Chapter 21
The Impact of Physicochemical and Molecular Properties in Drug Design: Navigation in the "Drug-Like" Chemical Space

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Abstract Physicochemical and molecular properties influence both pharmacokinetic and pharmacodynamic process, as well as drug safety, often in a conflicting way. In this aspect the current trend in drug discovery is to consider ADME (T) properties in parallel with target affinity. The concept of "drug-likeness" defines acceptable boundaries of fundamental properties formulated as simple rules of thumb, in order to aid the medicinal chemist to prioritize drug candidates. Special attention is given to lipophilicity and molecular weight, since there is a tendency for those parameters to increase in regard to complex compounds generated by new technologies, with potential consequences in bioavailability, while high lipophilicity is also associated with undesired effects. Such rules have the advantage to be very simple and are easy to interpret; however their drawback is that they do not take into consideration uncertainties in measurements and calculations as well as the receptor requirements. The case of PPARs, a nuclear receptor family, is discussed in detail in regard to the chemical space covered by the ligands, focusing on the high demands of the ligand binding domain in both lipophilicity and molecular size. Such paradigms indicate that it would be more appropriate to adapt drug-like properties according to specific drug discovery projects.

Keywords Drug discovery • Lipophilicity • Drug-likeness • PPARs

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21.1 Introduction

The impact of physicochemical properties in drug action has been rationalized since the early work of Hansch in the middle of the 1960s [1]. According to the first QSAR papers biological activity was considered as a function of lipophilicity, and electronic and steric properties [1–3]. Since those early years the evolution of the QSAR field has seen remarkable growth. Nowadays, a large arsenal of more than 4,000 molecular descriptors can be treated by sophisticated chemometric techniques to model biological activity [4]. At the same time the strategy of drug design has shifted to a more holistic approach considering absorption, distribution, metabolism, elimination (ADME) characteristics, as well as safety issues in parallel with target affinity [5, 6]. Drug candidates should possess favorable physicochemical and molecular properties that would elicit more chances for them to reach the market, reducing the attrition rate. The concept of drug-likeness associated mostly with pharmacokinetics and safety considers simple properties which should obey certain rules to guide chemical space navigation [7]. In the present paper the effect of the most important physicochemical and molecular properties is discussed in regard to both receptor requirements and pharmacokinetic process. A paradigm concerning PPAR ligands is presented.

21.2 Lipophilicity–Solubility–Ionization

The role of traditional physicochemical properties such as lipophilicity, solubility, and ionization is well established. Lipophilicity, expressed by the octanol–water partition coefficient (logP) or distribution coefficients (logD for ionizable compounds), is of paramount importance, influencing both pharmacokinetic and pharmacodynamic behavior as well as toxicological aspects [1–3, 8]. On the other hand aqueous solubility is associated with formulation and oral dosage administration, being a prerequisite for drug absorption to start through the gastrointestinal system [9]. Solubility, within the physiological pH range in conjunction with permeability, is included in the Biopharmaceutical Classification System (BCS) which categorizes drugs according to four classes [10]. BCS is of great interest for pharmaceutical industry since for drugs belonging to class I—high solubility/high permeability—bioequivalence studies are waived.

The majority of drugs contain ionizable groups, mostly basic functions. Acidic function is in certain cases an essential receptor requirement; strong acidity however is an unfavorable characteristic for permeability. Ampholytes constitute a particular class of drugs with their own physicochemical characteristics influencing their pharmacokinetic behavior in a more complex way, especially when they exist in zwitterionic form [11]. Within a series of chemically congeneric compounds however, as it is often the case in medicinal chemistry, there is no much variation in

the pKa values. More to the point distribution coefficients, logD, incorporate both logP and pKa.

A huge amount of research has been conducted in regard to lipophilicity. Experimental octanol–water partition coefficients (logP) have been compiled in commercially available databases [12, 13] while several algorithms have been developed and implemented in various software for logP or logD predictions [14]. Binding to proteins correlates linearly with logP, while permeability may follow parabolic or bilinear relationships with logP or logD. Thus optimum logP values (logPo) have been defined for the penetration through certain biological barriers [15]. There is however strong evidence that high lipophilicity is associated with undesired drug features, like extensive and unpredictable metabolism, high plasma protein binding, or accumulation to tissues. The minimum hydrophobicity concept formulated in 1987 by Hansch et al. dictates that drug design should be oriented to molecules with no more lipophilicity than that required for their biological action (permeability and affinity) [15]. This principle is applicable either for compounds designed to act in the periphery as well as for molecules designed to stimulate receptors in the CNS. For the latter case there is evidence that optimum lipophilicity for BBB penetration (logP ~ 2) is related to undesirable sedative activity. More to the point hydrophobic binding by displacing water molecules from the binding pocket is nonspecific interaction increasing the chance to off-target binding and nonspecific toxicity. Ten years later upper limits for logP values [16] were proposed by Lipinski et al. who included lipophilicity in the well-known rule of 5 (RoF).

