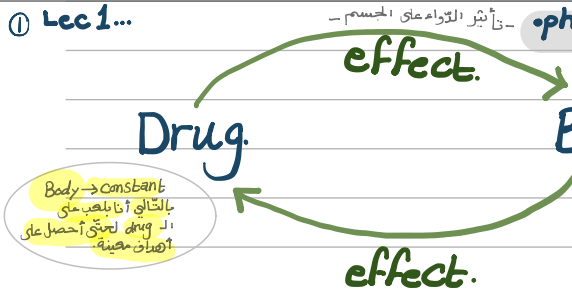
① Lec 1...

- pharmacodynamic: تأثير الدواء على الجسم



- pharmacoKinetic: تأثير الجسم على الدواء

pharmacoKinetic: the study of how the body interacts with administered substances for the entire duration of exposure.

pharmacodynamic: the study of a drug's molecular, chemical & physiologic effects or action.

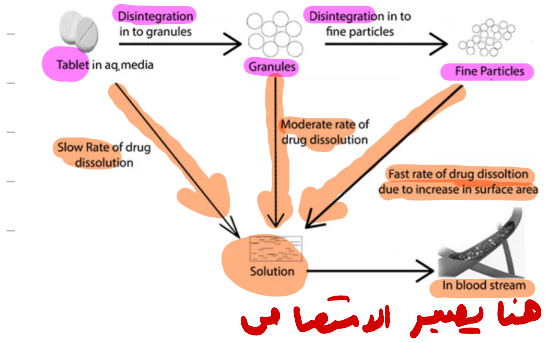
→ pharmacoKinetics: (ADME)
- A: Absorption. امتصاص
- D: Distribution. توزيع
- M: Metabolism. أيض
- E: elimination. خروج

1. Absorption:

بداية إحنا بنهتم بـ (oral dosage form) ← why? رضى الناس عنها عالي. ↓ side effect.
وخاصة "أغلب الأمراض chronic
- بعض باختصار مارح بيفع أفضل أعطي IV !! -

في medicinal 1 رح نركّز على (oral)

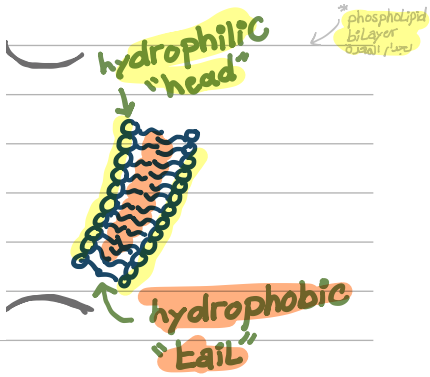
now:
بمر solid drug بمراحل وهي كالتالي:
يتفكك ينحل يمتص
Disintegration → Dissolution → Absorption



الصورة لحتى تكتمل الفكرة وتلتهم ^^

هنا يصير الامتصاص

② 



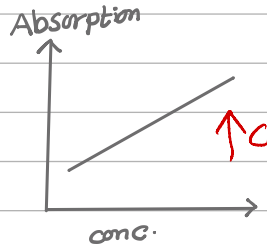
* نتعامل مع الـ (drug) : as chemical structure
إيش معنى هالحكي؟ يعني رح أهتم بـ: functional group

functional group
- polar
  1. Hydrophilic
  2. H-bound عادةً بعملو ↑
  3. ionic
  - ↳ hydroxyl group OH
  - ↳ carbonyl group
  - ↳ carboxyl group
  - ↳ amino group NH_2
  - ↳ sulfhydryl group SH
- non-polar
  - Hydrophobic
  - ↳ Aromatic ring
  - ↳ halide Cl F Br I

← لحتى يصير عندي Absorption فأنا بحاجة لوجود كل من: (hydrophilic & hydrophobic)
وأغلب أدويتنا بنلاقي فيها الشقين.

← الدوا لمّا يمر من (GIT) ويصير له امتصاص رح يمر عن طريق different transport processes
- passive
- Active

إيش بنفضّل يكون لدوانا؟ passive



↑ conc ↑ absorption bypassive.
بسبب فرق التركيز Concentration gradient.
*by passive.

active ⇝ carriers

← هل وجدت الـ carriers للأدوية؟ X، هي موجودة لـ :
... natural substrate
← عنّا الـ glucose (polar) بصرله امتصاص عن طريق الـ carriers
← Amino acid :
عنّا بجسمنا (20 a.a) كلهم (L) ولا واحد (D) ...
(D) موجودين بس بالبكتيريا -

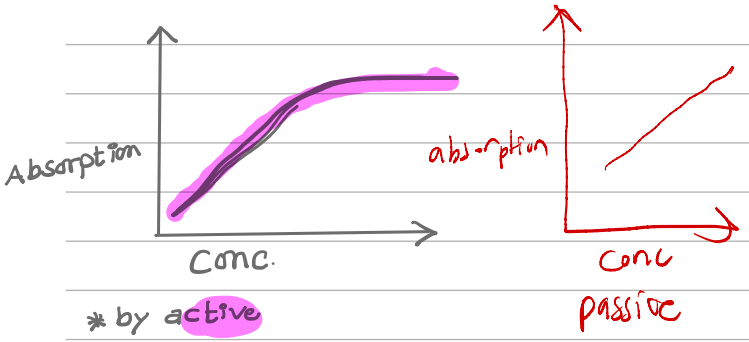
20 a.a
← 19 منهم chiral
← واحد منهم A chiral
glycine a.a

ذرة الكربون مرتبطة بأخوات مختلفة

* في الزمنات كان في دوا اسمه (Thalidomide)
- ثاليدومايد - كانت توخده المرأة الحامل بالـ (1st trimester) عشان يقلل symptoms ...
بعد سنين وجدوا الأطفال يلي أمهاتهم أخذوا هاد الدوا عندهم تشوهات ...
والسبب؟ stereochemistry
تحولات الدوا ما بين الـ (S) و (R)!
ومن هنا تتضح أهمية stereochemistry

والفكرة هي كالتالي:
الـ (enzyme) مكون من شو؟ amino acid
وهما عبارة عن chiral يعني تبعًا لهالحكي
الـ (enzyme) = chiral!
وهو مسؤول عن (metabolism)
فبالتالي قد يعمل metabolism لـ (X) ما يعمل لـ (Y) أو قد يعمل لـ (X و Y)!

* وملحوظة: amino acid = ~~non polar~~
بصيرلها امتصاص عن طريق الـ (carriers) ...



* by active

: now
بنفس الـ membrane of GI tract وجدوا proteins عاملة قناة بنسميها :
water channels
↳ it is very small in size
لا تسمح بمرور أدويتنا
(أ) فقط بستطيع العبور
ـ ليثيوم

مثلاً...
في لحتى يستطيع antibiotic يقتل البكتيريا
لازم يمر من water channels (gram -ve)
فأغلب الأدوية يلي بتشتغل على (G-ve) بتكون :
* very hydrophilic *

functional group:

① $CH_3CH_2CH_3$– : hydrophobic substituent — hydrophobic interaction — solubility عالية

② –COOH : polar ... H-bond بتعمل H-bond interaction — good solubility

Carboxyl

note:

*(carboxyl group): COOH

7.45

pH of blood > pKa of the drug that contains COOH

وهذا يعني رح يصير للدّوا: ionized in the blood

③ *(amine): NH_2

ionized in stomach

pH of stomach < pKa of amine

now: why is ionization important?

