تفريغ ميديسينال

محاضرة: Lec 1 part 1

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لجان الدفعات

Soul Academy

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.

من اهم الأشياء اللي رح ندرسها بال medicinal chemistry حيث drug discovery

بحيث بنطع دوا وبنعدل وبنشوف تأثيره بالجسم وبنشوف chemical respond

بناءً على ذلك بال drug discovery رح نقسم بشغلتين

① chemical properities: للدوا بحيث انه نبجيب الدوا لحالو ونحلله ونحاول

نعمله نفس ال pharmaco form اي هو الجزء المسؤول عن ال effectiveness بال

structure زي ال β-lactan الموجودة بال Penicillin فلما اصنع حلول اخلي ال

pharmacoform للدوا مشابه لدوا بعمل نفس ال effect وبعدها بعدل عليه.

التعديل بكون بناءً على ال chemical properities وبعدها بجربه على animal

او Hyman

② pharmacokinetic = لازم نحنا منعرف شو تأثيره على الـ pharmacokinetic (تأثير الجسم على الدواء)

هل رح يصير إله absorption / distribution / metabolism / excretion

③ pharmacodynamic = (تأثير الدواء على الجسم) بالجسم في receptor فلازم الـ

binding site للدوا يكون بشبه الموجود على الـ receptor فلما يرتبطوا مع بعض رح يصير

عندي interaction بين الدواء والـ binding site ورح يعمل complex بسمى drug-receptor complex

الحطي فوق بشكل عام !

• اي رح يعطي الـ effect

صون الأشي الموجود بالشرح

الـ drug discovery رح ندرس هاي الأشياء

1- Lead compound 2- Potency 3- Selectivity 4- toxicity

Lead compound :- هو المركب الاول اي تم اكتشافه وهلي الاغلب يكون جاي من Natural Product و يعطي اا Pharmalogical effect •

Natural drug :- morphen from opiod

semi synthsis :- Salicylic acid → acytyl salicylic acid اللي بعدل عليه ليتحول لـ

Fully synthsis :- بلجأ لهاي الطريقة لعدة اسباب منها انه لحمية المادة اي بدي استخلصها من النبتة بتكون قليلة وبوخذ لها بدي اعمل separetion لمكونات النبتة رح ياخذ وقت طويل •

drug potency :- concentration of drug that give up 50% from respond

عشان هيك الدوا لما أكتشفه لازم يكون potent وصمت ال therapeutic window لانه إذا كان

اعلى رح يكون toxic واذا كان اقل ما رح يكون إله تأثير (sub therapeutic)

selectivity ← الدوا لازم يكون selective بس لل target cell اذا كان للبكتيريا مثلاً يكون

selective بس عليها • وزي ما بنشوف بأدوية ال chemo therapy انه بالحط (non-selective) cancer

يسبب ضعف كبير للحمايين بال cancer وفي ممكن تاخد تموت منه

toxicity ← اي دوا يعطى للشخص لازم يصير ال elimination عشان مايفل بالجسم ويصير

• toxic

بعدما حكينا عن ال drug discovery رح ننتقل لل development: بعدل ال structure حتى احصل

على ال effect عن طريق ال structure activity realation ship (SAR) بحيث اي اقل اغير بال structure حتى يعطيني

different effect عشان هيك رح نهتم بال Pharmaco kintic لانه بهمني انه الدوا يمر بال absorption

distribuatio --- etc. مثلاً الدوا ما يكون oral availble عشان هيك بعمل اله improvment ويمر

oral availble وممكن الدوا ما يصير اله elimination فبعمل اله development حتى يمر بال metabolism + excereatio

وهسا رح نحكي عن identification and interpretation لِ نهتم فيها انه الدوا يرتبط بال binding site

ويعطي ال effect Pharmacoligical

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.

وآخر الشي الـ metabolic product : ليش يهتم فيها؟؟ لانه ممكن يكون عندي ادوية Pro-drug

اي تكون inactive وبعد ما metabolism وبتتحول لـ active يعطي الـ Pharmacological-effect

شو تعريف الـ drug

drug : chemical compound use for treat disease •

و ممكن استخدمه لحمان كل الـ micro-organism

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:

إلي صحوا الدوا ما صنعوا دوا واحد هما صنعوا الـ structural unit الـ هي الـ pharmaco form المسؤولة عن الـ activity . إذا انا بصنع different-compound الهم نفس الـ structural-unit بس انا بلعب بباقي الـ structur عشان يعطيني التغيير بالـ activity للأدوية وهذا الاشي اي بنتعامل معه بالـ (SAR) .

باك SAR رح نشوف الـ drug-design بحيث اني ارسم بـ software شكل الـ receptor (3D) بعد هيك بجيب الـ compound وبقربه من الـ receptor اي رسمته وبشوف هل معقد يدخل بالـ binding site ؟؟ هل بعمل attraction ؟؟ اذا صار إله attraction بعرف انه رح يصير drug-receptor complex وهيك رح يصير effet

Structure activity relationship (SAR)

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

- Optical isomerism → معظم الأدوية لها optical center إلي بخليها لها أكثر isomer
- Geometrical isomerism cis/trans
- Conformational isomerism
- isosterism → بيكون الادوية متشابهة كثير بس بشيل OH مثلاً او اضيف اشي ثاني

- Attraction forces:

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

هاي ال bond الي ممكن تصير بين ال drug وال binding site

ADME

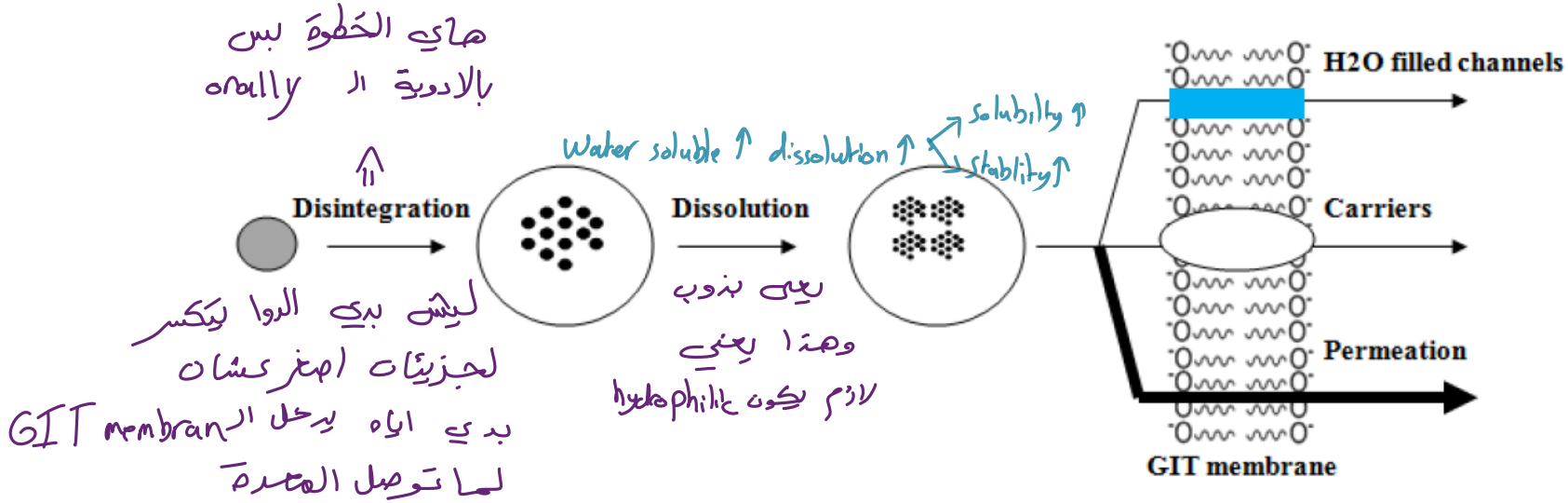
- Absorption
  - how do the drugs enter the body? → هل رح يصير إمتصاص
- Distribution
  - how are the drugs distributed in the body → كيف رح تتوزع بالجسم
- Metabolism
  - chemical modification of drugs (breakdown, increase of hydrophilicity to improve clearance)
- Excretion
  - how do the drugs leave the body → كيف بطلع من الجسم

