Revised Third Edition

Medicinal Chemistry

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Weak bases

وشايف Base كل الدنيا القاعدية ما بصيرله ionization يعني صعوه شايف الـ H^+ قليلة بضل يضغ الـ H^+ فبضل على شكل B ← مابصير تاين معناها شايف الدنيا قاعدية

$1 \geq pKa$

* الـ H^+ منخفض بالسيستم فما بده ياخده بضل unIonized

- 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.

رح يضل يعمل shifting لهون باتجاه الـ B

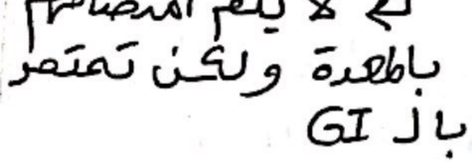
$$B \overset{H^+}{\rightleftharpoons} BH^+$$

B ↓ unionized

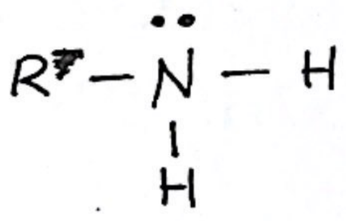
What is a basic compound

- 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.

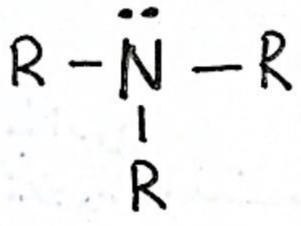
pKa = 9 ← They are considered intermediate Basic



Primary amine بشبه الامونيا

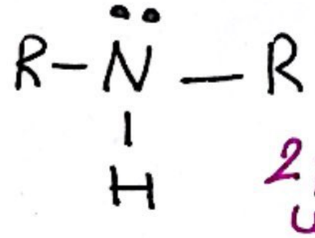


Tertiary amines



هلا هون شرحت عن ال intermediate acid /base
بس رح احطلكم الشرح لقدام

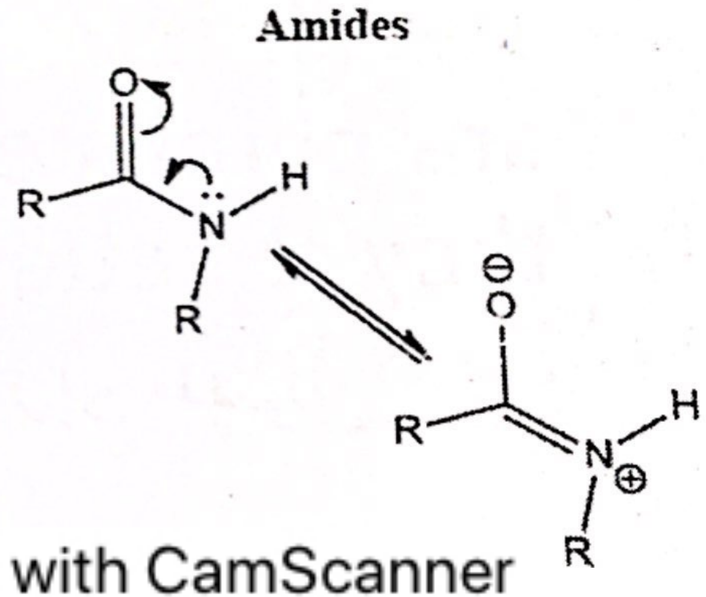
Secondery amines



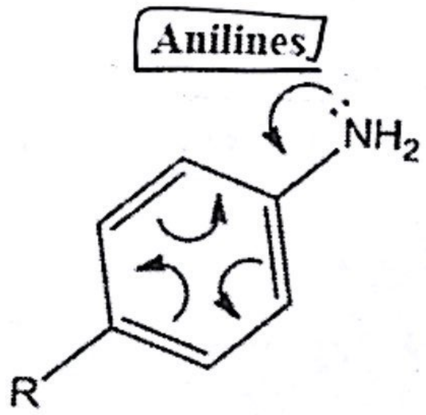
* ال Basic compound هو المركب القادر على اعطاء 2pairs of unshared electrons