نصّت pH partition hypothesis (theory) في على أنّ:

ionized form of the drug = hydrophilic

un-ionized form of the drug = hydrophobic

⇒ only ***un-ionized, non-polar drugs will penetrate a lipid membrane...

⇒ Body → GI / Blood / Liver / Kidney

*Chemical struc. لا تأثير على:

- physicochemical.
- pharmacokinetic.

كيف؟ الدّوا رح يصيرله امتصاص من GIT

ورح يصيرله distribution من خلال blood

ورح يصيرله elimination & metabolism من Kidney & Liver

... تمام؟

• الدّوا حتّى يصيرله امتصاص لازم يعبر GIT membrane (Lipophilic) ...

بالتّالي بهاي المرحلة أنا بحاجة إنّو يكون دواي (hydrophobic) ...

• مرحلة ما قبل الامتصاص ← (dissolution)

الدّوا لازم يكون soluble ...

↑ ionization ↑ solubility

↑ polar functional group ↑ solubility

• بالدّم أنا بحاجة إلى (functional group) يعمل interaction مع الألبومين (Albumin) ...

بحيث إذا الدّوا ترسّب بالدّم بعمل جلطة.

• in Liver:

The Liver is the main organ responsible for drug metabolism.

drug ← يعتبر → foreign substance

بالتّالي: زي ما دخل لازم يطلع

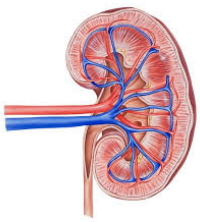
so: the drug must be pass through the Liver wall. (pass to hepatocyte)

* يعني لازم يكون hydrophobic ←

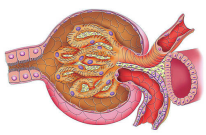
* وأيضًا لازم يصير interaction with ← Liver enzyme

the result should be: water soluble metabolite (excretion)...

• in Kidney:



Kidney



glomerular capsule.

glomerulus membrane ↕ very porous

ملحوظة: كل (membrane) في جسمنا هي نفس (basic structure)، الاختلاف الوحيد: porosity

مثلاً BBB الـ porosity تاعتها قليلة.

Summary:

for drug ... we need to have a balance between:

Hydrophilic funtional group & Hydrophobic functional group

ما بدنا الدّوا يكون (Totally hydrophobic) لأنّو لو كان هيك:

1) الـ(solubility) رح تكون v.Low.
2) الـ(absorption) رح تكون v.good.
3) في الدّم ممكن يصير له (precipitation).
4) بالكبد رح يجبر.

بعد وصول الدّوا للدّم رحلة الدّواء بشكل سريع:

Blood → → Target

↓

interaction

↓

response

يؤثّر ← (Chemical structure) على:
pharmacoKinetic & pharmacodynamic

→ Drug — interaction with — Target

بحاجة إنّو يكون الدّوا عندو:

1. proper functional group.
2. proper size.
3. proper orientation.

ملحوظة: كل ما كان الدّوا proper interaction كل ما احتجت منه dose أقل ...

ومش كل functional group بتدخل بالـ(interaction).

Introduction

→ physicochemical properties = biopharmaceutical properties

- The importance of physicochemical properties of the drug and the relationship of such properties to the pharmacological responses.
- Because these properties play an important role in determining biological action of pharmaceuticals, it is appropriate to refer to these properties as **biopharmaceutical properties** of drug substances.
- Examples of such properties include solubility, partition coefficients, degree of ionization, and polymorphism, which in turn are determined by the chemical structure and stereochemistry of drug substances.

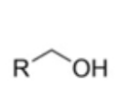
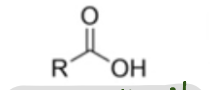
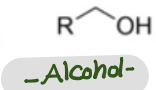
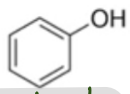
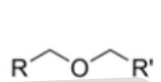
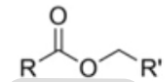
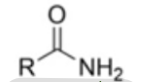
Introduction

- Drug molecules must cross various biological membranes and interact with intercellular and intracellular fluids before reaching the elusive region termed the "**site of action**."
- Under these conditions, the biopharmaceutical properties of the drug must contribute favorably to facilitate absorption and distribution processes to augment (زيادة) the drug concentration at various active sites (Pharmacokinetics)

Introduction

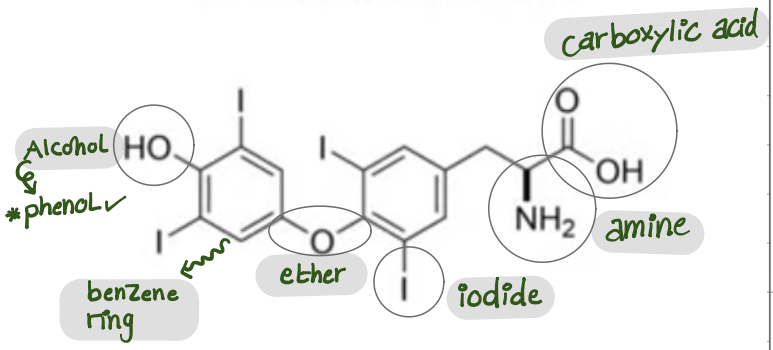
- ***Pharmacokinetics*** may be simply defined as what the body does to the drug
- Pharmacokinetics is divided into several areas including the extent and rate of absorption, distribution, metabolism and excretion. This is commonly referred to as the ADME.

Identifying functional groups:

 -Alcohol-	 -carboxylic acid-
 -Alcohol-	 -phenol-
 -Ether-	 -ester-
 -amine-	 -amide-

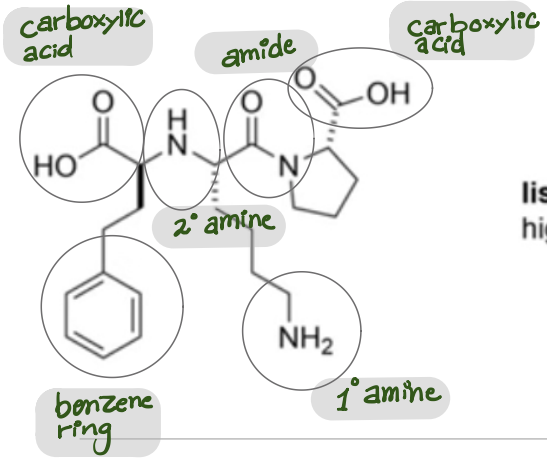
→ Examples:

PROBLEM #1



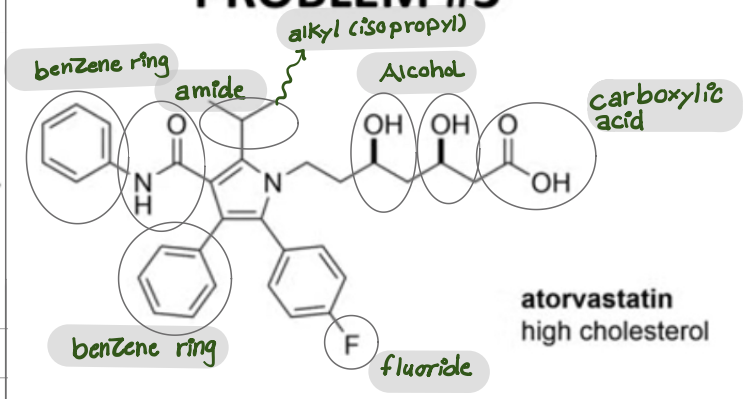
levothyroxine
thyroid hormone replacement

