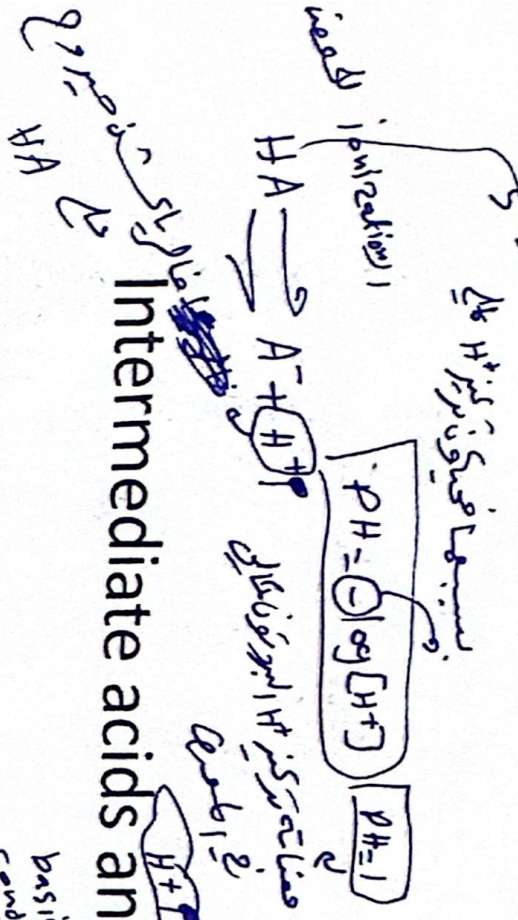
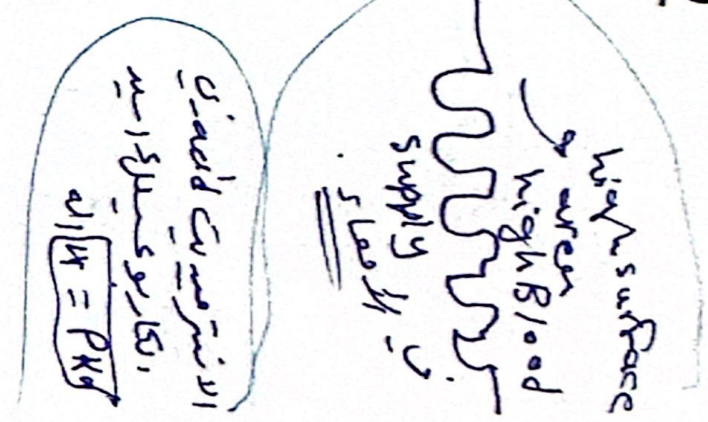


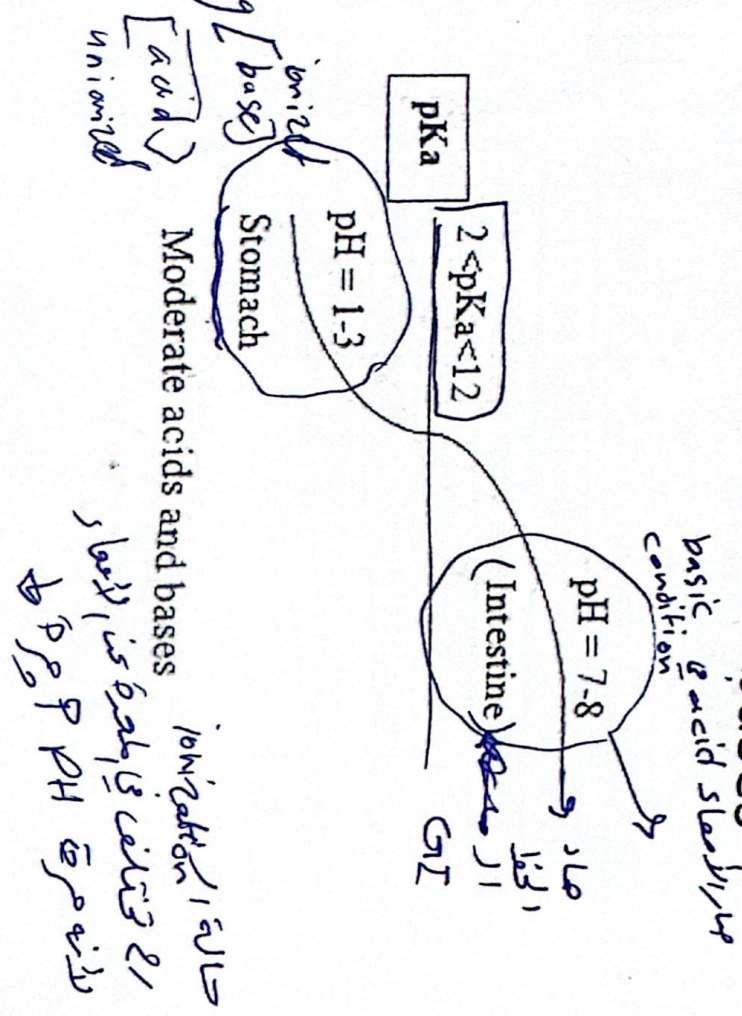
Pharmacokinetics 2



unionized in the stomach



Intermediate acids and bases



Intermediate acids

- In the stomach the conditions are acidic so the equilibrium is shifted toward HA therefore they're unionized and absorbed; while in the intestine the conditions are basic so the equilibrium is shifted toward A- therefore minimal absorption happen.
- Nevertheless in stomach happens the major absorption (50%), 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.