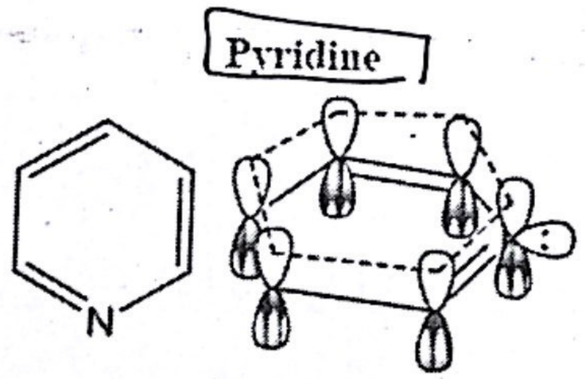
- **Amide** functional group have weak basic character! You may say it's a weak acid as we discussed before, when compared to carboxylic acids, BUT compared to amines, the amide's pair of electrons is less available for donation, and they're being withdrawn by the carbonyl.
- So, they're actually not 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.

* امتصاصه جيد بال GI



Other weak bases are aromatic amines such as:



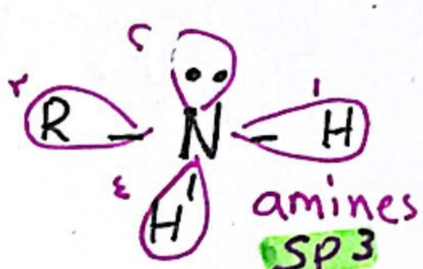


- **Aniline**, the pair of electrons of the N enter the resonance of the benzene ring therefore weaker base than amines (pKa=9.5; moderate base); Aniline **pKa=5-6** and varies with substitution; it's considered a moderate base.

- **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).

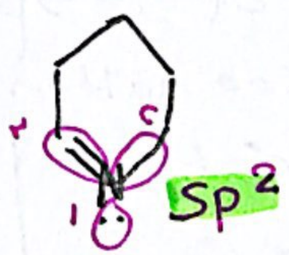
$sp^2 \rightarrow 3$

$sp^3 \rightarrow 4$



فيكون 1/4 يكونو 2pairs of unshared ele

* حصول ال N البعد عن ال



* اما هون 1/3 فيكونو

اقرب لل N لما يكون اقرب بكون اعطاءه اضعف بالتالي weaker Base يكون

pyridine < amines

weaker

لـ السبب

1 resonance

2 electronegativity

متوزع على عدد اقل

1/3

Other weak bases are aro...

Other weak bases are aromatic amines such as:

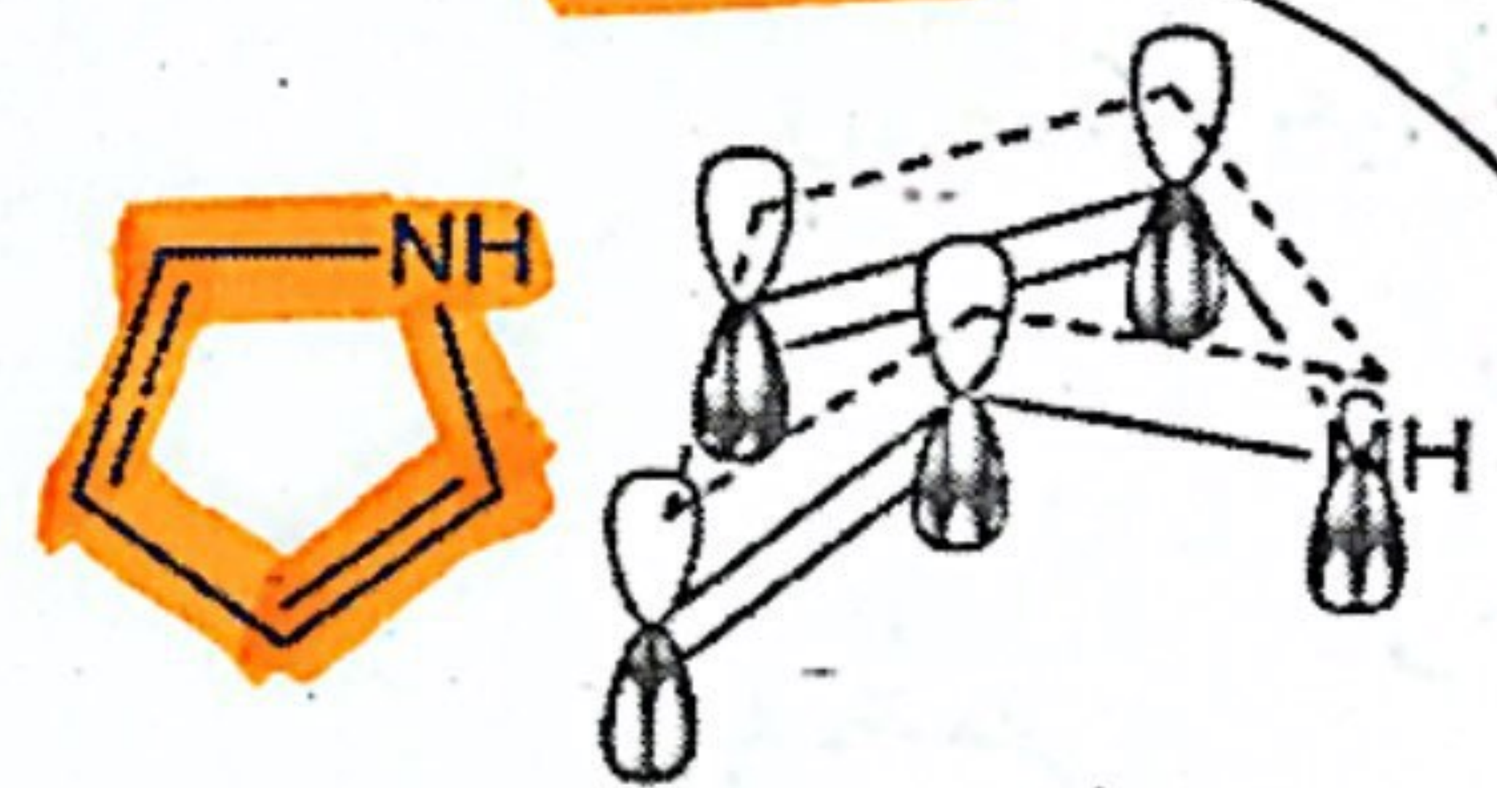
- **Pyrrole**, the N is sp3 hybridized. Yet, the pair of electrons are part of the aromatic ring conjugation, therefore not available for donation.

  × not Base it is an acid

- So, pyrrole is a much weaker base; it's very weak and belong to the group of compound that's permanently unionized

بس حكت هاي القصص المتبحبحة ما يتسأل عنها انسوا

Pyrrol



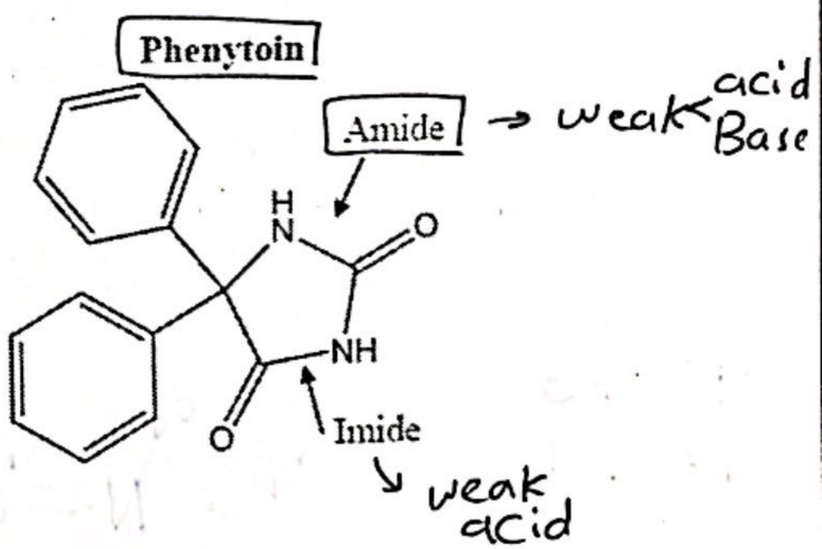
2pair of ele
بال pyrrol هي جزء
من ال aromatic ring
غير متوسطة. انها تعطي

* يعتبر weak acid هوه

Examples

ما عنده مشكلة بالامتصاص
so it's not a acid or base

- **Phenytoin** (antiepileptic) ← لمرض الصرع
- 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.



