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RULE OF FIVE: THE FIVE MEN ARMY TO CROSS THE BLOOD BRAIN BARRIER FOR THERAPEUTICALLY POTENT

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ABSTRACT

Drug is a chemical substance having definite structural framework, obtained either from synthetic source, semisynthetic source or natural source [animal or plant source] having capability to fit on bioreceptor platform having controlling capacity to check the malfunction of normal homeostatic cycle; whereas medicine is an application of drug into a formulation so that it can be easily administered into the body by maintaining therapeutic index to get desired pharmacological response. ***All drugs are chemical substance but all chemicals are not drug*** *which is well accepted in the arena of medicinal chemistry because chemistry is a playground of functional groups which follows the four coins: how, when, why & where as medicinal chemistry runs on it's two legs: chemistry & biology. Chemistry word is the combo effect of Chemist+Try, so try, try, try and try until you get your positive result. This positive result is based and characterized by structural network which is authenticated by spectral analysis [IR, NMR, Mass] to establish the backbone of chemical molecule. All drugs are xenobiotics [Xenus=outer source+Bioticon=active in-vivo] which are active inside the body until and unless that follows RO5 [Rule of Five]. The molecule which follows Lipinski's rule of five can show biological action inside the living system.*

KEYWORDS: Drugs, Medicines, Bioavailability, Bioequivalence, Metabolism, Pharmacodynamics, Pharmacokinetics, Receptor, Renal clearance, Blood Brain Barrier, Rule of Five, Lipinski rule, Xenobiotics, Polar, Nonpolar, Surface tension, Parachor, Therapeutic Index, High Throughput Screening, Partition coefficient, Docking.

History: Christopher A Lipinski is a medicinal chemist who is working at Pfizer, Inc. He is known for his "rule of five", an algorithm that predicts drug compounds that are likely to have oral activity.[1-5]

Lipinski received his PhD from the University of California, Berkeley in 1968 in physical organic chemistry. The Advanced Drug Delivery Reviews article reporting his "rule of five" is one of the most cited publications in the journal's history. In 2006, he received an honorary law degree from the University of Dundee and he has won various awards, including being the Society for Biomolecular Sciences' winner of the 2006 SBS Achievement Award for Innovation in HTS.[6-8]

Figure 1: Dr. Christopher A Lipinski [Founder of RO5].

- ✓ 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 coefficient (log P) that does not exceed 5.
- ✓ Not only does logP help predict the likely transport of a compound around the body. It also affects formulation, dosing, drug clearance, and toxicity. While the best mode of application of a chemical may be spraying as an aqueous solution, the active compound must be lipophilic enough to resist leaching into waterways.
- ✓ The logP value of a compound, which is the logarithm of its partition coefficient between n-octanol and water $\log(c_{octanol}/c_{water})$, is a well-established measure of the compound's hydrophilicity
- ✓ Low hydrophilicities and therefore high logP values cause poor absorption or permeation.

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.[9-12]