السوا يقدر بالمعدة فترة قصيرة أما في الأمعاء

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

في ١٠٪ في الأمعاء
و ٥٠٪ في المعدة

Intermediate acids

* زى ال Carboxylic acid
 unionized
 في المعدة (Ionized) في الأمعاء

- 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 $pH=pK_a$ then 50% is ionized; if $pH>Pka$ with 1 unit then 90% is ionized and 10% unionized); intestines have:

* المساحة السطحية area
 لها منخفضة
 والوقت time
 قليل كحشر عارث
 بقدرة الواحدة طريقة
 أما الأمعاء فتتميز بطولها
 يصل تقريباً 10 أمتار
 والى high Blood supply

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.

فذلك ال Carboxylic acid unionized
 في المعدة امتصاصه
 في غير
 لأنه الأمعاء لها
 اللون الزهري
 حدد

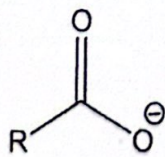
منها كبريتات صلبة
 للأغذية المتوسطة

وحداتها تكون ionized في الأمعاء في يتم امتصاصه في الأمعاء لكن بشكل غير جيد

Functional groups that make drugs of intermediate acid character

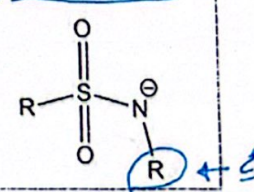
فيها تصد أصباً
 الخشائبي

Carboxylic acid 3-4.5 pKa
 (conjugated to EWD)



والتي تفاعلية R قروب
 electron withdrawing group
 6.5-10 pKa

Sulfonamides 3
 (without EWD)

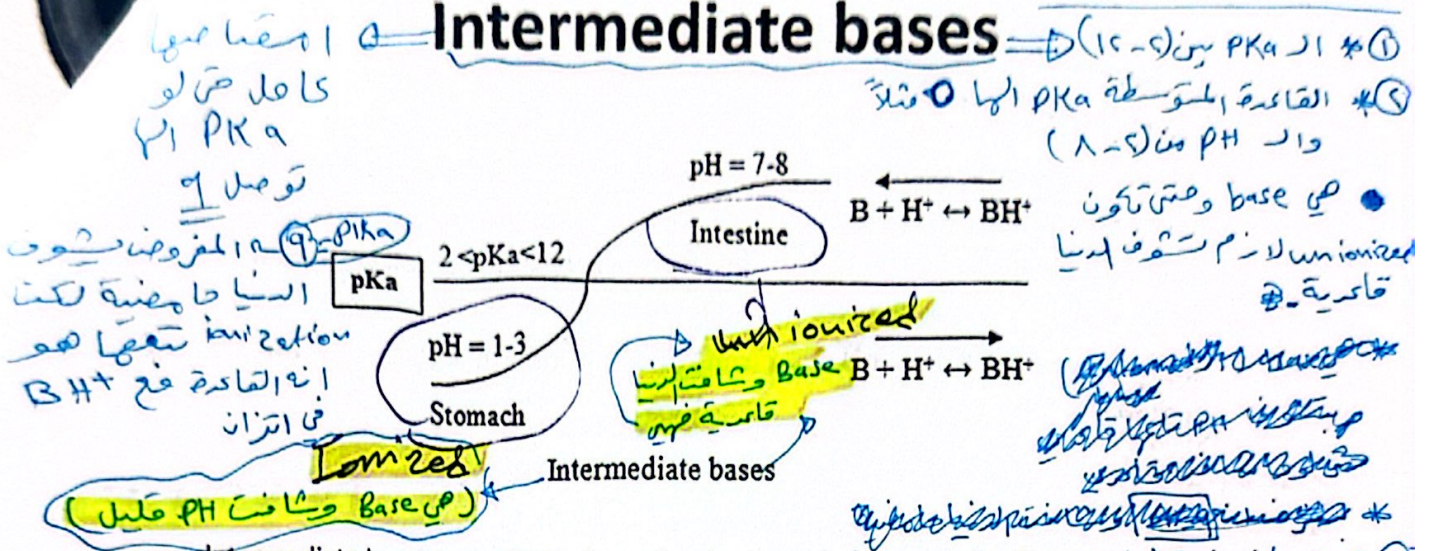


أهم مثال على الوسطية

Carboxylic acid with $pK_a=3-4.5$ 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 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.