* completly unIonized

Lipinski's rule of 5 → حكينا للزم

[1] M.w < 500 dalton
[2] N HBD < 5
[3] N HBA < 10
[4] logp → 5

* كل هاي الصفات موجوده بالـ phenytoin
امتصاصه كامل ٪100

Examples

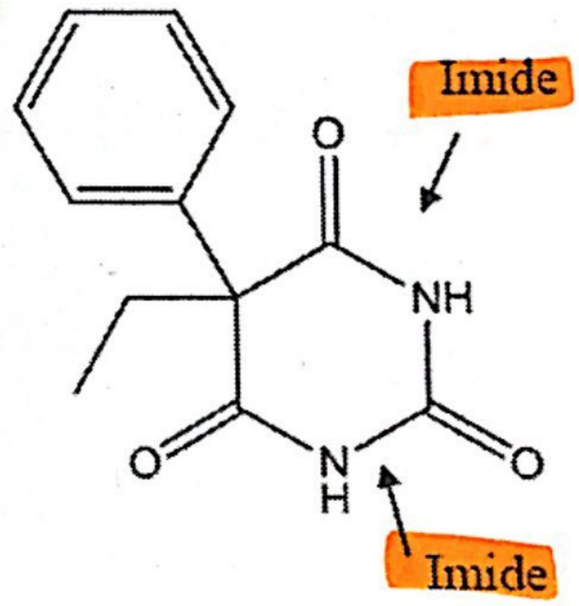
- **Phenobarbitone**
- Very similar to phenytoin; its structure contains 2 imides; the N pair of electrons is being withdrawn by 2 carbonyl so it's a weak acid. Therefore, permanently unionized through GIT and gets absorbed readily.

بعد الـ unIonization ← completly unionized كمان *

↳ lipinskis بيحكي عل rule of 5

بنطلع عليهم بعد ما نشوف الـ unIonization

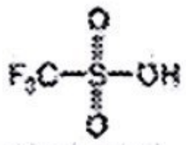
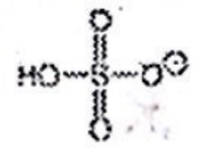
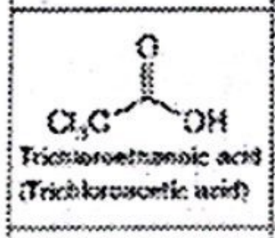
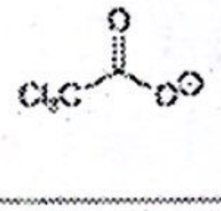
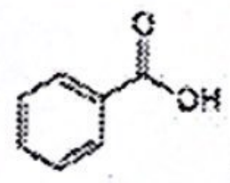
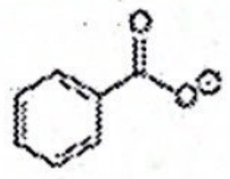
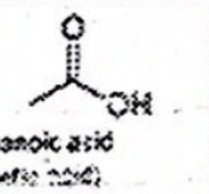
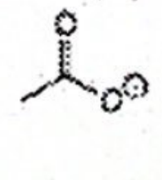
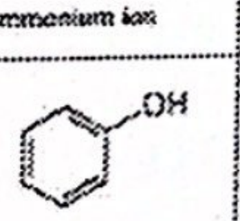
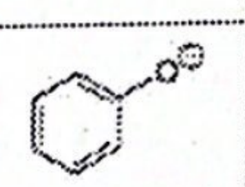
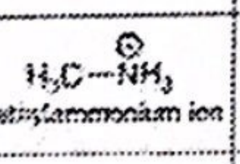
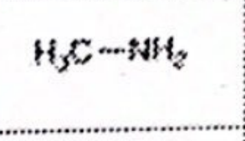
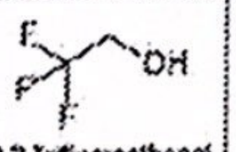
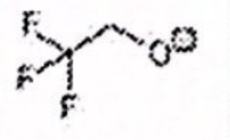
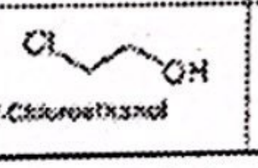
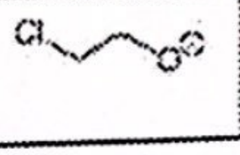
Phenobarbitone

