

MEDCHEM 562

Kent Kunze

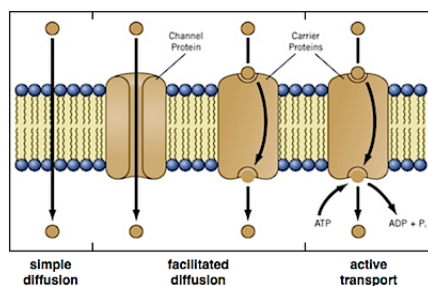
Lecture 1

Physicochemical Properties and Drug Disposition

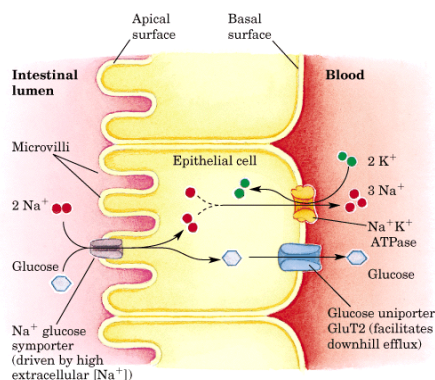
The ADME properties of most drugs strongly depends on the ability of the drug to pass through membranes via simple diffusion.

Greater than 80% of all drugs contain one or more ionizable groups. Only the uncharged form of a drug can pass through a membrane by simple diffusion. Thus it is important to be able to recognize the fraction of a drug that will be charged in a given compartment such as the intestinal lumen, the kidney tubules and the blood. Therefore it is important that you be able to relate drug structure to charged state. For ionizable drugs the percent of drug that is ionized will depend upon the pH of the solution.

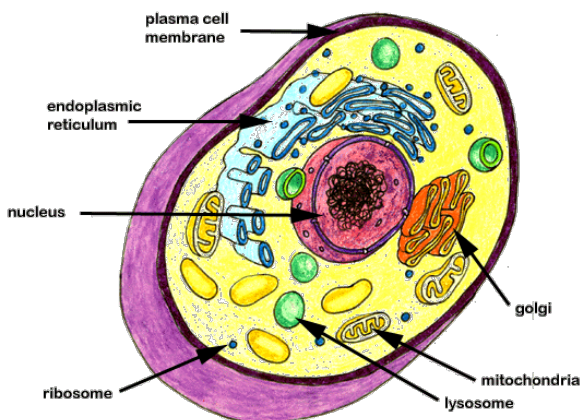
However, charged and uncharged forms of drugs can also pass membranes via influx and efflux transporters. Transporters are critical to the ADME properties of many drugs and other biochemical. For instance the absorption of amino acids (zwitter-ionic) and simple sugars (very polar) from the diet requires transporters.

**ADME**

Absorption: The majority of drugs are administered orally and absorbed from the GI tract. Dissolution, lipid solubility, ionization state (pKa) and transporters all affect net diffusion of a drug through the intestinal membranes into the portal blood (absorption) and overall availability of the drug to the systemic circulation (systemic bioavailability). Two membranes (apical and basolateral) are highly differentiated and contain different types of transporters



Distribution: Drugs are distributed into various compartments in the body where they find targets that include receptors and metabolic enzymes. These drug targets may be extracellular or intracellular. In many cases these drugs must pass through additional membranes such as the blood brain barrier as well as the cytoplasmic and nuclear membranes of the cell and/or invading microorganisms or cancer cells).



Metabolism: Most metabolic enzymes that biotransform drugs and often activate prodrugs are located in the hepatocytes. Generally, but not always, metabolism creates more polar less active metabolites that are readily excreted. This means that metabolism generally marks the termination of drug effect. Metabolism usually controls the rate at which a drug disappears from the body. It also can control systemic bioavailability of an oral dose. Lastly metabolism can be used to activate prodrugs to bioactive forms.

Excretion: Drugs are largely excreted as metabolites and unchanged drug by the kidneys. Among other factors, renal clearance depends upon the extent to which drugs are reabsorbed from the filtrate. This depends in part upon the ionization state of the drug in the tubule. We also see biliary excretion via transporters located on the canalicular membrane of the hepatocytes.

Ionization State of the Drug: The ADME properties of a drug depend heavily upon the ionization state of the drug in the physiological fluids. The extent of ionization depends on the functional group pKa value(s) and the pH of the aqueous phase of interest. We usually use pH of 7.4 as a reference value.

