LIPINSKI RULE OF FIVE

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Outline

- Lipinski rule
- Physicochemical properties
- How this rule benefits your project
- Variation to the rule of five
- Disadvantages/ Drawback

Objectives

- Our main aim is to understand the Lipinski rule of five and various variations related to this rule followed by drawbacks.

Lipinski rule

- Lipinski's rule of five also known as the Pfizer's rule of five

or

- 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 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 medication drugs are relatively small and lipophilic molecules [Lipinski et al. 1997, 2001 & 2004].

❖**Lipinski's rule states that:**

❖The biologically active molecule must implement these below mentioned conditions to be potentially used as a drug for oral administration otherwise it will show poor absorption or permeation.

or

❖ An orally active drug has no more than one violation of the following criteria:

- ❖Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms).
- ❖Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms).
- ❖A molecular mass less than 500 daltons.
- ❖An octanol-water partition coefficient log P not greater than 5.

Compds	% ABS	Vol (A3)	TPSA (A2)	NROTB	HBA	HBD	Log*P*	M W	Lipinski's Violations
Rule	-	-	-	-	<10	<5	≤5	<500	≤1
ABQ1	97.0182	295.28	34.73	2	3	0	3.68	341.02	0
ABQ2	97.0182	323.64	34.73	2	3	0	5.06	411	0
ABQ3	88.6485	385.91	58.99	5	6	0	3.1	431	0
ABQ4	94.272	322.23	42.69	3	4	0	3.53	371	0
ABQ5	91.0635	301.17	51.99	2	4	1	3.01	357	0
ABQ6	88.266	334.07	60.1	3	5	1	2.97	387	0
ABQ7	88.6312	386.38	59.04	5	6	0	3.5	431	0
ABQ8	96.2661	340.18	36.91	3	3	0	3.6	384	0
ABQ9	88.7175	385.75	58.79	5	6	0	3.36	431	0
ABQ10	91.0704	302.23	51.97	2	4	1	3.22	357	0
ABQ11	97.0182	311.56	34.73	2	3	0	3.94	355	0
ABQ12	94.1271	322.47	43.11	3	4	0	3.53	371	0

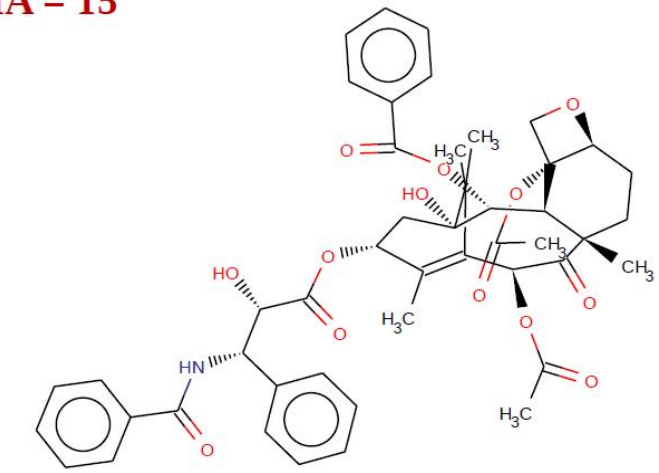
❖Based on the ROF, the rating of an orally active drug is between „0“ and „4“ which means that a potential drug has no more than one violation of the exposed criteria. However, Lipinski points out that such molecules should not be completely removed from further consideration; it is known that many drugs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

Examples of exceptional drugs violating more than one rule:

1. **Lipitor** Pfizer's best-selling drug and a major player in their success, violates two of the four basic Lipinski rules (MW & ClogP), comes close to violating a third (HBD), and also violates the variant rule of the number of rotatable bonds.

2. Paclitaxel: Violates 2 rules.

MW = 837
logP=4.49
HD = 3
HA = 15



Physicochemical properties

❖**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.

clogP is a method that computes the lipophilicity of a molecule by computing the sum of the logP of the fragments that comprise it.

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.

❖**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

❖**Hydrogen-Bond Acceptors**

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 co-workers observed that simply summing the numbers of nitrogen and oxygen atoms in the molecule serves as a good surrogate to correlate to oral bioavailability.

How this rule benefits your project?

- 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.
- This rule helps Pharmaceutics/Industrial Pharmacy students in proper selection of the drug and knowing whether the drug is suitable for oral formulations.
- For Medicinal chemistry students involved in drug designing, CADD, understanding this rule will help you a lot in designing suitable homologues of drugs and fine tuning your drug with suitable modifications.

Variations to the rule of five

❖**Veber's flexibility rules**

- ➢ 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 $Å^2$
- ➢ compounds with more than ten rotatable bonds generally have poor permeability.

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

❖ **Rule of three-**It is used to display small fragments and for screening set design, that desirable fragments possess:

- ➢ 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.

Disadvantages/ Drawback

- The equal weight given to each of the rules and the sharp boundary that marks the violation of a given rule.
- It does not include natural and biological compounds.
- ROF does not incorporate criteria relevant to metabolism.

References

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Thank
you