PROBLEM #2



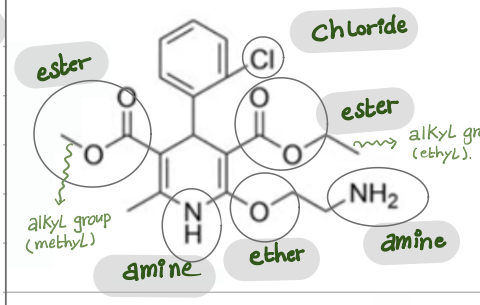
lisinopril
high blood pressure

PROBLEM #3



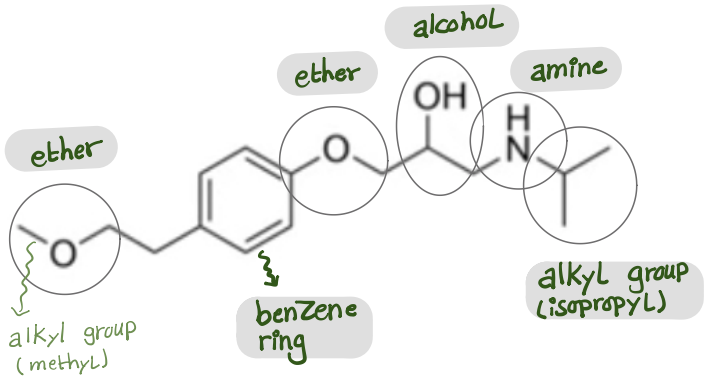
atorvastatin
high cholesterol

PROBLEM #4



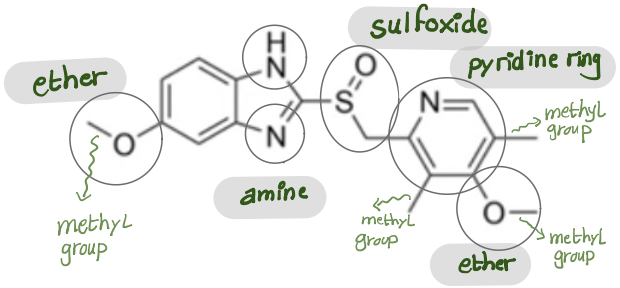
amlodipine
high blood pressure

PROBLEM #5



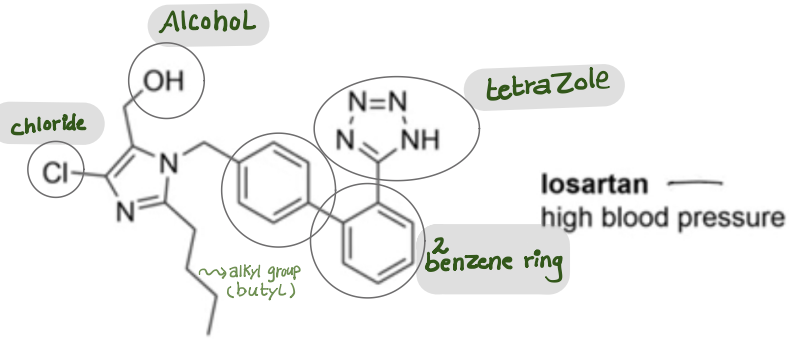
metoprolol
high blood pressure

PROBLEM #6



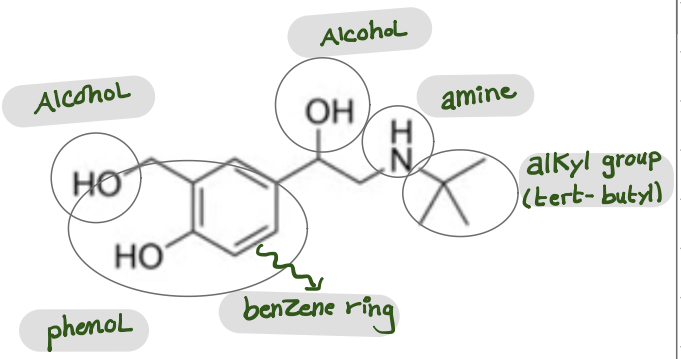
omeprazole
acid reflux

PROBLEM #7



losartan
high blood pressure

PROBLEM #8



albuterol
asthma

the effect of chemical structure of the drug on Absorption...

- Drug → A → ionization
- Drug → D → partitioning
- Drug → M
- Drug → E

* Ionization:

- depend on:
  1. pH of biological system...
  2. pKa of the drug

(بشكل عام pH ثابتة ⇐ pKa متغيرة).

- pKa
  - acidic
  - basic

مثلاً لو كان عندي:
pKa for acidic = 5
pKa for basic = 5
هل رح يكون إلهم same behavior؟

in stomach (acidic medium):

acidic drug = un-ionized form
☑ Absorption.

basic drug = ionized form.
☒ Absorption.

ملحوظة: قيمة الـ(pKa) ما بتخبرنا فيها لو كان الدوا (base or acid)، لذلك بطلّع بداية على functional group وبعديها ببني أفكاري عليها.

Acid

Strong	Intermediate	weak
pKa < 2	pKa: 2-10	pKa > 10

ملحوظة: في تصنيف تاني كالتالي:

strong pKa < 2
weak pKa: 2-10
very weak pKa > 10

نفس الأشي بس مسميات يعني ⇐ نفس (weak) نفس (intermediate) و(v. weak) ... (weak)

- acid: proton doner, e^- accepter
- base: proton accepter, e^- doner

$HCl \longrightarrow H^+ + Cl^-$ (complete dissociation)

$CH_3CH_2OOH \rightleftharpoons CH_3\overset{H}{C}OO^- + H^+$ (partial dissocia.)

why HCl is strong while CH_3CH_2OH is not?

(stable conjugated base) كل ما كانت عندي
... (strong acid) كل ما كان

Cl^- | $CH_3CO_2^-$

إجت الـ(-ve charge) على
(O: good electronegative atom)
لكنها مش لدرجة (Cl^-)

بالجدول الدوري:

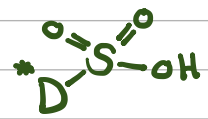
C, N, O, F → بتزيد electroneg.

more stable conjugted base:
لمّا بتكون موجودة على (-ve charge)
(electronegative atom)

* إذا شفتها بعرف إنّو (functional group) المركب عندي (strong acid):

1. sulfonic acid

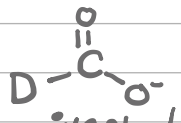
D: Drug



conjugated base

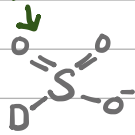
بتتوزع (e^-) على (3 electrone. atoms)

طيّب لو عندي:



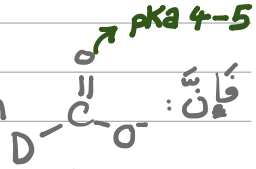
conjugated base

pKa<2



more stable than

pKa 4-5



فإنّ: (e^- توزّعت على 2 O)

صون (3 O)

more acidic = ↓pKa

كل ما كان الحمض أقوى رح يقدر يعمل (dissociation) أسرع ...

