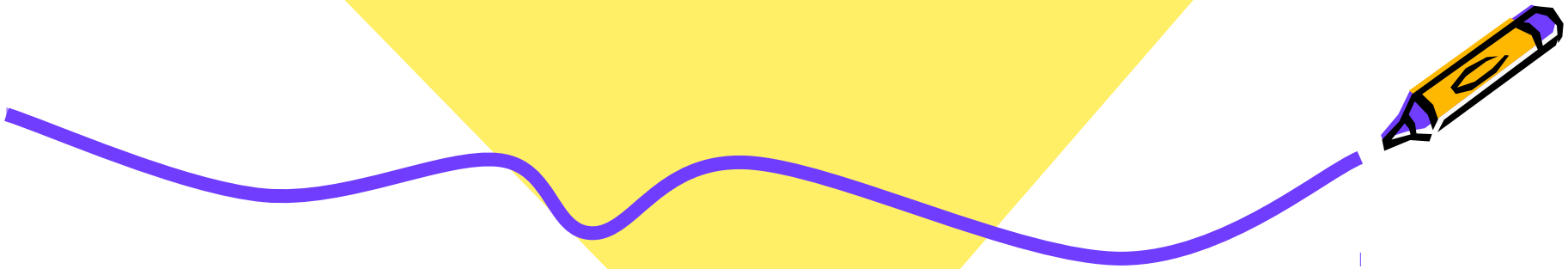
Lipinski's rule of five



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

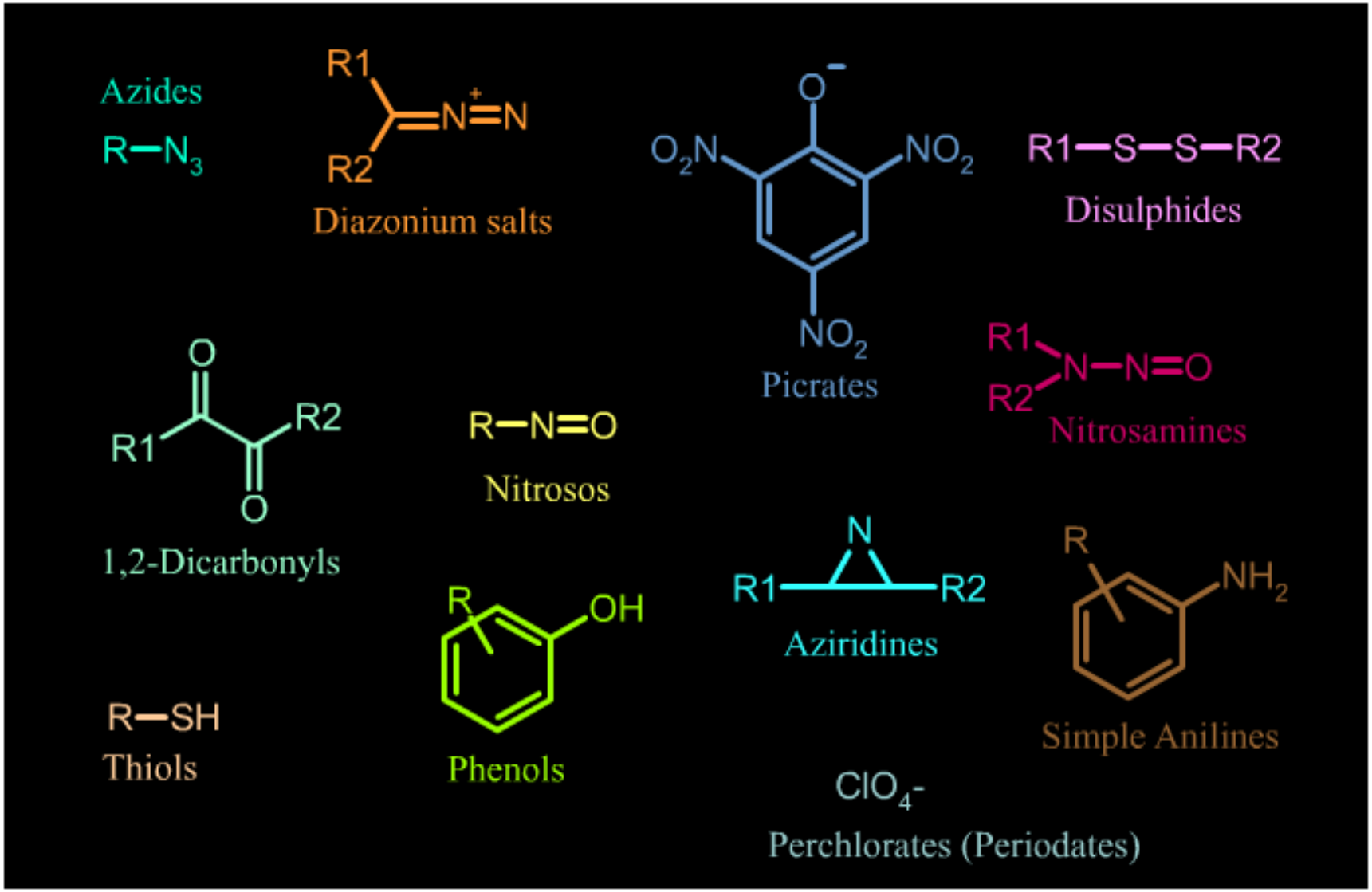
Table 2b: Pharmacokinetic Properties important for good oral bioavailability for the compounds of ABQ series.