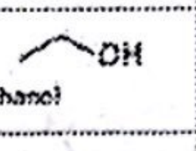
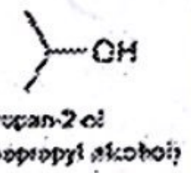
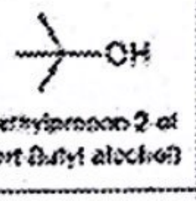
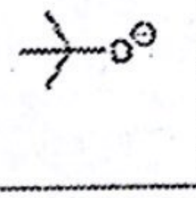
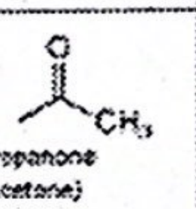
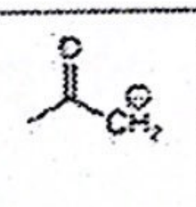
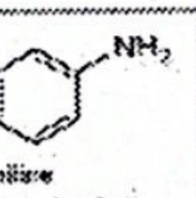
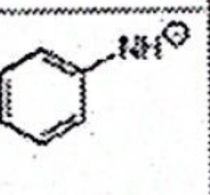
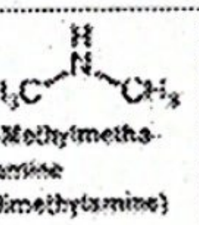
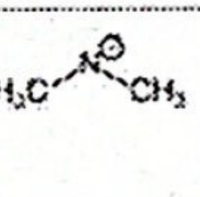
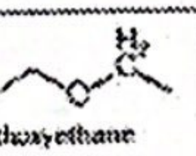
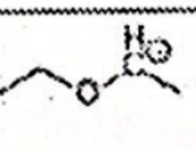


To summarize

- So far, we have discussed the following: حكيناه قبل
- - 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.

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^{3}	~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		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^{-18}	18
 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^{-36}	36
$H_2C{=}CH_2$ Ethene (Ethylene)	$H_2C{=}CH^{\ominus}$	1×10^{-44}	44
 Ethoxyethane (Diethyl ether)		$\sim 1 \times 10^{-45}$	~45
CH_4 Methane	$H_3C^{\ominus}$	1×10^{-48}	48
CH_3CH_3 Ethane	$CH_3CH_2^{\ominus}$	1×10^{-50}	50

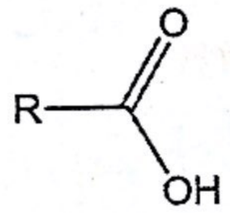
[a] $pK_a = -\log K_a$. The less positive (or more negative) the pK_a value, the stronger the acid relative to another acid.

جدول موحظ

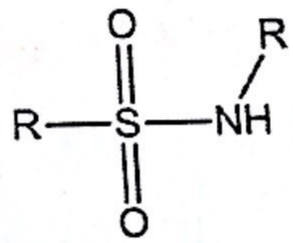
Common acidic functional groups in pharmaceutical chemistry and their pKa values

هدول حفظ

carboxyl

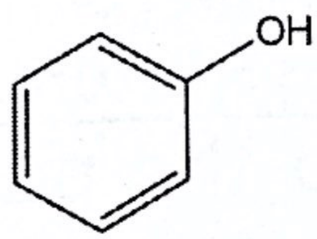


4-5

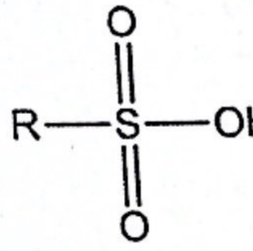


10

phenol



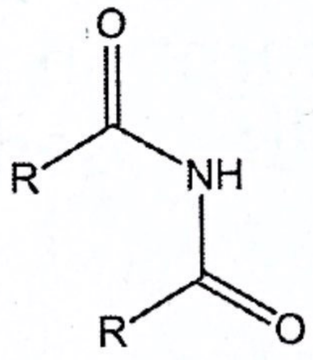
~~9.9~~ 17



<2

salfunic acid

imides
weak acids



8-10

ال pka/ structure لكل مركب
مهمين كتير

Remember the followings

* تلخيص *

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

Pharmacokinetics 2

الي بعد هاي همه الي شرحتهم بالبداية 👍🏻

weak bases

amines < intermediate Bases

Intermediate Bases
↳ pka = 9 ,

لا يتم امتصاصهم باطعدة
ولكن يتم امتصاصهم
(intestine) GI) با

* الـ Amines ← pH اقل منه باطعده وبالintestinal زيه
او اكتر عشان هيك

Basic ← intestine دح يشوفو
unIonized
Ionized ← acidic ← stomech

ما يتم امتصاصهم

* هلا لانه بالـ intestine ← unIonized
والـ Transit time بالامعاء طويله (لانو الامعاء طويله)
كل الدوا رح يتم امتصاصه زيه زي الـ weak

