Pharmacokinetics from medicinal point of view

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A definition of medicinal chemistry

- A definition of medicinal chemistry was given by a specialized IUPAC commission:
- “Medicinal chemistry concerns with the discovery (lead compounds, improvement of potency, selectivity and toxicity), the development (improvement of pharmacokinetic properties), the identification and the interpretation of the mode of action of biologically active compounds at the molecular level.

Definition of Medicinal Chemistry

- Medicinal chemistry is also concerned with the study, identification, and synthesis of the metabolic products of these drugs and related compounds. ”
- Drugs – natural and synthetic alike – are chemicals used for medicinal purposes. They interact with complex chemical systems of humans or animals.

Definition of Medicinal Chemistry

- So, it is the science that studies the relationship between the chemical structure of the drug/ molecule with its biological activity.
- In our course, this relationship will be studied from different aspects:

1- Structure-activity relationship (SAR):

- Topological match (3D structure match)
- Attraction forces

2- structure-pharmacokinetics relationship:

- Absorption, distribution, metabolism and excretion (ADME)

3- Metabolism

4- Prodrugs

Structure activity relationship (SAR)

- 3D match: brings the drug closer to the receptor, thus increases attraction forces

- Optical isomerism
- Geometrical isomerism
- Conformational isomerism
- isosterism

- Attraction forces:

- Electrostatic, Van der Waal, covalent, H- bonding

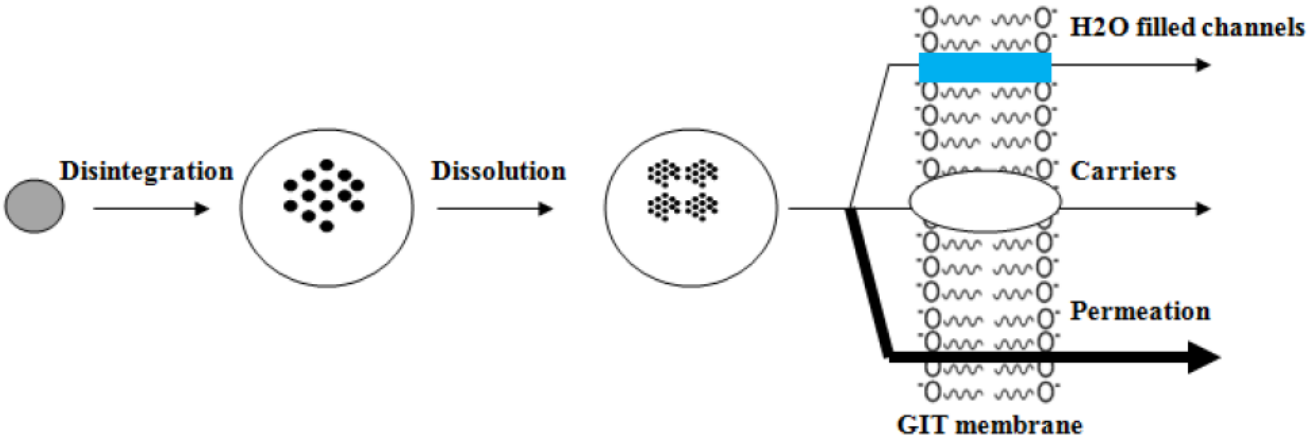
ADME

- Absorption
  - ➡ how do the drugs enter the body?
- Distribution
  - ➡ how are the drugs distributed in the body
- Metabolism
  - ➡ chemical modification of drugs (breakdown, increase of hydrophilicity to improve clearance)
- Excretion
  - ➡ how do the drugs leave the body

- Structure - Pharmacokinetics relationship which means we'll study
- Structure – Absorption relationship
- Structure – Distribution relationship
- Structure– Metabolism relationship
- Structure – Elimination relationship
- how the chemical structure affect all these pharmacokinetic profiles

Structure - Pharmacokinetics relationships

- Structure - Absorption relationships
- in order for a drug to be bioavailable the first condition is to be water soluble, if it doesn't dissolve in water (insoluble) it won't be available for absorption



Routes of GIT penetration

- The drugs penetrate the GIT by 3 routs (H_2O filled channels; Carriers; Permeation):
- 1- Water filled channels (minor route)
- Are actually integral proteins forming passage filled with water through which a drug molecule can cross, but they have some restrictions:

a. The molecule must be totally water soluble.

b. The molecule must be very small in size (< 4 Angstrom).

EXAMPLE

- The only known drug to cross the membrane through this route is Li^+ ion which is used in certain psychotic disorders such as bipolar depression
- Lithium is approved by the US Food and Drug Administration (FDA) as a prescription medication for bipolar disorder. It helps stabilize patients quickly.

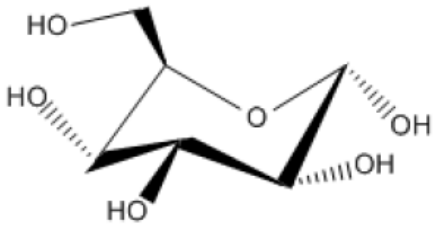
Routes of GIT Penetration

- 2- Carriers (minor route)
- They are integral protein which can carry molecules across the cellular membrane of the GIT.
- Carriers are meant to be used for hydrophilic molecules which are essential for biological activity and don't have the optimal hydrophilic-hydrophobic properties needed to cross the phospholipids bilayer of cellular membranes.

Routes of GIT penetration
2- Carriers (Example)

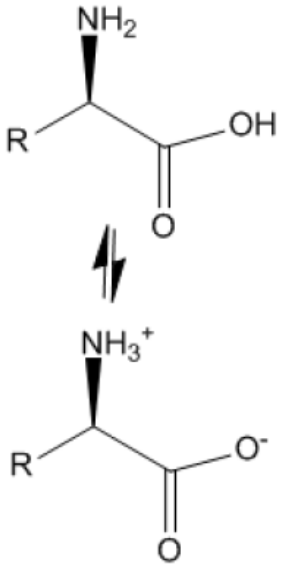
Glucose (α-D-glucose)

Is very essential and is hydrophilic due to the presence of hydroxyl groups in its structure and it can't cross the phospholipid bilayer by simple diffusion, it needs a carrier.



Amino acids

Are essential compounds which contain a carboxyl and an amine group in their structure which are ionized under physiological pH carrying +ve and -ve charges at the same time (zwitterion), so they need carriers.



In order for a drug to cross through a carrier, it must be very similar to one of the essential molecules found in nature because those carriers have 3 special characters:

- a. Very stereoselective: They can distinguish certain arrangement of atoms in the 3 dimensional space.
- Example: Amino acids in natural are "L" form (= S form), so it will recognize the L form not the D form amino acids.

- b. Saturable: They can carry limited number of molecules per unit time, so increasing the dose will increase the bioavailability of a particular molecule up to a certain limit.

To overcome this problem in clinical practice those drugs are given in small divided doses instead of single large doses, or using controlled release formulations.

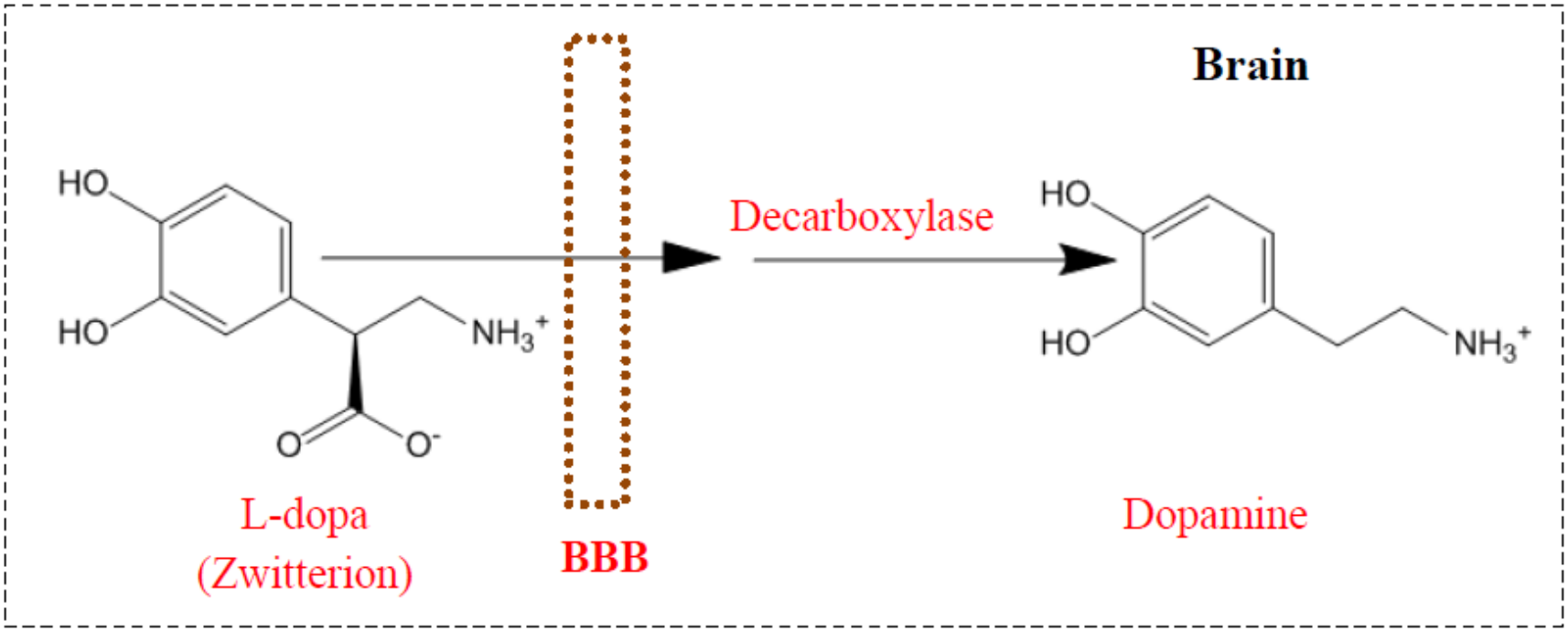
- c. They either use energy or not.