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

Table 3b: Osiris calculation for bioavailability and toxicity prediction of series ABQ

BIOAVAILABILITY AND DRUG SCORE[a]					TOXICITY RISK PREDICTION[b]			
Cmpds	Solubility	Mol wt	Drug likeness	Drug score	Mutagenic	Tumorigenic	Irritation	Reproductive effect
ABQ1	-4.46	341	2.73	0.68				
ABQ2	-5.94	409	3.76	0.44				
ABQ3	-4.52	431	5.8	0.64				
ABQ4	-4.48	371	2.9	0.67				
ABQ5	-4.17	357	2.97	0.72				
ABQ6	-4.19	387	3.14	0.7				
ABQ7	-4.52	431	3.32	0.63				
ABQ8	-4.5	384	1.77	0.37				
ABQ9	-4.52	431	5.8	0.64				
ABQ10	-4.17	357	2.97	0.72				
ABQ11	-4.81	355	1.42	0.58				
ABQ12	-4.48	371	2.91	0.67				
ABQ14	-4.76	367	1.63	0.58				

Remove compounds with toxic groups



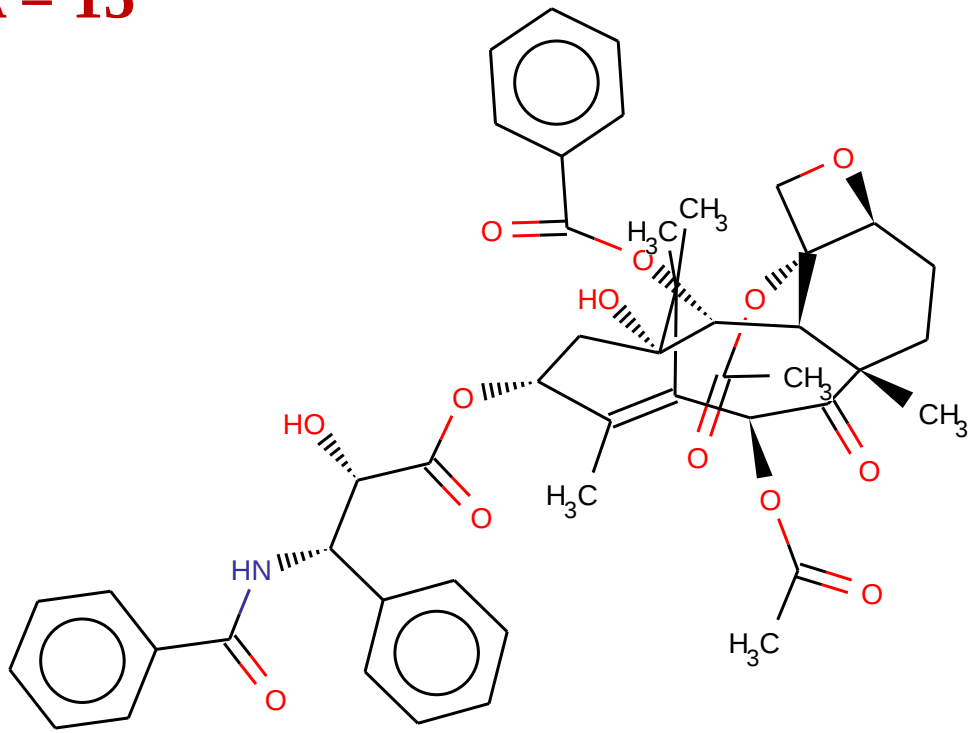
Paclitaxel (*Taxol*): violation of 2 rules

