



# تفريغ ميديسينال

Lec 1 Part 2

محاضرة:

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الصيدلانية:



لجان الرفعات



تنگرانه  
 ال pH بالعدد = 1-3  
 ال pH بالاصحاء = 6-7

# Weak acids

1-alcohol  
 2-imid  
 3-amid  
 عندما لا يتغير  
 يتصرف مثل weak acid  
 weak base

- There **pKa is 12 or more**, which means in the GIT (pH= 1-8) conditions they 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.

ال pKa ال weak acid = 12 or more اذا ال  $pH < pKa$  يكون unionize بالعدد والاصحاء  
 بس هتو مثل شرط عشان يتغير ال BBB لازم يكون! لهم optimal-hydrophilic hydrophobic

لما يكون weak acid ② optimal hydrophilic-hydrophobic ① يكون orally

Permeation وسهيك ما رالم bioavailable

Lipinski's rule - degree of dissociation (ر تحي عنها بعد رينه)

مثال

اذا كان الدواء unionize پس insoluble ما ر يتوب بال water

وسهيك ما ر يكون orally bioavailable

# Weak acids

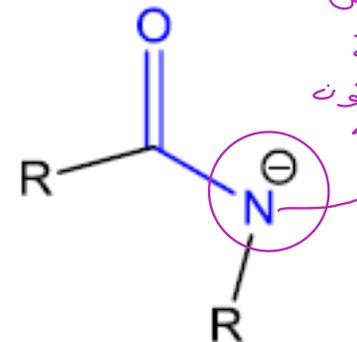
يمكن اعتبارهم weak base لأن

- **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**.

ال N مش سهل يكون  
كلها charge (-)

لأنه ال N weak electronegativity فلما يبر deprotonated ال charge (-)  
ما يرح تكون stable بسهولة وبالنتيجة تعتبر ← very weak acid  
و بتكون بال BI بالعادة من 12

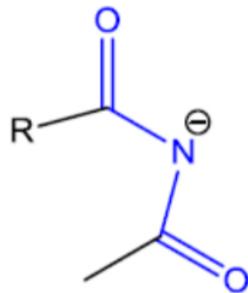
Amides  
(pKa ≥ 12)



عندما H تقدر  
تتبرع فيها بس  
ال pKa لها عالية  
عشان سهل يتكون  
weak

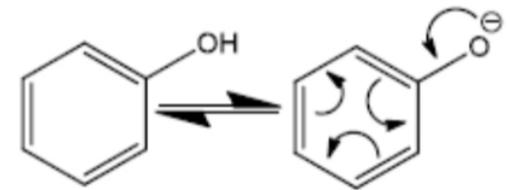


**Imides**  
(pKa=8-10)



# Weak acids

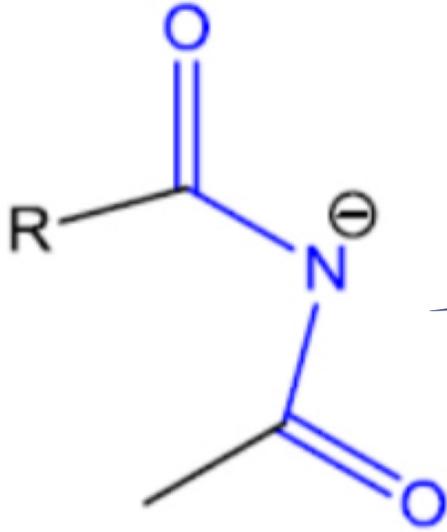
**Phenols**  
(pKa=17)



- **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**

# Imides

(pKa=8-10)



هذا الجزء عبارة  
عن amid

وهذا Carbonyl

بسبب ال Carbonyl في ضعفها صار ال Imid stronger than Amid يس

مع هيلك بسبب ال (-) charge في على له ما رج يسر stable بسهولة ويقلد

weak

ال aliphatic alcohol كالم (primary / secondary / tertiary) يعتبروا very very weak acid وال

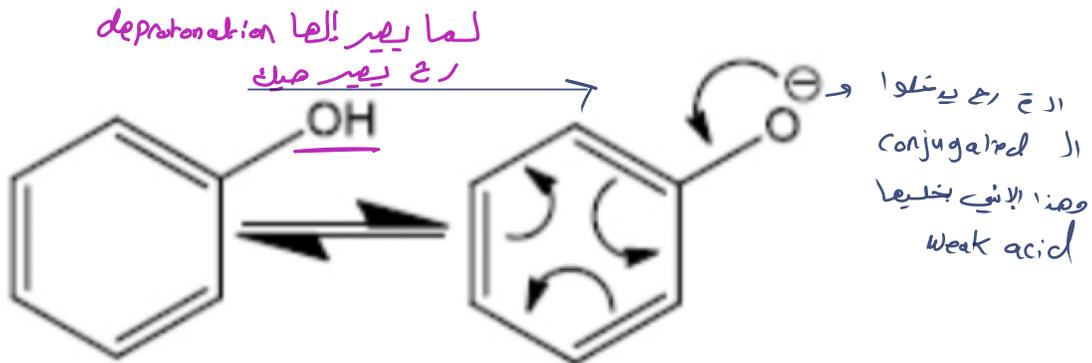
Phenol لهم  $pK_a$  25 بس اذا ال alcohol مرتبنا ب aromatic Ring زي ال Phenol

ال  $pK_a$  بيهر 17 .