- Facilitated diffusion: transport with the concentration gradient and don't need energy.

- Active transport: against the concentration gradient so it needs energy.

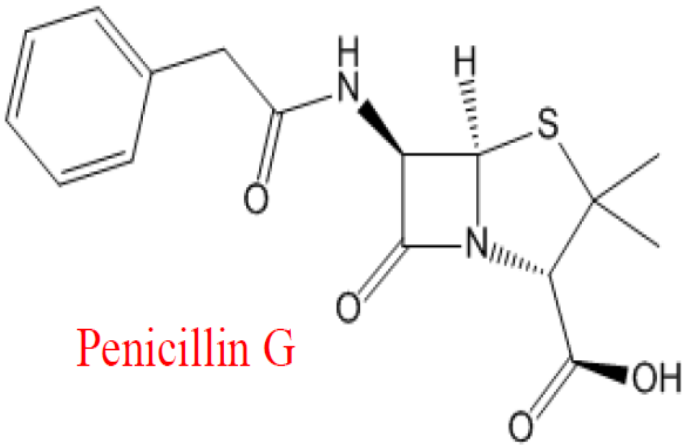
- EXAMPLE (Important)
- L-dopa
- Parkinson's disease is related to deficiency of dopamine which is an amine (pKa=9.5).
- Under physiological conditions (pH=7.4) which are acidic conditions having enough hydrogen to keep it protonated (+vely charged) so it's difficult to administer dopamine because it can't cross the BBB due to its charge. If dopamine was given orally, it will cause peripheral side effects (hypertension due its adrenergic activity).
- To overcome this problem, we changed dopamine to its corresponding amino acid form L-dopa which is a liable substrate for the amino acids' carriers found on the BBB.
- Inside the brain, L-dopa is converted to dopamine under the action of L-dopa decarboxylase. L-dopa is carried throughout both the BBB and GIT membrane. (BBB is similar to GIT membrane even tighter).

L-dopa

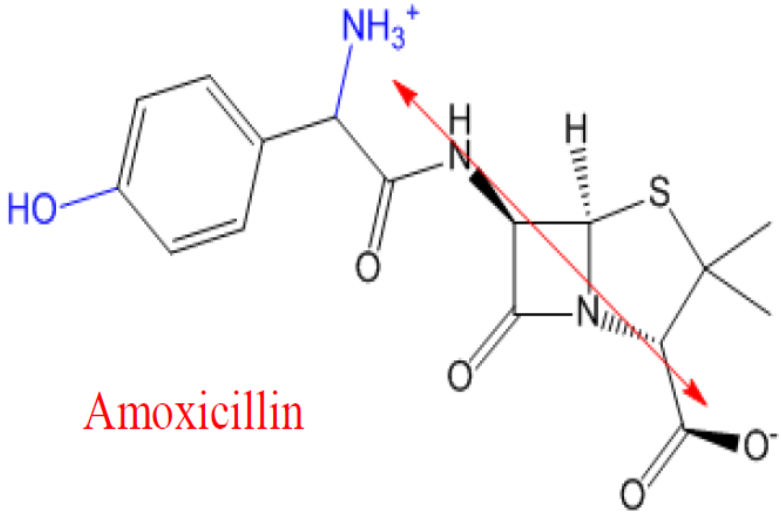

Brain
HO
HO
NH3+
O
O-
L-dopa
(Zwitterion)
BBB
Decarboxylase
HO
HO
NH3+
Dopamine

2- Carriers: Example

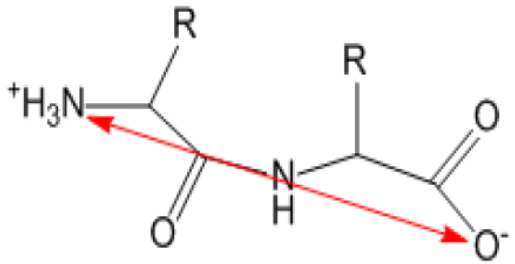
- Penicillin's
- 1st discovered is Penicillin G which is orally inactive, but when converted to Ampicillin
- the carboxylic acid (pKa= 3) is ionized to carboxylate which is -vely charged and the amine +vely charged through GIT (pH= 1-8).
- Ampicillin structure is similar to dipeptides, making it a good candidate to be carried across the GIT by carriers originally found to carry di- and tri-peptides formed by protein break down.
- Ampicillin bioavailability can reach a maximum of only 60-66% because the carriers are saturable.



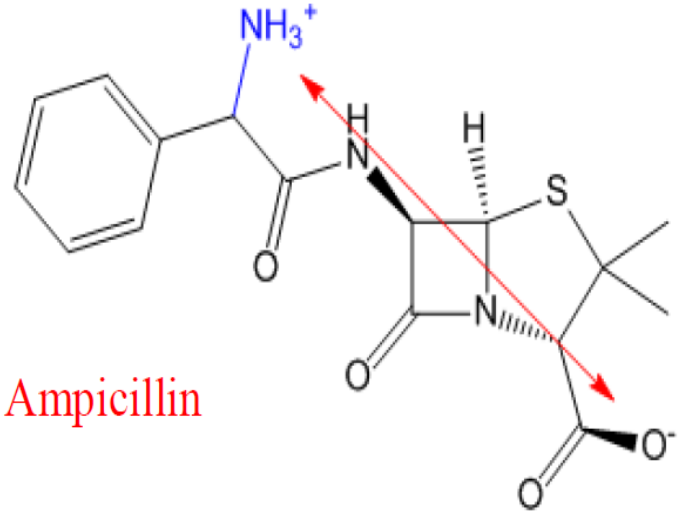
Penicillin G



Amoxicillin



Dipeptides



Ampicillin

2- Carriers: Example

- Other EXAMPLES on drugs that cross through carriers are a group of anticancer drugs called Antimetabolites which are compounds very similar to natural metabolites.
- Uracil is a nitrogenous base that gets incorporated into RNA by being converted to nucleoside (+Ribose sugar) then to nucleotide (+Phosphate).
- If we make isosteric replacement of a hydrogen H by flour F (size wise) we produce Fluorouracil which can compete with uracil carriers therefore blocking its absorption to cells and blocking RNA production killing the cell, so it's used as an anticancer agent.

Uracil **Fluorouracil**

3. Permeation by partitioning (major) The 3rd route of absorption

- Permeation is to cross the membrane by dissolving in the phospholipid bilayer in a process called partitioning.
- If a drug has optimal hydrophilic/hydrophobic properties, then the drug can partition itself and dissolve in both phases (water and oil) to certain limit. After dissolving in water outside the cell it starts to partition in both phases, and then after saturating the oil phase (phospholipid bilayer)
- it starts to partition toward the other water phase inside the cell.

3. Permeation by partitioning (major)

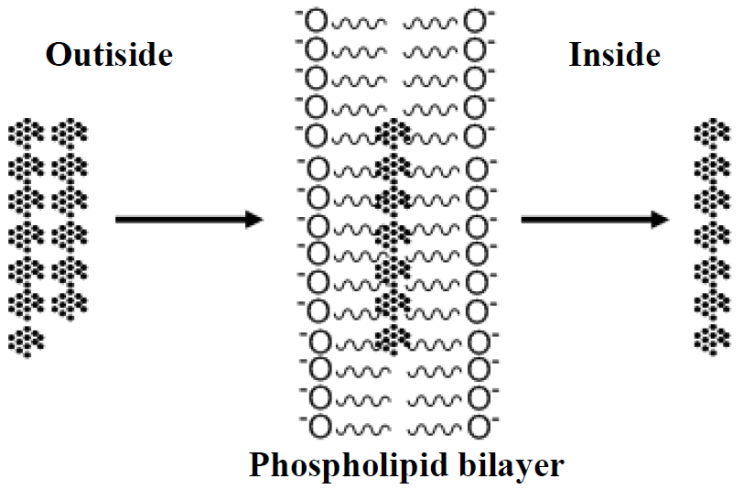
In order for partitioning to occur, 2 conditions must exist:

a. The drug must be unionized

If it was ionized: the +vely charged drug will be adsorbed to the -vely charged phospholipid bilayer heads; while repulsion between -vely charged drugs and the –vely charged phospholipid bilayer heads. Also the charge will make the drug hydrophilic therefore insoluble in the lipid bilayer.

b. The drug must have optimal Hydrophilic/Hydrophobic properties

In order to get partitioned between water and fatty layers.



Drug ionization very important

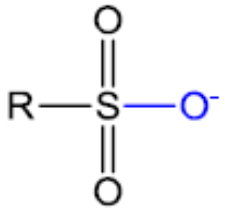
- Drug ionization
- We can classify the drugs found in pharmacopeia according to ionization to 3 classes:
- 1. Strong acids and bases.
- 2. Weak acids and bases.
- 3. Intermediate acids and bases.

- Strong acids and bases
- Strong acids...
- Their pKa is 2 or less, and the stomach pH= 1-3 while intestine pH= 7-8; the pH through all the GIT is higher than the pKa which represents basic conditions for this strong acid shifting the equilibrium toward A- side, therefore it will be ionized through all the GIT and its ionization accounts for high hydrophilicity making it unavailable for absorption through oral route.

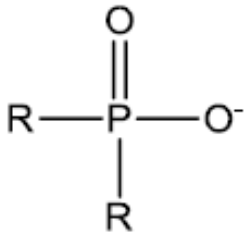
- EXAMPLES
- Sulfonic acid group pKa<1 so it's always ionized and we expect the drug carrying sulfonic acid group to be totally ionized through the GIT therefore orally unavailable.