الادوية بتكون إما reversable او irreversable وطبعاً انا بفضل الـ reversable لانه بس يخلص الـ effect بفك من الـ receptor ويطلع برره الجسم اما الـ irreversable رح تفل مرتبطة بالـ receptor ورح تعمل toxic-effect

- **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



بالأدوية ال oral الدوا لازم ينتقل من GI للدم وبالعادة بصير إلها First pass

metabolism يعني انه الدوا لما بكون بال stomac وال intestine رح ينتقل جزء من الدوا لل liver ويصير له

metabolism ورح يطلع من الجسم فحسب انا بكلو بدي بالدوا فمثلاً ما بدي يصير إلها إمتصاص

بالدم بدي ال effect يكون بالمعدة او الأمعاء ... الخ

الدوا لازم تتوفر فيه عدة خصائص عشان يصير له إمتصاص منها انه hydrophilic عشان

يذوب . عشان هيك معظم الادوية اللي تباع بالصيدليات بتكون salt ليكون فيها جزء hydrophilic

معلومة سريعة:

ال D اذا مثال على الادوية ال lipophilic

عشان هيك لازم ناخده مع اكلة دسمة

Routes of GIT penetration

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

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

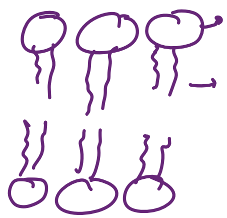
- **2- Carriers** (minor route)
- They are integral protein which can carry molecules across the cellular membrane of the GIT.
- Carriers are meant to be used for hydrophilic molecules which are essential for biological activity and don't have the optimal hydrophilic-hydrophobic properties needed to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

مشو يعني hydrophobic - hydrophilic optimal ؟؟

مش ال cell membran بتكون من head و tail

head ⇓ Carboxlic acid ((–) charg)

tail ⇓ Fat



عشان يدخل الدوا لازم يكون جزء منه hydrophilic ليدخل من ال Head وجزء lipophilic

عشان يذوب بال lipid ويطلع من الجهه الثانيه

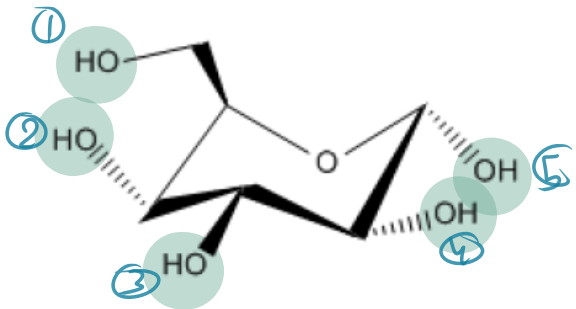
Routes of GIT penetration

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.

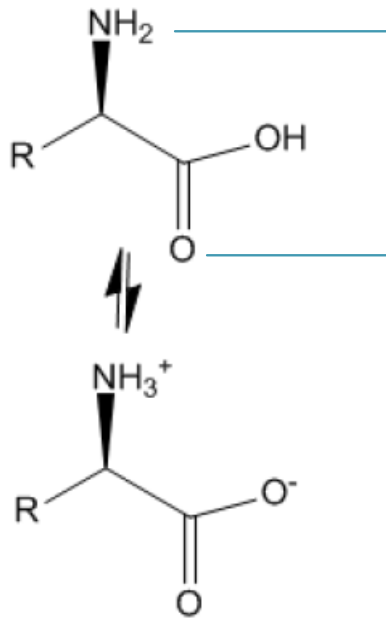
5-carboxylic لهيك group



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.

Amphoteric يتصرفوا ك



ionized لما تصير (+)charge لما يكون

ionized لما تصير (-)charge لما يكون

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:

مثلاً " إذا كانت الـ carrier تحمل D-glucose إذا بس رح تحمل الأدوية الـ D

- **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.

برضه إذا كانت بس L-amino acid رح تحمل بس L

- **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.

يعني انه اعطي مثلاً dose 100mg وانه بس 300mg حمار للهم إمتصاص عن طريق الـ carrier وصارو fully saturable إذا رح يصير excreation من 100mg من الدوا إذا" خسرت 70% من الدوا بالـ metabolism فشو الحل؟؟

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.