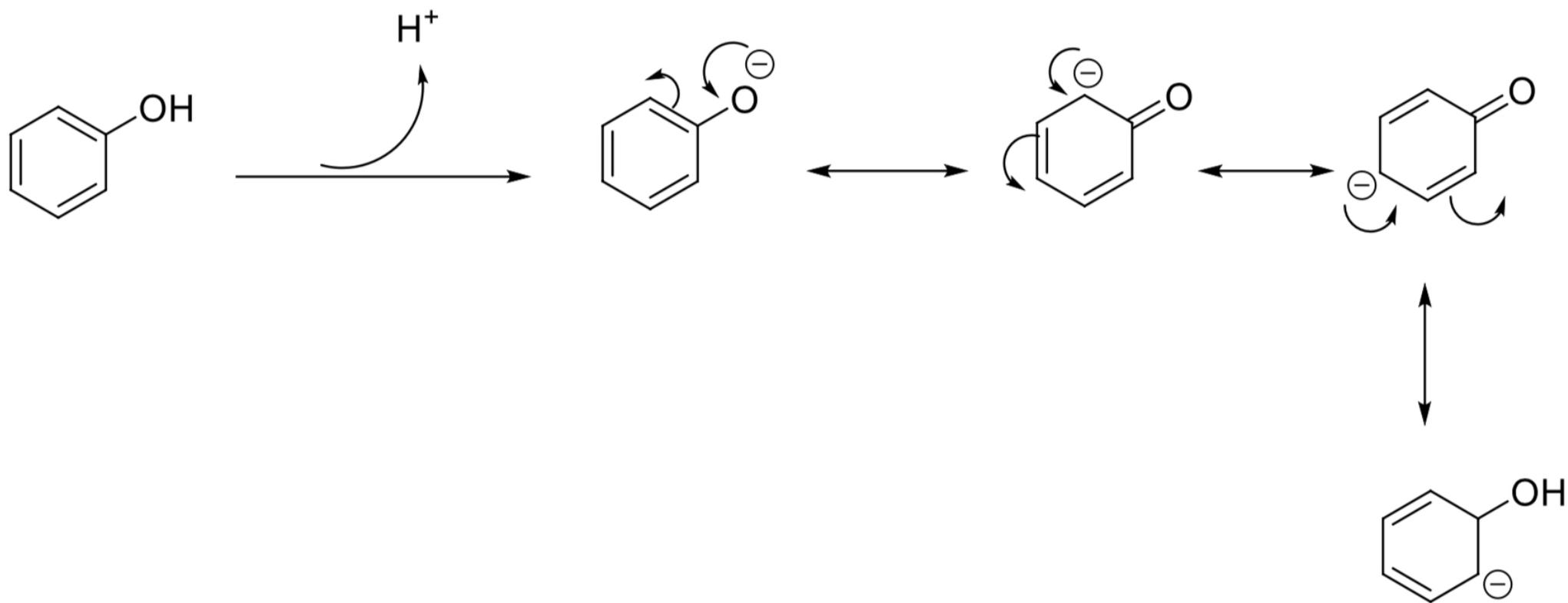
ليش ال Phenol يعتبر weak من strong inter-mediate ؟؟

## Phenols

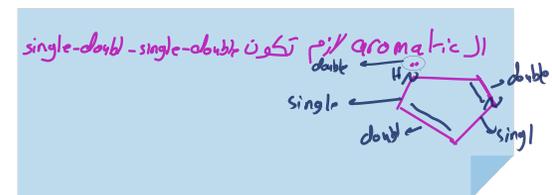
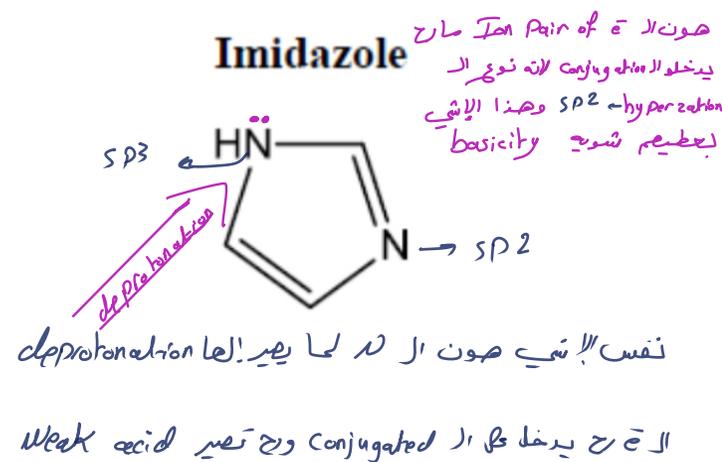
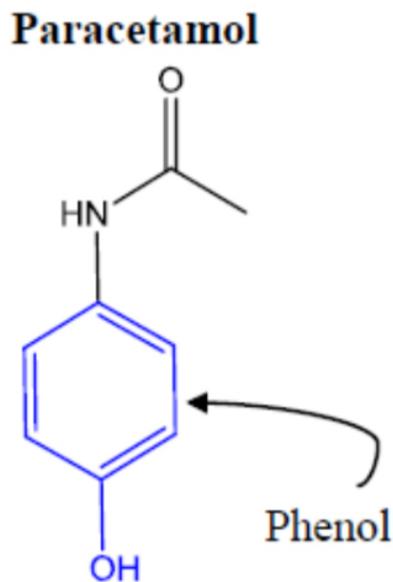
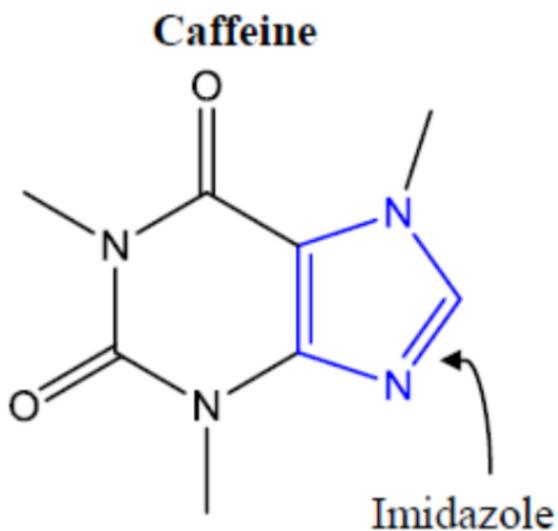
( $pK_a=17$ )



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.