Base:

كذلك الأمر مع القاعدة ... كل ما كان عندي (stable conjugated acid) كل ما كانت (strong base).

* مين من بينهم stronger base؟

why?

الإلكترونات هون موجودة على N بالمقابل في الأنلين الإلكترونات جزء من الوقت موجودين على N والجزء التاني داخلين بـ (resonance)

لازم الإلكترونات تكون Localized لحتى يكون strong base، لذا كل ما كانوا (e⁻) موجودين كان stronger base.

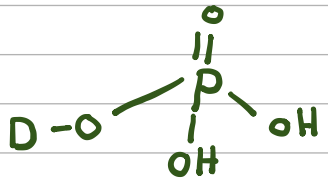
ملحوظة: بالـ (base) لحتى أعرف بنفسك الـ (base) نفسه، لكن في (acid) بجسك تاعته (conjugated base)...

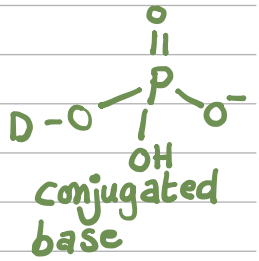
نعود لموضوعنا الـ Acid:

* إذا شفتها بعرف إنو (functional group) المركب عندي (strong acid):

1. sulfonic acid

2. phosphoric acid



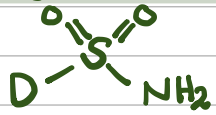


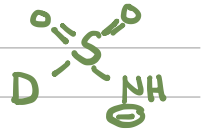
conjugated base

-نفس الحكي-

3. sulfonamide

-conjugated with carbonyl group-



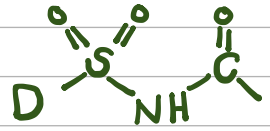


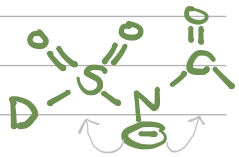
conjugated base

- N less electronegative than O-

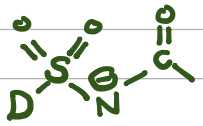
بالتالي لو بدي أقارنه بـ (sulfonic acid) أو بـ (phosphoric acid) يعتبر weaker ...

ولو بدي أخليه أقوى بضيف بدل H: carbonyl

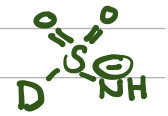




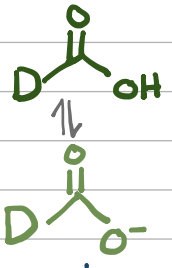
هيك (-ve charge) رح تيجي مرة على (C=O) وجزء على (S=O) ...

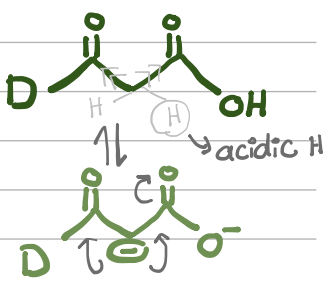


more stable than



4. carboxylic acid conjugated with carbonyl.





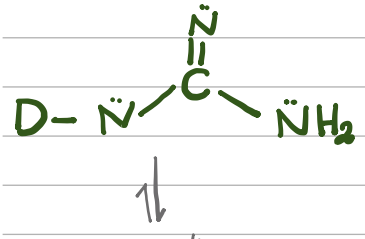
*note:

if carboxylic acid is conjugated with carbonyl group, it will be stronger.

-more stable conjugated base-

* إذا شفتها بعرف إنّو function group المركب strong base :

1. Guanidine



* strong basic drug.

* pKa > 10 / 12

$[I]^+$

I: Ionized ✓

- strong basic drug in stomach = ionized form.
  - pKa of drug > 10 & pH of stomach 3
  - pKa > pH ... ionized

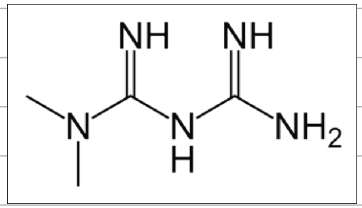
- strong acid & strong bace = ionized throughout GIt

strong acid $[I]^-$ } ☒ absorption
strong base $[I]^+$ }

- لكن:
  - وجدوا في أدوية إلها (+ve charge) وصارلها ... absorption
  - absorption ما رح يصرلها ⇔ -ve charge.
  - ممكن ⇔ +ve charge

طيّب ليش بعطي orally ؟
Local treatment ✓
يعني أنا أصلاً ما بدي يصيرله امتصاص حتّى يشتغل على GIt ...

(Glucophage - Metformin :)



hydrophilic group ✓
hydrophobic group X
Drug taken orally ✓
← طيّب كيف؟ حكينا لازم يكون في الشقين.

...

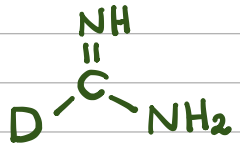
- strong basic drug → charge يحمل → ionized → absoption ✓

ممكن أعطي الدّوا لشخصين، واحد يستجيب والثّاني لا ... والسّبب: الأوّل اختلف عن الثّاني بالـ (carrier) ...

* -ve protein = carrier
والدّوا +ve
بصير (ion complexation)
وهيك بعبر الدّوا.

← طبعًا مش كل (+ve) برتبط معها هالحكي ^^

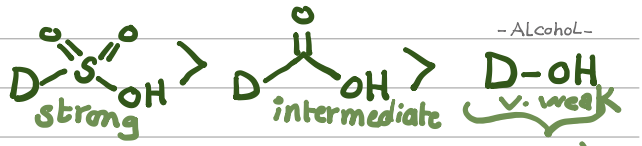
2. Amidine



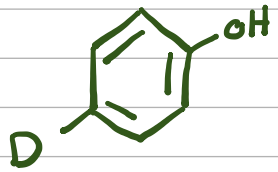
* strong basic drug

* (functional group) يعتبروا intermediate :

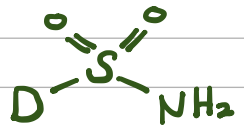
1. carboxylic acid - acid-



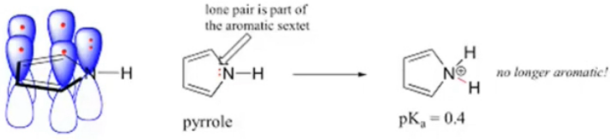
ionization ← معلومة: الجسم ولا يمكن يعمل لـ (OH)!
(very weak).
مشان هيك وجود (phenol) بالدّوا بساعد على امتصاصه.

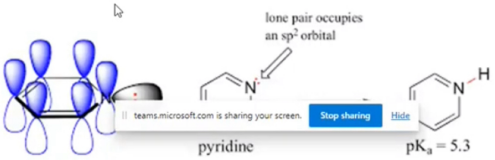


2. Sluphonamide - acid-



وحدة من N ح
تكون (e⁻) تاعها داخلة
بالـ(resonace) ووحدة
لا ح تكون (e⁻) available

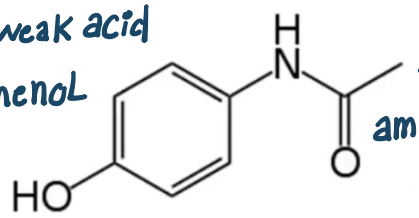




مش هيك :
pyridine more basic than pyrrol...

