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Lipinski's rule of five, famous extensions and famous exceptions

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ABSTRACT

Mathematical models show qualitative and quantitative dependencies between the structure, physico-chemical properties and activities of the investigated compounds. There are different rules for the prediction of good bioavailability, and one of the most well-known is the Lipinski rule. The rule is related to the molecular properties important for a drug's pharmacokinetics in the human body: absorption, distribution, metabolism, and excretion (ADME). In addition to the Lipinski rule, there are reported different combinations of criteria that are important predictors of permeability. An additional rule was proposed by Veber. He compared the oral bioavailability of the compound and the permeability of the compound with the molecular flexibility.

Keywords: absorption, acceptors, biological activity, donors, exceptions

Introduction

Most scientific studies today are focused on the discovery and synthesis of biologically active compounds, the study of their action, efficiency and possible toxicity to the environment. In order to save time and money, before the synthesis of a new bioactive compound, the application of various mathematical models establishes qualitative and quantitative dependencies between its structure, physico-chemical properties and activities. The molecular descriptor most commonly used to predict the potential of a compound as bioactive is lipophilicity. According to IUPAC, lipophilicity represents the affinity of molecules or parts of molecules towards the lipophilic environment. In addition to lipophilicity, the rules of good bioavailability are applied for the theoretical assessment of the existence of biological activity of compounds, among which the most well-known is the Lipinski rule (Apostolov and Vastag, 2017).

Once in the body, the pathway of a biologically active compound is determined by its absorption, distribution, metabolism, excretion and toxicity (ADMET). To evaluate and optimize the action and efficiency of a bioactive compound, it is necessary to know its pharmacokinetics. Since most bioactive substances are not administered intravenously, the pharmacokinetic predictor that may indicate the level of intestinal absorption is the human effective permeability in the jejunum. Molecules with higher lipophilicity have better permeability through the phospholipid bilayer of enterocytes, so the level of permeability is directly conditioned by the lipophilicity of the molecules.

The activity of the compound in the central nervous system is conditioned by its passage through the blood-brain barrier. The blood-brain barrier (BBB) is a mechanism that controls the passage of substances from the blood into the cerebrospinal fluid, and thus into the brain and spinal cord. The value of the pharmacokinetic parameter, log BBB, indicates the possibility of using a molecule as neurologically active. The early stages of modern design of a biologically active compound require the study of its impact on the environment, which is most often reflected in the assessment of its danger to various test organisms (Apostolov and Vastag, 2017).

Lipinski rule of five

In order to advance the discovery and development of new drugs, great efforts are being made to evaluate the similar ‘drug-like’ properties of molecules in the early stages of the discovery-research process. There are different approaches to solve this problem, but the simplest and most used approach is developed by Chris Lipinski and his colleagues at Pfizer, which is generally referred either as the Lipinski Rules or the Rule of Five (ROF) (Petit et al., 2012).

Rule of five (ROF) is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans(Lipinski et al., 1997).

The biologically active molecule must implement five conditions to be potentially used as a drug for oral administration. Poor absorption or permeation are most likely if:

- Molar mass >500,
- Number of H-bond acceptors >10,
- Number of H-bond donors > 5,
- LogP> 5 (or MlogP>4.15)

(Lipinski et al.,1997).

Based on the ROF, the rating of an orally active drug is between „0“ and „4“ which means that a potential drug has no more than one violation of the exposed criteria. However, Lipinski points out that such molecules should not be completely removed from further consideration; it is known that many drugs do not undergo ROF (Petit et al., 2012).

Although the rule of five has a wide application, there are certain deficiencies. The two major weaknesses are the equal weight given to each of the rules and the sharp boundary that marks the violation of a given rule. Another disadvantage of this rule is that it does not include natural and biological compounds. ROF does not incorporate criteria relevant to metabolism.

Lipophilicity

Lipophilicity, a description of the ability of a molecule to partition into octanol versus water, is a physicochemical property commonly considered to be highly relevant to the rate of absorption. Lipophilicity is defined as the logarithm of the ratio of drug that partitions into organic phase to that in aqueous phase, and is referred as logP. While this property can be physically measured in various ways, numerous methods for computation of logP exist, each of which has its own advantages and shortcomings. For example, clogP is a method that computes the lipophilicity of a molecule by computing the sum of the logP of the fragments that comprise it. These fragmentary values were generated by least-squares fitting to a training set, and include correction factors for electronic and steric effects. The cLogP method works well for molecules that possess typical drug-like functional groups, and fragments that are closely related to the training set. An atomic-based prediction of logP (AlogP, MlogP) utilizes the atomic contributions of each atom in the molecule, also fit to a training set with experimentally determined partition coefficients. During the development of the Rule of Five, Lipinski compared the use of the fragment-based cLogP computation to that of the atomic-based MlogP parameter. While the cLogP method produced highly accurate results in classes of compounds where all the fragments of a given compound were defined within the training set,

the rule-based Moriguchi method always provided an answer, even at the expense of accuracy. Therefore, within a series of related compounds (generated within a medicinal chemistry optimization program), the more-accurate cLogP is typically used, and, for assessment of lipophilicity of large collections, the more general MlogP computation was applied.

M log P: log P by the method of Moriguchi

The calculation of log P *via* the method of Moriguchi begins with a straightforward counting of lipophilic atoms (all carbons and halogens with a multiplier rule for normalizing their contributions) and hydrophilic atoms (all nitrogen and oxygen atoms). The Moriguchi method applies 11 correction factors: four that describe the hydrophobicity and seven that describe the lipophilicity (Lipinski et al., 1997).