1 or less = weak base لا النسبه لا pKa لا



# Weak bases

يتكون أقل من الـ pH للحمض والايونات إذا رح تكون unionize

← equilibrium اتزان

- 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.

weak and intermediate base ← 75% من الادوية

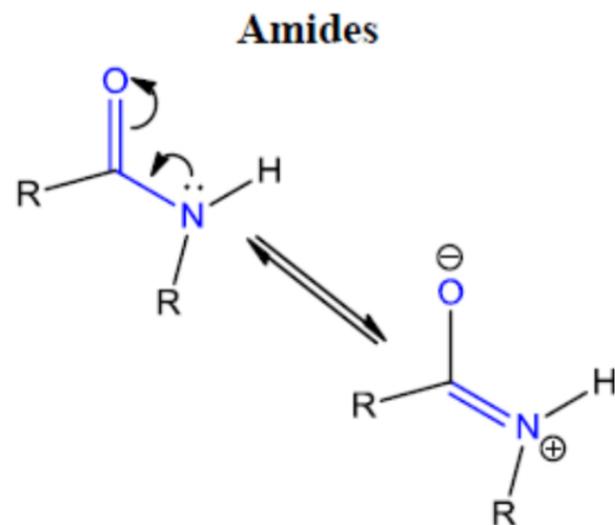
- That means inside all the GIT (pH=1-8) the conditions are constantly basic shifting the equilibrium toward B therefore weak bases are permanently unionized across GIT and so they're better candidates for oral absorption.

# 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.

amine بقدر اعتبارهم Weak and intermediate base

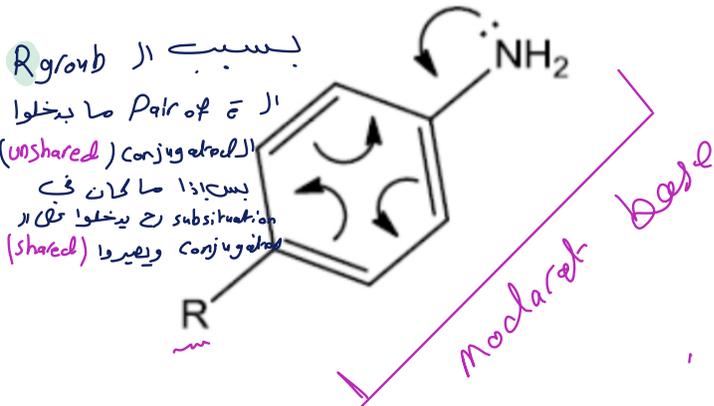
- **Amide** functional groups have weak basic character! You may say it's a weak acid as we discussed before, when compared to carboxylic acids, BUT compared to amines, the amide's pair of electrons is less available for donation, and they're being withdrawn by the carbonyl.
- So, they're actually not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



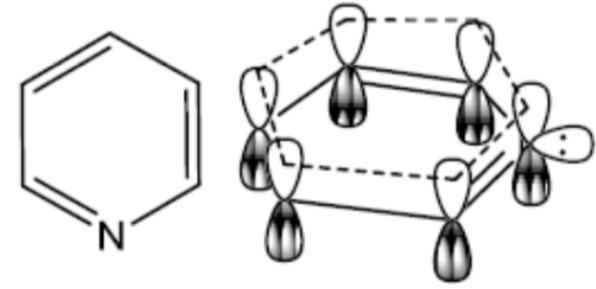
# Other weak bases are aromatic amines

such as:

Anilines



Pyridine



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

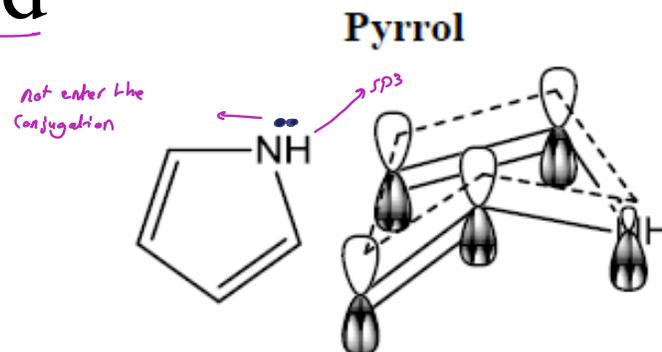
↳ in stomach ionize (not absorbed in stomach) , but in intestine unionize (absorbed in intestine)

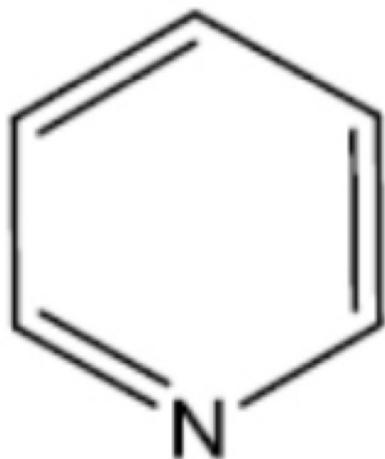
- **Pyridine**, is also considered a moderate base with  **$pK_a= 5-7$** ; when looking at the 3D structure you'll notice that the orbital of the pair of unshared electrons is out of the conjugated system and available for donation therefore considered bases, yet unlike amines' N with  $sp^3$  (s orbital is 1/4 of total  $sp^3$ ), while pyridine N is  $sp^2$  (s orbital is 1/3 of total  $sp^2$ ) therefore the pair of unshared electrons are closer to the N of pyridine and so less available for donation than amines; so pyridine ( $pK_a=5-7$ ) is weaker base than amines ( $pK_a=9.5$ ).