* لا تنسوا احنا بنحكي عن الـ intermediate bases

* الـ weak / strong pH وحده على طول الـ GI
بس الـ intermediate مختلف الوضع

amines → pKa = 9

في منهم weak bases ومنهم intermediate Bases

Intermediate ACiDs pKa = 5-9

They are not ionized in the stomech

لكن امتصاصهم مختلف تماماً بال intestine

لانو ال intestine فال Transit time طويلة طويل بالتالي

يمكن امتصاصهم بال intestine

بس بالمعدة مع انهم unIonized لكن بسبب

تركيب المعدة الكيمائي فهي ليست للإمتصاص اصلا

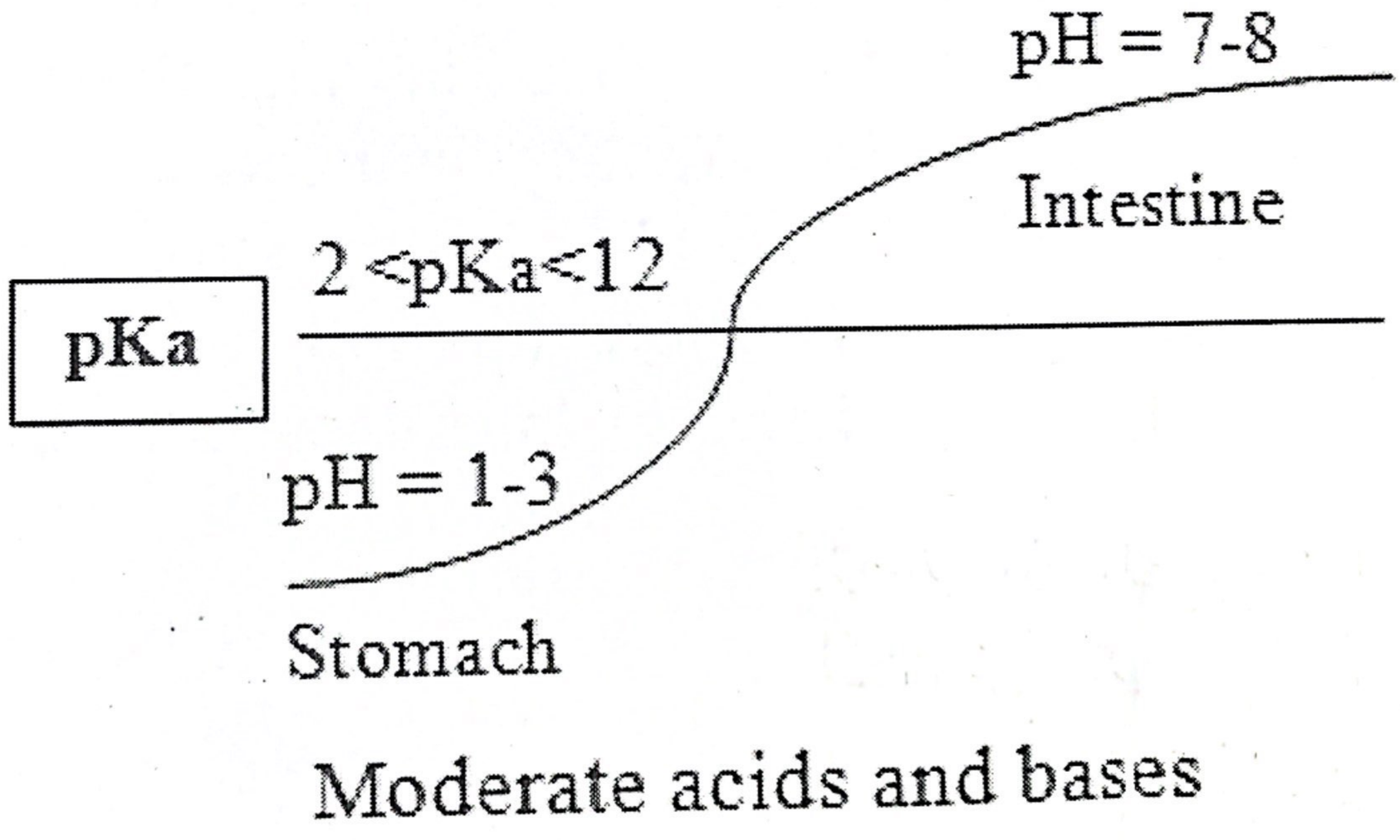
فما بنستفيد + الـ Transit time بالمعدة قصير