الحل انه اقسم الـ dose مثلاً" 500mg مرتين باليوم أو 300mg ثلاث مرات باليوم

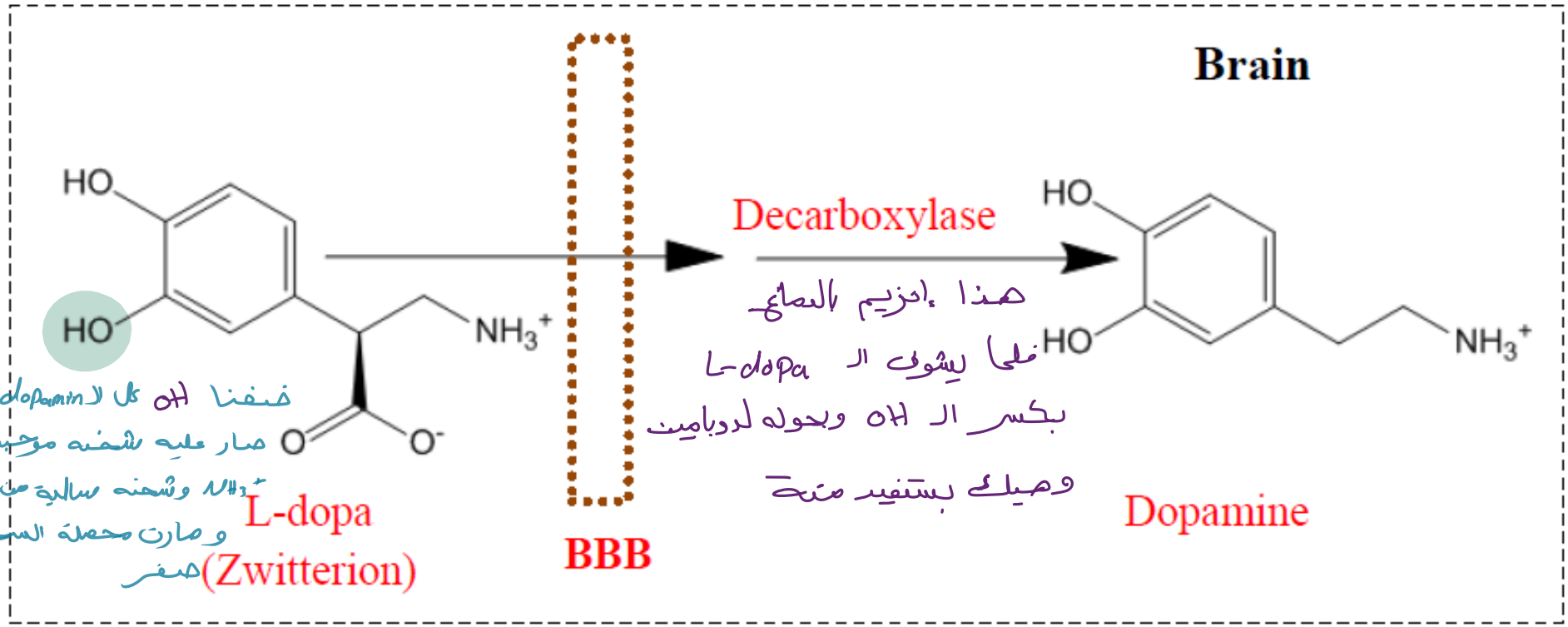
- **c. They either use energy or not.**

- Facilitated diffusion: transport with the concentration gradient and don't need energy. → from high to low con
- Active transport: against the concentration gradient so it needs energy. from Low to high con

- **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).

L-dopa

بالعادة الـ dopamin يعطى orally بس هو يعتبر basic drug اذا pH < pKa الـ يصير الـ ionization بالمعدة وصارح تقدر يعبر من الـ BBB



خسفنا OH الـ dopamin وهيك صار عليه شحنه موجبة من NH_3^+ وشحنه سالبة من الـ OH وصارن محصلة الشحنات صفر (Zwitterion)

هذا انزيم بالصائغ لما يشوف الـ L-dopa بكسر الـ OH ويحوله لدوبامين وهيك بستفيد مرتين

وهيك غيرنا من الـ dopamin بحيث اني خليته Amphoteric بدل ما تكون amino-salt وهيك صار يصير الله ionization بالمعدة وهيك رح يصير الله absorption وينتقل عن طريق الـ carrier لـ BBB ويصير الله امتصاص بالصائغ

2- Carriers: Example

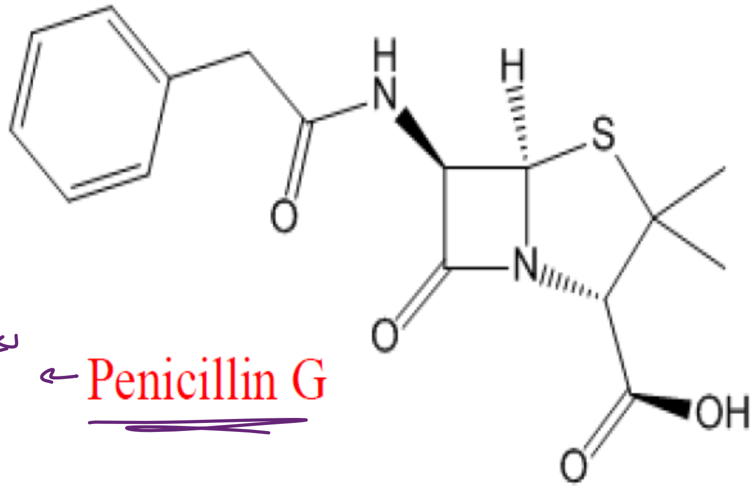
- **Penicillin's**

لسبب orally inactive عشان β-lactran Ring وبتتكسر بالجسم

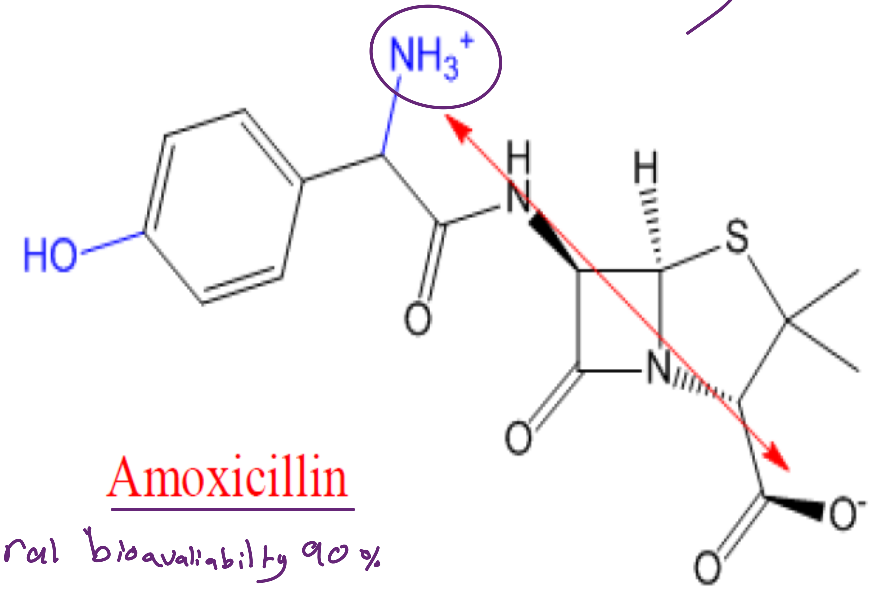
- 1st discovered is **Penicillin G** which is orally inactive, but when converted to **Ampicillin**
- the carboxylic acid (pKa= 3) is ionized to carboxylate which is -vely charged and the amine +vely charged through GIT (pH= 1-8).
- Ampicillin structure is similar to dipeptides, making it a good candidate to be carried across the GIT by carriers originally found to carry di- and tri-peptides formed by protein break