# Other weak bases are aromatic amines such as:

- **Pyrrole**, the N is  $sp^3$  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

ال pyrrole تعتبر weak acid لانها لا تحتج على  
deprotonation وتعتبر weak base بسبب  
انه لا Pair of e لا يتصرف shared





→ Pair of  $e^-$  not enter  
the conjugation

sp<sup>2</sup> → Pair of electron unshared

Moderate base عشان هيك يعتبر

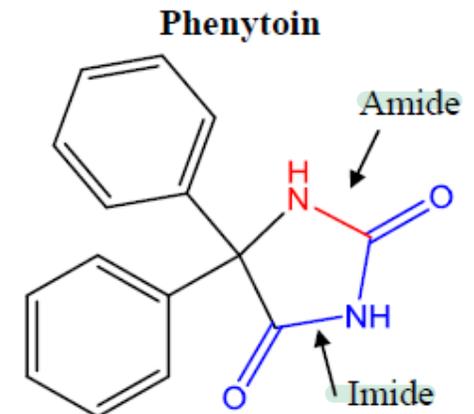
$$pK_a = 5-7$$

وبرضه لا يكون ionize بالهده

، لا يات un-ionize بالاهده

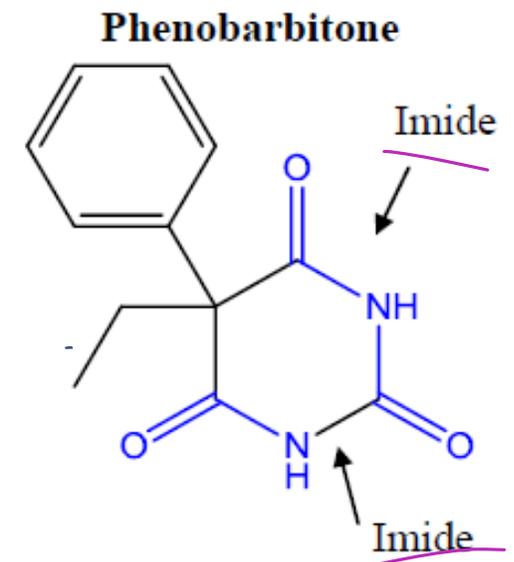
# Examples

- **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

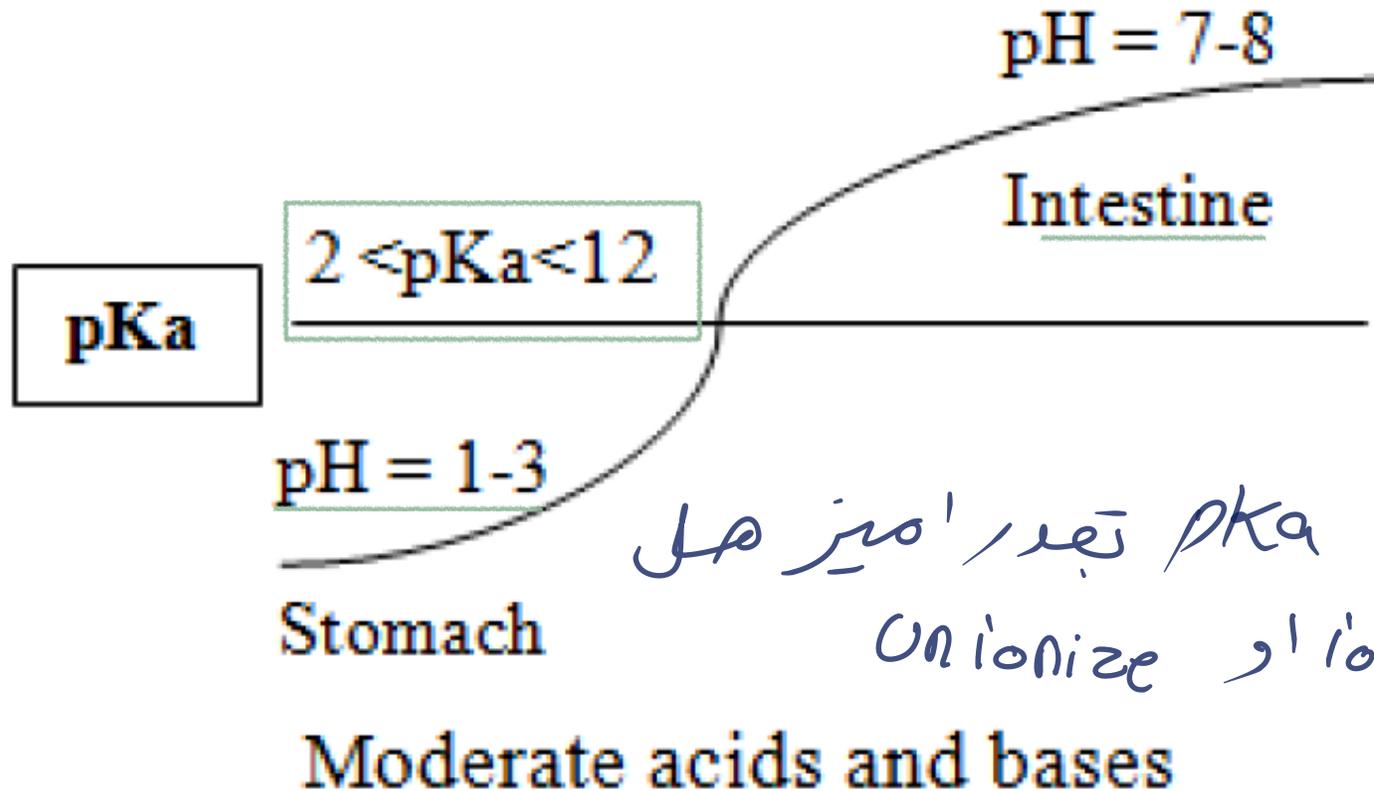
- **Phenobarbitone** (*antiepileptic*)
- Very similar to phenytoin; its structure contains **2 imides**; the N pair of electrons is being withdrawn by 2 carbonyl so it's a **weak acid**. Therefore, permanently unionized through GIT and **gets absorbed readily**.



# 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



# 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<sup>-</sup>. 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.