Summary examples on strong acids expected to be orally not available

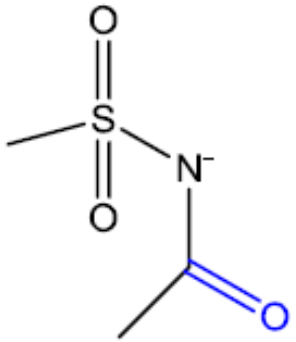
Sulfonic acid



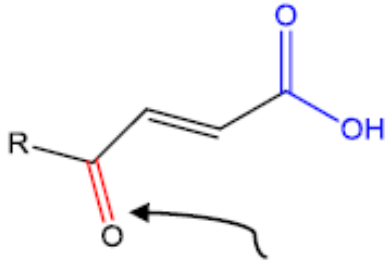
Phosphoric acid



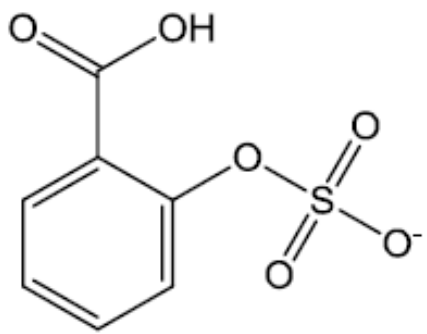
Sulfonamides
(with carbonyl at N)



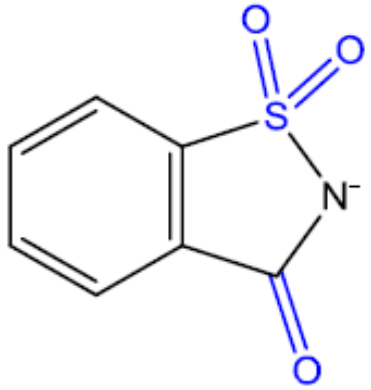
Carboxylic acid
(conjugated to EWD)



Sulfosalicylic acid

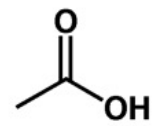


Saccharine

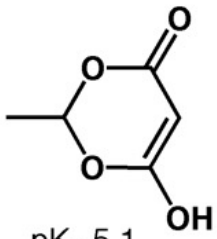


roduction

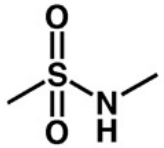
Acidic bioisosteres



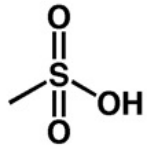
pK_a 4.75
tPSA 37.3
cLogP -0.19
CMR 1.29



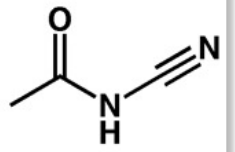
pK_a 5.1
tPSA 55.7
cLogP -0.26
CMR 2.86



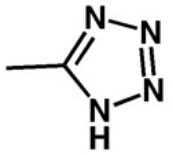
pK_a 10.7
tPSA: 46.17
CLogP: -0.868
CMR: 2.3462



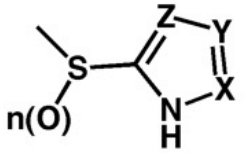
pK_a -1.9
tPSA: 54.37
CLogP: -2.424
CMR: 1.6668



pK_a 8.2
tPSA: 52.89
CLogP: -1.594
CMR: 1.9871

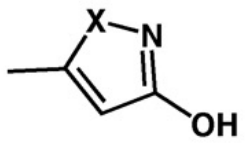


pK_a 4.5
tPSA: 49.11
cLogP: -0.194
CMR: 1.9486



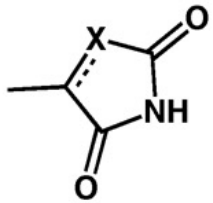
pKa 4.7 - 11.6

X, Y, Z = N, C, CO



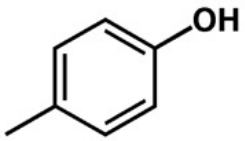
pKa 3.4 - 5.0

X = O, S, NMe

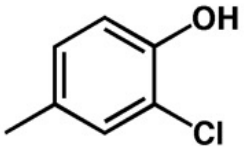


pKa 5.0 - 6.5

X = O, S, N, C

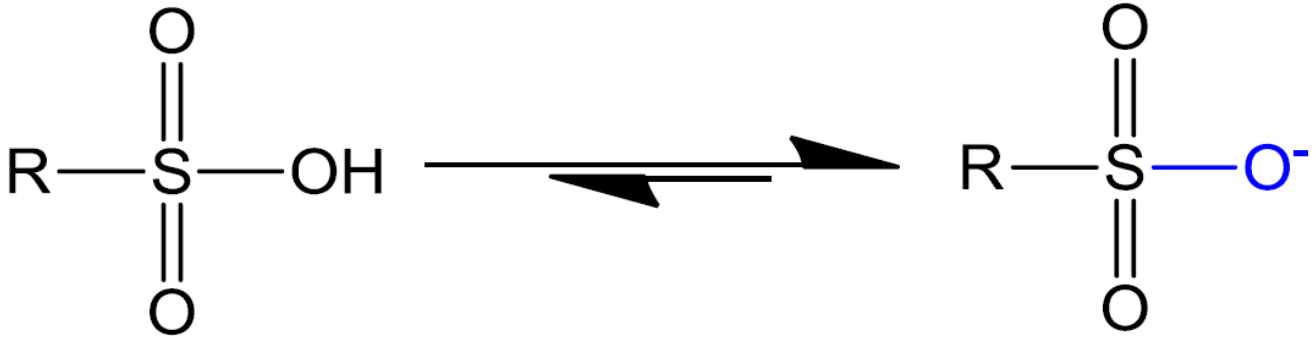


pKa 9.9



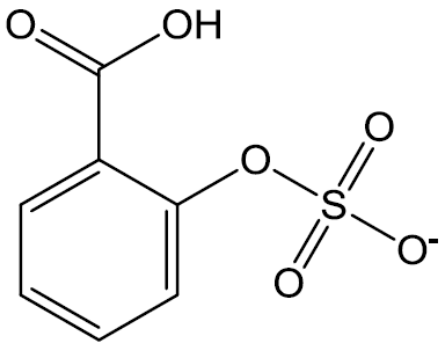
pKa 8.5

- Salicylic acid is the active form of Aspirin (acetylsalicylic acid), salicylic acid is absorbed through the GIT; if I want to treat a local inflammatory condition in the GIT such as Crohn's disease or ulcerative colitis, we can attach a sulfonic acid group to salicylic acid forming sulfosalicylic acid which is not absorbed orally and treat inflammation of the GIT in a local sense minimizing side effects.



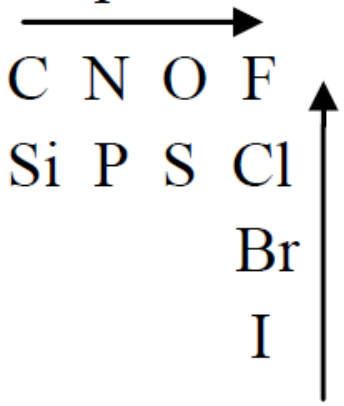
Sulfonic acid

Sulfosalicylic acid



Electronegativity

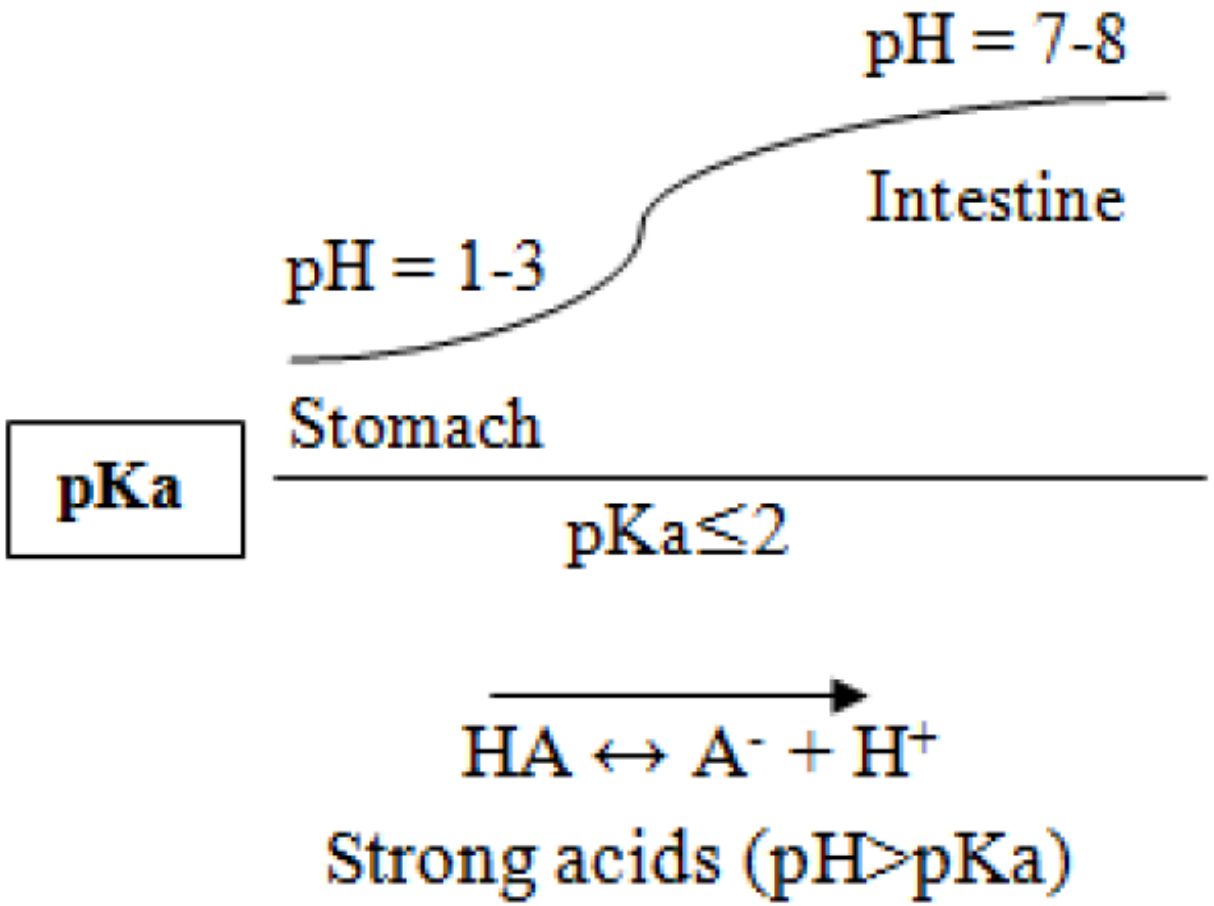
we most concern about this part of the periodic table:



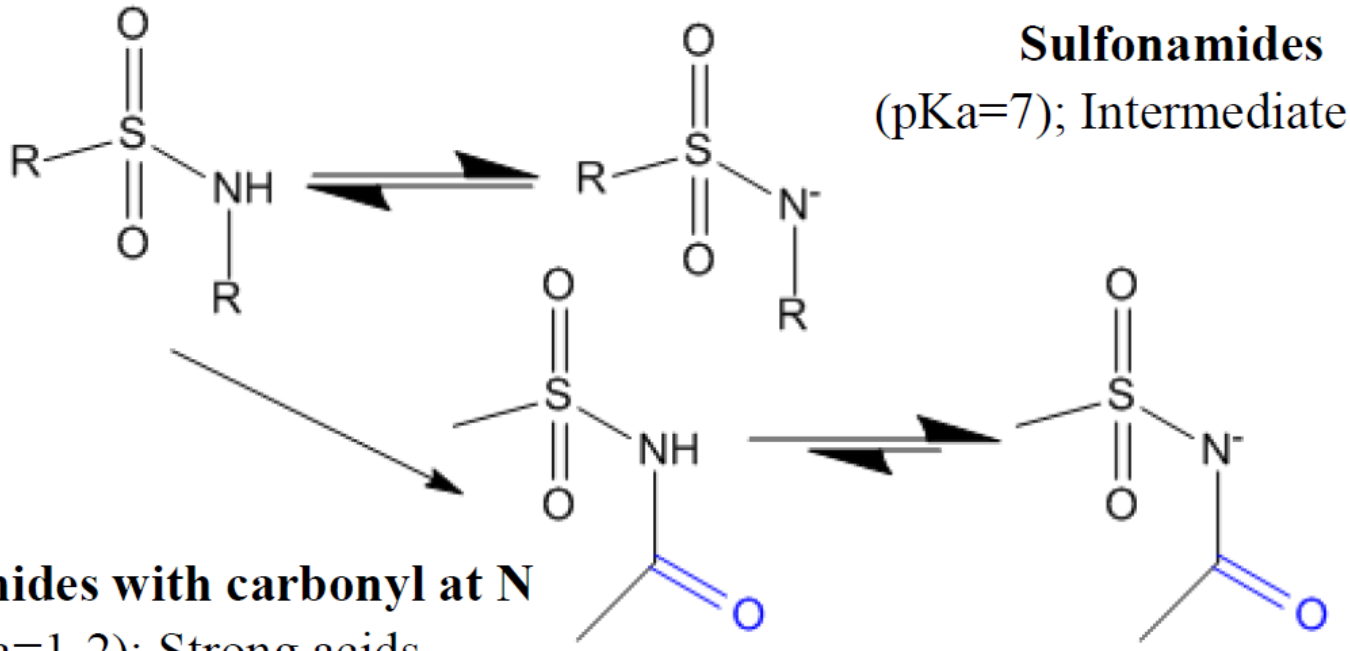
higher electronegative atoms tend to attract the electrons more.

Ex. O withdraw electrons from S in sulfonic acid.

Strong acids...



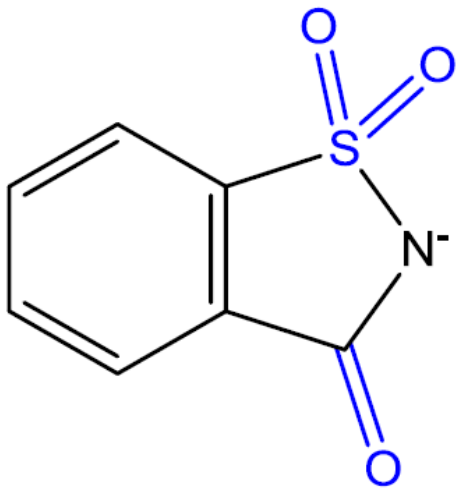
- Another group is sulfonamids which is per say an intermediate acid pKa=7, but if we attach an extra carbonyl to its nitrogen it becomes strong acid pKa=1-2.



- sulfonamide with the carbonyl at the N is nearly as strong as the sulfonic acid with a pKa=1-2; therefore, its orally unavailable.

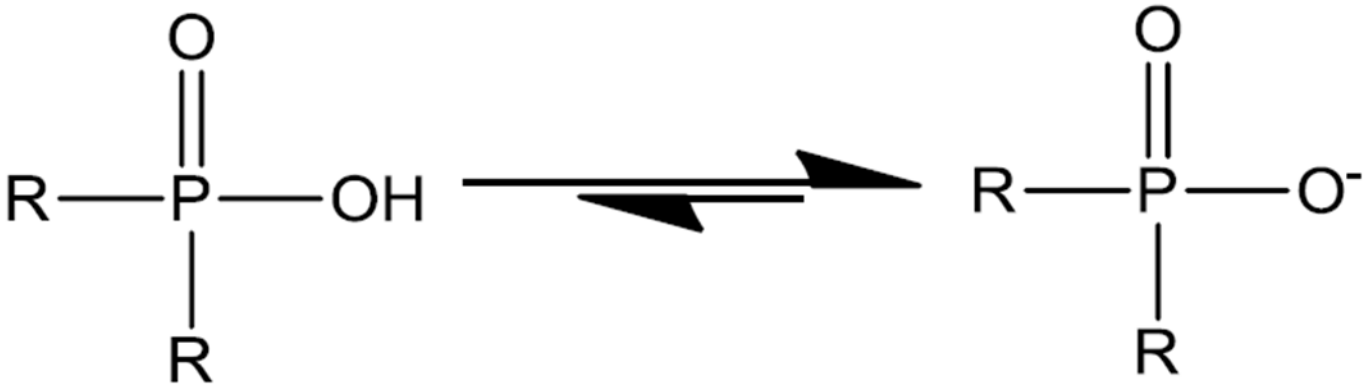
An example is Saccharine produced as Na-Saccharine which is a diabetic sweetening agent; diabetic patient can feel its sweetness without concerning about elevating blood sugar levels because it's eliminated through the fecal system without being absorbed.

Saccharine



- Another example on strong acidic groups which if found in drugs they make them orally unavailable is phosphoric acid;.

Phosphoric acid



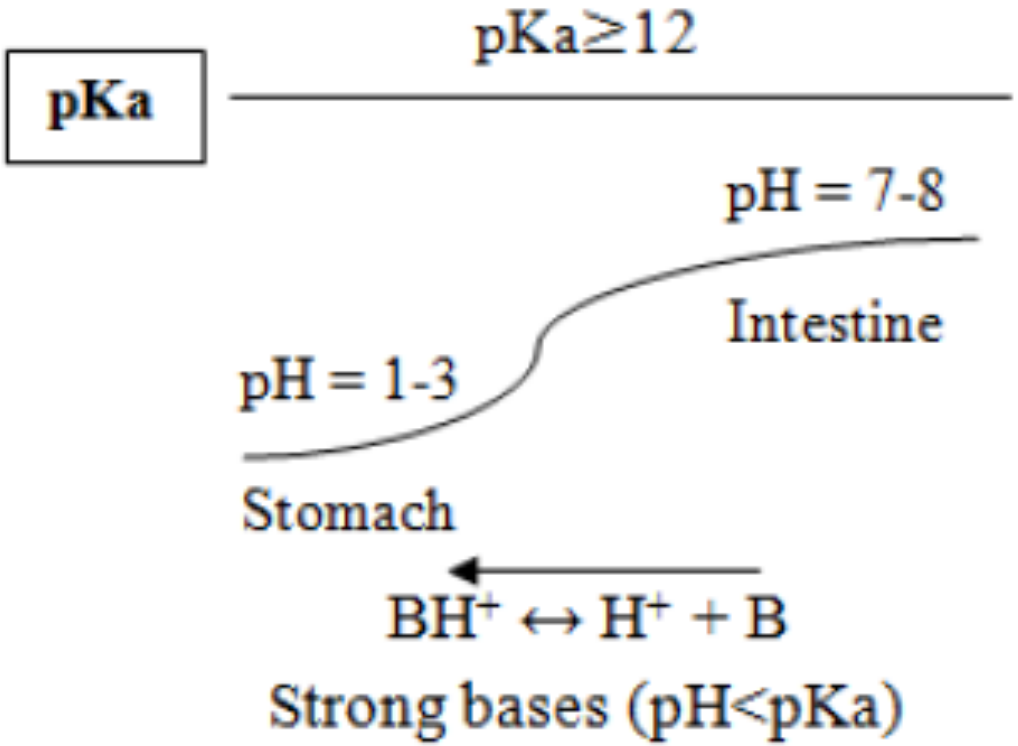
Another example on strong acidic groups

- Carboxylic acid is another group to discuss, even though it's solely intermediate acid with pKa=3-4.5 but if it was conjugated to an electron withdrawing group like carbonyl it will become a strong acid.