---

v.weak acid
phenol
amide
v.weak acid

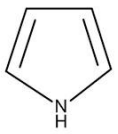


Paracetamol
(analgesic and antipyretic)
•* unionized across the GIT ✓ absorption ✓
•* fulfilling all lipinski's rule of 5
•* 100 % Bioavilabilty

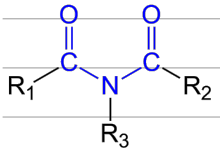
---

*يعتبروا (functional group) weak :

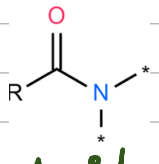
1. Alcohol.
2. phenol.
3. Amides
4. Imides
5. Imidazole
6. pyrrole



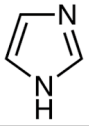
Pyrol



Imide



Amide



Imidazole

D-$\ddot{N}H_2$

all = basic drug

من بين منهم التلات الـ(e⁻) متاحة ؟ available e⁻

-الأول-

R: e⁻ donating
more electro. ← N بتخلي
available e⁻ يضي

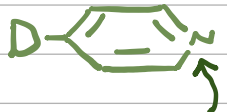
-التاني-

متاحين مرّة على N ومرّة
وللـ(resonance) ...

*بالتالي : الأول < التاني
-more basic-

-التالت- (زي الـ amine تمامًا)

lone pair
داخلة ؟
إذًا هي
available
good base
إذًا هي



Hybridization
of N atom :
sp^3

→ Many drugs are either weak acids or weak bases in the largely aqueous environment of the body, meaning that they either donate or accept protons depending on the pH...

At neutral pH, weak acid tends to donate or lose a proton to become negatively ionized or charged, while a weak base tends to accept or gain a proton to become positively charged

This charge can influence a drug's absorption, its distribution between compartments, and its elimination from the body
since a molecule which is charged whether positively or negatively will have a reduced ability to cross biological membranes by passive diffusion.

The proportion of drug that is ionized in a given compartment will depend on the pH of the compartment relative to the drugs pKa...
Many compartments have different pH:
- The stomach is acidic.
- The small intestine can be weakly basic.
- The blood has a pH of about (7)
- The pH of urine in the kidney tubules & bladder can vary from acidic to basic.

At the low pH of the stomach, an acidic drug will be uncharged & may therefore be efficiently absorbed from this compartment.

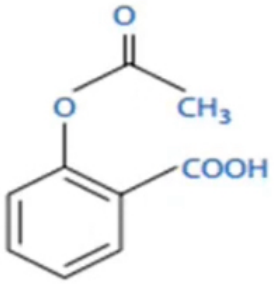
on the other hand, a basic drug will accept a proton to become positively charged in the stomach & will therefore be poorly absorbed.

conversely, at the high pH of the small intestine, an acidic drug will be negatively charged & poorly absorbed, whereas a basic drug will be uncharged & therefore efficiently absorbed.

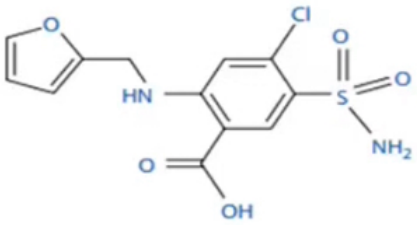
The law of mass action covers the available drug that can leave a compartment... As the uncharged portion of the drug leaves the compartment, the number of charged molecules will decrease to maintain the balance of charged & uncharged molecules at the given pH.

clinically we can alter the pH of compartment to change the drug's degree of ionization in order to influence its ability to leave that compartment...

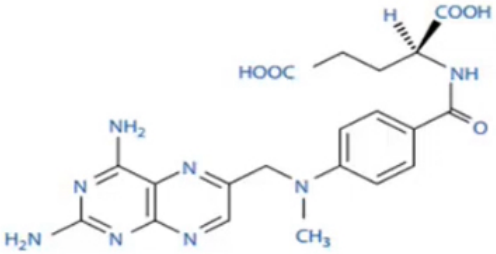
For example, in some instances of drug overdose, we can increase the pH of the fluid being filtered by the kidney by giving a solution of sodium lactate to sequester or trap an acidic drug in the urine, because it will be readily filtered by the kidney glomerulus. But in a compartment with a high pH, such as the tubule fluid of kidney, it will be more charged, and therefore reabsorption will be reduced from the renal tubule back into body. It is therefore more efficiently cleared from the body by excretion in the urine.



Aspirin



Furosemide



Methotrexate

-carboxyl-

•For aspirin and furosemide acid with pKa values of 3.5 and 3.9, the answer is that 99.99% of a given dose of drug will be ionised at the pH of blood or intracellular fluid.

•For methotrexate, the answer will be slightly less, but still greater than 99%

LIPINSKI'S RULES (rule of five)

لو ليش خمسة؟ كل الأرقام يلي بتحكي فيها من مشتقات الرقم خمسة.

- molecular weight (g/mol) ≤ 500
- num. of H-bond acceptors ≤ 10
- num. of H-bond donors ≤ 5
- log P (lipophilicity) ≤ 5

NH
OH

exception في؟ yes!

- انتهاكات

≥2 rule violations → high risk of low solubility & membrane permeability

- الفيديوهات القصيرة -

(1)

→ Lipinski's rules don't make a molecule more potent or have greater efficacy or lower toxicity.
Lipinski's rules are just about absorption...

→ Barriers to absorption:
1. solubility aqueous
2. permeability
3. first-pass effect.

① The molecule must dissolve at least a bit in either gastric fluid or intestinal fluid
Log p addresses this idea somewhat if a molecule has too high of a lipophilicity it won't be water soluble

② Drugs must cross membranes & membranes tent to be crossed passively by drugs...
They diffuse across the membran... membrans are non-polar, so oral drugs need to not interact too strongly with water...
if the molecule binds water too tightly, the molecule will not enter the non-polar membrane, which is designed to block the movement of water.
H-bond donors & H-bond acceptors interact with water
These are intermolecular forces between the drug & water...
So, Lipinski's rules limit the number of H-bond donors & H-bond acceptors in the potential drug

② Another idea for permeability is size.
Big molecules are slower to diffuse across a membrane, so the molecular weight is capped at 500