The pH of other biological fluids can be significantly different. What this means is that a pH gradient often exists across a membrane. For ionizable drugs a pH gradient often determines total concentration of drug on each side of a membrane and the direction of movement of a solute.

Here are the pH values for various fluids.

Blood and intracellular fluid pH =: 7.4
 Urine pH =: 5-8 (normal is 7)
 GI tract pH =: 1-7 (stomach 1; intestine 3-7)
 CSF: pH = 7.3

We can use the Henderson-Hasselbalch equation to determine the precise ratio of the concentrations of the conjugate acid and conjugate base at a particular pH. You should know this equation

$$pKa = pH - \log \frac{[\text{conjugate base}]}{[\text{conjugate acid}]}$$

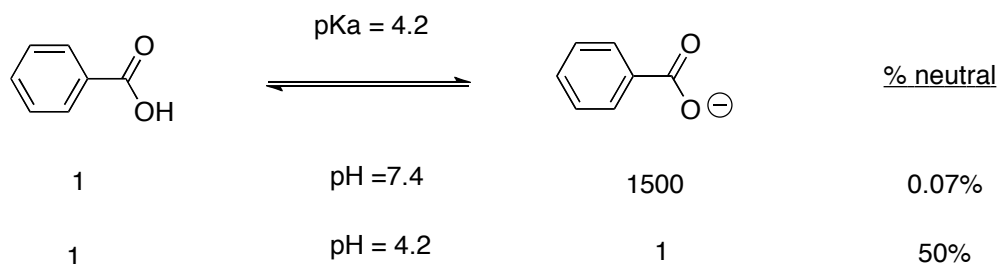
As you should definitely know by now, when the pH of a solution is equal to the pKa of the functional group the ratio of the conjugate base to the conjugate acid is equal to 1.

When the pH of the solution is significantly different from the pKa of a drug we can calculate the conjugate base/conjugate acid ratio in that environment.

$$\frac{[\text{conjugate base}]}{[\text{conjugate acid}]} = 10^{(pH - pKa)}$$

Here we are primarily interested in the ratio of unionized drug to ionized drug so we need to know whether the conjugate acid is charged (amine) or neutral (carboxylic acid).

Carboxylic acid example:



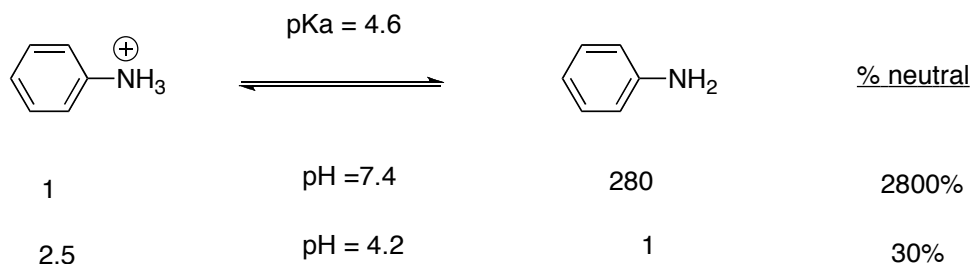
Lower pH favors the neutral conjugate acid

For benzoic acid (left column of the following table; pKa = 4.2) the protonated conjugate acid form is neutral and the benzoate anion conjugate base is negatively charged. We can calculate that the ratio of benzoate anion to benzoic acid (neutral) at pH 7.4 is $1 \times 10^{3.2}$ or roughly 1500:1. Thus carboxylic acid drugs are negatively charged in the blood and penetration into tissues will be dependent on the lipophilicity (log P) of the conjugate acid which is neutral. Also these types of drugs tend to be bound to plasma proteins (albumin) and have high unbound volumes of

distribution. Almost all of the compound is in the anion form that cannot pass through membranes. If we consider the GI tract which is more acidic at the upper end this ratio shifts in favor of the neutral species. For instance at pH = 4.2 approximately 50% is present as the neutral form and absorption of carboxylate containing drugs in general is fine as long as there are not other ionizable groups such as is present in amino acids.

The presence of other ionizable groups complicates the relationship. For instance, amino acids are amphoteric (zwitterionic) and always charged. Amino acids can only pass membranes via transporters and we see examples where transporter deficiencies for particular essential amino acids can cause disease due to a lack of adequate levels of the amino acid absorbed from the diet. Many drugs are zwitterionic due to critical binding interactions with the target.