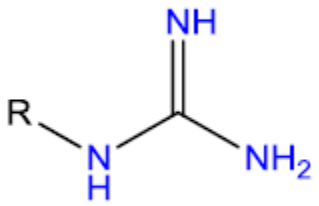
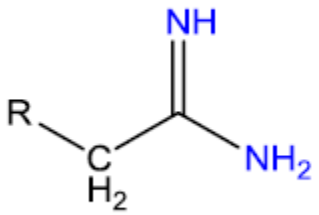
Strong Bases...

- Strong bases have high pKa 12; in GIT
- (pH=1-8) the conditions are continuously acidic and the reaction is shifted toward BH+, as previously said, in order for a compound to be absorbed it has to be unionized but strong bases are permanently +vely ionized through GIT.

Absorption of strong bases

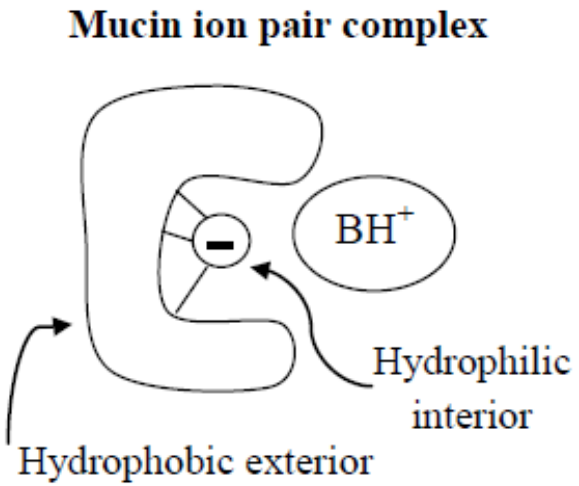


- There are some functional groups if found in a chemical structure they indicate that this structure is permanently +vely charged during passage of GIT; most important ones are:
- Guanidine and Amidine both with pKa 12.

Guanidine	Amidine
	

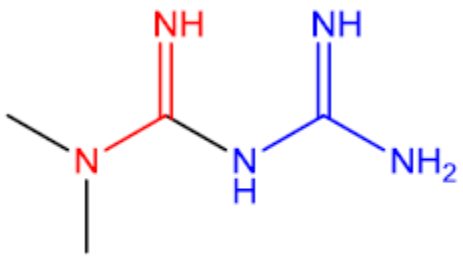
- So, both Guanidine and Amidine if they were found in a chemical structure we can conclude that this structure is permanently cationic (+vely charged) through all the GIT, therefore we expect them to be not available for absorption BUT that's not the case,
- Strong bases actually are of poor bioavailability, unlike strong acids which are completely not available for absorption This poor bioavailability of strong bases is due to the presence of Mucin which is a hydrophobic protein produced by GIT cells bearing a -ve charge on its interior while its exterior is hydrophobic therefore it's able to form complexes with the +vely charged bases forming ion-pair complexes protecting them from water and they're hydrophobic enough to cross the GIT cellular membrane.

What applies to strong bases applies for quaternary ammonium salts; they're permanently ionized however because of the presence of mucin we do have some bioavailability however it's not more than 40%.

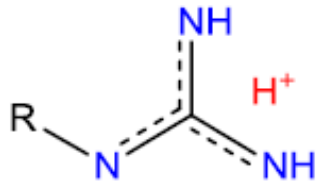


- EXAMPLES
- Metformin (diabetic medication) Its trade name is Glucophage ® ; it has biguanide groups in its structure so it's a strong base with pKa 12 yet it's administered orally!
- It is given in high doses and the physician needs time adjusting the dose for a particular patient due to its erratic bioavailability as the presence of biguanide groups make it permanently ionized and permanently +vely charged as well as variation in the amount of mucin among individuals

Metformin
(biguanide)



The proton in strong bases rotate among the basic groups and so called **tautomerism** which is best drawn as below structure:



Weak acids

- There pKa is 12 or more, which means in the GIT (pH= 1-8) the
- conditions are constantly acidic shifting equilibrium toward HA, therefore weak acids are permanently unionized across GIT so they've well bioavailability not necessarily excellent but they're better candidate to be absorbed orally because there are other important factors controlling bioavailability we mentioned, and we'll discuss in more details later.
- such as optimal hydrophilic/hydrophobic properties represented by lipinski's rule of 5. (we will discuss it later)

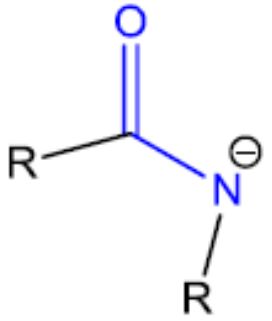
- For example, if the compound is unionized and highly insoluble in water for some reason it won't be bioavailable, therefore we should keep in mind to check on all the factors to judge bioavailability.

Weak acids

- Amides by looking at their conjugate base, they contain an electron withdrawing carbonyl building up a -ve charge on N, yet N isn't strong electronegative enough to stabilize -ve charge efficiently therefore considered a weak acids; their pKa is 12 or more.

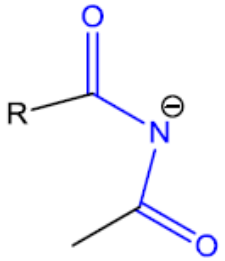
Amides

(pKa≥12)

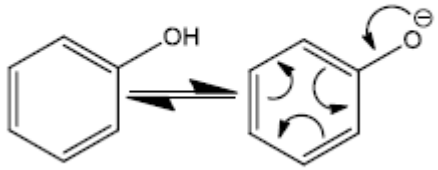


Weak acids

Imides
(pKa=8-10)

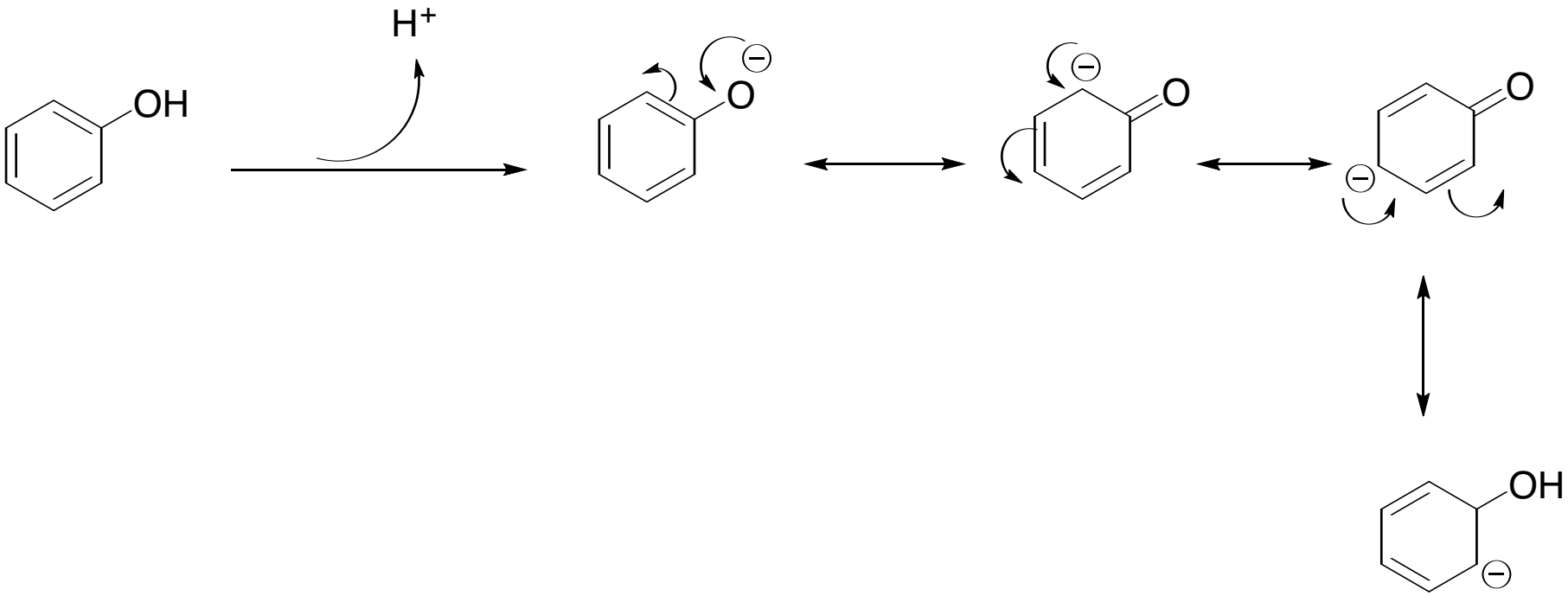


Phenols
(pKa=17)



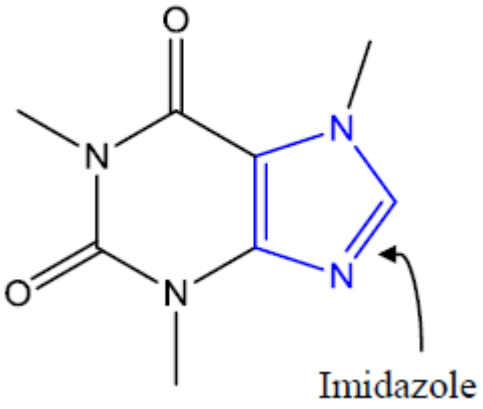
- Imides in fact are also considered weak acids even though they contain 2 electron withdrawing carbonyl which can further stabilize -ve charge on N; their pKa=8-10 so imides are stronger acids than amides but still considered fairly weak acids.
- Alcohols are very weak acids with pKa= 25 and it's impossible to be ionized under normal physiological conditions; Phenols instead are considered weak acids because the -ve charge on the O is stabilized by the conjugated benzene ring resonance; their pKa=10

Phenoxide anion is stable by resonance. This means that phenol can give stable anion upon donating its proton
“They act as an acid"

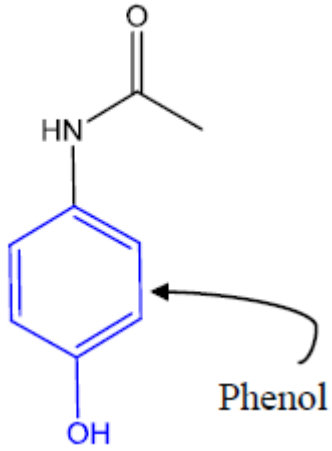


- Heterocyclic nitrogen structures such as in Imidazole group is also considered quite weak acid.
- So, we mentioned Amides, Imides, Phenols and Imidazoles as examples on functional groups which represent weak acids. Also, Alcohols are very weak acids.
- Therefore, if found in a chemical structure, it's expected to be unionized through GIT.