ضفت هاي ال NH_3^+ لحتى تكون نفس المسافة بال di piptied

ما أقدر اعطيه orally

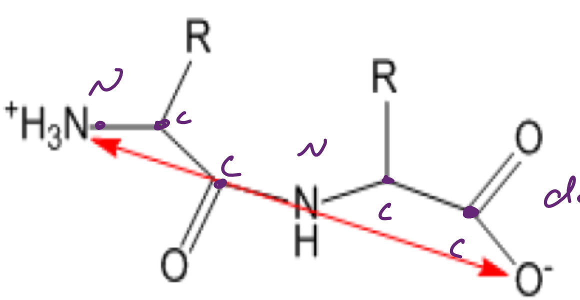


I يعطى ← Penicillin G



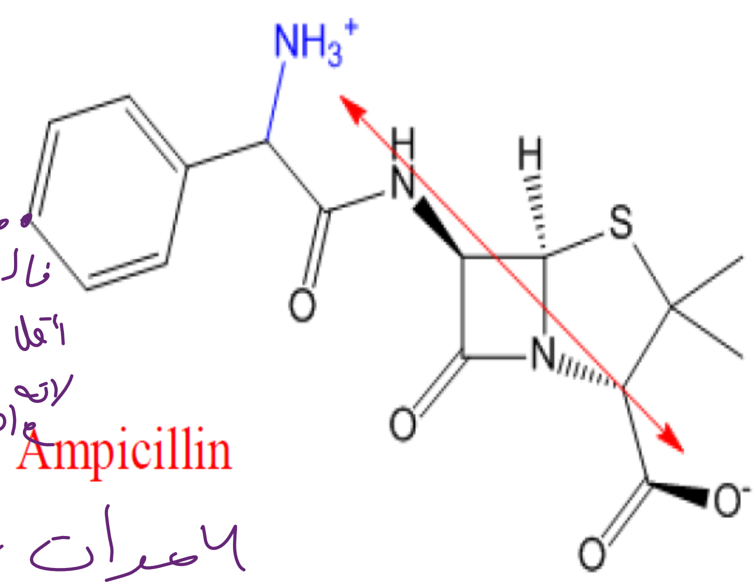
Amoxicillin

oral bioavailability 90%



Dipeptides

ما في OH فال bioavailability أقل فلازم أزيد ال dose لانه fally saturable



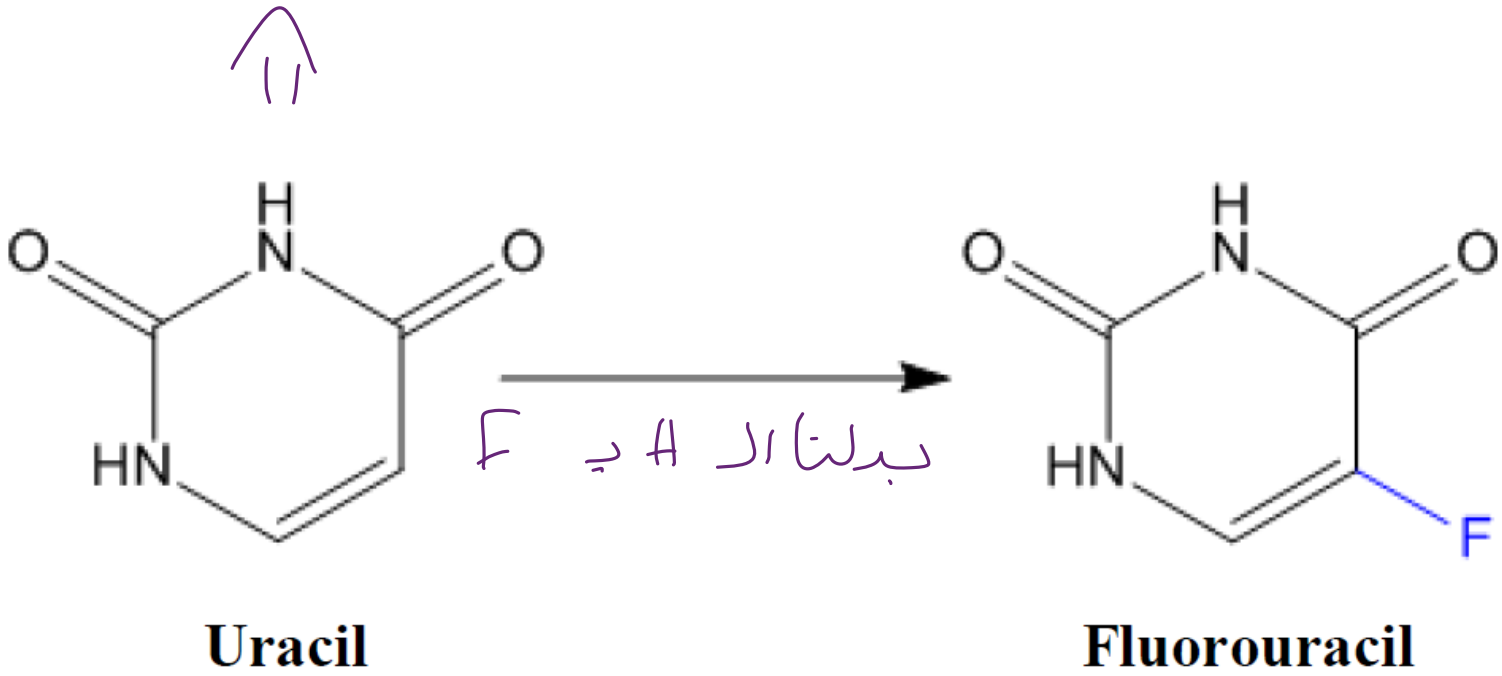
Ampicillin

لهون اليوم

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

structure of RNA بكون بال



Uracil **Fluorouracil**

قلما يرتبط ال Fluorouracil بال RNA يمنع تكون ال RNA ويعمل killing for cancer cell بهذا التغير

قدرو يكتشفو anti-cancer جديد. والمعروف انه ال uracil يرتبط مع ال Ribos لحتى يعمل ال blocking عملت لها nucliked لهاي العملية

إلها شرطين
① unionize ② optimal hydrophilic – hydrophobic

3. **Permeation** by partitioning (major)