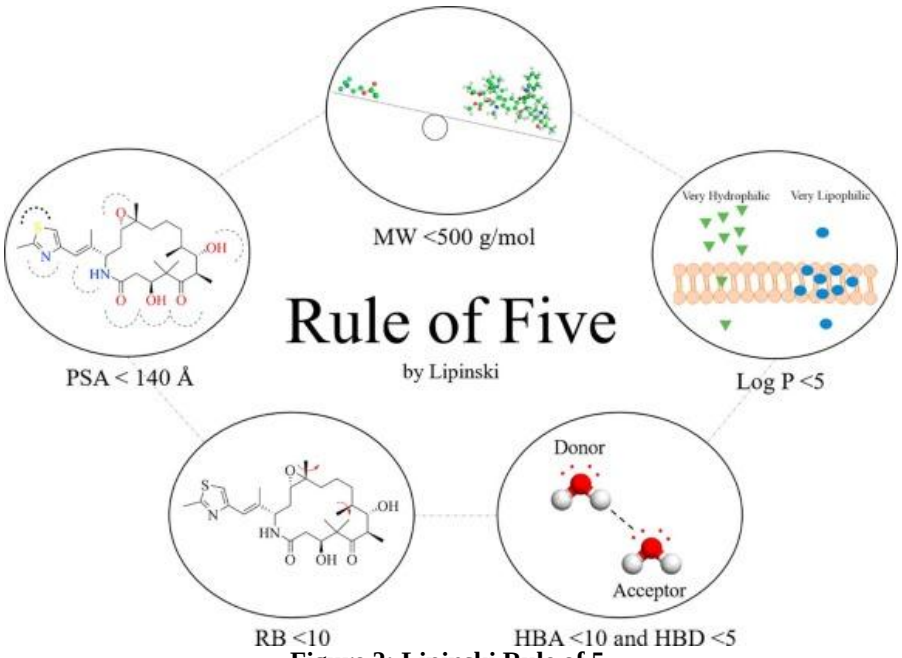


Figure 2: Lipinski Rule of 5.

The drug which enters into the body system undergoes biotransformation followed by metabolic pathway. Some part of drug gets liver's first pass mechanism and gets metabolised by following phase-I [functionalization step: oxidation, reduction & hydrolysis] then gets converted into non-polar state into semi-polar state and then enters into phase-II [conjugation step: glucuronidation conjugation, glutathione conjugation, sulfate conjugation & amino acid conjugation] and becomes semipolar to polar and easily excreted out through renal clearance as well as through rectal route.[13-15] 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 drug molecular structure undergoes following profiles like pharmacodynamics & pharmacokinetics. Pharmacodynamics profile follows the physicochemical & biochemical parameters:

Lipophilic [Partition coefficient, π-constant, Chromatography, Solubility], Electronic [Hammett constant, pKa, Resonance, Quantum number, Spectroscopy] & Steric [Molecular weight, Molecular formula, Elemental percentage, Molar refraction, Molar volume, Parachor, Surface tension, Density, Dielectric constant, Polarizability, Connectivity indices], Biologic [k_m=Michaelis–Menten kinetics constant for enzyme-substrate conjugate, k_i=Ionisation constant, pA_2=Agonist-antagonist constant, pA_1=Dielectric constant for enzyme, IC_{50}=Antagonist drug potency]

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. 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. This famous "rule of 5" has been highly influential in this regard, but only about 50 % of orally administered new chemical entities actually obey it. Studies have also demonstrated that some natural products break the chemical rules used in Lipinski filter such as macrolides and peptides.[16,17]

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 coefficient (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.[18]

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

1. Partition coefficient log P in −0.4 to +5.6 range
2. Molar refractivity from 40 to 130
3. Molecular weight from 180 to 480
4. 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 further questions a 500 molecular weight cut-off. 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. In particular, compounds which meet only the two criteria of:

1. 10 or fewer rotatable bonds and
2. Polar surface area no greater than 140 Å2

are predicted to have good oral bioavailability.

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 lipophility 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.[19,20]