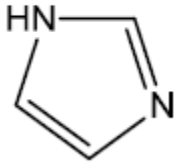
Caffeine



Paracetamol



Imidazole



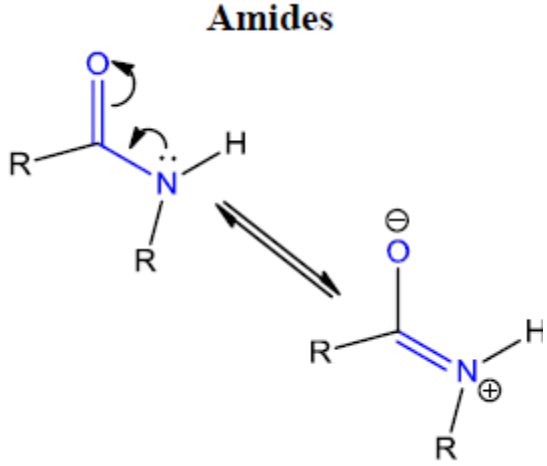
Weak bases

- Their pKa is 1 or less; they're completely the opposite of strong bases like guanidine or amidine which as we said their pKa is 12 or more.
- That means inside all the GIT (pH=1-8) the conditions are constantly basic shifting the equilibrium toward B therefore weak bases are permanently unionized across GIT and so they're better candidates for oral absorption.

What is a basic compound

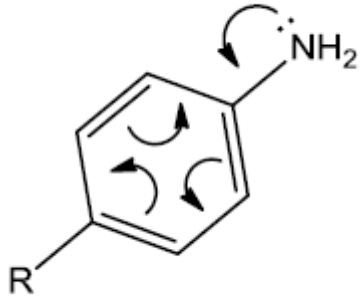
- What makes any chemical group basic is its ability to donate pair of unshared electrons.
- Amines are the most important basic functional group in most chemical structures, because its N is able to share pair of unshared electrons unlike O in case of alcohols, which has 2 pairs of unshared electrons but doesn't share them, because O is more electrophilic.

- Amide functional group have weak basic character! You may say it's a weak acid as we discussed before, when compared to carboxylic acids, BUT compared to amines, the amide's pair of electrons is less available for donation, and they're being withdrawn by the carbonyl.
- So, they're actually not available for donation because of resonance with the nearby carbonyl.
- So, Amides are also weak bases with pKa 1 or less therefore unionized in GIT.

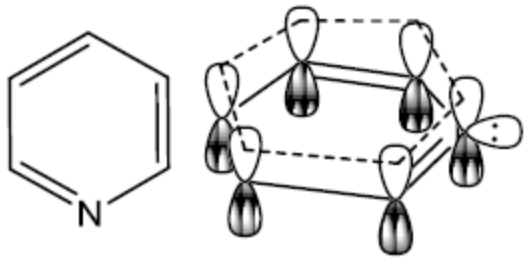


Other weak bases are aromatic amines such as:

Anilines



Pyridine

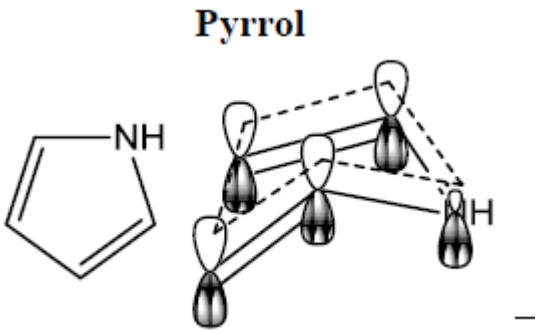


- Aniline, the pair of electrons of the N enter the resonance of the benzene ring therefore weaker base than amines (pKa=9.5; moderate base); Aniline pKa=5-6 and varies with substitution; it's considered a moderate base.

- Pyridine, is also considered a moderate base with pKa= 5-7; when looking at the 3D structure you'll notice that the orbital of the pair of unshared electrons is out of the conjugated system and available for donation therefore considered bases, yet unlike amines' N with sp3 (s orbital is 1/4 of total sp3), while pyridine N is sp2 (s orbital is 1/3 of total sp2) therefore the pair of unshared electrons are closer to the N of pyridine and so less available for donation than amines; so pyridine (pKa=5-7) is weaker base than amines (pKa=9.5).

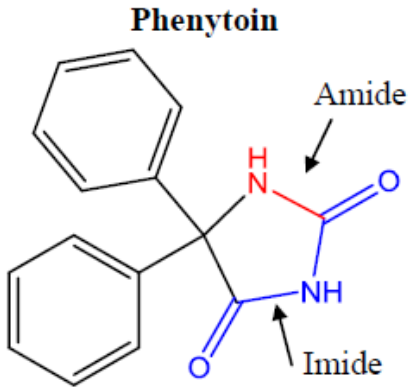
Other weak bases are aromatic amines such as:

- Pyrrole, the N is sp3 hybridized. Yet, the pair of electrons are part of the aromatic ring conjugation, therefore not available for donation.
- So, pyrrole is a much weaker base; it's very weak and belong to the group of compound that's permanently unionized



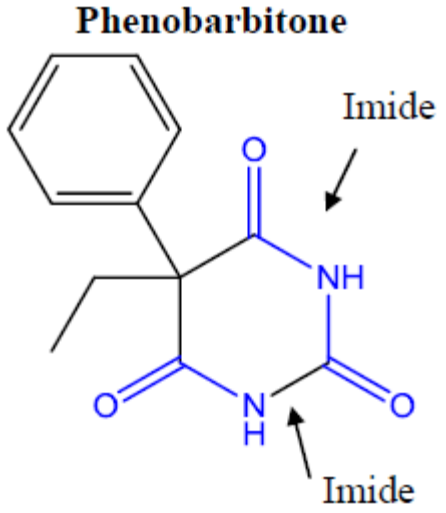
Examples

- Phenytoin (antiepileptic)
- Its structure contains both amide and imide functionalities. so it's both weak acid and weak base; phenytoin is totally absorbed, totally distributed, and can cross the blood brain barrier that is even tighter than GIT membrane.



Examples

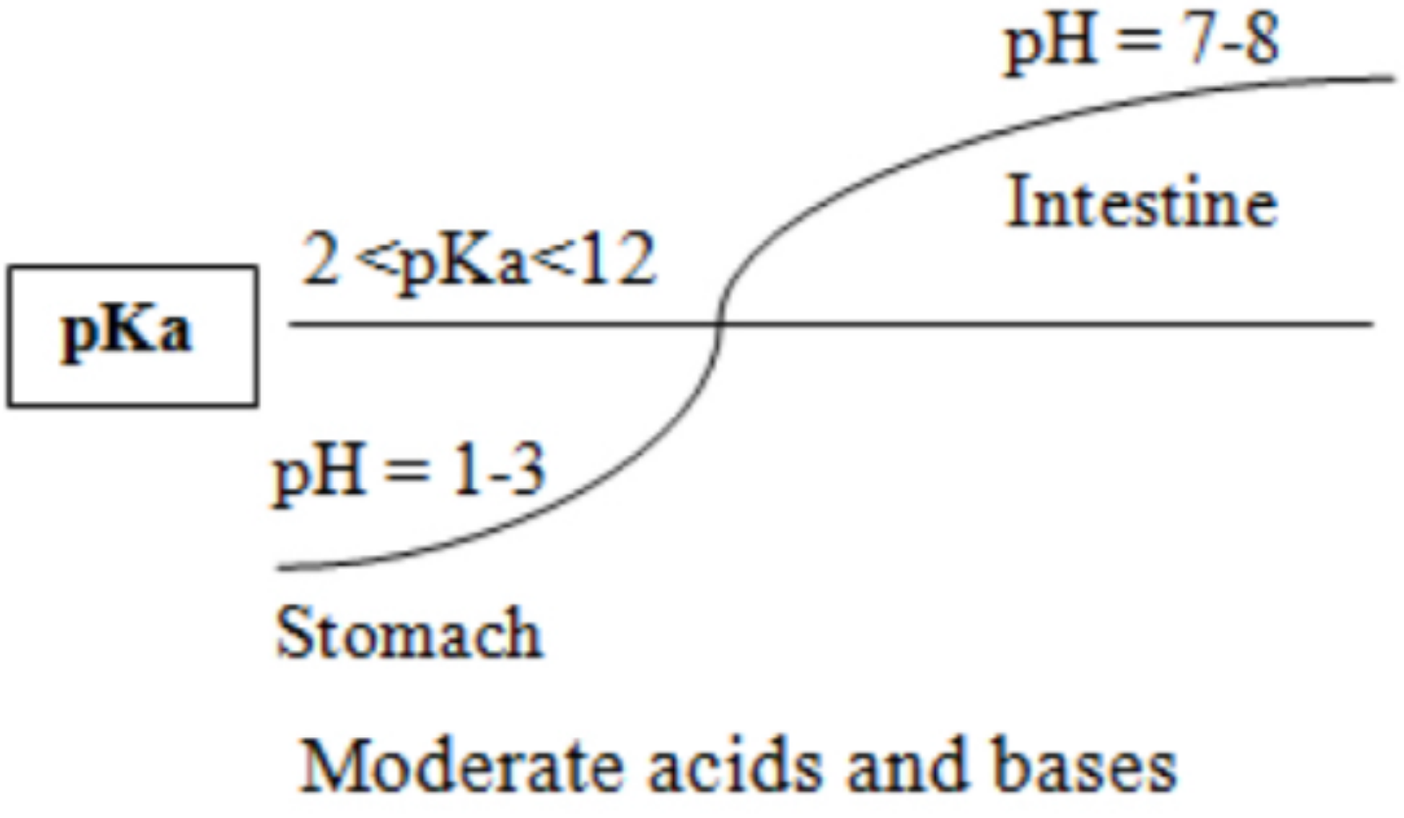
- Phenobarbitone
- Very similar to phenytoin; its structure contains 2 imides; the N pair of electrons is being withdrawn by 2 carbonyl so it's a weak acid. Therefore, permanently unionized through GIT and gets absorbed readily.