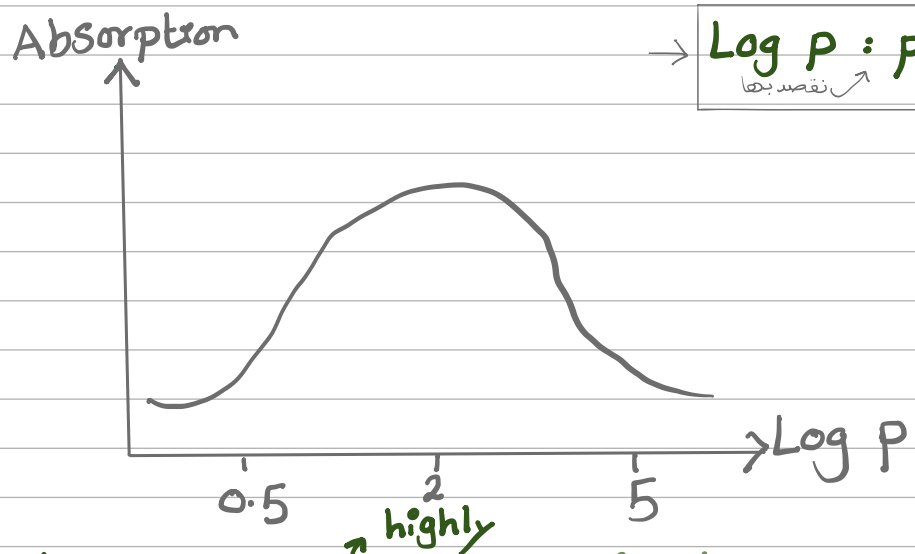
③ if a molecule undergoes extensive first-pass metabolism, it will have poor bioavailability & show low absorption into the central compartment.
Lipinski's rules do nothing to prevent the first-pass effect or hepatic clearance...
if anything, keeping a molecule smaller makes the molecule a better possible fit into the active site of the metabolic enzymes.

Therefore, Lipinski's rules focus only on improving solubility & membrane permeability in order to maximize the oral absorption of a molecule.

Physiochemical Factors Affecting Dru Absorption Lipinskis rule of

- **Lipinskis rule of five**
- As a rule of thumb, orally absorbed drugs tend to obey what is known as Lipinskis rule of five. The rule of five was derived from an analysis of compounds from the **World Drugs Index database**, aimed at identifying features that were important in making a drug orally active. It was found that the factors concerned involved numbers that are multiples of 5:

1) a molecular weight less than 500
2) no more than 5 hydrogen bond donor groups
3) no more than 10 hydrogen bond acceptor groups
4) a calculated log P value less than +5



→ Log p : partitioning Coefficient.
نقصد بها

* Log p < 0.5 & ↑ Hydrophilic (good solubility ... poor Absorption).
* Log p > 5 & highly Hydrophobic (poor solubility ... Low Absorption).

So: if Log p less than 0.5 or more than 5 = bad for absorption.

* The optimum absorption → Log p around 2
* In General:

لهيك يكون Log p = 2 يعني رح يعبر BBB وبأدويتنا ما بنفضّل هالشي،
يعتبر side effect، هيك أدويتنا بنحاول يكون log p تاعها بعيدة عن 2

* molecular weight:

C:12 O:16 N:14
F:19 H:1 S:32

* H-bond donor & H-bond acceptor:

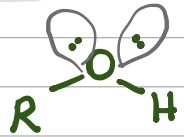
HBD HBA

HBD: functional group contains (H) atom...

HBA: functional group contains Lone pair of electron (..)

← حتى يستقبل البروتون H^+

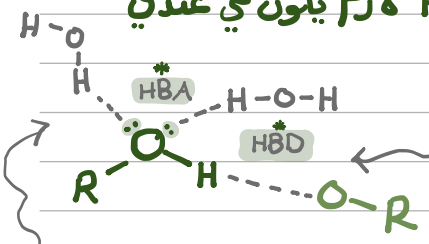
EX1: R-O-H



HBD? or HBA?

لحتى تكون HBD لازم يكون في عندي ... (e^- deficient)

وقد وُجد بالتالي



وبنفس الوقت أنا في عندي:
stable Lone pair of e^- in (O) atom
so: it act as HBA

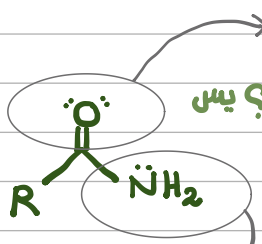
EX2: - 1° Amide -

HBD? HBA? or both?

تذكير:

X ⇐ H
X: N, O

X: e^- rich -lone pair of e^--
H: e^- deficient.



هل عندها H ؟ X
إذاً هي مش HBD
عندها lone pair e^- ؟ يس
✓ يس ؟ HBA

lone pair e^- عندها

والسؤال الذي يتبعه
هل هما localized ؟
والجواب لا؛ لإنّهم داخلين ... resonance!

They are not available all the time...
SO:
not HBA!

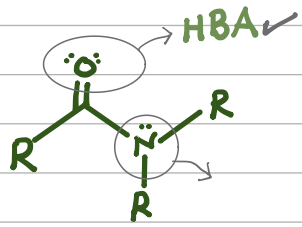
والآن بنشوف في عنّا (H) وكمان في عندي e^- deficient لإنّو
N = electronegative atom
N ⇐ H

SO:
it is HBD...

* ملحوظة على الهامش:
Localized يعني الإلكترونات موجودة على الذرة طول الوقت...

-فيديو اليوتيوب القصير-
-Hydrogen Bond Acceptors & Donors-

Ex3: -3° Amide-

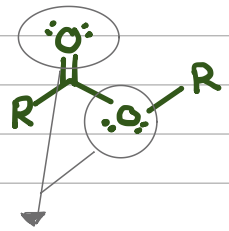


صون (N) ماعندها localized e⁻ بالتالي مرّة تانية ليست HBA والآن لو شفنا فصي لا تمتلك H وبالتالي ما رح تكون HBD ...
HBD✗ HBA✗

Ex4: -Ether-

heteroatom + localized e⁻ + No (H) atom = HBA✓

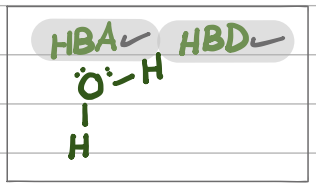
Ex5: -ester-

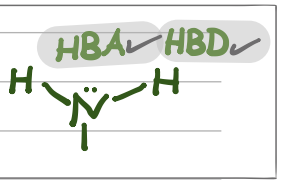


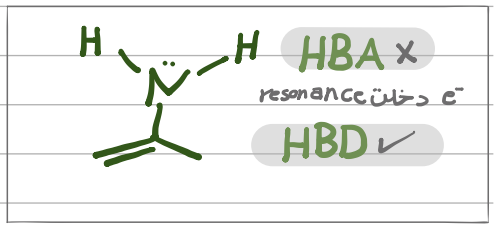
كلاهما = HBA✓

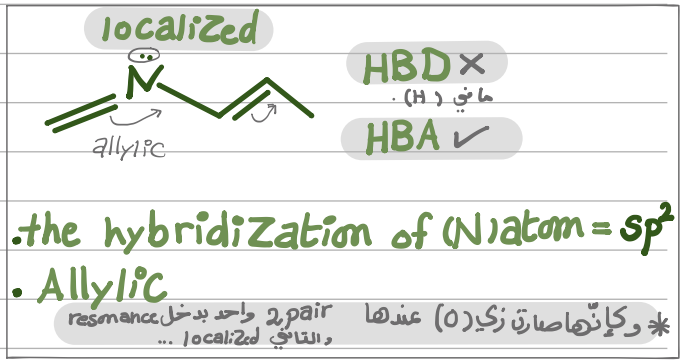
note:
(N) atom in Amide = 1 Lone pair of e⁻
(O) here = 2 Lone pair of e⁻
1 pair resonance — 1 pair Localized.