* هذه مناصب من ربي الكونف المتوسط امتصاصها جزئي
 في الأمعاء في امتصاصها 10% حتى لو تأنيث في المعدة / لأن الزمان الذي يقعد فيه السوا بالأمعاء طويلة فامتصاصها Time
 (large surface area) high Blood/supply

note (المعدة لم تخلت للامتصاص)
 لما كانت متأنيثة في المعدة الامعاء امتصاصها قليل
 لأن الزمان الذي يقعد فيه السوا بالأمعاء طويلة فامتصاصها 10%
 (Blood supply) long transient time
 weak base Pyridine or Intermediate like N Base

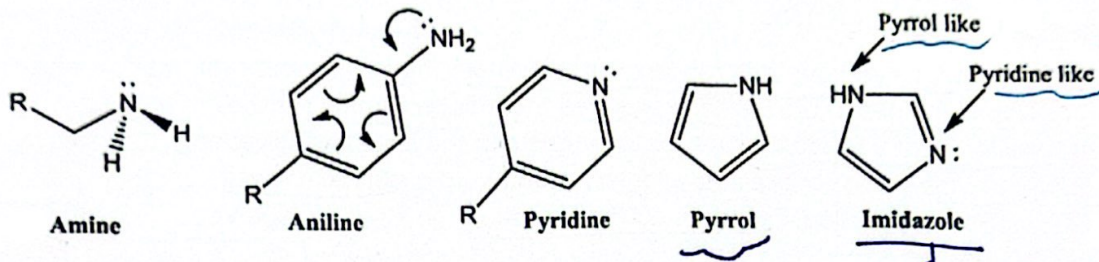
Groups which make drugs with intermediate basic character,

- 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^2 hybridized so electrons are closer to nucleus $pKa=5-6$

Intermediate bases

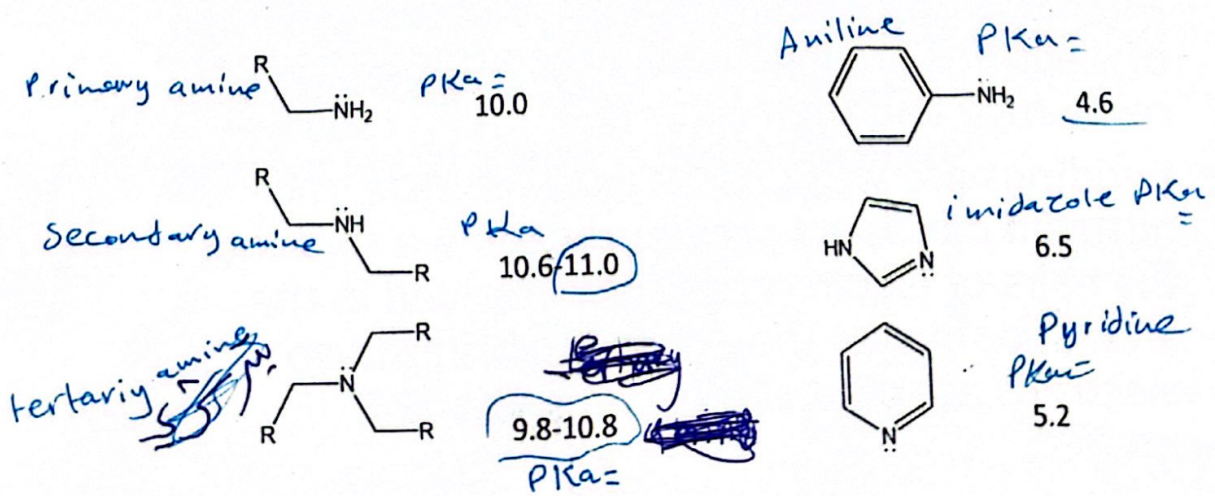
Intermediate and weak base

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



*هنا في إيميدازول
histidine
في إيميدازول
هنا إيميدازول*

Common basic functional groups in pharmaceutical chemistry and their pKa values



Remember the followings

For acids:

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

$pH < pK_a$ by 2 units, 99% unionised

$pH > pK_a$ by 2 units, 99% ionised

For bases:

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

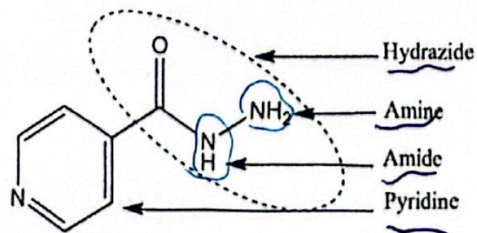
$pH < pK_a$ by 2 units, 99% ionised

$pH > pK_a$ by 2 units, 99% unionised

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.



Handwritten notes: "Isoniazide" and "GIT" with a checkmark.

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