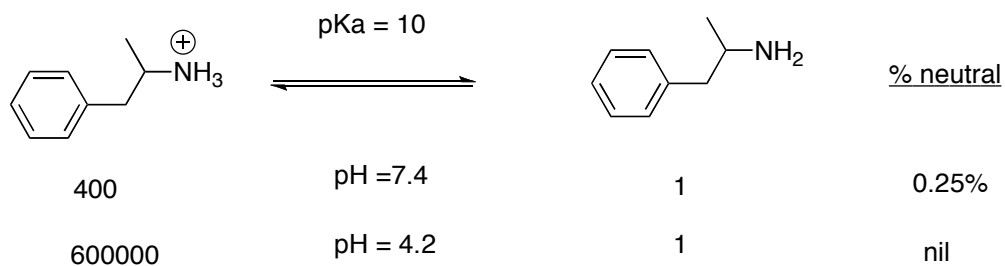
Aromatic amine example:



Lower pH favors the charged conjugate acid

The pKa of aniline is 4.6, which is very similar to benzoic acid. However in the case of aniline the conjugate acid, the anilinium ion, is charged and the conjugate base, aniline is neutral. This is opposite to benzoic acid that has a similar pKa see above. We can calculate that the ratio of the conjugate base (aniline) to the conjugate acid (anilinium ion) at pH 7.4 as above which yields a ratio of $1 \times 10^{2.8}$ or roughly 280:1 in favor of the neutral form. Thus we would expect that absorption of an aniline type drug to be rapid and to occur towards the distal (more basic) portion of the GI tract. We would also expect logP to be less problematical as a determinant of absorption and distribution since the neutral form usually predominates.

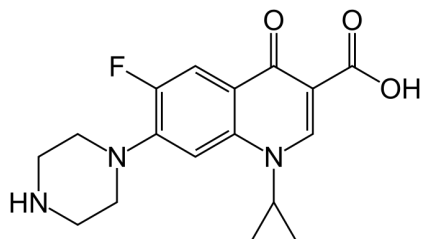
Aliphatic amine example:



Lower pH favors the charged conjugate acid

The pKa of amphetamine is 10 thus the charged conjugate acid predominates at most physiological pH values. The neutral conjugate bases of amine drugs are generally highly lipid soluble and most simple amines are well absorbed. The blood brain barrier is more problematical for neuroactive agents.

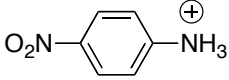
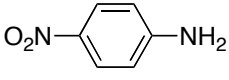
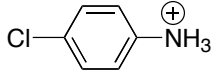
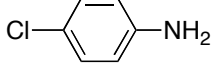
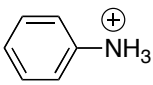
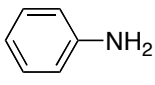
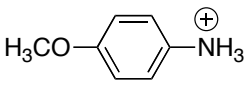
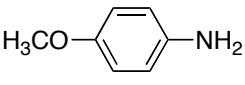
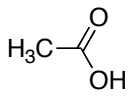
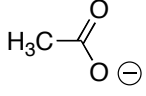
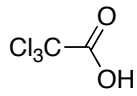
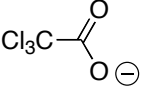
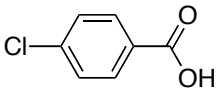
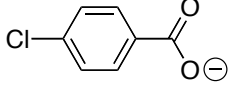
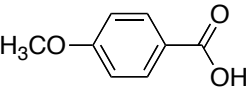
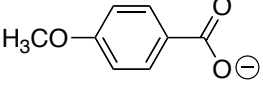
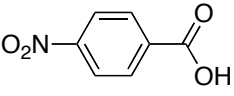
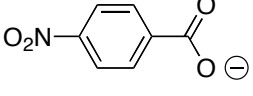
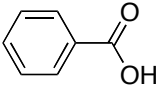
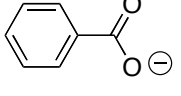
Multiple ionizable groups are often present in drugs.