الـ inter mediat acid بالـ stomach بالعادة يكونوا unionize

معظم الـ inter mediat acid يكون الـ  $pKa \approx 3-4.5$  طبعاً يكون اقل من

الـ  $pH$  بالعدة فيكونوا unionize يعني سير الـ absorption

ليس الـ absorption! لهم بالعدة قليل؟

① الـ surface area قليل بالمقارنة مع الـ intestine الوقت! يعني يفضل فيه الـ blood بالعدة قليل

③ low vascularize يعني ما في blood supply كثير

# Intermediate acids

- Under stomach conditions (acidic conditions), intermediate acids are unionized (HA) while in intestines (basic conditions) are ionized (A<sup>-</sup>). 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

1)  $pH \approx 3-4.5 = pK_a$  ! intermediate acid - drug

2)  $pH > pK_a$  ! ionize ! 7-8 intestine

intestine ↓

إذا كانت الفرق بين  $pK_a$  و  $pH$  بمقدار one unit

يكون 90% un-ionize و 10% ionize

أما إذا كان الفرق two unit يكون 99% un-ionize و 1% ionize

أما إذا كان الفرق three unit يكون 99.9% un-ionize و 0.1% ionize

لازم تعرف الـ  $pK_a$  للـ intermediate acid على أن تعرف

جميع الـ intermediate acid drug

يجب أن يعرف الـ absorption بالمعدة

بس هذا لا يعني أنه يجب أن يكون

100% لازم تعرف كم الـ  $pK_a$

والثبات للفرق بينه وبين الـ  $pH$

لكن تعرف كم يجب أن يعرف الـ ionization

الـ degree of ionization

بالسلايد الجاي يجب أن يكون العكس

لأنه في الـ intestine يكون

ionize



# Intermediate acids

الإنزيمات في الأمعاء في حالة توازن مع الشكل الأيوني A<sup>-</sup>

- Through intestines even though it's mostly ionized because ionization is in equilibrium between HA and A<sup>-</sup> 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.

بال intestinal لا يكون نفس ال stomach لأنه ال  $pK_a < pH$

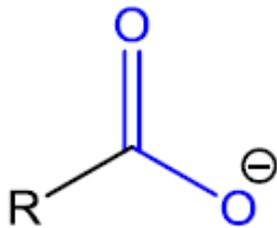
إذا كان الفرق 1 unit لا يكون 90% ionize و 10% unionize

إذا كان الفرق 2 unit لا يكون 99% ionize و 1% unionize

إذا كان الفرق 3 unit لا يكون 99.9% ionize و 0.1% unionize

# Functional groups that make drugs of intermediate acid character

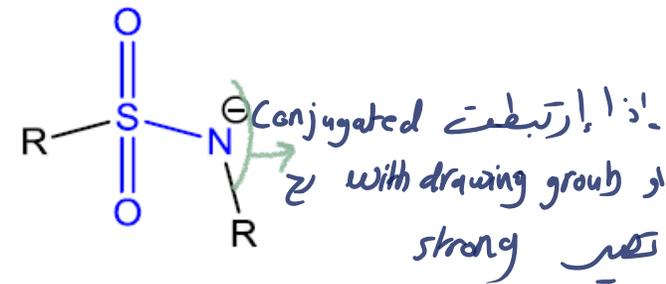
## Carboxylic acid



إذا ضمنت  
withdrawing  
group  
زیرا کاربونیل  
strong  
نقص

**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

## Sulfonamides (without EWD)



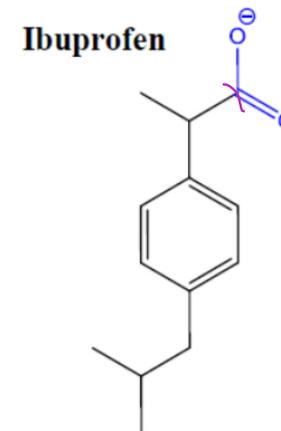
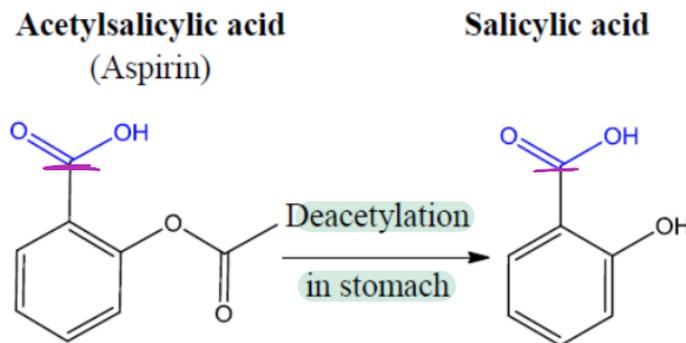
**Sulfonamide**, you remember from the previous lecture if the R group is an electron withdrawing group, then it will become strong acid as in case of Saccharin but Sulfonamides without having an electron withdrawing group on R their **Pka=6-7** they're intermediate acidic therefore they're unionized in the stomach and in the intestine is ionized on the N. *totally unioniz in stomach pKa-pH 7.3*

*in intestine pH ≈ pKa 50% unioniz 50% ionize*

Aspirin → NSAID

# 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**.

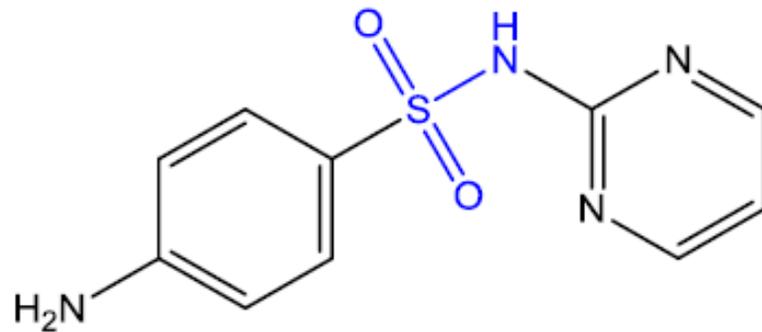


- Drugs containing sulfonamides are usually used as antibacterial agents. However, some sulfonamide drugs are used as anti-diabetics (Sulfonylurea:  $pK_a \sim 3.8-6$ ), anti cancer agents and diuretics (Thiazides:  $pK_a \sim 6.8-9.8$ ).
- Example of antibacterial agent: **Sulfadiazine**.

