The traditional physical-property-based argument for drug attrition is developed and extended to one that incorporates drug–transporter interactions. A new algorithm is proposed that facilitates the evaluation of this hybrid property space.

A new paradigm for navigating compound property related drug attrition

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Improving the efficiency of drug discovery remains a major focus for the pharmaceutical industry. Toxicity accounts for 90% of withdrawals and major early-stage terminations relate to suboptimal efficacy and safety. Traditional oral drug space is well defined with respect to physicochemical Q3 **properties and ADMET risks but increased focus on ligand-lipophilicity efficiency, maximizing enthalpy contributions and new target classes challenge this paradigm. A hybrid space has been identified that combines physical properties and key interactions attributable to drug transporters. A novel algorithm is proposed that incorporates drug–transporter interactions and its utility evaluated against popular ligand efficiency indices. Simply reducing the bulk properties of compounds can exchange one problem for another and creates high-risk areas that challenge the successful delivery from a balanced portfolio.**

Introduction

Q4 Recent statistics indicate that the well-documented challenges facing the pharmaceutical industry continue with rising costs and attrition together with increased pressure from regulators and payors being major contributors [1–4]. For over a decade now, companies have rightly focused on Q5 compound properties to stem ADMET-related attrition and increase the likelihood of candidates surviving early toxicity assessment, progressing into humans and ideally achieving appropriate exposure. The latter should not only be viewed from the systemic circulation but also at the target tissue for efficacy without paying the penalty at tissues associated with (often) off-target safety concerns.

Clearly, intrinsic drug affinity at desired or nondesired (potentially toxic) targets is governed by a combination of bulk physicochemical properties [5] and specific structural features for example Q6 basic pK_a for hERG [6,7], phospholipidosis (PLD) inducers [8], structural motifs for reactive metabolites [9,10] and transporter interactions such as with the bile salt excretory pump (BSEP) [11]. Nevertheless, sufficient exposure at the target tissue will still be required in addition to inherent affinity. Optimizing the exposure of potent compounds at the desired site of action and in tissues associated with toxicity is fundamental to addressing attrition via efficacy and safety

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[12,13]. In turn, key determinants of drug exposure are the molecular properties of the drug candidate [14–16]. The overarching goal therefore remains to achieve good pharmacokinetics and optimized exposure from a modest dose often preferring the oral route. Therefore, an enhanced understanding of the interplay between molecular structure and exposure remains paramount to successful drug discovery and we move to a paradigm based upon 'design better, develop faster and succeed more often' from the rather uninspiring but often quoted mantra of 'fail fast and fail cheap'.

Drug-like metrics: rules and indices

Emphasis has therefore been placed on defining a series of rules and indices for compounds at various stages of preclinical development. It is important to distinguish between efficiency metrics that incorporate the affinity of compounds for their targets from more-generic drug-like properties. The term drug-likeness is applied in drug discovery to identify virtual or real molecules that occupy what is considered to be drug-like chemical space, based on physicochemical properties [17–19]. Often this entails examining the calculated physicochemical properties of molecules and favoring those found in marketed drug molecules or clinical candidates. It is now widely accepted that drug-like compounds tend to demonstrate certain favorable ADMET properties such as aqueous solubility and cell permeability. One approach is to use property cutoff filters above which compounds fail, for example the now famous Rule of Five (Ro5) [20].

Clearly, the value of these filters depends on the method used for their calculation and their associated errors [21]. Nevertheless, this concept and resulting rules have gained popularity as a result of their simplicity; they are easy to interpret and the molecular properties on which they rely can be readily calculated and it is easy to identify compounds that meet or fail the criteria and to develop optimization strategies. The underlying rationale is to increase the probability of designing, prioritizing and thereby developing compounds with an acceptable ADMET profile and to minimize property space that is sparsely populated with marketed drugs (exception space). Precedence for the success of the latter group is rare and would be exceptional [22].