معظم الأدوية تعبر بهاي الطريقة

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

3. Permeation by partitioning (major)

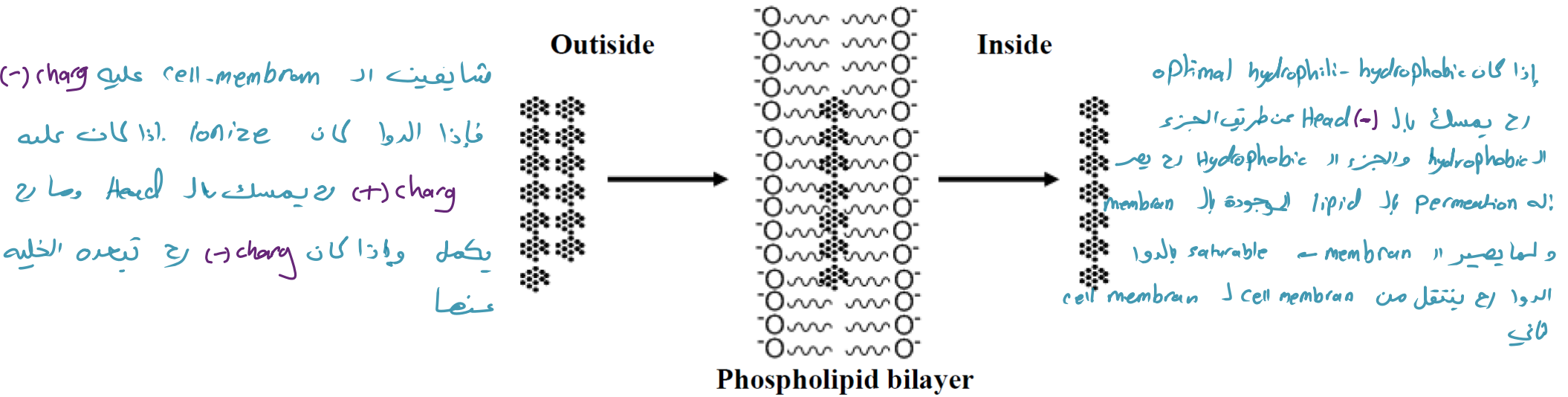
In order for partitioning to occur, 2 conditions must exist:

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.



unionze	ionize
acid pH < pKa	acid pH > pKa
base pH > pKa	base pH < pKa

هذا الجدول احفظوه
عشان يسهل عليكم
معرفة مين ionize و non

خلونا نشوف مثال:

الادوية ال strong acid إلها pKa < 2 فلما اقارن ph ال
بالمعدة والامعاء رح الاحظ انه ال pH اكل من ال pKa
وهذا يعني انه ionized

pH

stomac (1 - 3)

intestin (7 - 8

الادوية ال strong acid ما بنقدر نعطيها only لانه رح تكون ionize
بالمعدة والامعاء وصارت يصير إله absorption وحيكون poor bioavailability يعني كمية
الدوا اللي حتوصل ال blood circulation قليلة

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.

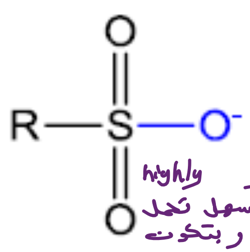
Summary examples on strong acids expected to be orally not available

ionize دائماً

Sulfonic acid

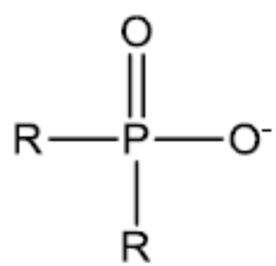
R – S – OH ح يكسرها وح يصير ionized

pKa < 2



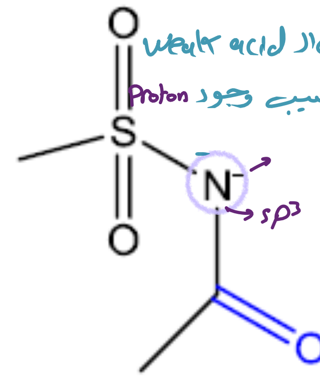
ال O تعتبر highly electronegativity فسهل تحمل ال charge وبتكون عليه stable

Phosphoric acid



Sulfonamides (with carbonyl at N)

ال structure قريب لـ sulfonic acid

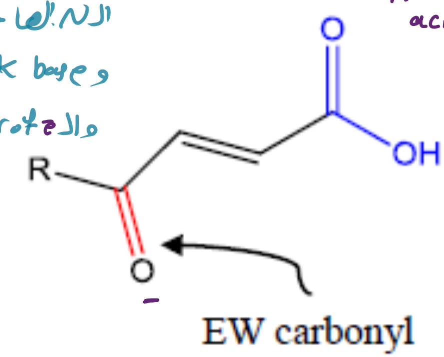


ال N لها خصائص ال weak acid و weak base بسبب وجود proton والـ ion pair

sp3

Carboxylic acid (conjugated to EWD)

moderated acid



Sulfosalicylic acid

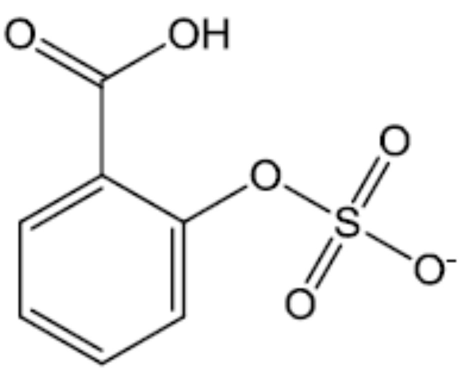
لانها تحتوي ع sulfonic acid

اللي اله pKa 2- ح يصير ionization

ويضل بالمعدة والامعاء وح

يعطي ال effect بشكل locally

لتعالج ال inflammation



sulfonic acid

Saccharine

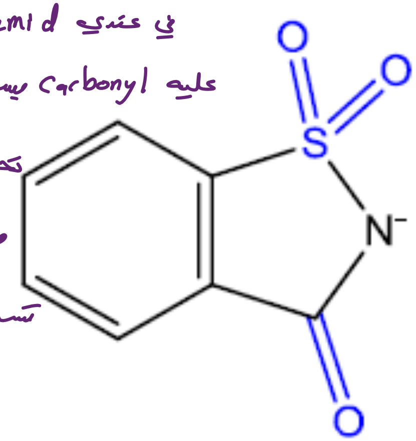
في عندي sulfonamid ضفت

عليه carbonyl بسبب هاي الإضافه

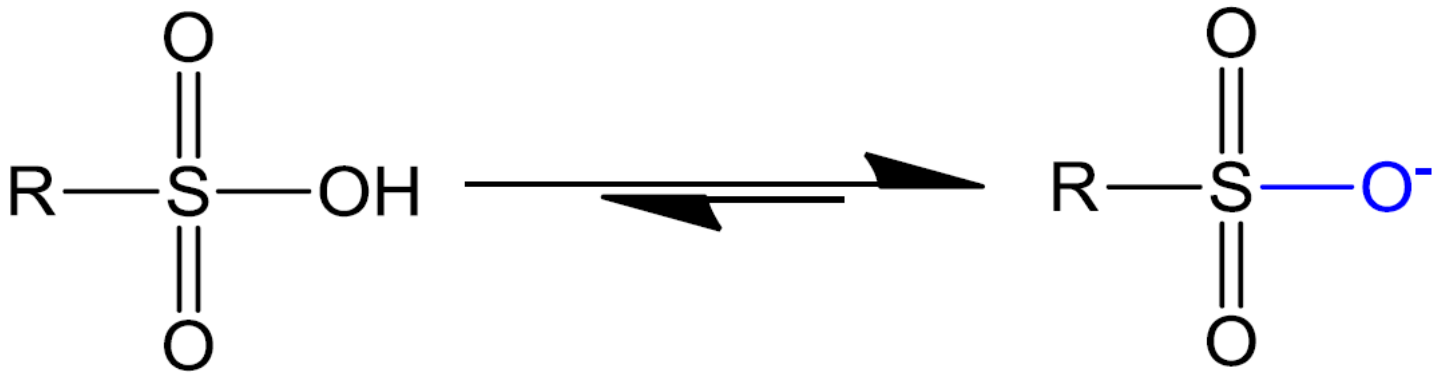
تحولت لـ strong acid

وصارت ال pKa

تساوي (1-2)