مثال عليها ← المركبات اي فيها OH

Carboxylic acid

pka
الرهم بالنص

← Intermediate acids and bases



Moderate acids and bases

unIonized in the stomech

← 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.

← مع ما يتم امتصاصه Max = 50% بصيرله امتصاص

← الـ Blood supply اكتر بالامعاء

عشان هيك بحكيلك لو حد صابه سرطان المعولون هاد السرطان لوما تم اكتشافه ع بكير بكون خطير جداً لانو كل الدورة الدموية بتصب بالامعاء

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

الاكل بقعد باطعده

٥٠٪ من الجرعة امتصت كحد اقصى
لكن في ١٥٪ لانو الدوا بقعد بالامعاء
لفتره طويلة فإمتصاص الدوا الحقن
يكون ٦٥٪ = ١٥٪ + ٥٠٪
* حمضات الامعاء ممكن تحفز امتصاص الدوا
بنسبة ١٥٪ *

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:

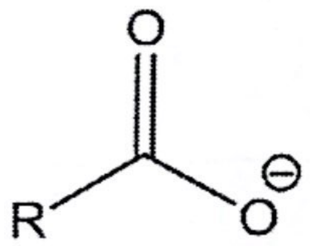
فعلان الامعاء

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

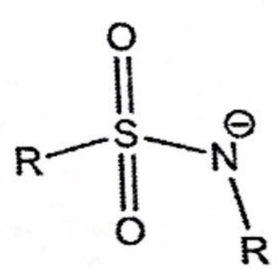
- approximately 60-75% absorbed provided that they satisfy Lipinski's rule of 5 which we'll discuss later on.

Functional groups that make drugs of intermediate acid character

Carboxylic acid
(conjugated to EWD)



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

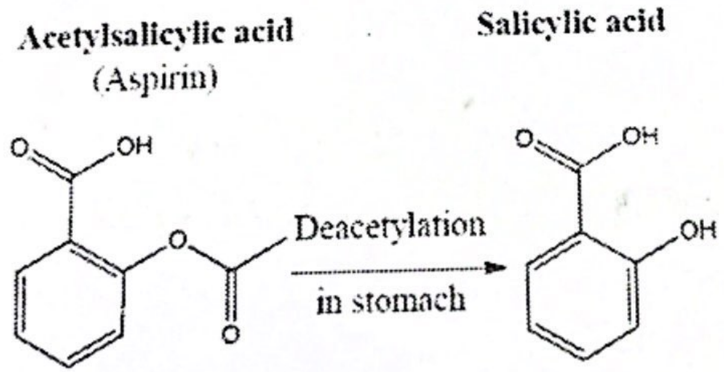
Sulfonamide, you remember from the previous lecture if the R group is an electron withdrawing group then it will become strong acid as in case of Saccharin but Sulfonamides without having an electron withdrawing group on R their **Pka=6-7** they're intermediate acidic therefore they're unionized in the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

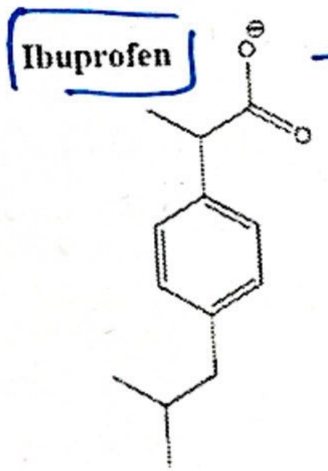
intermediate ممكن يكون strong acid

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** and this group is cleaved in the stomach to become salicylic acid itself which is an anti inflammatory, in the past used as analgesic, and now used 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.**

