Lipinski and Veber rules

The Lipinski and Veber rules are rules for compounds being investigated for drug discovery. Drugs that fit these rules SHOULD have good oral bioavailability.

Lipinski rules

Lipinski's rules of 5 are as follows…the drug should have

- A molecular weight <500
- A value of logP<5
- Less than 5 –OH or –NH groups (hydrogen bond donors) in total
- Less than 10 O or N atoms in total (hydrogen bond acceptors

Explained

- A molecular weight of less than 500. There is a known relationship between molecular weight and permeability-high molecular weight means poor permeability. Presumeably due to compound size
- P is the partition coefficient, a measure of hydrophobicity. In an experimental setup, it is a ratio of the concentration of a drug on octanol, or an immiscible solvent, divided by the concentration of the drug in aqueous solution.
- 5 –OH and –NH bonds, and 10 O or N atoms is to determine hydrogen bonding. Any more than this and too many hydrogen bonds form. This is key to its water solubility, but these bonds must be broken if it is to cross the lipid membranes.

Stats relating to the rules

- About 80% of current drugs on the market have molecular weights under 450.
- On average, commercial drugs have molecular weight of 360, an average of 2.5 –OH and –NH groups, an average of 6.3 O and N atoms, and a lop value of 1.6.

Veber rules

Veber et al, in a paper released in 2002, proposed the following:

- 10 or fewer rotatable bonds (though if its less than 7, oral bioavailabilty is much greater than 7 or more)
- Less than 12 H bond donors or acceptors in total
- A polar surface area of less than 140 A (angstroms) squared
- These rules don't give a molecular weight value

Why are the rules important-a bit on oral bioavailability

There are many different drug administrative routes-intravenous, subcutaneous, intramuscular…but arguably the best is oral, because it doesn't involved sticking a needle into the body and all the risks associated with that.