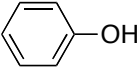
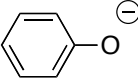
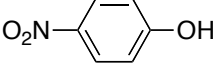
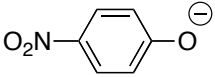
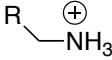
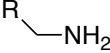
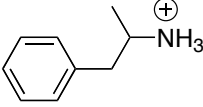
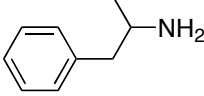
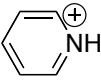

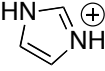

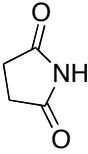
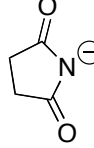
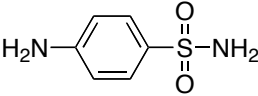
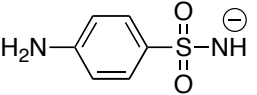
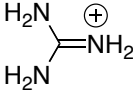
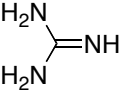


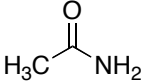
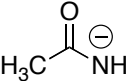


Ciprofloxacin is zwitterionic due to three ionizable groups (carboxylic acid (pKa = 4.5); aliphatic amine (pKa = 9-10); aromatic amine (pKa 4.5)). It bears at least one charge over the pH range of interest (2-9) and will not pass through membranes. Thus one would predict poor bioavailability. However, ciprofloxacin is absorbed from the GI tract due to uptake transporters however the bioavailability is limited (60%).

Note: The structures of most drugs are usually shown as the neutral species along with an associated pKa. This can be confusing/irritating if it is not readily apparent whether the neutral species is the conjugate acid (phenols, aliphatic or aromatic carboxylic acids, sulphonamides, imide (barbituates)) or the conjugate base (aromatic amines, alkylamines, pyridines, imidazoles, azole). Obviously if you are given the name of a drug and it's pKa without structural information you cannot know how it will behave at different pH values and what the ionization state is at pH 7.4. Sometimes this can be really difficult, particularly on exams. Over the course of the next three quarters you will see many examples where the pKa's of functional groups drive properties such as receptor affinity and absorption so you will develop a working knowledge as you go along and an intuition about ionizable groups.

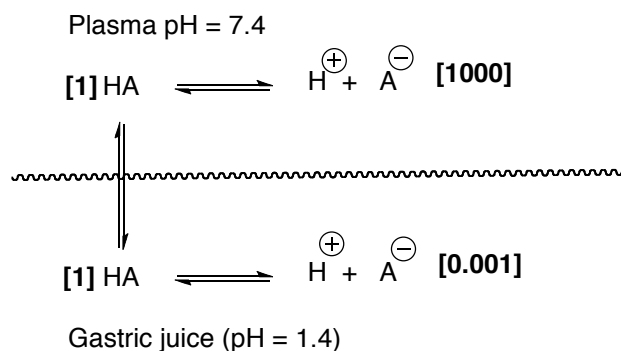
Some characteristic functional groups and pKa's are shown below. The list is not exhaustive by any means but should trigger your long-term memory from MedChem 400.

Conjugate Acid	pKa	Conjugate Base
	1.0	
	4.0	
	4.6	
	5.3	
	4.8	
	0.8	
	4.0	
	4.5	
	3.4	
	4.2	

Conjugate Acid	pKa	Conjugate Base
	9.6	
	7.2	
	10	
	10	
	5.0	
	7.0	
	10	
	11	
	14	
	16	
	18	