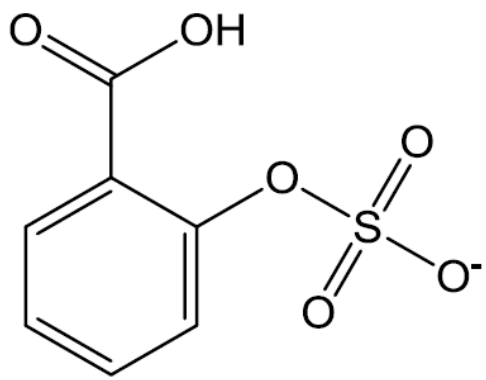


- Salicylic acid is the active form of Aspirin (acetylsalicylic acid), salicylic acid is absorbed through the GIT; if I want to treat a local inflammatory condition in the GIT such as Crohn's disease or ulcerative colitis, we can attach a sulfonic acid group to salicylic acid forming **sulfosalicylic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



Sulfonic acid

Sulfosalicylic acid

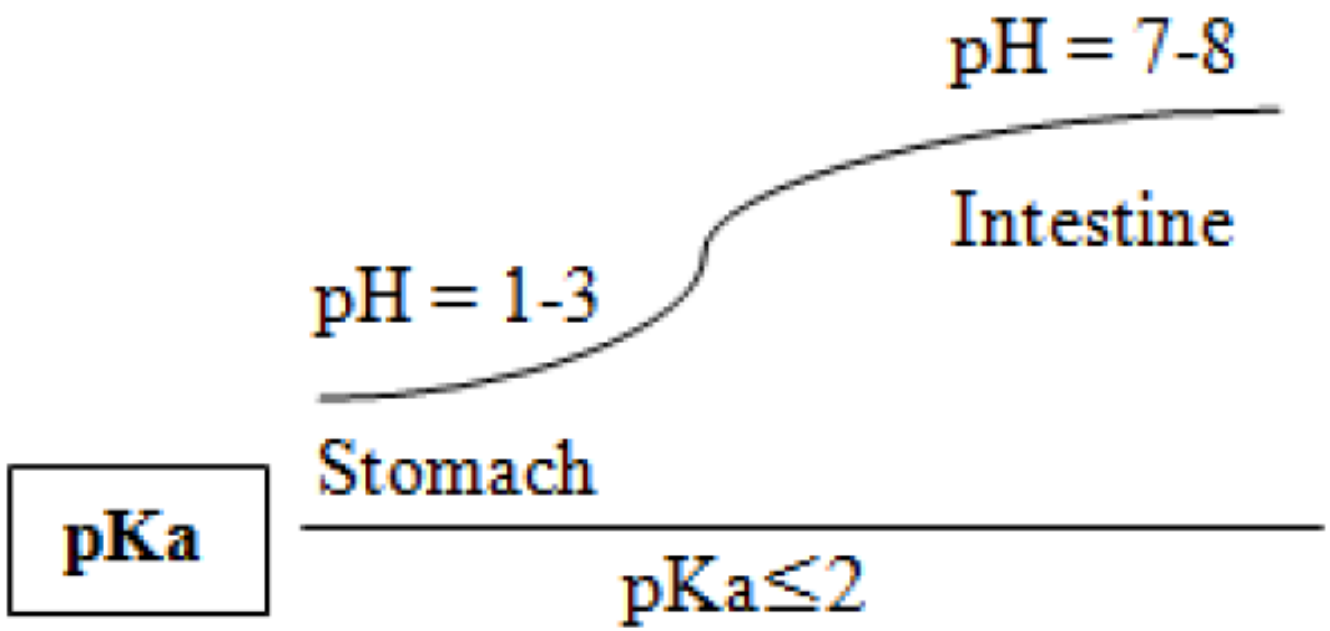


⇒ sulfonic acid ، carboxylic acid عبارة عن

$HA \longrightarrow A^- + H^+$

التفاعل باتجاه اليمين (A^- ionized)

Strong acids...

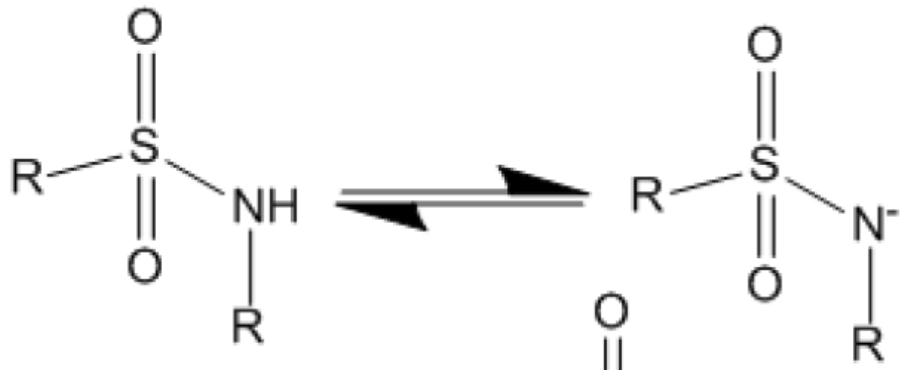


$$HA \leftrightarrow A^- + H^+$$

Strong acids (pH>pKa)

- 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**.