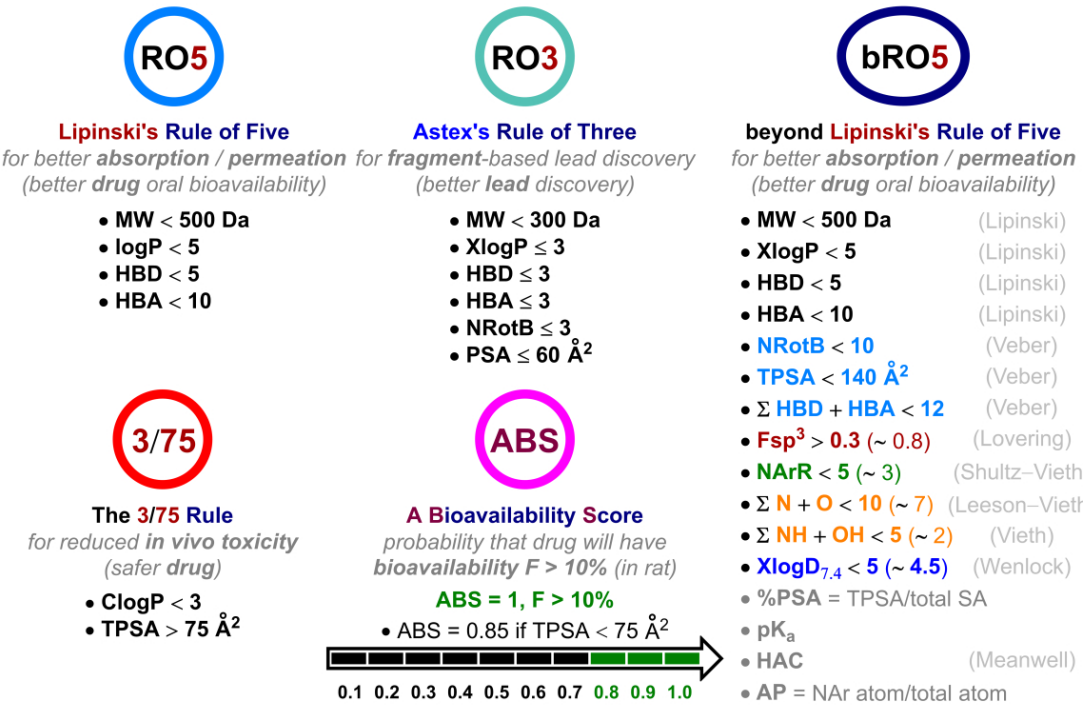
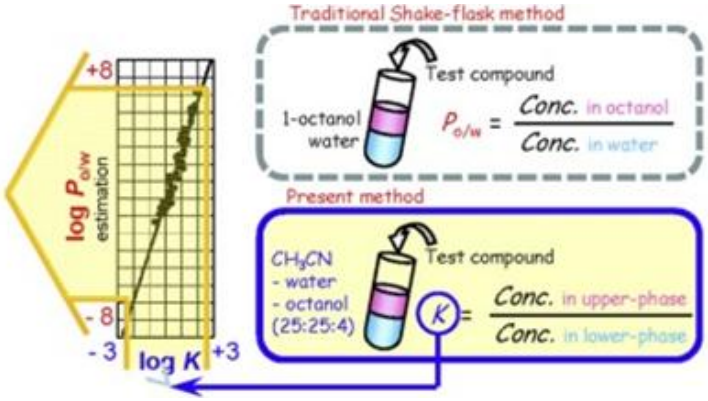
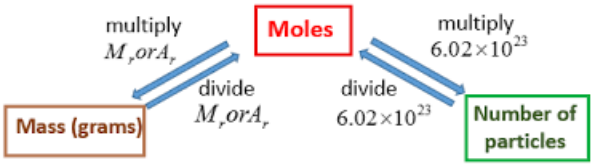


Figure 3: Comparison between RO5, RO3 & bRO5.

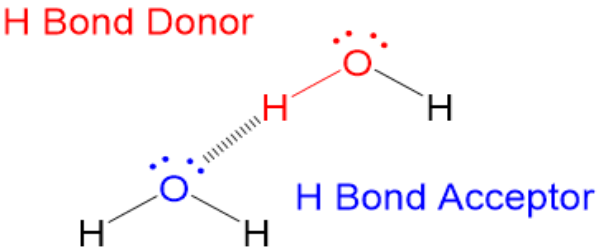
A rule of three compliant compound is defined as one that has:
octanol-water partition coefficient log P not greater than 3