in type 1  
diabet

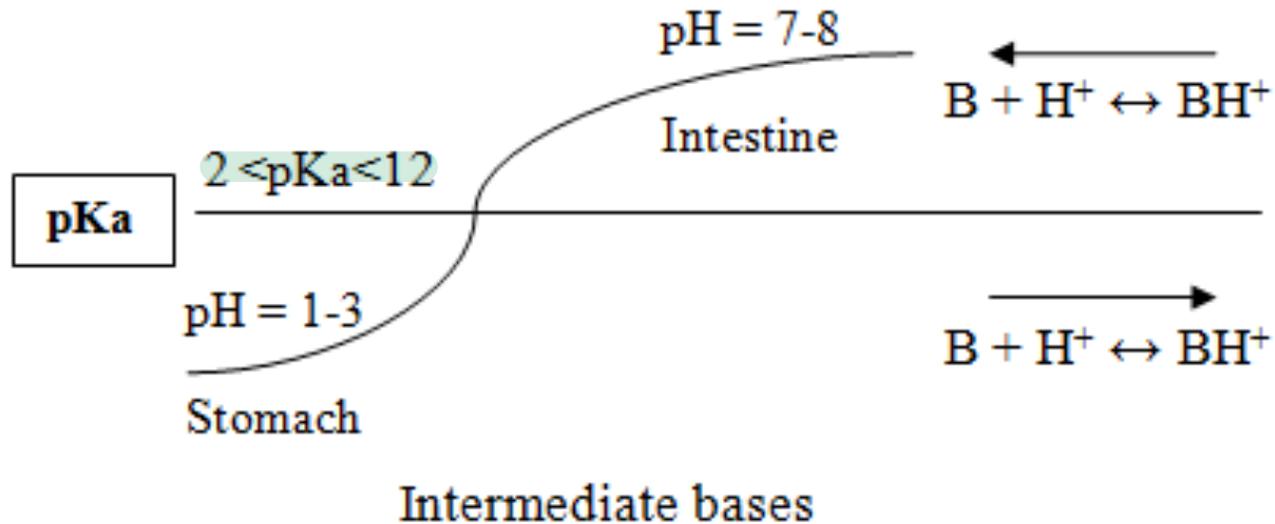
in GI

**Sulfadiazine**



⇒ totally absorbed  
in stomach  
 $pK_a = 3-5$

# 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.

بفضل الاويه انما تكون Basic drug ليست؟

للتفاح تكون Ionize بال Stomach وصاح يصر لها absorption فيها

لانه بال Intestine رح يصر لها unionization وبالتالي absorption ولما انه لها Surface area

كالي و high vasculariz وال drug رح يقعد فيها تقريباً 12 ساعة كل هاي الأشياء بتحسنت

ال 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 sp<sup>2</sup> hybridized so electrons are closer to nucleus **pKa=5-6**

توضووا الشرح  
بالملايرات  
المسابقه

بالنسبة الى Amin حكيما انهما ممكن تكون intermediat

base ال  $pK_a$  ايلها = 9-9.5 بال stomach ال  $pH = 1-3$  اذا ال  $pK_a$   $pH$

ال يكون ionize فيها بس بال intestine ال  $pH = 7-8$  اذا الفرق

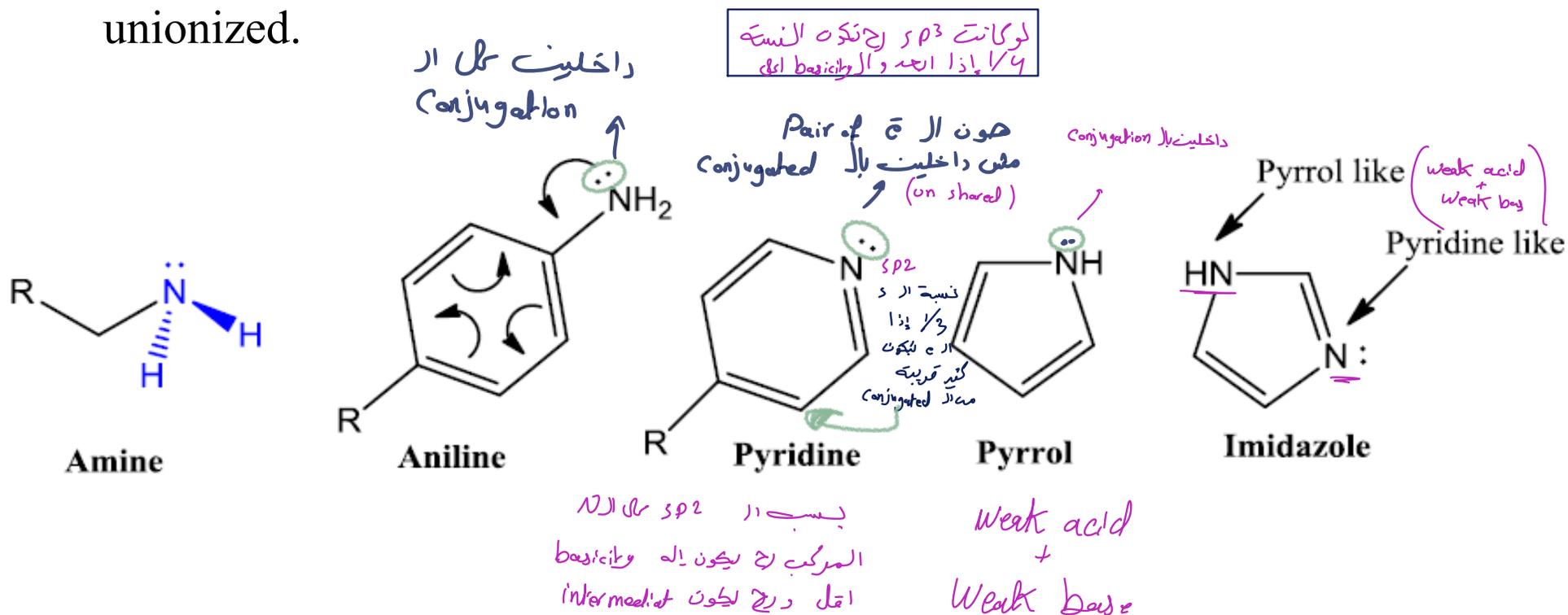
بينها ديت ال  $pK_a = 1$  ال يكون unionize 90% و ionize 10%