MW = 837

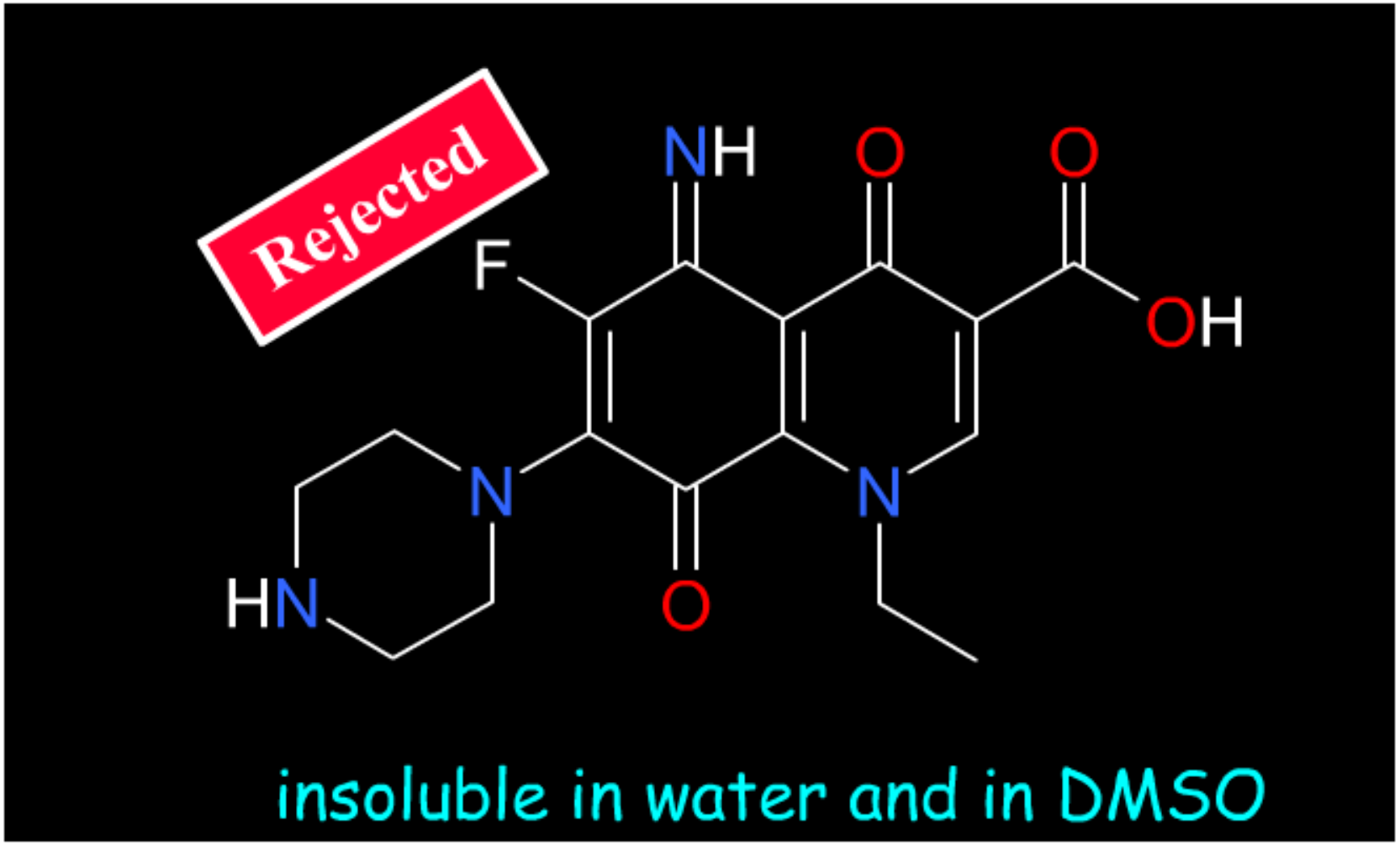
logP=4.49

HD = 3