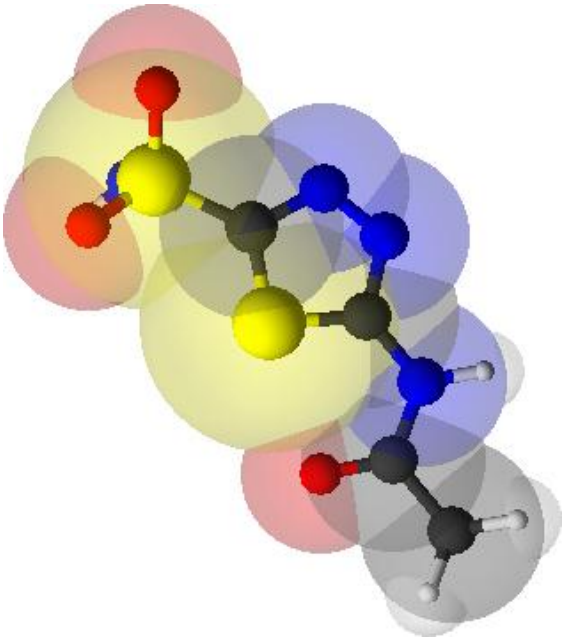
Molecular mass less than 300 Daltons



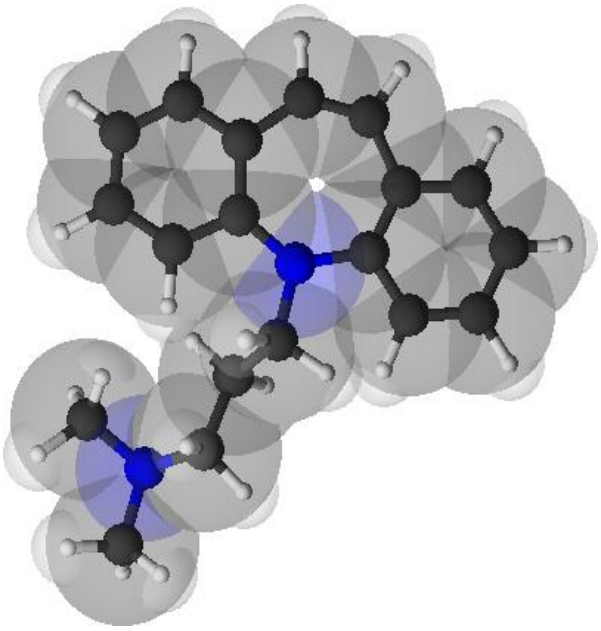
Not more than 3 hydrogen bond donors



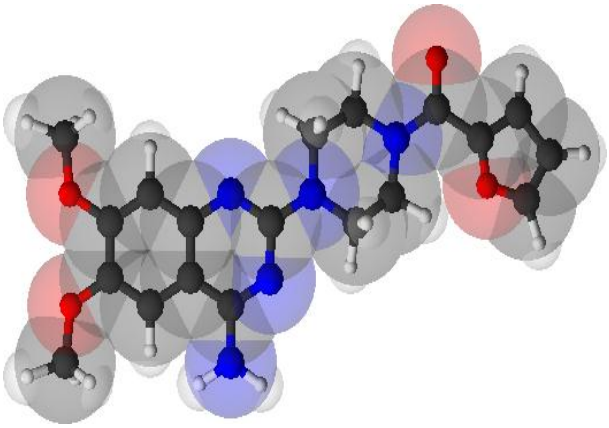
Not more than 3 hydrogen bond acceptors
Not more than 3 rotatable bonds



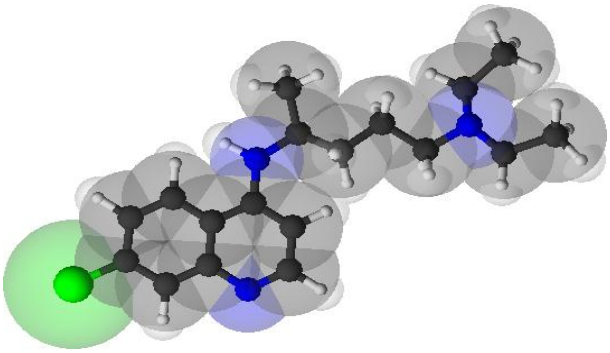
Acetazolamide [MW: 222; logP: -0.26; c-logP: -0.39]



Imipramine [MW: 280; logP: 4.80; c-logP: 4.53]