21.3 Descriptors, Descriptors, Descriptors... Which Molecular Properties Are We Looking for in Medicinal Chemistry?

Molecular descriptors are derived from different theories, such as quantum chemistry, organic chemistry, physical chemistry, computational chemistry, information theory, graph theory, and so on [4]. In addition constitutional descriptors count the presence of certain structural characteristics like heteroatoms, rings, bonds types, hydrogen bond acceptor, or donor sites. To extract relevant information from a large descriptor pool, and transform this information to knowledge incorporated in a model, different chemometric techniques are applied. The interpretation of the models however as well as the back conversion of the ensemble of the included molecular descriptors to chemical structure is not always an easy task. In fact, molecular descriptors may be further categorized to those useful for predictions of the biological activity of new compounds or for screening compound libraries and those which are easily interpretable giving insight on the mechanism of action. The latter are more familiar to the medicinal chemist and are helpful to guide further synthesis within a given chemical category. In principle, receptor–ligand interactions involve electrostatic interactions, hydrogen bonding, van der Waals and

hydrophobic interactions. Further to the traditional electronic substituent constants, energy parameters like E_{HOMO}, E_{LUMO}, maximum or minimum electrostatic potential, dipole moments, partial charges, protonation states, or acidic/basic ionization constants may express the influence of electronic properties. The count of hydrogen bond acceptor and donor sites, hydrogen bond acidity and basicity parameters, and polar surface area (PSA) are among the most common descriptors to describe hydrogen bonding. Octanol–water logP as well as nonpolar surface area or volume reflects hydrophobic interactions, while bulk parameters like molecular weight, or molecular volume, polarizability, and molecular refractivity may reflect size requirements or/and (in the case of the last two) the contribution of van der Waals interactions. Flexibility usually expressed by the number of rotatable bonds is also an important straightforward interpretable property influencing binding affinity. Constitutional descriptors can describe additional structural requirements for the stabilization of drug–receptor interactions. Among these properties lipophilicity, molecular size, hydrogen bonding, PSA, and flexibility are important also in regard to bioavailability and safety issues of drug candidates, often in conflict with receptor requirements [17].

21.4 Drug-Likeness: The Development of Metrics

The evolution in synthetic possibilities and biological testing elicits new experimental data to be generated on a regular basis, following research into new chemistries and the advantages of high-throughput screening and combinatorial chemistry [18]. Such conditions and the society requirements for the development of new safer drugs faster brought forth the establishment of simple rules or metrics to guide the initial design of drug candidates from a vastly expanding chemical space. The first and still mostly applicable rule was formulated by Lipinski et al. in 1997, known as the rule of 5 (RoF) which sets upper limits (multiples of 5) for four fundamental molecular descriptors. According to RoF, molecular weight (MW) should not exceed 500 Da, calculated lipophilicity (clogP) should not exceed 5, hydrogen bond donor sites (HD) should not be more than 5, and hydrogen bond acceptor sites not more than 10. Upon pairwise violation of these limits, bioavailability problems may occur in the case of orally administered drugs [16]. RoF was further extended including cutoff values or ranges for additional properties, the most common being: PSA (<140), number of rotatable bonds (<10), Molar Refractivity (40–130), number of aromatic rings (<3), total number of atoms (20–70) [19]. Concerning safety, increased relative risk (6:1) for an adverse event in toxicology studies may be anticipated for compounds possessing both high lipophilicity (ClogP > 3) and low topological polar surface area (TPSA < 75 A) [20]. Stricter cutoff values are suggested for compounds active in the Central Nervous System (CNS-likeness) [21]. The development of Fragment-Based Drug

Design (FBDD) led to the establishment of the rule of 3 for lead compounds according to which MW < 300, logP < 3, HD < 3, and HA < 6 [22].

In fact, the establishment of these rules of thumb intended to hamper the increase in size and complexity of drug candidates which were generated by the new techniques mainly the combinatorial chemistry and FBDD. The advantages of smaller and less lipophilic drug candidates were further recognized in terms of receptor binding. A new category of metrics emerged according to which affinity is normalized against molecular size, expressed as the number of heavy atoms N_H, and/or lipophilicity. Ligand Efficiency (LE) [23] and Ligand Lipophilicity Efficiency (LLE) [24] may be used to prioritize drug candidates with quasi equal potency.

$$LE = \Delta G/N_H = RT \times pIC_{50}/N_H = 1.4 \times pIC_{50}/N_H$$
$$LLE = pIC_{50} - logP$$

In terms of thermodynamics, according to LLE drug–receptor interaction should be optimized in regard rather to the enthalpic component through specific interactions. Increase in entropy through hydrophobic binding increases the risk of undesired effects (next to poor ADME properties) in agreement with the minimum hydrophobicity concept.