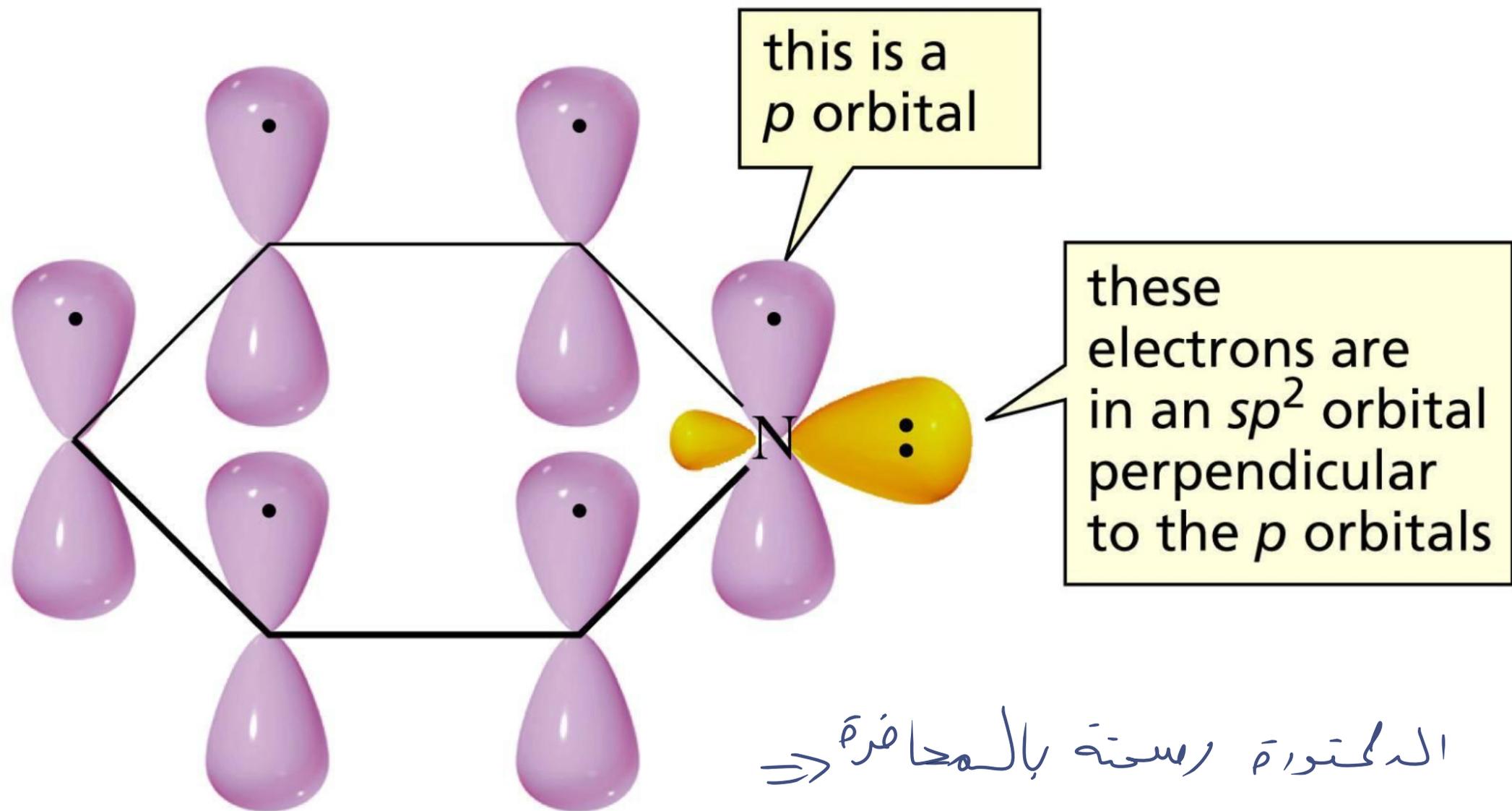
حكيما انه ال Amin يكون intermediat base لانه ال N كليها e Pair of