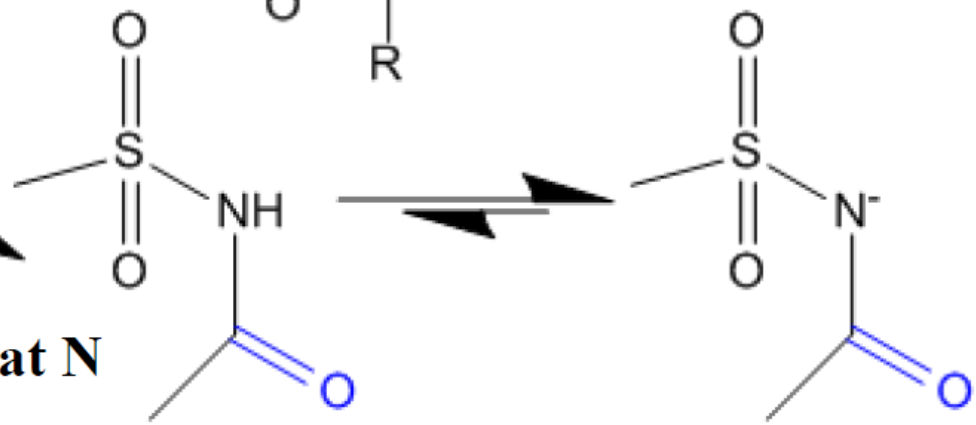
acidic الها طرف
basic وطرف



Sulfonamides
(pKa=7); Intermediate acids

لانه ذرة N الها electronegativity قليلة السحنه السالبه ⇐ صعب يصير الها stablize عشان صيغ تتكون N

intermediate acid



Sulfonamides with carbonyl at N
(pKa=1-2); Strong acids

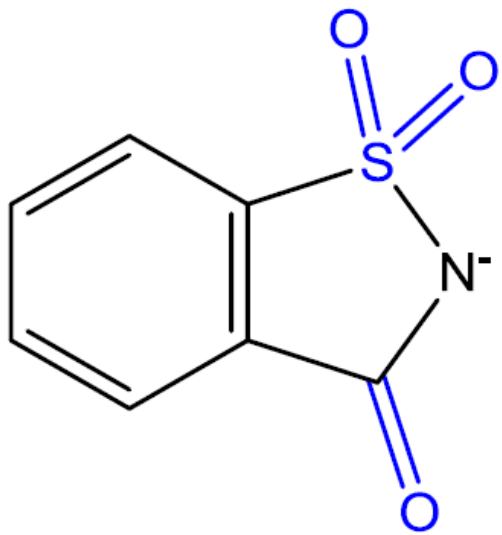
بسبب اضافة الـ carbonyl صارت strong acid

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

محلي صناعي بستخدمة
مرضى السكري ليحسوا بطعم
الحلو بدون ما يرتفع السكر بالدم

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

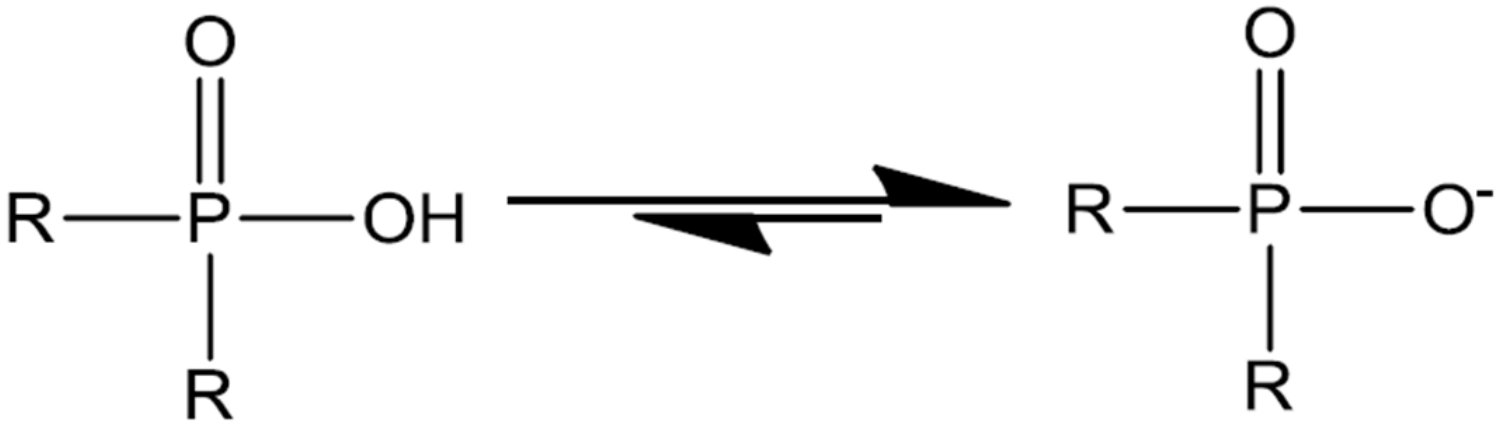


لانه تحتوي على ال sulfonic acid مرتبط بـ ال carbonyl بـ يصير

له ionization صار يصير إله امتصاص بالدم وهيك صار برفع مستويات السكر بالدم

- 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.

PKa 7 pH لانه ال unionization فبصير اله بالعدة intermediat acid بعتبر

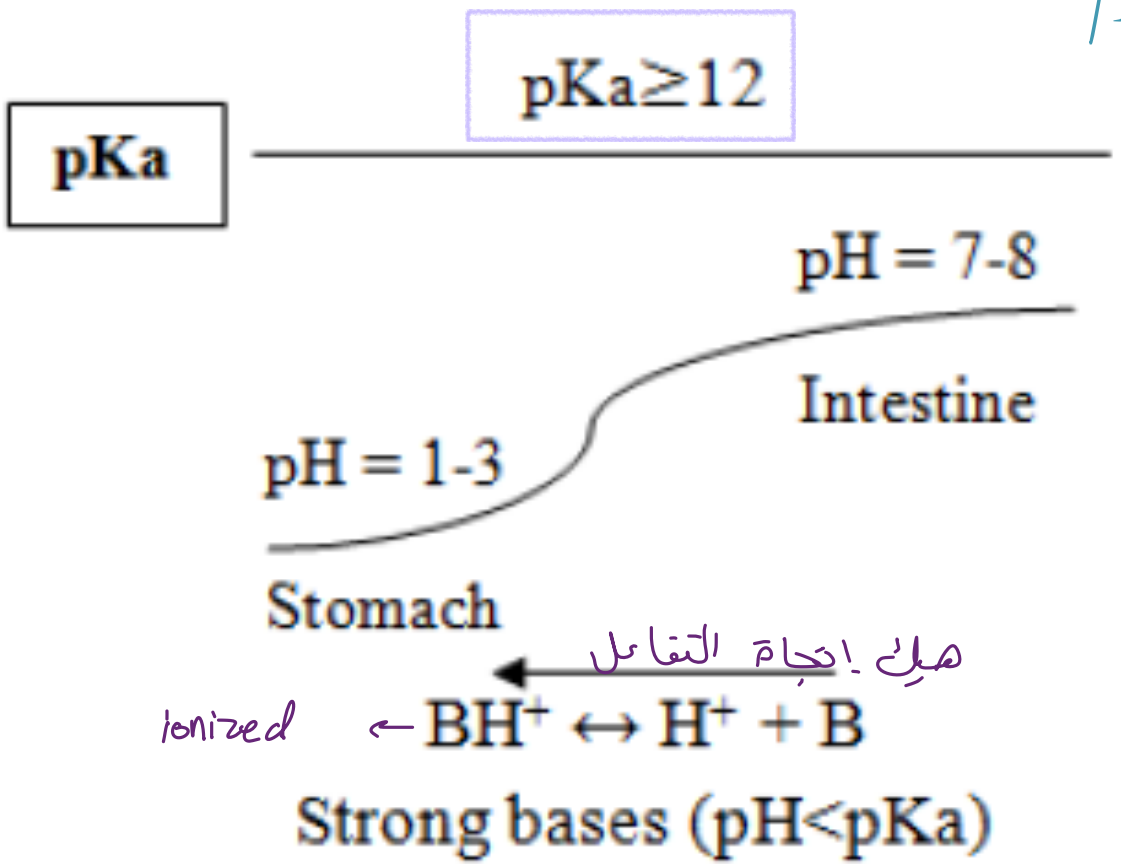
strong acid ل بتحول ح withdrawing group بس اذا كان في