Ex:



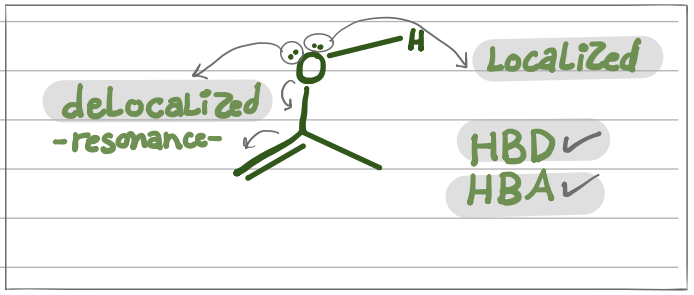


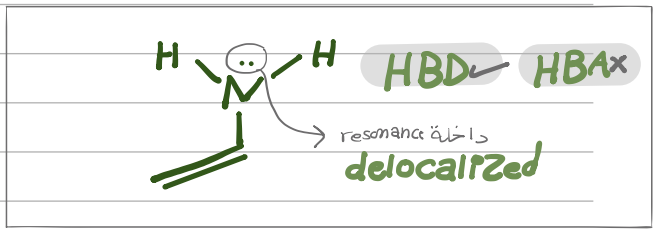




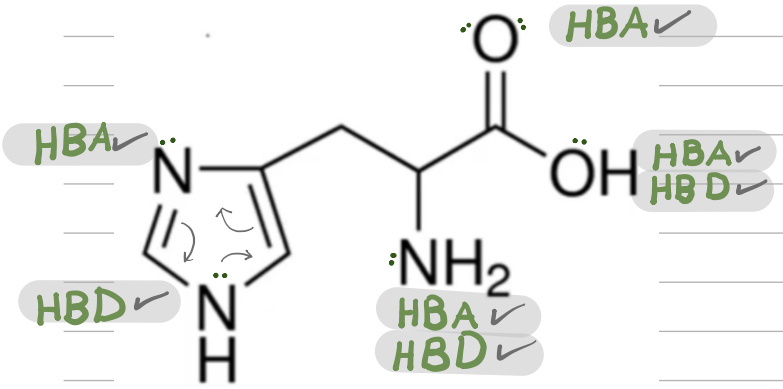
- the hybridization of (N) atom = sp^2
- Allylic

* وكإنّها صارت زي (O) عندها 2 pair واحد بدخل resonance والتاني localized ...





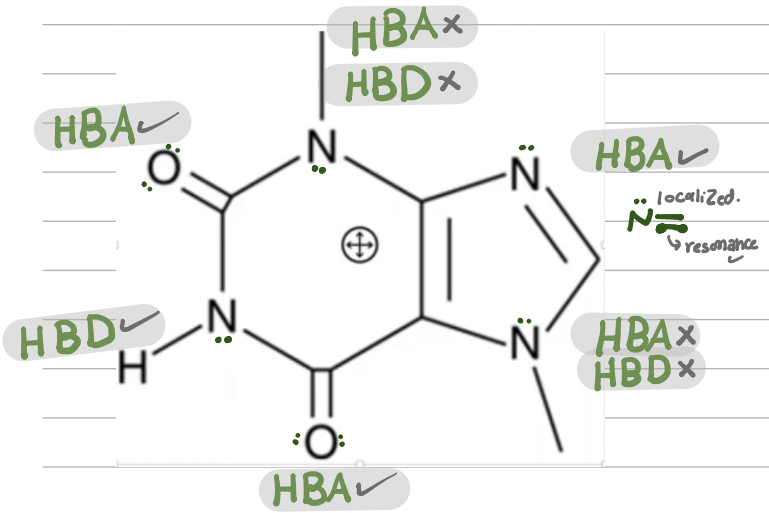
→ Histidine/amino acid :

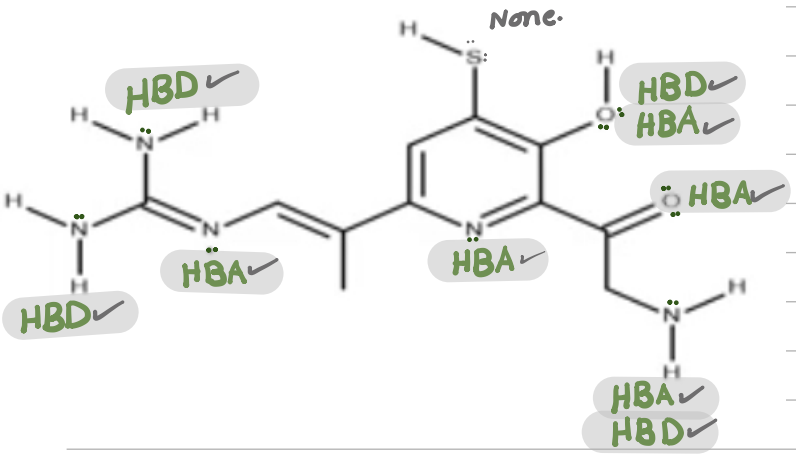


(N=); allylic : HBA → N

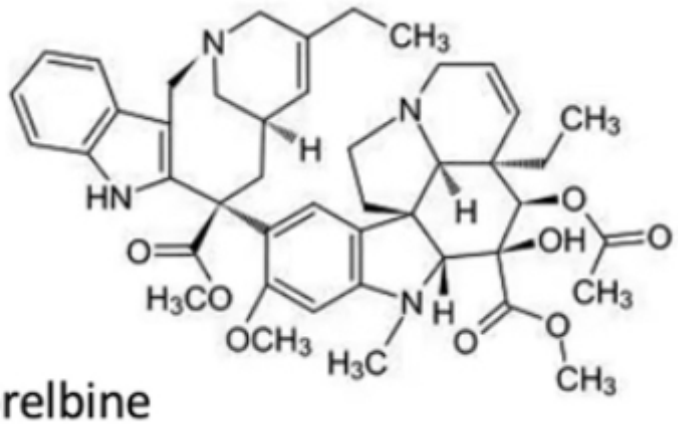
(N—); HBD

→ Theobromine :





- **Lipinskis rule of five**
- The rule of five has been an extremely useful rule of thumb for many years, but it is neither quantitative nor foolproof. For example, orally active drugs such as atorvastatin, rosuvastatin, cyclosporin and vinorelbine do not obey the rule of five.