Recognition of the property inflation or molecular obesity associated with compound progression has led to more rigorous rules or filters, for example Rule of Four for leads [23] and the Rule of Three for fragment-based lead generation [24]. However, their specificity can be poor and concern has also been expressed that these rules or indices should not be seen as hard cutoffs but rather guidelines given the errors in their measurement [25,26], and that application of multiparametric optimization methods would add considerable insight and benefit [27,28]. Moreover, several valuable therapeutic discoveries lie in chemical space beyond typical oral drug space – so-termed exception or beyond the Ro5 (bRo5) space [22].

It can therefore be concluded that adopting the rules for drug-like properties biases the odds in favor of finding a successful compound, but applying these rules as rigid filters runs the risk of rejecting valuable compounds. Consequently, several groups have cautioned that such assessment should go beyond such simple rules. The introduction of the term ligand efficiency (LE) was the first of several expressions that have recognized the importance of combining physicochemical properties and potency at the intended target [29,30]. A comprehensive review of the development of these metrics or indices is beyond the scope of this work. The interested reader is directed to Fig. 1, which provides the chronology of major developments in this area.

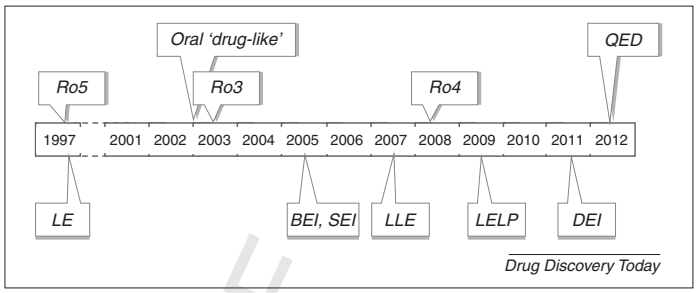

FIGURE 1

Schematic timeline illustrating major developments of generic drug-like properties (above timeline) and efficiency metrics (below timeline). Rule of Five (Ro5) [20], ligand efficiency (LE) [59], oral drug-like [15,49], Rule of Three (Ro3) [60], binding efficiency indices (BEI) [49], surface efficiency indices (SEI) [49], ligand-lipophilicity efficiency (LLE) [29,30], Rule of Four (Ro4) [23], lipophilicity-corrected ligand efficiency (LELP) [61], drug efficiency index (DEI) [62], quantitative estimate of drug likeness (QED) [25].

Analysis of historical oral marketed drug data might not be reflective of future trends in preclinical drug discovery because increasingly different approaches are adopted particularly for target engagement. These include optimization of receptor kinetics through consideration of enthalpy binding [31], novel target classes [32,33], allosteric modulators [34] and targeting novel signaling pathways such as β-arrestin [35]. These relatively recent approaches could yield compounds with a physical property distribution distinct from that previously observed and characterized. If this is coupled to classical strategies for the optimization of ADMET properties using traditional methodologies with established compound collections, vigilance and the early identification of chemical space which could deviate from our previous experience is paramount. Maintaining compound properties that are based on historical drugs while targeting novel mechanisms for efficacy might not serve the industry well. Therefore we need to be able to respond rapidly to an ever-changing concept of what constitutes drug-like space.

Compound properties and their relation to attrition

A recent study by Pfizer [36] reported an analysis of compound attrition resulting from preclinical toxicity in rat demonstrated an increased likelihood of failure if compounds were basic and had $\log P > 3$, PSA < 75 Å^2. One interpretation of these findings would be that lipophilic, relatively promiscuous compounds with little polar functionality tend to have an increased incidence of toxicity. A similar finding was also reported around this time for a range of veterinary drugs [37] and reports have indicated the importance of lipophilicity in hepatotoxicity with a $\log P > 3$ being suggested as a threshold, together with considerations of total daily dose. A similar analysis by AstraZeneca [38] on their compound failures revealed a different profile, with the majority of attrition occurring with PSA > 75 Å^2 and $\log P < 3$. Although attrition in the high-log *P*–low-PSA space can readily be rationalized via consideration of promiscuity and interactions across a range of systems [30], the

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