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

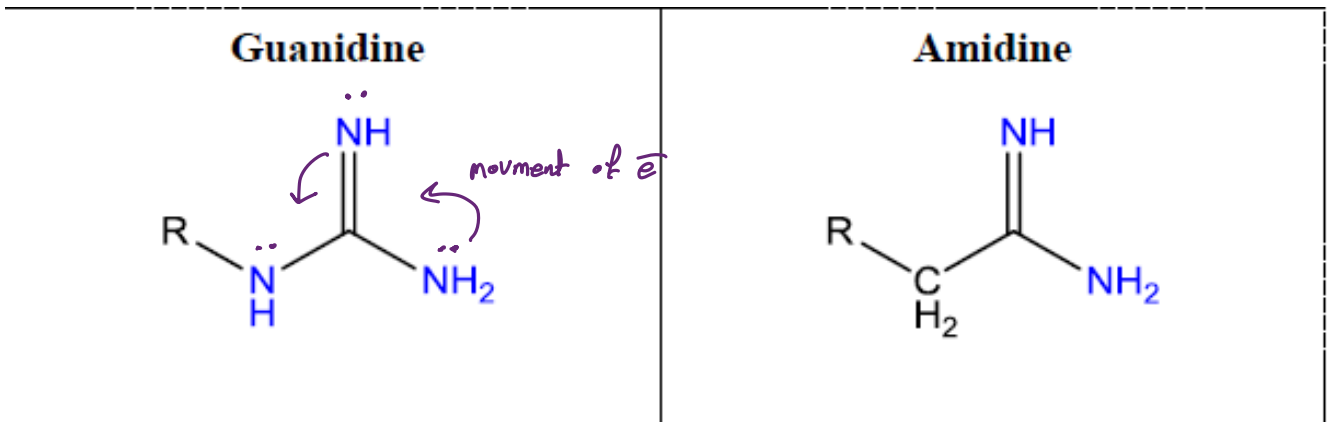
pH < pK



Strong bases (pH<pKa)

- 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.

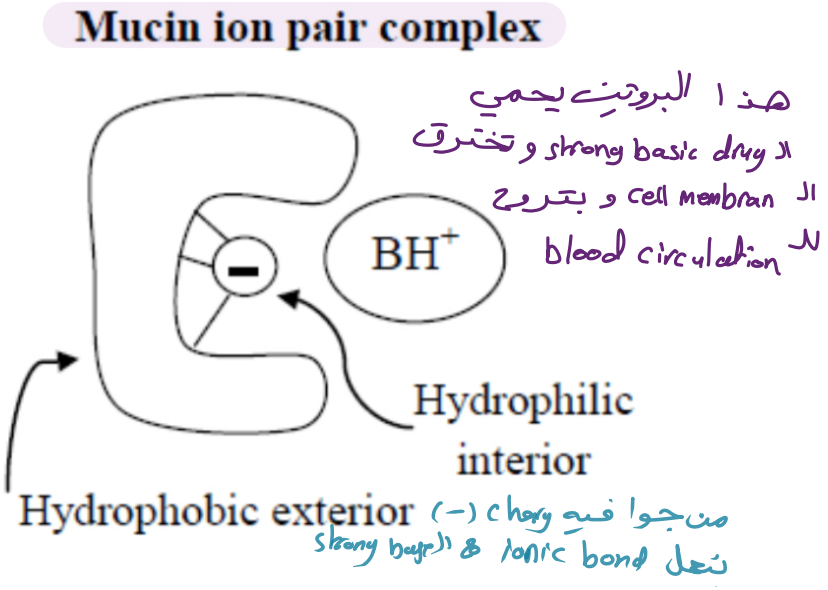
ionize يعني GI بال



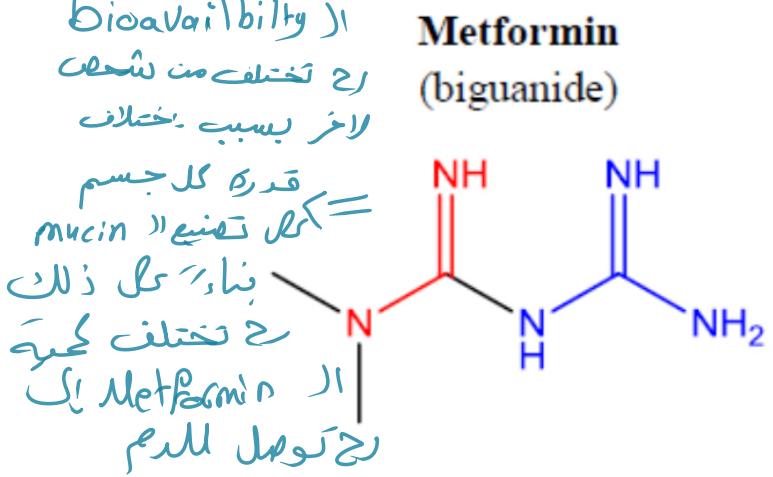
مع انه الـ strong base بتكون ionize بالـ GI إلا انه فيه إلها bioavailability = 40% تقريباً بسبب
وجود بروتينات الـ mucin الشرح بالسلايد القادم

- 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.

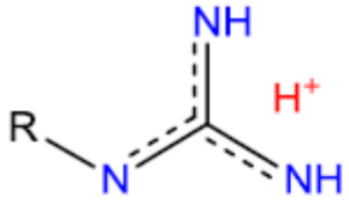
What applies to strong bases applies for quaternary ammonium salts; they're permanently ionized however because of the presence of mucin we do have some bioavailability however it's not more than 40%.



- **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



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



معلومة تكل السريع .

الـ stomac الها surface area اقل من الـ intestin فحتى الادوية الي

بالها intermediate bioavailibity ح يصير الها absorption ويسبب وجود الـ Microvilli الموجودة بالـ

intestine تلعب دور بتحسين الـ absorption