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Ligand Filtration of Large chemical database



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Lipinski's rule of five

- **Lipinski's rule of five**, also known as **Pfizer's rule of five** or simply the **rule of five (RO5)**, is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has chemical properties and physical properties that would make it a likely orally active drug in humans.
- The rule was formulated by Christopher A. Lipinski in 1997, based on the observation that most orally administered drugs are relatively small and moderately lipophilic molecules.
- The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion ("ADME"). However, the rule does not predict if a compound is pharmacologically active.
- The rule is important to keep in mind during drug discovery when a pharmacologically active lead structure is optimized step-wise to increase the activity and selectivity of the compound as well as to ensure drug-like physicochemical properties are maintained as described by Lipinski's rule.^[3] Candidate drugs that conform to the RO5 tend to have lower attrition rates during clinical trials and hence have an increased chance of reaching the market.



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Components of the rule

Lipinski's rule states that, in general, an orally active drug has no more than one violation of the following criteria:

- No more than 5 hydrogen bond donors (the total number of nitrogen–hydrogen and oxygen–hydrogen bonds)
- No more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms)
- A molecular mass less than 500 daltons
- An octanol-water partition coefficient¹ ($\log P$) that does not exceed 5

Note that all numbers are multiples of five, which is the origin of the rule's name. As with many other rules of thumb, such as Baldwin's rules for ring closure, there are many exceptions.



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Variants

In an attempt to improve the predictions of drug likeness, the rules have spawned many extensions, for example the Ghose filter:

- Partition coefficient $\log P$ in -0.4 to $+5.6$ range
- Molar refractivity from 40 to 130
- Molecular weight from 180 to 480
- Number of atoms from 20 to 70 (includes H-bond donors [e.g. OHs and NHs] and H-bond acceptors [e.g. Ns and Os])

Veber's Rule

Veber's Rule further questions a 500 molecular weight cutoff. The polar surface area and the number of rotatable bonds has been found to better discriminate between compounds that are orally active and those that are not for a large data set of compounds in the rat.^[8] In particular, compounds which meet only the two criteria of:

- 10 or fewer rotatable bonds and
- Polar surface area no greater than 140 \AA^2

are predicted to have good oral bioavailability.



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Lead-like

- During drug discovery, lipophilicity and molecular weight are often increased in order to improve the affinity and selectivity of the drug candidate. Hence it is often difficult to maintain drug-likeness (i.e., RO5 compliance) during hit and lead optimization. Hence it has been proposed that members of screening libraries from which hits are discovered should be biased toward lower molecular weight and lipophilicity so that medicinal chemists will have an easier time in delivering optimized drug development candidates that are also drug-like. Hence the rule of five has been extended to the **rule of three** (RO3) for defining **lead-like** compounds.
- A rule of three compliant compound is defined as one that has:
 - octanol-water partition coefficient $\log P$ not greater than 3
 - molecular mass less than 300 daltons
 - not more than 3 hydrogen bond donors
 - not more than 3 hydrogen bond acceptors
 - not ⁵more than 3 rotatable bonds



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Lipinski Rule of 5

not more than **5**
hydrogen bond
donors

not more than
10 hydrogen bond
acceptors

molecular
weight less
than **500**

ClogP not
greater than **5**
(lipophilicity)

physicochemical properties