To summarize

- So far, we have discussed the following:
- - Strong bases: Guanidine and Amidine.
- - Weak acids: Amides, Imides, Phenols and Imidazole.
- - Weak bases : Amides, Imides and aniline.
- - Moderate bases: Aniline, Pyridine and Amines were discussed for comparison.
- Strong acids are totally not absorbed while strong bases have some absorption, due to the presence of mucin; weak acids and bases are totally unionized therefore are good candidates for absorption taking in concern the other factors that will be discussed later.

Intermediate acids and bases



Moderate acids and bases

Intermediate acids

- In the stomach, conditions are acidic. Which means that the equilibrium is shifted toward HA therefore they're unionized and absorbed. On the other hand, conditions are basic in the intestines. So, the equilibrium is shifted toward A-. Therefore, minimal absorption happens.
- Nevertheless, major absorption (50%) happens in the stomach, absorption isn't complete because the stomach is not designed for absorption itself:

1. It has small surface area,
2. Short transient time (around 6 hours)
3. Less blood supply compared to intestine which has large surface area, long transient time (around 12 hours) and highly vascularized.

Intermediate acids

- Under stomach conditions (acidic conditions), intermediate acids are unionized (HA) while in intestines (basic conditions) are ionized (A-). That's why nearly 50% of the administered dose is being absorbed in stomach even though transient time is short (around 3-6 hours) in stomach, on the other hand in intestines only 15% are absorbed

Intermediate acids

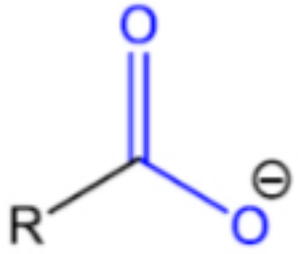
- Through intestines even though it's mostly ionized because ionization is in equilibrium between HA and A- not absolute and a fraction of unionized form is always present (if pH=pKa then 50% is ionized; if pH>Pka with 1 unit then 90% is ionized and 10% unionized); intestines have:

1. large surface area
2. long transient time (around 12 hours).
3. Very good blood supply which aid in absorption. Eventually intermediate acids are

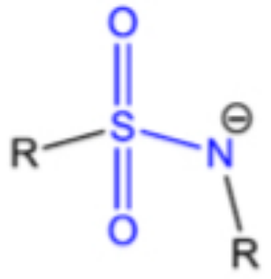
- approximately 60-75% absorbed provided that they satisfy Lipinski's rule of 5 which we'll discuss later on.

Functional groups that make drugs of intermediate acid character

Carboxylic acid



Sulfonamides
(without EWD)

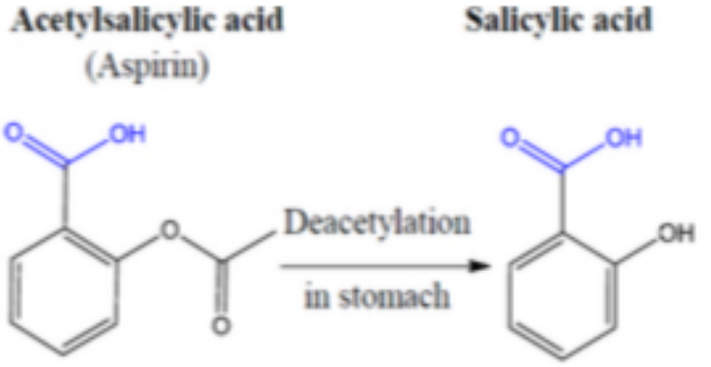


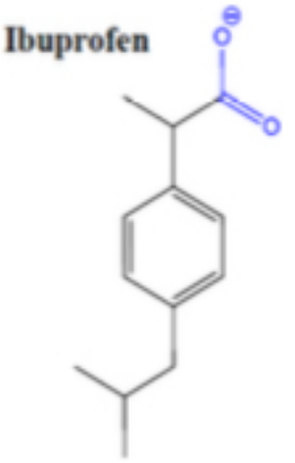
Carboxylic acid with **pKa=3-4.5** depending on the substitution if it's attached to an electron withdrawing group it becomes more acidic while if it's attached to electron donating group it becomes less acidic

Sulfonamide, you remember from the previous lecture if the R group is an electron withdrawing group, then it will become strong acid as in case of Saccharin but Sulfonamides without having an electron withdrawing group on R their **Pka=6-7** they're intermediate acidic therefore they're unionized in the stomach and in the intestine is ionized on the N.

EXAMPLES

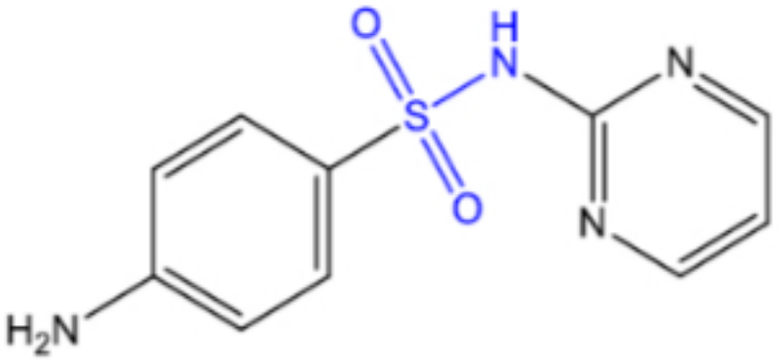
- Drugs containing carboxylic acid like **salicylic acid** which is a non-steroidal anti-inflammatory drug NSAID when attached to acetyl group it becomes **acetylsalicylic acid** which is found in **Aspirin,** an anti inflammatory, used as analgesic, and as antiplatelet. In fact, all the family of NSAIDs are characterized by the presence of aromatic ring attached with a carboxylic acid. Therefore, if you attach a carboxylic acid with an aromatic ring in any configuration, you'll form an NSAID, such as **ibuprofen**.



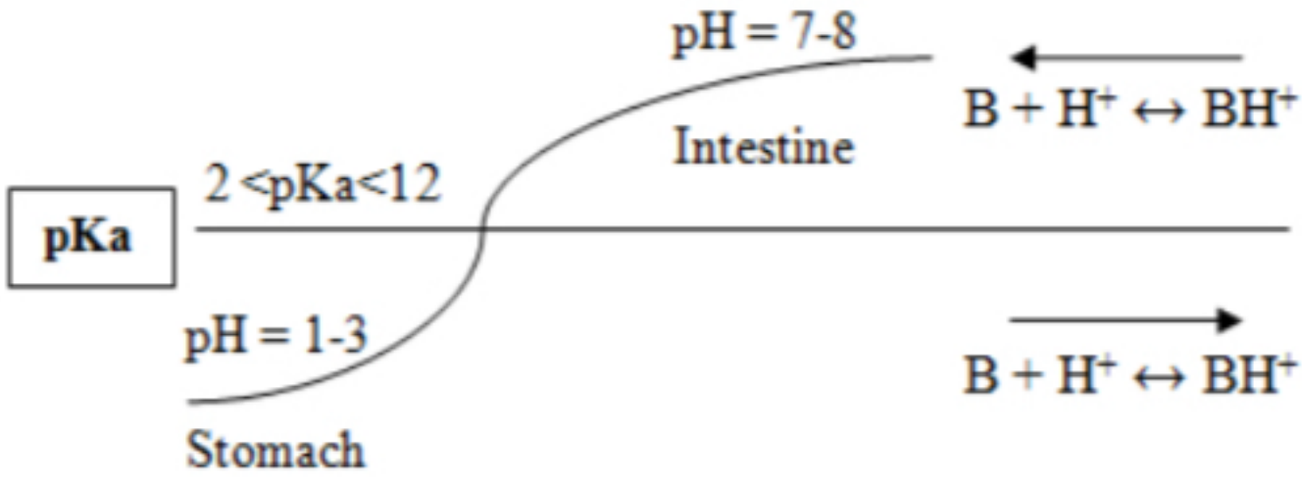


- Drugs containing sulfonamides are usually used as antibacterial agents. However, some sulfonamide drugs are used as anti-diabetics (Sulfonylurea: pKa ~ 3.8-6), anti cancer agents and diuretics (Thiazides: pKa ~ 6.8-9.8).
- Example of antibacterial agent: **Sulfadiazine**.

Sulfadiazine



Intermediate bases



Intermediate bases

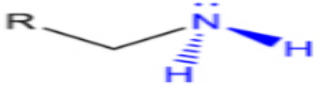
Intermediate bases have **ZERO** absorption in stomach, however significant absorption happen in the intestine provided that the compound satisfies Lipinski's rule of 5 because drugs are unionized and the intestines have long transient time, large surface area and very good blood supply so it's well designed for absorption, can reach 100% absorption.