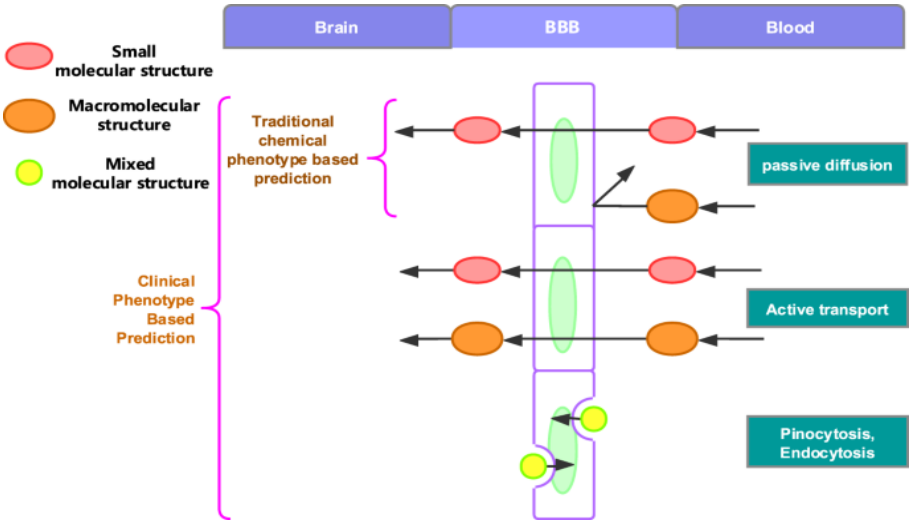


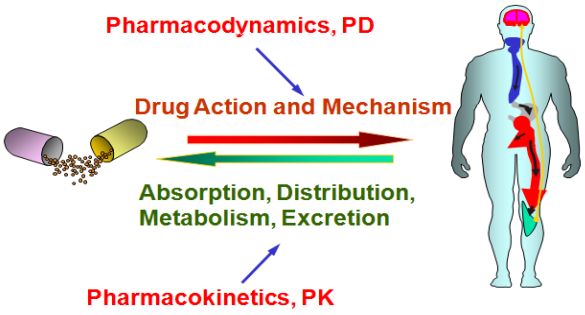
Prazosin [MW: 383; logP: 1.47; c-logP: 1.65]



Chloroquine [MW: 319; logP: 4.69; c-logP: 3.93]

Figure 4: Electronic 3D structures of few drugs with Molecular Weight <500 Dalton & logP <5.





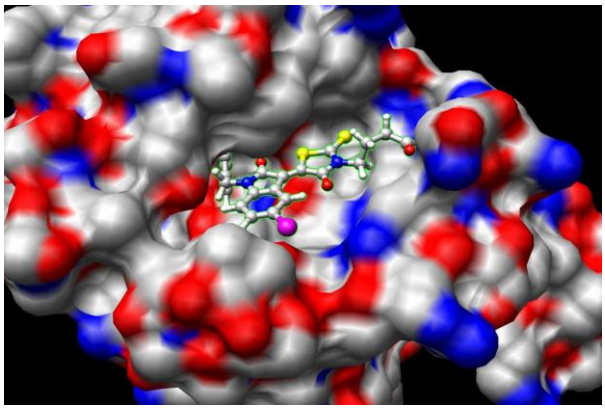


Figure 5: Lipinski Rule of Five in Drug Receptor Binding & Pharmacodynamics/Pharmacokinetics.

CONCLUSION

Unique rule of five targets the drug molecule below a molecular mass less than 500 Daltons and logP -0.4 to +5.6 potentiates the permeability of molecule through Blood Brain Barrier to reach at drug target to fit on receptor to possess drug action in system. Every drug has some logP & c-LogP which follows partition coefficient between lipid and water system inside the body system to categorise in lipid and water solubility. In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using, for example, scoring functions. The associations between biologically relevant molecules such as proteins, peptides, nucleic acids, carbohydrates, and lipids play a central role in signal transduction. Furthermore, the relative orientation of the two interacting partners may affect the type of signal produced (e.g., agonism vs antagonism). Therefore, docking is useful for predicting both the strength and type of signal produced. Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterisation of the binding behaviour plays an important role in rational

design of drugs as well as to elucidate fundamental biochemical processes.

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