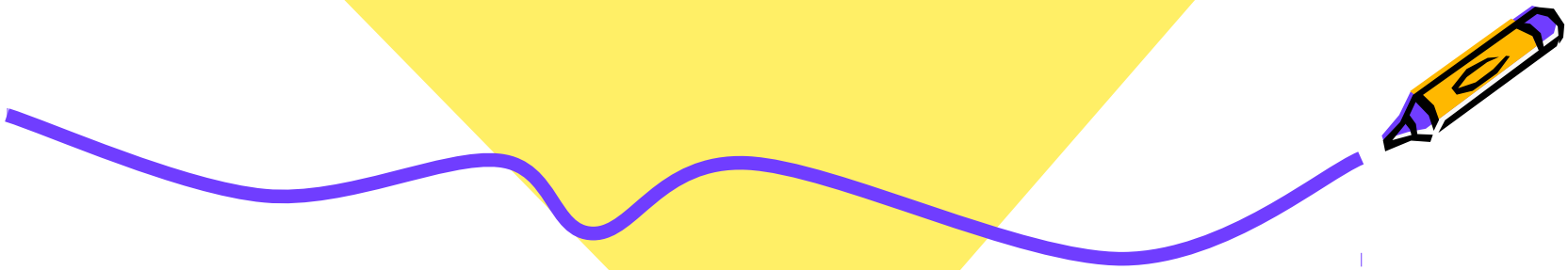
Lipinski's rule of five



Lipinski's rule of five

Lipinski's rule of five also known as the 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 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, in general, 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

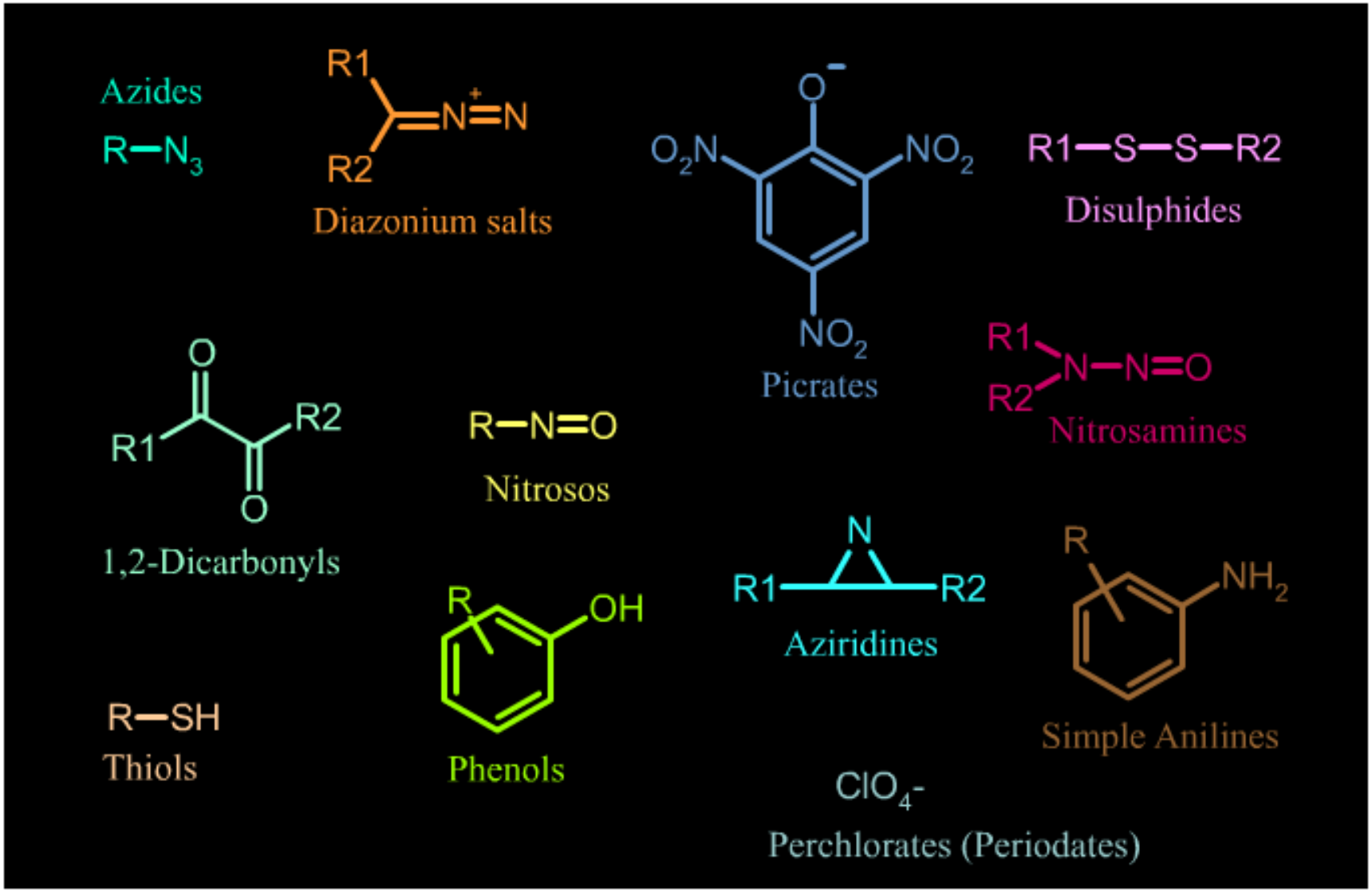
How this rule benefits your project?

