.8), indicating that there is greater attrition for more lipophilic compounds in both discovery and development. Clinical safety attrition was assessed by comparing the compounds failing to show clinical safety in Phase I with compounds successfully reaching Phase II. Notably, there was a statistically significant difference between the mean clog *P* values of compounds failing due to clinical safety (3.8) compared to those progressing (3.1); yet, the same trend did not occur in analysis of the preclinical toxicology data. Importantly, these findings reinforce the need to continue to control lipophilicity and suggest a new and important link between lipophilicity and clinical failure due to safety issues [12].

Control of lipophilicity during compound optimization can be accomplished using lipophilic efficiency indices. Ligand lipophilicity efficiency, defined as LLE = pIC_{50}–log *P*, can be used to evaluate the quality of research compounds, linking potency, and lipophilicity in an attempt to estimate drug-likeness [8]. The optimal target range for LLE is generally considered to be between 5 and 7 and can be applied during optimization to identify improved leads [13]. The ligand efficiency-dependent lipophilicity index (LELP), defined as the ratio of log *P* and ligand efficiency (LE), combines lipophilicity, molecular size, and potency into one descriptor and allows both fragments and lead-like and drug-like compounds to be evaluated [14]. LELP is negative only when log *P* is negative and thus the higher the LELP score, the less drug-like the compound. In a study by Tarcsay et al. that assessed these indices, both helped to identify compounds of better quality with regard to ADME, binding thermodynamics, and safety properties; however, LLE was deemed more applicable in the later development stages, while LELP was more practical for ADME- and safety-related issues [15]. Overall, application of lipophilic efficiency metrics like LLE and LELP during optimization could help identify improved drug candidates.

3. Expert opinion

Despite the fact that the average lipophilicity value has changed little for approved oral drugs over the past few decades, patents from 18 pharmaceutical companies during 2000–2011 indicate that most companies are working with more lipophilic molecules [16]. This shift toward increased lipophilicity has been observed in compounds failing due to clinical safety in Phase I compared to those progressing to Phase II [12]. The inflation of physicochemical properties in most medicinal programs is attributed to a variety of causes, including diversity of new target biology, risk/benefit, and varied drug discovery practices [17]. Thus, it appears that drug design practices have drifted away from a focus on optimized design based on physicochemical parameters, like optimal lipophilicity, that have stood the test of time and are characteristic of approved oral drugs. Accordingly, greater focus on drug design practices to reflect optimal lipophilicity profiles during lead optimization is warranted.

A key challenge for successful drug discovery is finding a balance between the constraints on the physicochemical properties of drug candidates and maintaining adequate potency to provide an effective dose. Monitoring of lipophilic efficiency metrics like LLE and LELP could help to improve the overall quality of candidate drugs by controlling physiochemical parameters, especially log *P* or log *D*, while maintaining compound potency throughout optimization. Additionally, log *P* should be experimentally evaluated for a representative set of compounds in order to predict log *P* for a given chemical series. This can be accomplished using chromatographic techniques such as reversed-phase high performance liquid chromatography [3,4]. The use of confidence in log *P* prediction would allow higher resolution and discrimination with regard to selection of reliable and non-reliable predictions, thus increasing design efficiency. Although there is a heightened awareness of the importance of lipophilicity of a drug candidate to its long-term success, the integration of multiple parameters into drug design will be essential if improved molecules with greater potential to succeed are to be identified. Indeed, lipophilicity is one of the key molecular properties to address in early stages of drug design to increase chances of selection of compounds that would not fail in development because of poor ADMET characteristics; thus, improving the likelihood of therapeutic success.

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