هي ال ال ال اعطيه خصائص basic

# 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.





orbital structure of pyridine

الذاتورة رسته بالمحافرة =>

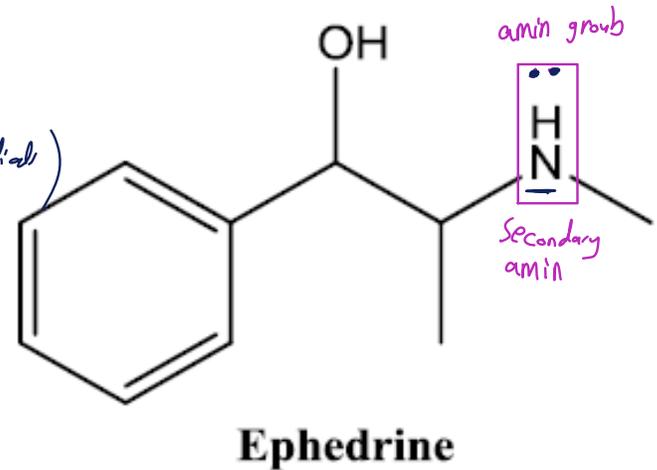
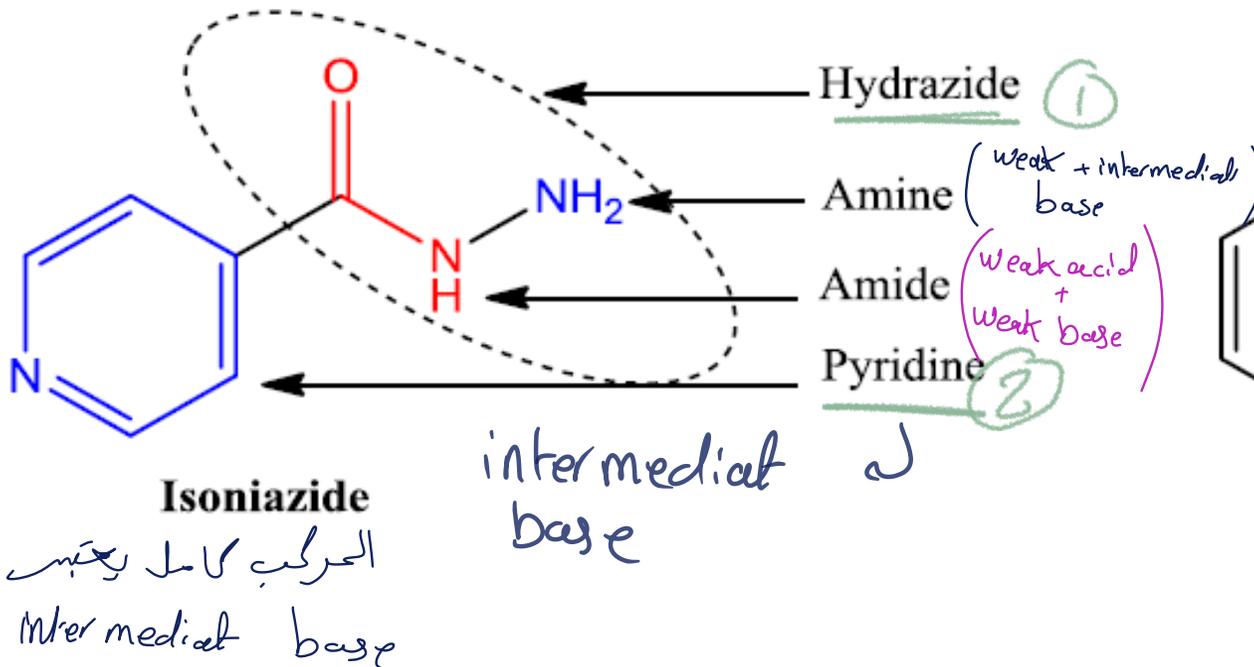
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# Intermediate Bases: Examples

## Isoniazide (for tuberculosis)

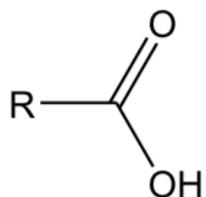
contains pyridine N and hydrazide function (consecutive N attached to a carbonyl) containing amide which is a weak base, and an amine which is an intermediate base. Therefore, Isoniazide is a drug administered orally and well absorb in the intestine for sure.

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



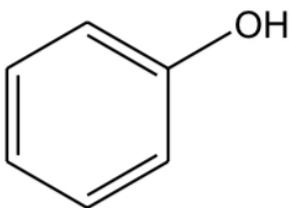
# Common acidic functional groups in pharmaceutical chemistry and their pKa values

1- Carboxylic acid



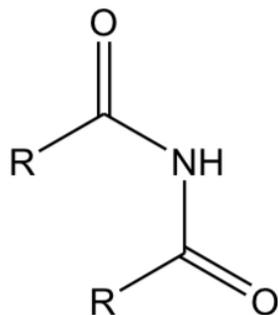
4-5

2- Phenol



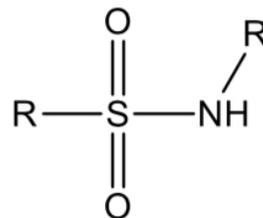
9.9

3- Imid



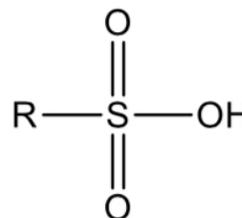
8-10

4- sulfonamid



10

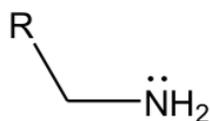
5- sulfonic acid



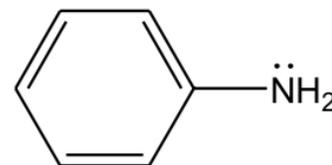
<2

# Common basic functional groups in pharmaceutical chemistry and their pKa values

1- Amin

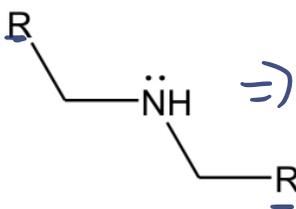


10.0



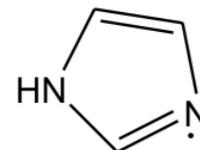
4.6 5-Aniline

2- secondary Amin



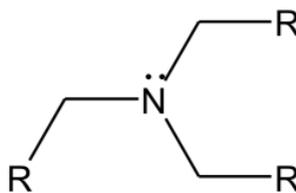
⇒ pKa اقل من ال Primary بسبب وجود ال  
 donation group ال N تغير withdrawing group طرح  
 لتسحب الة اكتر وتزيد ال basicity

10.6-11.0

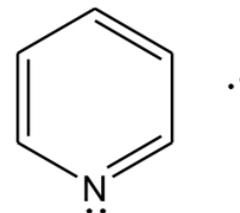


6.5 6-imidazol

3- tertiary Amin



9.8-10.8



5.2 7-Pyridine

هون صارت ال pKa اقل لان صندل  
 ال 3 مركبات صاروا ضعيف ال ال  
 فقلت ال basicity

# 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*