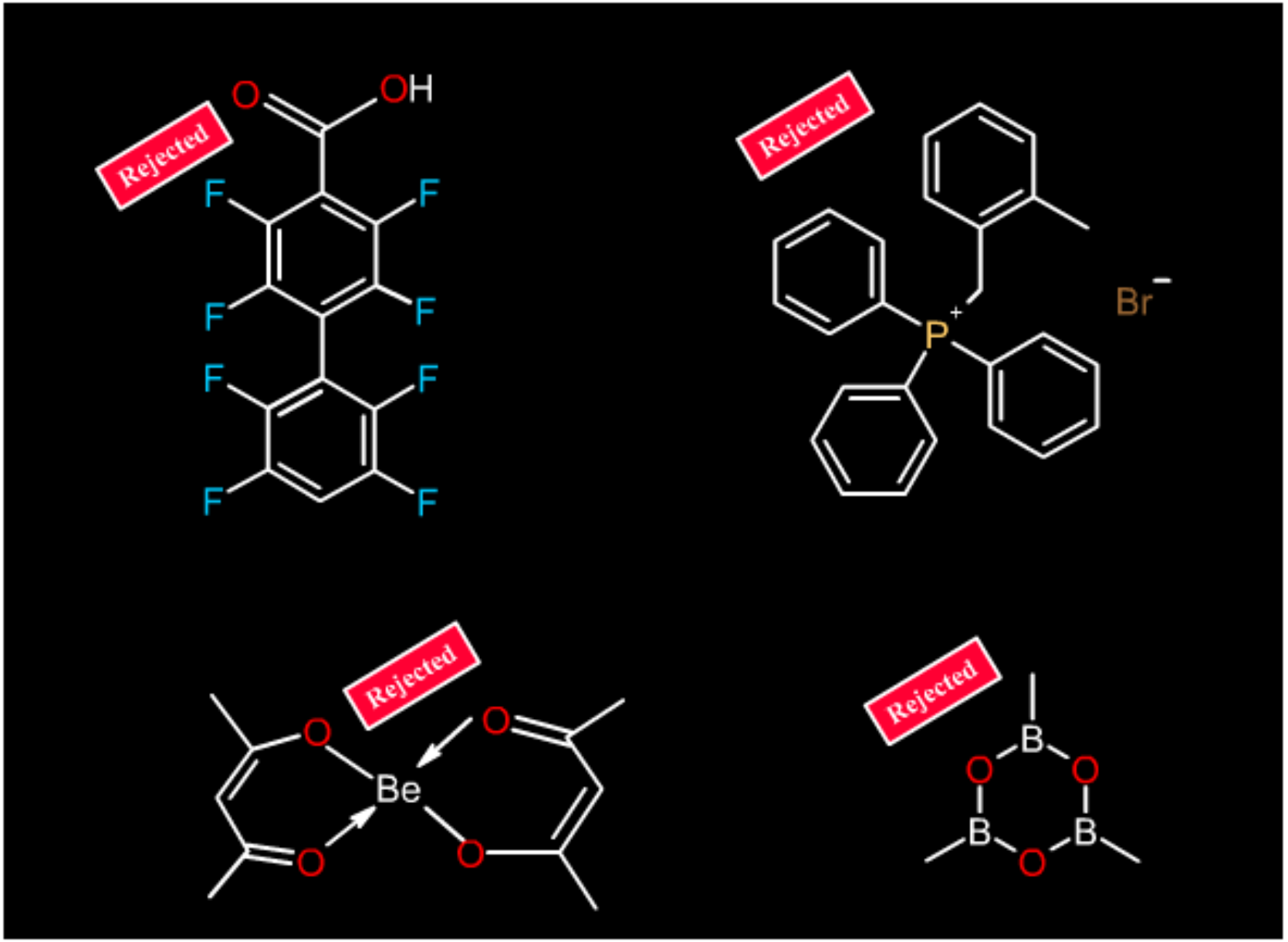
HA = 15



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.