Other metrics include: Percent Efficiency Index, PEI = f(Inh)/Mw and Binding Efficiency Index BEI = pIC_{50}/Mw normalizing activity against molecular weight expressed in kDa. The Surface Efficiency Index, SEI = pIC_{50}/PSA considers Polar Surface Area (in 100 s Å) while Ligand Efficiency Dependent Lipophilicity, LEDL = logP/LE considers both lipophilicity and size to normalize potency [23, 25].

The advantages of such metrics are that they are simple and easy to interpret. These same features however may be considered as drawbacks since such metrics can be easily "over-interpreted." In addition, they do not account for uncertainties mainly in the calculation of lipophilicity. More to the point, although they are considered as universal, they are not since they do not account for different therapeutic categories and thereupon for receptor requirements.

21.5 Navigation in Drug-Like Chemical Space: The PPAR Paradigm

Peroxisome–Proliferator Activated Receptors (PPARs) belong to the nuclear hormone receptor superfamily, which includes three subtypes PPAR-α, PPAR-β/δ, and PPAR-γ [26]. Each of these subtypes appears to be differentiated in a distinct tissue-specific manner, playing a pivotal role in glucose and lipid homeostasis. PPAR-α offers a target for the treatment of dyslipidemia, with fibrates being well-known approved drugs. PPAR-γ, the most investigated subtype, is a molecular target for

the treatment of type 2 diabetes mellitus with rosiglitazone and pioglitazone of the thiazolidinedione family being marketed drugs [26, 27]. Recently considerable interest has been oriented in combining the beneficial effects of dual PPAR-α and PPAR-γ activation, according to the concept of multi-target approach, in the aim to achieve synergism and to circumvent side effects of PPAR-γ, such as weight gain, fluid retention, and edema [28]. The implication of PPARs, mainly of the β/δ and γ subtypes, in CNS disorders and in particular in Parkinson disease, multiple sclerosis, and CNS trauma injury is under investigation [29]. A particular feature of the Ligand Binding Domain (LBD) in PPARs is the very large Y-shaped cavity within the protein. It includes a very flexible entrance allowing large ligands to enter the cavity and then branches into two arms, approximately equally long [27]. Arm I is the only region with substantially polar residues, which form part of a hydrogen-bond network with the ligands upon binding. It includes the AF-2 helix that contains the transcriptional activation domain. In PPAR-δ isoform the area next to AF2 is smaller than in the other two subtypes. The hydrophobic arm II and the interior of the entrance are mainly hydrophobic. This receptor topology implies particular requirements which are reflected in the molecular properties of PPAR agonists and which may contradict the upper limits defined by the different metrics.

Tracking the property space for a large data set of PPAR-γ agonists ($n = 1{,}152$ compounds) 24 and 59 % of compounds showed violations of RoF concerning excess MW and clogP, respectively [29]. 21 % of compounds exceed both clogP and MW upper limits. Classifying the compounds according to their activity, in the case of highly active ligands ($pEC_{50} > 7$) 40 % of them exceeded both MW and clogP upper limits showing a twofold violation of RoF. Although hydrogen bonding is essential to stabilize the ligand–receptor complex no violations in the number of hydrogen bond donor and acceptor sites were observed. An analogous study restricted to two chemical categories, mainly to tyrosine and thiazolidinedione analogues, has shown however that high activity can be achieved with moderate lipophilicity [30, 31]. In contrast, in the case of indole analogues with dual PPAR-α/γ activity high demands in both lipophilicity and molecular weight are required [32]. Further comparative studies on PPAR-α/γ ligands demonstrated that high lipophilicity is more important for PPAR-α subtype, while high molecular size is imperative for PPAR-γ. Careful inspection of the differences in amino acid residues in the LBD of PPAR-α and PPAR-γ and molecular simulation supported the different impact of the two properties in binding [33]. Since however, for safety reasons, a careful balance in PPAR-α and PPAR-γ activity is desirable, drug candidates may not be selected among the most active compounds. Summarizing, the high demands on lipophilicity and molecular size of PPAR-α/γ although contradictory to drug-like properties are essential receptor requirements and should be taken into account in a consensus manner for the design of new candidates.

Conclusions
The term "drug-likeness" has gained prevalence in the drug discovery community. It defines acceptable boundaries of fundamental properties formulated as simple rules of thumb. Such rules however do not take into consideration receptor requirements, as shown in the PPAR paradigm. In this aspect it would be more appropriate to adapt drug-like properties according to specific drug discovery projects.

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