من اطرحيات الي قدها carboxyl و امتصاصها جيد لكن لايتجاوز ال 70٪

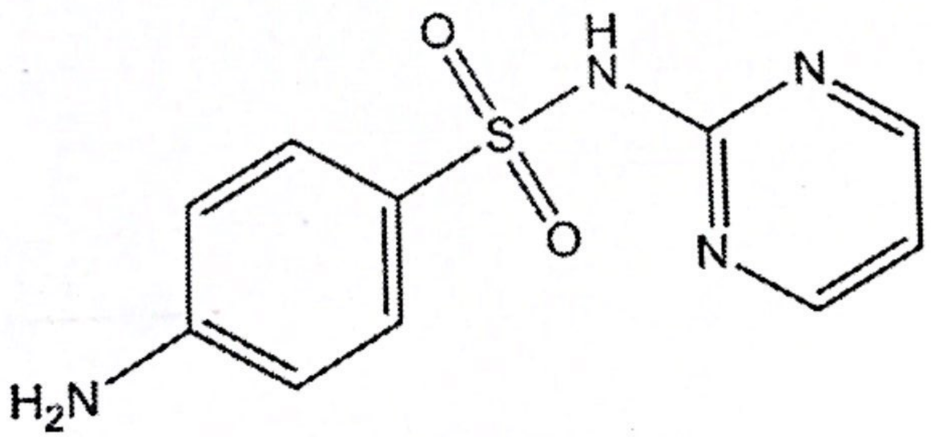




امتصاصه ممتاز برضو

- 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.**

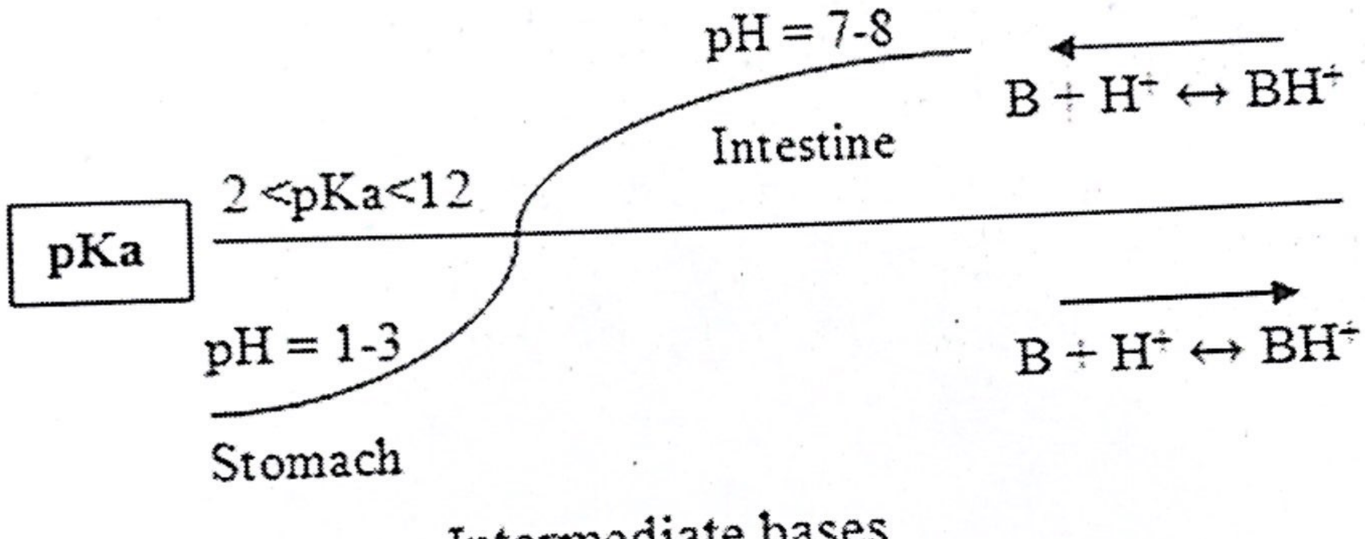
Sulfadiazine



unionized ← in the intestine

Intermediate bases

امتصاصهم بالامعاء ✓
باطحه Zero X



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.