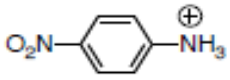
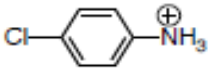
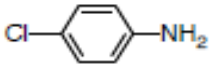
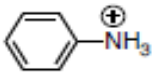
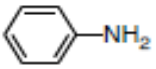
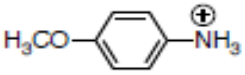
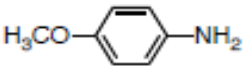
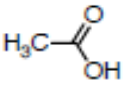
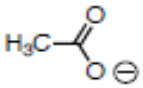
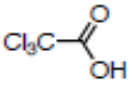
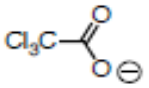
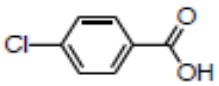
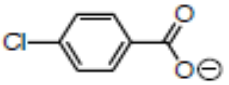
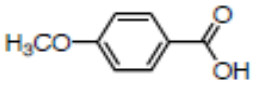
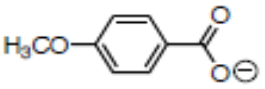
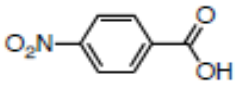
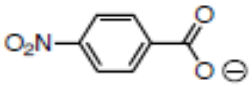
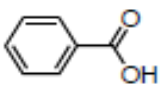
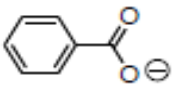
**Lecture 2: Physicochemical Properties** (continued)

Always keep in mind physiological pH when discussing pKa values. Blood (plasma/serum) pH is about 7. Stomach is about 1-2 and distal part of colon about 9-10.

| 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 |
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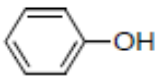
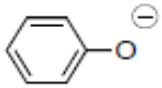
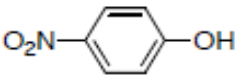
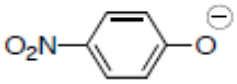
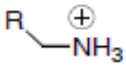
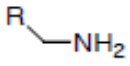
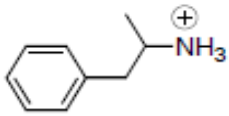
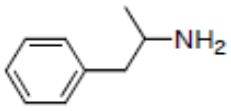
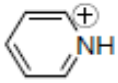
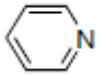
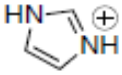
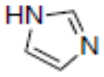
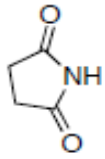
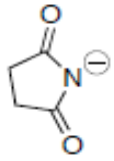
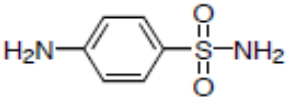
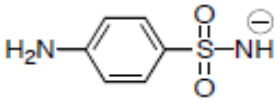
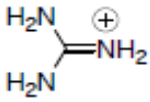
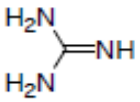
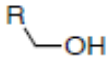
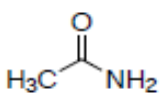
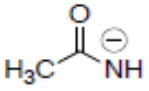
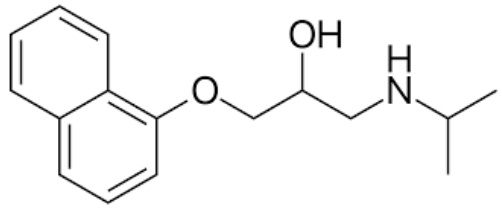
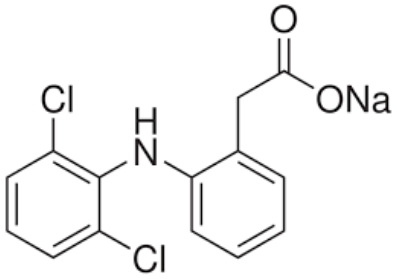
|  | 9.6 |  |
|  | 7.2 |  |
|  | 10 |  |
|  | 10 |  |
|  | 5.0 |  |
|  | 7.0 |  |
|  | 10 |  |
|  | 11 |  |
|  | 14 |  |
|  | 16 |  |
|  | 18 |  |