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 rugs and fine tuning your drug with suitable modifications

Remove compounds with toxic groups



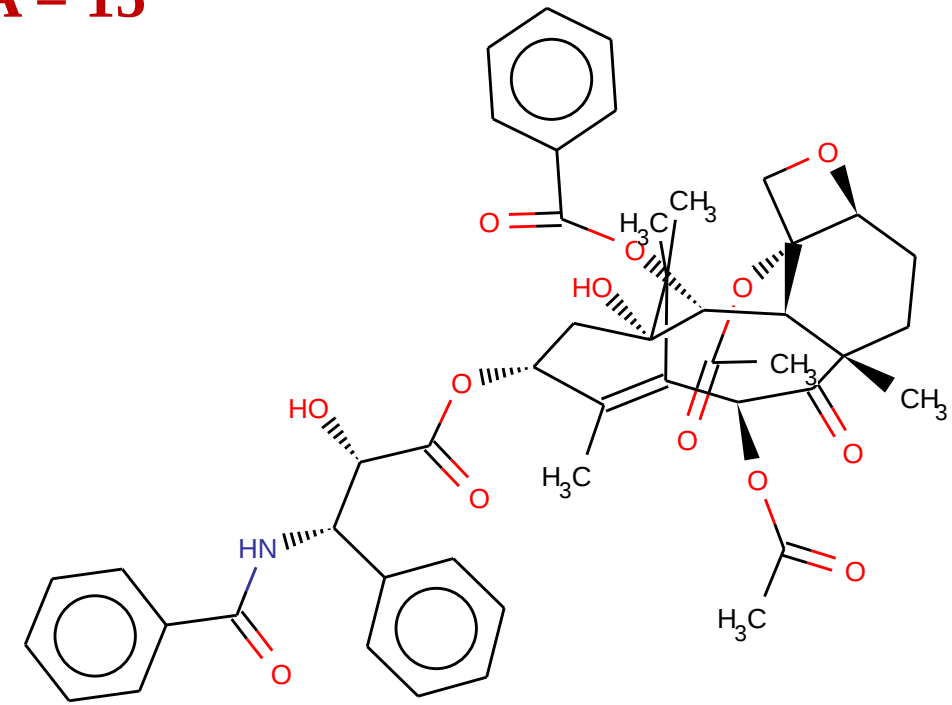
Paclitaxel (*Taxol*): violation of 2 rules