Groups which make drugs with intermediate basic character,

- most importantly are **Amines** which in fact are benchmark for organic bases; their **pKa=9-9.5**
- follow amines in order are **aromatic amines** like **Aniline**, they're weaker bases because their pair of electrons are involved in the aromatic system resonance and their **pKa= 5-7**
- **Pyridines** are weak bases with heterocyclic nitrogen discussed previously and we said that the pairs of electrons are not involved in the aromatic ring yet they're sp2 hybridized so electrons are closer to nucleus **pKa=5-6**

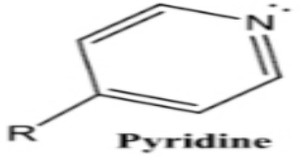
Intermediate bases

- Other heterocyclic compounds like **Imidazole** one of its N is pyridine like while the other is pyrrole like with the electrons being involved within the ring. So, they are not available for donation which makes pyrrole very weak base.
- It's very weak and belong to the group of compound that's permanently unionized.

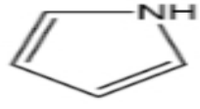


Amine

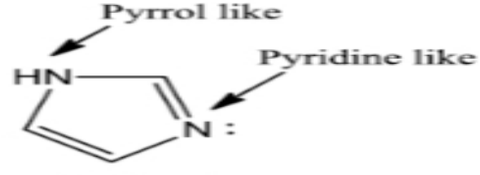
Aniline



Pyridine



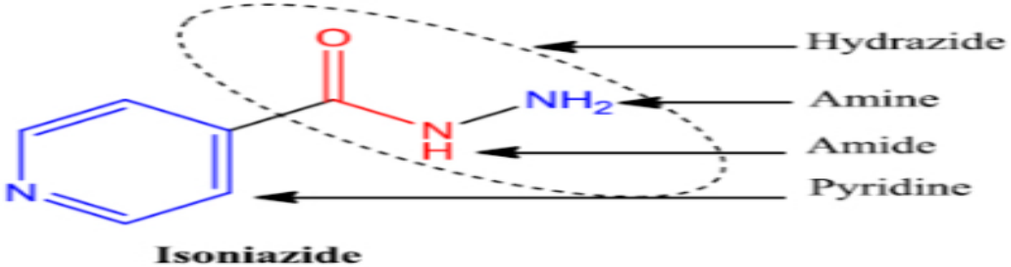
Pyrrol



Imidazole

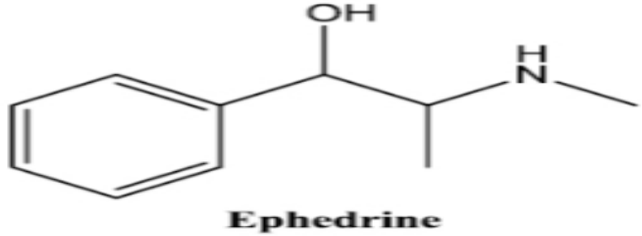
Intermediate Bases: Examples

Isoniazide (for tuberculosis)
contains pyridine N and hydrazide function (consecutive N attached to a carbonyl) containing amide which is a weak base, and an amine which is an intermediate base. Therefore, Isoniazide is a drug administered orally and well absorb in the intestine for sure.



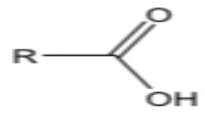
Isoniazide

Other drugs are like **ephedrine**, **pseudoephedrine** and **natural alkaloids** all of them are amine containing compounds and absorbed in the intestines



Ephedrine

Common acidic functional groups in pharmaceutical chemistry and their pKa values



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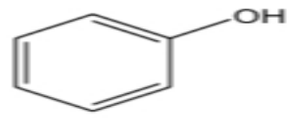

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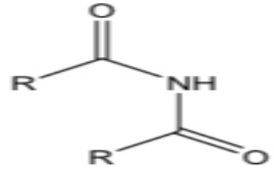

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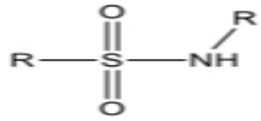

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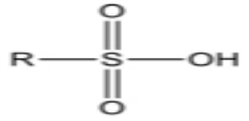

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Common basic functional groups in pharmaceutical chemistry and their pKa values

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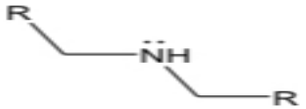
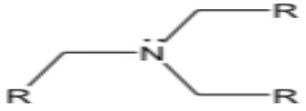
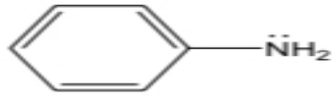


10.6-11.0



9.8-10.8



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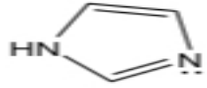

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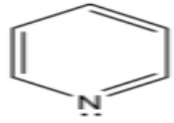
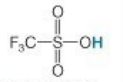
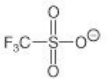
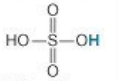
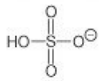
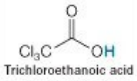
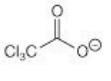
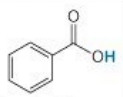
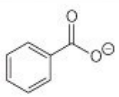
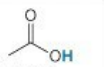
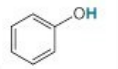
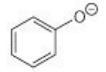
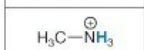
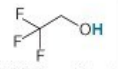
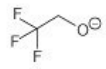
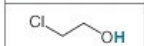
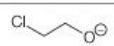
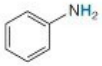
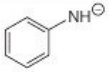
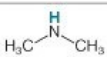
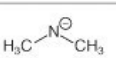
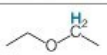
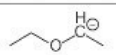


5.2

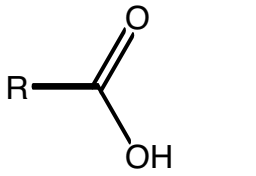
TABLE 6-1 Values of K_a and pK_a for Various Acids[a]

Acid	Conjugate Base	K_a	pK_a
 Trifluoromethanesulfonic acid		1×10^{13}	−13
 Sulfuric acid		1×10^{9}	−9
HCl Hydrochloric acid	$Cl^{\ominus}$	1×10^{7}	−7
$H_3O^{\oplus}$ Hydronium ion	H_2O	55	−1.7
 Trichloroethanoic acid (Trichloroacetic acid)		0.17	0.77
HF Hydrofluoric acid	$F^{\ominus}$	6.3×10^{-4}	3.2
 Benzoic acid		6.3×10^{-5}	4.2
 Ethanoic acid (Acetic acid)		1.8×10^{-5}	4.75
H_2S Hydrogen sulfide	$HS^{\ominus}$	6.3×10^{-8}	7.2
$H_4N^{\oplus}$ Ammonium ion	NH_3	4×10^{-10}	9.4
 Phenol		1×10^{-10}	10.0
 Methylammonium ion	H_3C-NH_2	2.3×10^{-11}	10.63
 2,2,2-Trifluoroethanol		4×10^{-13}	12.4
 2-Chloroethanol		1.3×10^{-13}	12.9

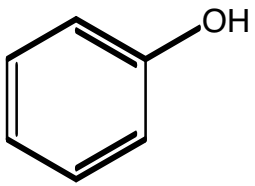
Acid	Conjugate Base	K_a	pK_a
CH_3OH Methanol	$CH_3O^{\ominus}$	3.2×10^{-16}	15.5
H_2O Water	$HO^{\ominus}$	2×10^{-16}	15.7
 Ethanol		1×10^{-16}	16
 Propan-2-ol (Isopropyl alcohol)		3.2×10^{-17}	16.5
 Methylpropan-2-ol (*tert*-Butyl alcohol)		1×10^{-19}	19
 Propanone (Acetone)		1×10^{-20}	20
$HC{\equiv}CH$ Ethyne (Acetylene)	$HC{\equiv}C^{\ominus}$	1×10^{-25}	25
 Aniline (Phenylamine)		1×10^{-27}	27
H_2 Hydrogen gas	$H^{\ominus}$	1×10^{-35}	35
 N-Methylmethanamine (Dimethylamine)		1×10^{-38}	38
$H_2C{=}CH_2$ Ethene (Ethylene)	$H_2C{=}CH^{\ominus}$	1×10^{-44}	44
 Ethoxyethane (Diethyl ether)		~1×10^{-45}	~45
CH_4 Methane	$H_3C^{\ominus}$	1×10^{-48}	48
CH_3CH_3 Ethane	$CH_3CH_2^{\ominus}$	1×10^{-50}	50

[a] $pK_a = -\log K_a$. The less positive (or more negative) the pK_a value, the stronger the acid relative to another acid.

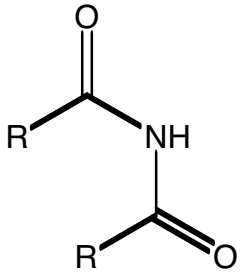
Common acidic functional groups in pharmaceutical chemistry and their pKa values



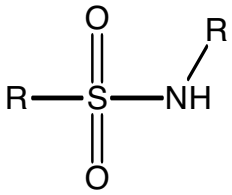
4-5



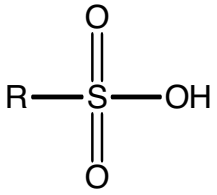
9.9



8-10



10



<2

Remember the followings

For acids:

1. a high pka means the species is predominantly unionised, is a bad proton donor, and a weak acid
2. a low pka means the species is predominantly ionised, is a good proton donor, and a strong acid

pH < pKa by 2 units, 99% unionised
pH > pKa by 2 units, 99% ionised

For bases:

1. a high pka means the species is predominantly ionised, is a good proton acceptor, and a strong base
2. a low pka means the species is predominantly unionised, is a bad proton acceptor, and a weak base

pH < pKa by 2 units, 99% ionised
pH > pKa by 2 units, 99% unionised