Some other trends of note

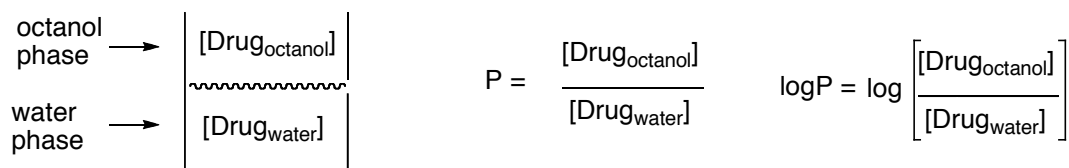
1. For series of similar compounds with different substituents, electron withdrawing groups tend to lower pKa values whether the effect is due to inductive effects or resonance. Electron donating groups tend to raise pKa values.
2. The pKa's of aliphatic and aromatic carboxylic acids are similar (pKa = 3-5) and they are all referred to as weak acids (Strong acids have pKa's less than 2 and are always ionized).
3. The pKa's for aromatic amines (3-5) are roughly 6 pKa units lower than aliphatic amines (8-10). Aromatic amines, pyridines and imidazoles are generally called weak bases. Aliphatic amines are called strong bases.
4. For most purposes the use of integer pKa values are sufficient for estimating % ionized. This makes it easy to calculate estimates of % unionized.
5. Lipophilicity is also important: Many drugs will pass passively and rapidly through membranes despite the fact that as little as 0.1% of the drug is in the uncharged form. This is because the relative lipophilicity of the uncharged form will contribute substantially to the overall rate of transfer across membranes (permeability).
7. Good systemic bioavailability is often hard to achieve. For some drug classes, both good bioavailability and pharmacological efficacy have not yet been achieved in a single compound.
8. Important concept: When a membrane separates compartments of different pH the total concentration of an ionizable drug will be different in each compartment while the concentrations of the unionized species will be the same. This is particularly important in the GI tract lumen and kidney tubules which are adjacent to the blood. What is the pKa of the drug (HA) shown below? Would you expect reasonable absorption in the intestine? Gastric absorption is limiting for many drugs. Here the pH gradient drives absorption and final equilibrium strongly favors the blood. Now think about the kidney where the proximal tubule pH is variable but usually slightly acidic.



Lipophilicity

The relative physicochemical properties of a drug or series of drugs can be related to ADME and pharmacological effect. In drug design lead compounds are modified to optimize these properties as well as others (like minimizing off target effects). Here a basic core structure called a pharmacophore is systematically modified by changing functional groups, lipophilicity, solubility, size and pKa values. In some cases, ADME can also be improved by creating a prodrug or altering the formulation. You will learn about some successes and failures as you study the various drug classes. Lipophilicity is a major factor and has it's own language.

Log P is partition coefficient that is a quantitative measure of lipophilicity. Here the solubility of the unionized form of the drug in a lipid phase (octanol) and water is compared and expressed as a ratio. Octanol and water are immiscible, so the solution has two phases with the octanol on top. Typically the drug is dissolved in the more soluble solvent, equilibrium established and the concentrations of the non-ionized species in the two phases is measured. Log P is measured for only the non-ionized species.



Equal solubility in both phases gives a $P = 1$ and a $\log P = 0$. Most drugs have positive $\log P$ values. Importantly Log P values are independent of pH.

Note that most drugs are partially ionized in water. This means that a direct measure of $\log P$ requires that we know the concentration of the non-ionized species and ignore the ionized species. Charged species are not soluble in octanol. While $\log P$ is known for many drugs based on experiment, we usually resort to a $\log P$ that has been calculated using a computer. This value is referred to a clogP (calculated $\log P$).

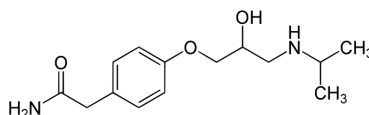
Log D is a partition coefficient that is quantitative measure of the ratio of **total drug** in each phase. For non-ionizable drugs $\log D$ and $\log P$ are the same. For ionizable drugs $\log D$ is highly dependent on pH of the aqueous phase. $\log D$ then is more representative of the partitioning between a membrane and the aqueous phase such as a drug in the GI tract. Lets look at an two examples. We use the earlier data at different pH values for benzoic acid and aniline.

	Benzoic Acid; pKa = 4.2; logP = 1.8				Aniline; pKa = 4.6; logP = 1.03			
pH	4.2		7.4		4.2		7.4	
Species	HA	A ⁻	HA	A ⁻	BH ⁺	B	BH ⁺	B
octanol	63	--	63	--	--	10.7	--	10.7
water	1	1	1	1500	2.5	1	.003	1
D	31.5		.042		3		10.7	
Log D	1.5		-1.4		0.5		1.02	
Log P	1.8		1.8		1.03		1.03	

We note that:

1. Log D for weak acids (conjugate acid is neutral) decreases as pH increases.
2. Log D for weak bases (conjugate acid is charged) increases as the pH increases.
3. Since log D is pH dependent the pH must be noted. Often seen in a subscript (Log D_{7.4}; Log D_{4.2}; etc).
4. pKa, logP and log D_{pH} values are related. If you know any two values you can calculate the third.

Let's look at some data for the absorption of various beta blockers which are all secondary aliphatic amines with no other ionizable groups. Atenolol below (pKa = 9.2).



