

three decades, indicating that they are important properties of oral drugs; in contrast, the number of O and N atoms, H-bond acceptors (HBA), rotatable bonds, molecular weight (MW), and number of rings increased in drugs between 1983 and 2002. Physicochemical properties determine important drug parameters like solubility, permeability, metabolic stability, transporter effects, and protein binding. These fundamental properties dictate oral bioavailability and exposure at the physiological site of action. The drug-likeness terminology, therefore, can be understood as a way to relate physicochemical properties to ADME and toxicological (ADME-T) properties and pharmacological profile. Drug-like properties are intrinsic molecular properties and simultaneous optimization of physicochemical properties along with pharmacological properties is critical to success in drug discovery.

During the multidimensional optimization process, the medicinal chemist needs methods to monitor the progress, as well as get feedback from the iterative learning process, of establishing the structure–activity relationships (SAR). The concepts of ligand efficiency (LE) and lipophilic ligand efficiency (LLE) are introduced in this chapter as simple measures to monitor and ultimately balance the pharmacological profile and the physicochemical properties. These concepts intend to integrate the need for drug-like properties with the hunt for affinity to the target. They can be used by project teams to make informed decisions and ultimately drive projects toward higher quality compounds that are less likely to fail in development due to compound-related issues. Importantly, compounds with properties that fail the criteria of drug-likeness have higher attrition. By nature, the concept of drug-likeness has to do with probabilities, so is not an absolute science. The goal is to increase the *probability* of prospectively designing molecules that are more likely to survive pre-clinical safety studies and that possess optimal pharmacokinetic and pharmacodynamic properties to test hypotheses in the clinic.

5.2 DRUG-LIKE PROPERTIES OF ORAL DRUGS

The discussion in this chapter relates to small-molecule drugs. The meaning of “drug-likeness” depends on the mode of administration. The highest patient compliance (i.e., the degree to which a patient correctly follows medical advice) is observed for the oral route of drug administration; this is also the most cost-effective and most convenient. Consequently, most drugs are administered as tablets or capsules. Oral drug space is a generic term that describes the region of chemical space in which oral drugs have a high probability of being found. It can in principle be defined using any number of physicochemical or theoretical descriptors. A descriptor is a structural or physicochemical property of a molecule or part of a molecule. Examples include lipophilicity (assessed by the log P and log D values), molecular weight, number of hydrogen bond donors and acceptors, and topological polar surface area (TPSA).

A drug-like molecule must have some solubility in both water and fat, since an orally administered drug needs to pass through the intestinal lining after ingestion, be carried in aqueous blood and penetrate the lipid-based cell membrane to reach the inside of a cell. A model compound for the lipophilic cellular membrane is 1-octanol (a lipophilic hydrocarbon). Lipophilicity is measured as the partition of a small molecule between octanol and water (log P) or aqueous buffer (log D, often at pH = 7.4) as depicted in Figure 5.1. For small-molecule drugs log P is typically 3–5 meaning that the molecule has a preference for octanol over water by a factor of 1,000–100,000. A hydrogen bond is the electrostatic attractive force between a polar hydrogen bound to an electronegative atom such as nitrogen or oxygen of one molecule and an electronegative atom of a different molecule. The name hydrogen bond is in fact a misnomer; as it is not a true bond but in fact a strong dipole–dipole attraction. The topological polar surface area (TPSA) of a molecule is defined as the surface sum over all polar atoms, primarily oxygen and nitrogen, and is therefore roughly a count of the number of polar atoms, each of which contributes with approximately 14 Å². The TPSA is not always “easy” to deduce directly from the chemical structure as not all polar heteroatoms contribute equally and due to the fact that the 3D conformation of a molecule is not