MW = 837

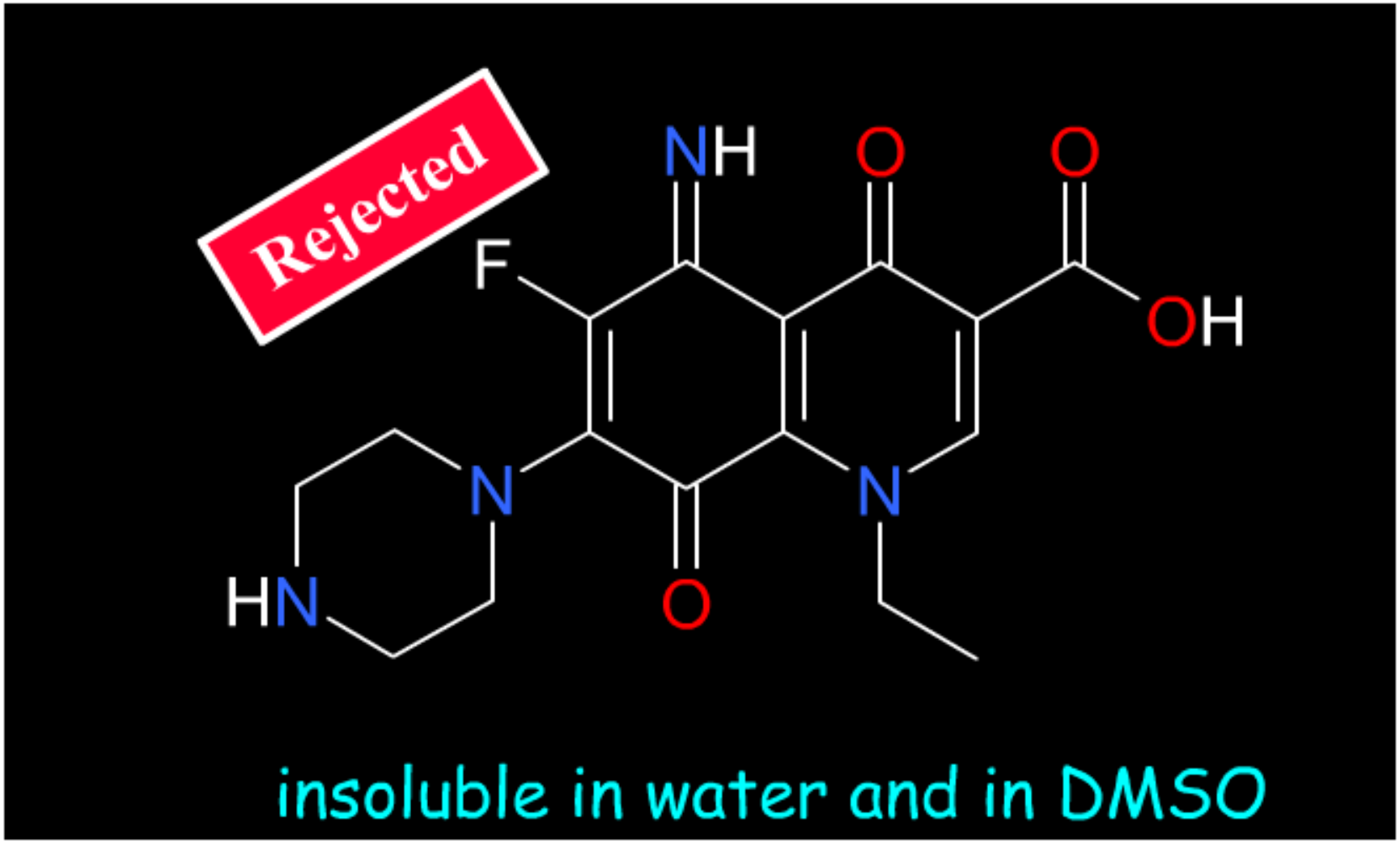
logP=4.49

HD = 3

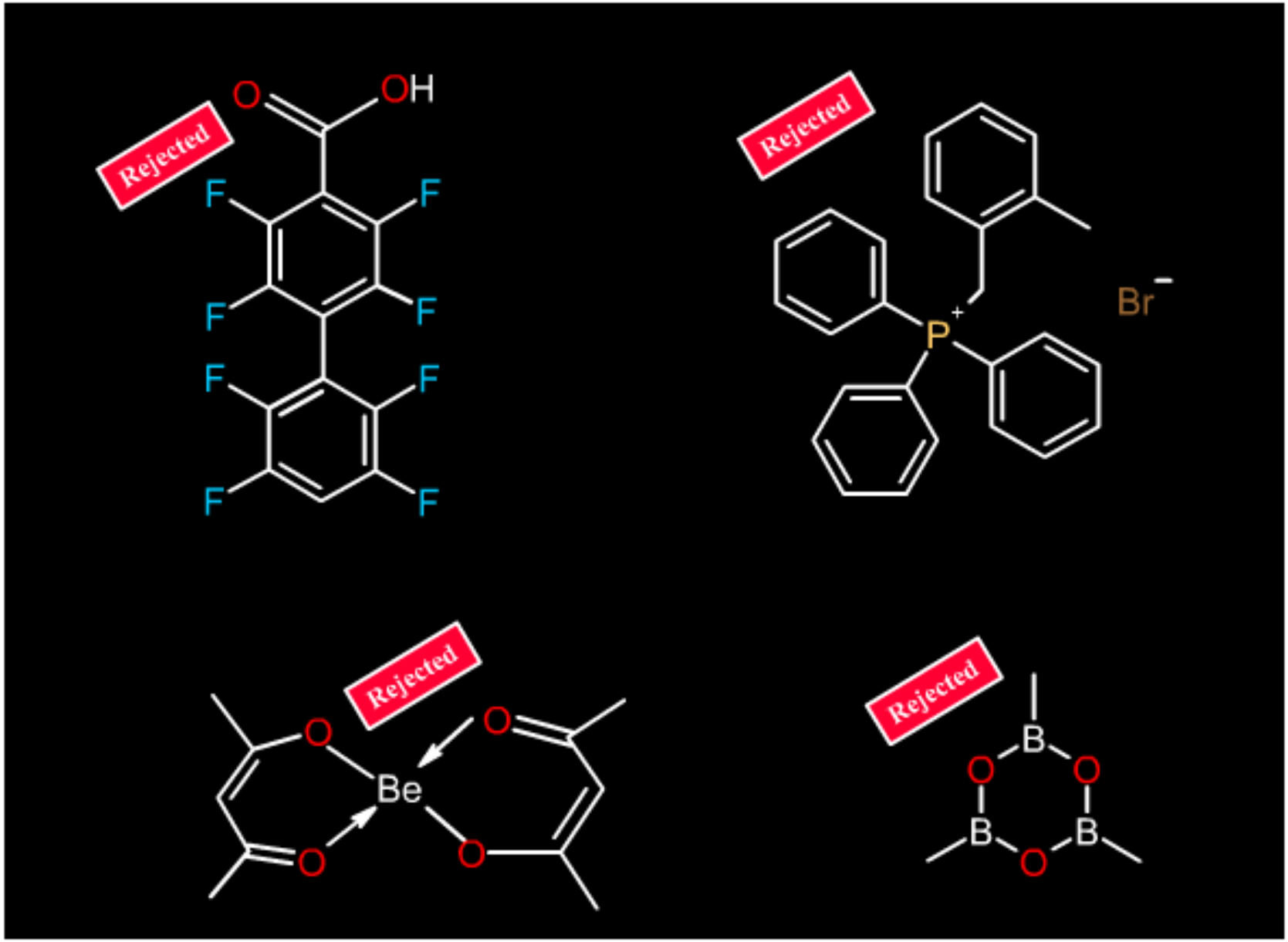
HA = 15



Remove poorly soluble compounds



Filter on inorganic and heteroatom compounds



This seems like a lot to remember!

There are various guidelines to help, the most well-known of which is the **Lipinski Rule of Five**

- molecular weight < 500
- logP < 5
- < 5 H-bond donors (sum of NH and OH)
- < 10 H-bond acceptors (sum of N and O)

An additional rule was proposed by **Veber**

- < 10 rotatable bonds

Otherwise absorption and bioavailability are likely to be poor. NB This is for **oral** drugs only.