Fraction Lipophilicity Index (FLI): A Metric for Assessing Oral Drug-Likeness of Ionizable Chemical Entities

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ABSTRACT

Fraction lipophilicity index (FLI) was developed as a metric for assessing oral drug likeness of ionizable chemical entities, as a weighted combination of $\log P$ and $\log D$ according to equation: $\text{FLI} = 2\log P - \log D$. The dataset included basic and acidic oral drugs introduced worldwide from 1994-2013. Using MedChemDesigner for logP and logD calculations, a drug-like FLI range of 1-8 is defined, whereas ClogP leads to a broader FLI(C) range of 1-10. A comparison of FLI with Rule of 5 showed that oral drugs with a two fold violation were well accommodated within the specified FLI ranges. Calculations of FLI and FLI(C) for 41 drugs with poor/moderately absorption showed that 40% of them have values outside the suggested drug-like ranges, while a distinct gap in the FLI and FLI(C) space permits the recommendation of ‘safer’ ranges: for bases between 5-8 and 5-10 for FLI and FLI(C), respectively, and for acids between 4-7. Application of FLI to a test set of investigational compounds placed all of them within the drug-like FLI/FLI(C) range, while discriminating two out of three low permeable molecules.

KEYWORDS

Acidic Drugs, Basic Drugs, Drug-Likeness, Fraction Lipophilicity Index, Oral Absorption, Rule of 5

1. INTRODUCTION

The evolution in synthetic possibilities and biological testing has exponentially increased the amount of experimental data and the rate of screening of compound libraries to identify new leads in pharmaceutical industry (Hertzberg and Pope, 2000). However, despite the advances of new technologies, drug development is still struggling against high attrition rates and rising costs, even up to as much as $11$ billion (Gunn and Rabiner, 2014), while more than ten years of intensive efforts are needed (Kola and Landis, 2004). Therefore, it is in a medicinal chemist’s best interests to seed out non-drug-like molecules as early as possible in the drug development pipeline in order to discover new and safer drugs more efficiently. In this respect, the establishment of simple rules, or metrics, based on one or more physicochemical properties, easily calculated at the early preclinical stages, was brought forth to identify drug-like molecules from a vastly expanding chemical space (Ursu et al, 2011; Zhang, 2012; Ritchie and Macdonald, 2014). Lipinski’s Rule of Five (Ro5) was the first among such metrics to be applied for compounds intended for oral administration (Lipinski et al, 1997). It suggests upper limits for four molecular properties, which include molecular weight ($M_w < 500$), lipophilicity ($c\log P < 5$), counts of hydrogen bond donor (HBD<5) and acceptor sites (HBA < 10).

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Compounds violating more than two of the Ro5 conditions are prone to gastrointestinal absorption problems (Lipinski et al., 1997). The Ro5 was followed by Jhoti’s Rule of Three (Ro3), which is based on the same properties and defines lead-likeness, applicable in particular for fragment-based drug design (Congreve et al., 2003). The drug-likeness concept was further expanded to include additional properties, the most common being: polar surface area (PSA) (<140), number of rotatable bonds (<10), molar refractivity (40–130), number of aromatic rings (<3), total number of atoms (20–70) (Veber et al., 2002; Oprea, 2002; Ritchie and Macdonald, 2009; Yusof and Segall, 2013).

Molecular size and lipophilicity were also used to normalize affinity, in order to avoid molecular obesity. Thus, small and less lipophilic molecules get prioritized. Ligand efficiency (LE) and lipophilic ligand efficiency (LLE) are the most popular among such metrics (Hopkins et al., 2004; Hopkins et al., 2014). The involvement of lipophilicity in most of the above metrics is in accordance with the minimum hydrophobicity concept formulated already in 1987 by Hansch et al. (Hansch et al., 1987). High lipophilicity can result in non-specific binding and has been associated with drug promiscuity, and thereupon side effects, as well as with accumulation in the organism and toxicity.

As imprinted in the above-mentioned metrics, it becomes evident that during drug development lipophilic compounds may face difficulties with both oral absorption and pharmacodynamic/toxicity aspects. However, for oral absorption, the pH-partition hypothesis dictates that, next to lipophilicity, which is the driving force for membrane permeability, ionization is also a key issue. For this reason, the Ro5 has received noteworthy criticism for ignoring the ionization degree of a molecule, and it often fails in the case of ionizable compounds (Martin, 2005; Vistoli et al., 2008). To face ionization, an optimum range between 1-3 has been proposed for log $D$ at physiological pH (Comer, 2003), while Waring established lower limits for log $D_{7.4}$ in a molecular weight dependent manner (Waring, 2009). It should be noted that the above suggestions underestimate the role of intrinsic lipophilicity of the neutral species. However, considering the dual nature of lipophilicity as the outcome of hydrophobicity minus polarity, in Waring’s approach the reference to molecular weight indirectly addresses the hydrophobicity component, which is related to the bulk and size of the molecule (Testa et al., 1996; Tsopelas et al., 2017).

In the present work we developed Fraction Lipophilicity Index (FLI), a new metric for assessing oral drug-likeness of ionizable chemical entities by weighted combination of both log $P$ and log $D$, considering that the two measures have a distinct role to play.

### 2. THEORETICAL BACKGROUND

Lipophilicity is conventionally expressed as the logarithm of the partition coefficient (log $P$), a measure which refers to the concentration ratio of the neutral species in equilibrium between octanol and water. In the case of ionizable compounds, the distribution coefficient (log $D$) is considered, which takes into account the intrinsic lipophilicity of the different species present (i.e. both neutral and ionized) and their relative concentrations. At a given pH, the log $D$ of an ionizable compound can thus be defined by Equation (1):

$$
log D = log f^{-N} P^N + \sum(f^I P^I)
$$

(1)

where $f^N$ and $f^I$ are the respective fractions of the neutral and ionized forms, which themselves are a function of pH and $pK_a$; $P^N$ and $P^I$ are the partition coefficients of the neutral and ionized species, respectively (Pagliara et al., 1997). In fact, the partitioning of the ionized species occurs in the relatively large amount of saturation water present in wet octanol or upon formation of partially neutralized ion pairs (Tsantili-Kakoulidou et al., 1997; Avdeef, 2003). Nevertheless, $P^I$ is very small in respect to $P^N$ (2-5 log units lower) and can be practically neglected; thus eq 1 is simplified to Equation (2) (Pagliara et al., 1997):
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