Drug	LogP	Log D(7.4)	% Absorbed
Nadolol	0.56	-2.1	30%
Atenolol	.033	-1.7	50%
Acebutolol	1.77	-0.3	90%
Betaxolol	2.53	0.43	100%
Propranolol	2.9	0.79	100%

Here we see the effect of lipid solubility on extent of absorption from the intestine into the portal blood. As expected increased log P and log D confers better absorption. Since the pKa values for the amines are similar we see parallel changes in Log P and Log D. Also be careful to differentiate between % absorbed and bioavailability. The bioavailability of atenolol is 40 to 50%. The bioavailability of propranolol is around 25% due to hepatic first pass metabolism.

Many of the beta blockers are relatively resistant to metabolism and are then excreted unchanged in the urine. Based on the principles you learned about renal clearance it should be logical to you that the % unchanged in the urine for a class of drugs with similar structure should be inversely related to log P and log D. In this case that relationship is observed.

Drug	Log D(7.4)	% excreted unchanged
Sotalol	-1.7	80%
Practolol	-1.5	90%
Atenolol	-1.7	85%
Metoprolol	-0.5	10%
Betaxolol	0.43	15%

High lipophilicity can be a bad thing.

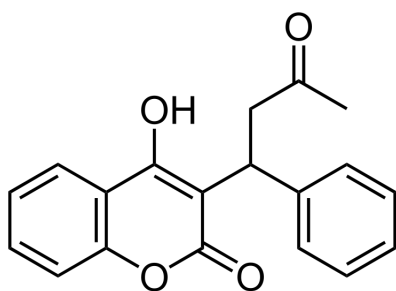
Highly lipophilic drugs ($\log P > 5$, octanol/water ratio $> 100,000$ to 1) are normally readily absorbed, however they partition into the lipid compartments (large V_d), have long half-lives (difficult to dose) and may persist in the brain. Examples of these kinds of drugs are amiodarone ($\log P = 7.8$), Proxicromil ($\log P = 4.9$) and Penfluridol ($\log P = 7$).

ADME and Lipinski's Rules

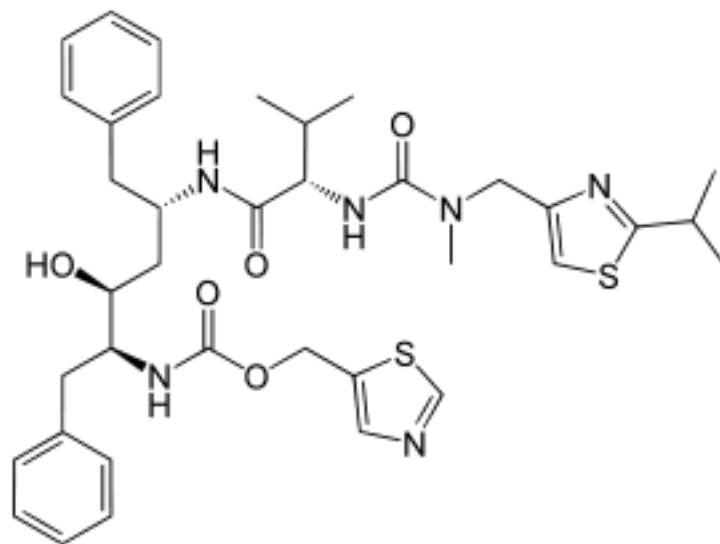
Lipinski's rule of was derived from analysis of large data base of known drugs and clinical failures for which extensive data had been collected. It was meant to provide a set of rules that could be used to guide the development of new drugs that would be orally active. These rules are empirical and impact each component of ADME to some extent. For instance an orally active drug has to escape first pass metabolism. They are most widely applied to creating drugs that are absorbed. These rules do not predict pharmacological activity (ie receptor binding). They are widely used in the industry and have undergone a number of refinements and additions. Obviously not all of the drugs on the market fit the rules.

Lipinski's rule states that, in general, an orally active drug has **no more than one violation** of the following criteria:

1. Not more than 5 hydrogen bond donors (R-O-H and R-N-H). (RTV = 4)
2. Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms) (RTV = 11)
3. A molecular weight less than 500 grams/mole (RTV= 728)
5. An octanol-water partition coefficient, $\log P$, not greater than 5 (RTV = 7.5).



Warfarin



Ritonavir (RTV)