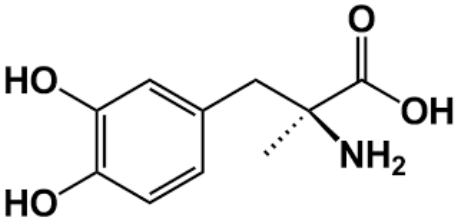
**Some examples of actual drugs:**



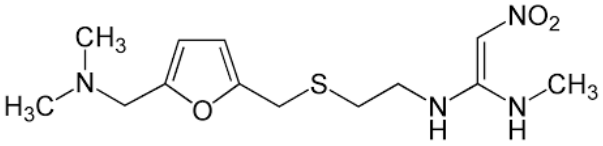

**Propranolol**



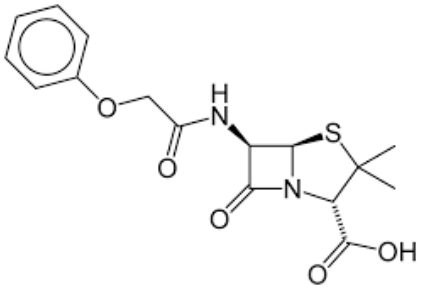

**Diclofenac sodium**



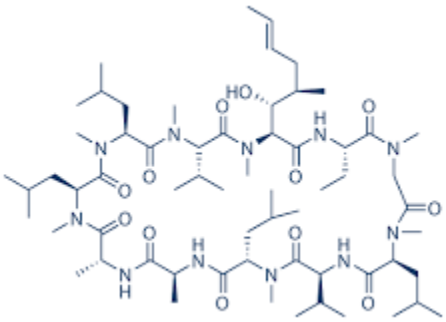

**Methyldopa**



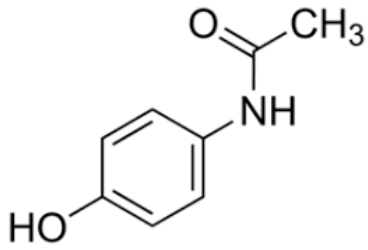

**Ranitidine**



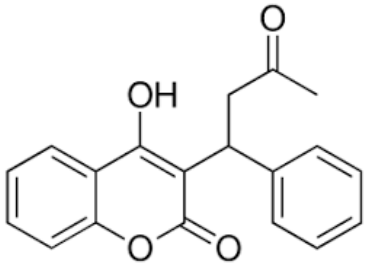

**Penicillin (G)**




**Cyclosporin**




**Acetominophen**



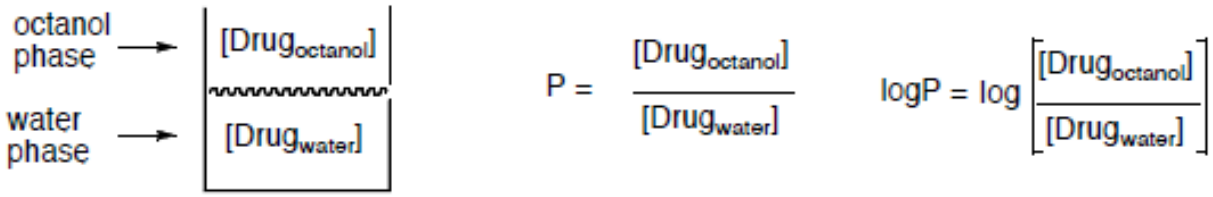

**Warfarin**

**Drug permeability and lipophilicity**

In addition to charge, liphophilicity can have a major impact on drug absorption. Lipophilicity is (lipo = fat) and (philicity = love) means “fat loving”. Recall from Figure 3, (Lecture 1) that membranes are rich in lipids (fat). Therefore, in general if a drug is lipophilic, it can dissolve into and through membranes more readily.

We have technical terms for describing lipophilicity and they are logP and logD. These terms are actually quite similar as they both reflect the partitioning of drug between an octanol phase and an aqueous phase (water or buffer). LogP is the logarithm of the ratio of drug in the octanol phase over the water phase. For **logP**, we measure the ratio of uncharged drug only. For **logD**, we include the effect of charge as we measure the ratio of total drug in each medium (octanol or buffer) and we specify the pH of the water.

**LogP:**

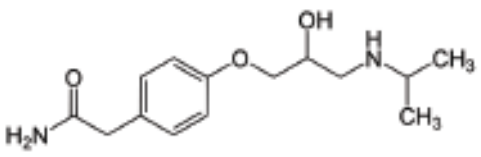



Regardless, in either case **high logP** and **high logD** values tend to increase drug absorption up to a limit. But if the value gets too high, then the drug becomes insoluble in water and can’t dissolve in water. Again, consider Figures 4 and 5 (lecture 1). The very first step in drug absorption by the oral route is dissolution of the drug into gastric and GI fluids (both aqueous).

Some example beta blocker drugs with LogP and LogD values along with the percentage of oral absorption are shown below. Notice that in general, as logP and logD values increase, so does the % absorbed.

| 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% |

The structure of these beta blockers are similar to that of atenolol, shown here. They all have an ionizable amino group with a pka value around 9.




**Atenolol**

What features in a drug cause increases in logP and logD?

Simply put, lots of carbon atoms and hydrogen atoms as well as halogens will cause increases in logP and logD values. So, -CH-, -CH2-, -CH3, and aromatic rings. Also F, Cl, Br atoms will increase logP and logD values.

On the other hand, lots of functional groups that increase polarity and engage in hydrogen bonds with water will cause decreases in logP and logD values. So, functional groups like -OH, -NH, -NH2.

**Lipinski's Rules** are listed below and were arrived at empirically by observation of the behavior of many orally absorbed drugs and their clinical effects.

1. Not more than 5 hydrogen bond donors (R-OH, and R-NH).
2. Not more than 10 hydrogen bond acceptors (oxygen and nitrogen atoms).
3. A molecular weight less than 500 grams/mole.
4. A logP value not greater than 5.

In general, the rule states that an orally active drug will not have more than one violation of the above rules. Of course, there are always exceptions. And this is especially true if a drug can be shunted by a transporter.

Finally, never confuse oral absorption with oral bioavailability. Remember that oral bioavailability is also impacted by first pass metabolism and transporters- mainly by the liver and the intestines. A drug can be orally absorbed quite well but undergo extensive first pass metabolism such that it has very low oral bioavailability.

And as stated above, the lipophilicity and/or charge(s) on a drug can play important roles in how the drug interacts with its target (receptor, enzyme, DNA, etc.).