The correction factors that describe hydrophobicity are:

1. UB (the number of unsaturated bonds except those in nitro groups);
2. AMP (the correction factor for amphoteric compounds): an α amino acid structure adds 1.0 to the AMP parameter, while each amino-benzoic acid and each pyridine carboxylic acid adds 0.5;
3. RNG: it has the value of 1.0 if the compound has any rings other than benzene-based with hetero-aromatic, or hydrocarbon rings;
4. QN (the number of quaternary nitrogen atoms).
5. The seven correction factors that describe lipophilicity are:
6. PRX (a proximity correction factor for nitrogen and oxygen atoms that are close to one another topologically): 1) addition of 2.0 for each two atoms directly connected and also for each two atoms connected *via* a carbon, sulfur, or phosphorus atom, 2) addition of 1.0 unless one of the two bonds connecting the two atoms is a double bond; 3) addition of an extra 1.0 for each carboxamide group, and for each sulfonamide group2.0;
7. HB: 1.0 if there are structural features that will make an internal hydrogen bond;
8. POL (the number of heteroatoms connected to an aromatic ring by only one bond or the number of carbon atoms attached to two or more heteroatoms which are also attached to an aromatic ring by only one bond);
9. ALK: 1.0 if the molecule contains only carbon and hydrogen atoms and not more than one double bond;
10. NO_2 (the number of nitro groups);
11. NCS: 1.0 for each isothiocyanate group and 0.5 for each thiocyanate group;
12. BLM: 1.0 if there is a beta lactam ring in the molecule (Lipinski et al., 1997).

Hydrogen-Bond Donors

In addition to high molecular weight and lipophilicity, large numbers of hydrogen-bond donor groups in a compound can reduce the ability of a molecule to permeate a membrane bilayer. Compounds that possess a large number of hydrogen-bond donors will partition into a strongly hydrogen-bonding solvent (such as water) rather than into the lipophilic environment present in a cellular membrane. The hydrogen bonding ability of functional groups in a molecule might be measured by simple accounting of N-H and O-H bonds in a molecule (Lipinski et al., 1997).

Hydrogen-Bond Acceptors

For the same reason that hydrogen-bond donors reduce the permeability of compounds into lipophilic environments, hydrogen-bond acceptors affect permeability by interacting favorably with a strongly hydrogen bonding solvents such as water. Again, while hydrogen-bonding parameters can be computed, Lipinski and coworkers observed that simply summing the numbers of nitrogen and oxygen atoms in the molecule serves as a good surrogate to correlate to oral bioavailability (Lipinski et al., 1997).

Variations of the rule of five

Recognizing the value of such retrospective analyses of drug candidates as originally performed and formalized by Lipinski, others have reported different combinations of criteria that are important predictors of permeability. An additional rule was proposed by Veber. He compared the oral bioavailability of the compound and compared the permeability of the compound with the molecular flexibility, which can be described in terms of the number of rotatable bonds. Estimation of the number of rotatable bonds allows correlation of permeability properties without consideration of molecular weight. It has been concluded that compounds with more than ten rotatable bonds generally have poor permeability. Also, Veber concluded that the high polar surface area affects the reduction of permeability (Pollastri, 2010).

Veber's flexibility rules complement the rule of five:

- The product must have no more than 5 hydrogen bond donor sites,
- It must have no more than 10 hydrogen bond acceptor sites,
- Its molecular mass must be less than 500 Daltons,
- Its molecules must contain between 20 and 70 atoms (50 on average),
- Its polar surface area must be smaller than 140 $Å^2$.

These criteria can predict intestinal absorption of a product and its ability to pass through the blood–brain barrier.

Linking computed molecular descriptors to central nervous system (CNS) permeability was proposed by Ajay. Computed properties, including molecular weight, molecular branching, hydrogen bonding, aromatic density and logP, were evaluated and compared to lists of drugs for which data about CNS activity were available. Molecular weight, degree of branching, number of rotatable bonds, and number of hydrogen bonds showed the highest correlation to CNS permeability, such that if these values are increased, CNS exposure is decreased. Similarly, increasing aromatic density, numbers of H-bond donors, or cLogP values predicted compounds are with higher CNS permeability (Pollastri, 2010).

A variation of ROF known as rule three, is used to display small fragments and for screening set design, that desirable fragments possess a:

- molecular weight <300,
- fewer than 3 hydrogen bond donors and acceptors,
- cLogP≤ 3.

The rule three also contains a variation of the Veber's criterion, so that the desirable fragments have three or less rotating bonds and a polar surface area ≤ 60 $Å^2$. These data imply that a rule of three could be useful when constructing fragment libraries for efficient lead discovery (Congreve et al., 2003).

The rule of five exceptions

The 'rule of 5' is based on a distribution of calculated properties among several thousand drugs. Therefore, by definition, some drugs will lie outside the parameter cutoffs in the rule. Very small number of therapeutic categories account for most of the USAN (United States Adopted Name) drugs with properties falling outside Lipinski rule. These orally active therapeutic classes are:

- antibiotics,
- antifungals,
- vitamins,
- cardiac glycosides.

These compounds have structural features that allow the drugs to act as substrates for naturally occurring transporters. If such classes are excluded from the USAN library, there are very few examples of compounds remaining that violate the ROF (Lipinski et al., 2001).

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