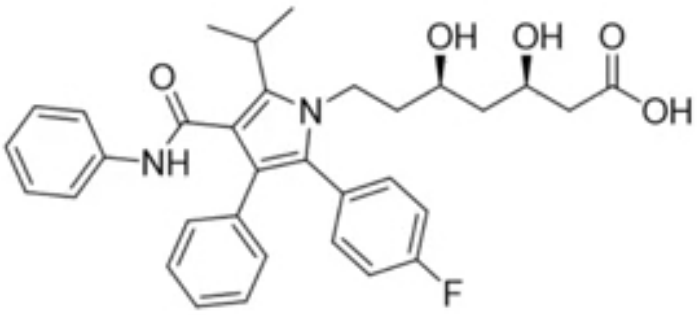


Vinorelbine

– (2) الفيديوهات القصيرة –

- The compouds that fall outside of Lipinski's rules :

ATORVASTATIN



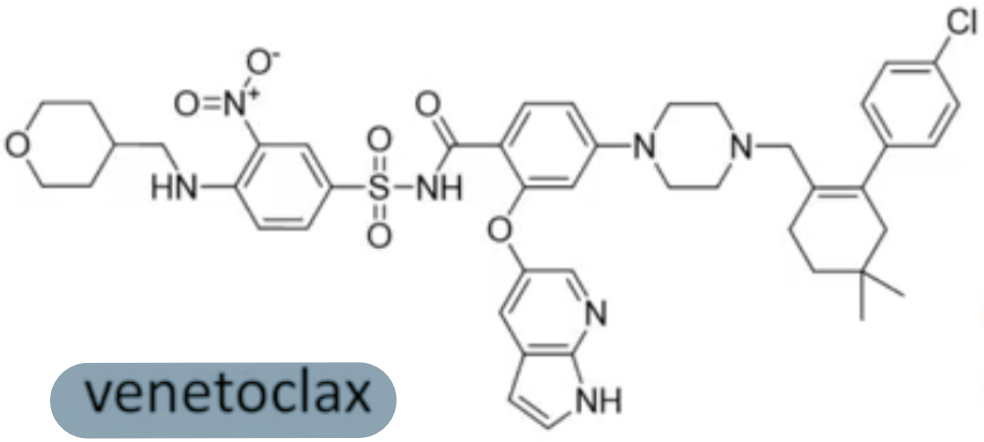
– لازم يكون أقل أو يساوي 500 – 500

- MW – 559 g/mol
- HBA – 6
- HBD – 4

– لازم يكون أقل أو يساوي 5

- log P – 6.36
- F – 14%

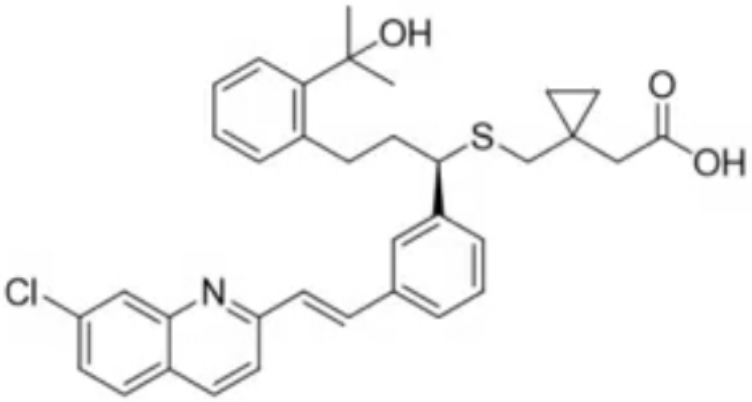
ومعنى ذلك : safe ✓ effective ✓



venetoclax

huge!

- MW – 868 g/mol
- HBA – 9
- HBD – 3
- clog P – 6.12
- F – 5.4%



montelukast

- MW – 586 g/mol
- HBA – 4
- HBD – 2
- clog P – 7.20
- F – 68%

parameter
تاني غير
Lipinski's rule.

Physiochemical Factors Affecting Drug Absorption

- Work carried out by **Veber** in 2002, demonstrated the rather surprising finding that **molecular flexibility** (as measured by the number of freely rotatable bonds present in the structure) plays an important role in oral bioavailability.
- **The more flexible the molecule, the less likely it is to be orally active.** Less surprisingly, the analysis showed that the **polar surface area** of the molecule could be used as a factor instead of the number of hydrogen bonding groups.
- These findings led to the following parameters for acceptable oral activity. Either:
- a polar surface area ≤ 140 A° and ≤ 10 rotatable bonds, or
- ≤ 12 hydrogen bond donors and acceptors in total and ≤ 10 rotatable bonds.

- The more flexible the molecule, the less likely it is to be orally active...

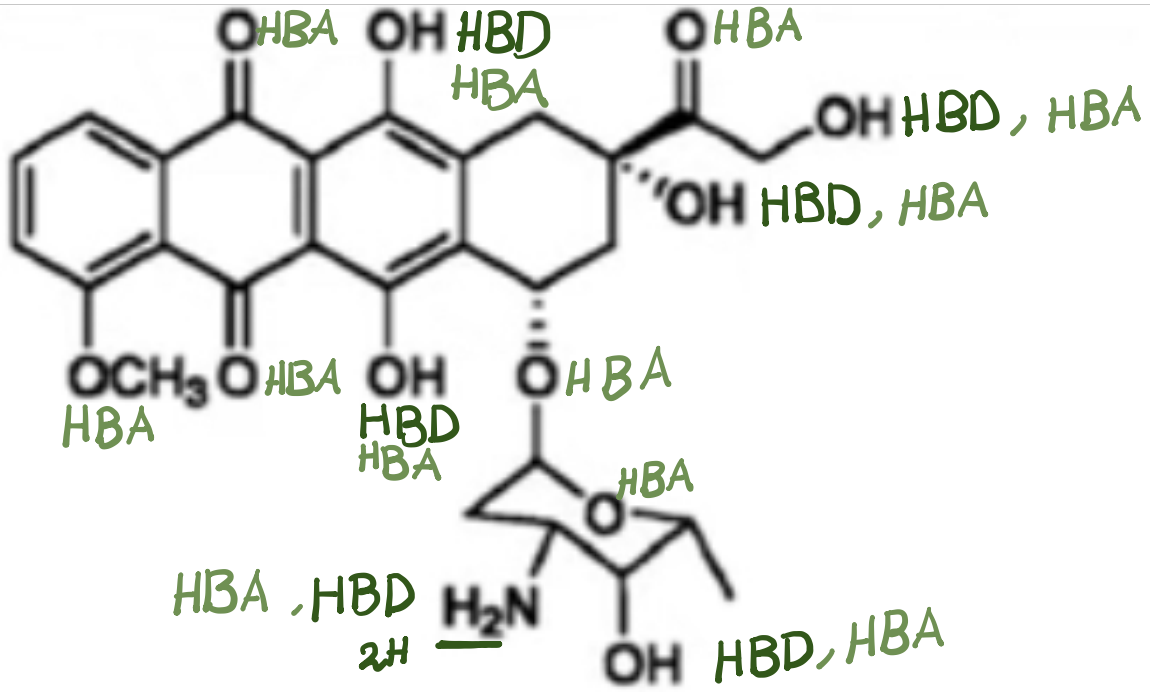
- The veber rules:

→ polar surface area ≤ 140 A°
&
rotatable bonds ≤ 10

OR

→ HBD + HBA ≤ 12
&
rotatable bonds ≤ 10

- Doxorubicin, has very low oral bioavailability.



Lipinski Rules

- H-bond donors = 7 HBD>5!
- MW = 543 MW>500!
- ClogP = −1.7 ✓ okay
- H-bond acceptors = 12 HBA>10!

*المعايير الصحيحة:

HBD≤5 ✓
MW≤500 ✓
log p≤5 ✓
HBA≤10 ✓

Doxorubicin

3 rules تتجاوز

!!

Veber Rules

- Rotatable bonds = 11 R.b>10!
- polar surface area PSA = 206 PSA>140!
- Total H-bonds = 19 Total>12!

*المعايير الصحيحة:

Rotatable bonds≤10
polar surface area≤140
HBD+HBA≤12

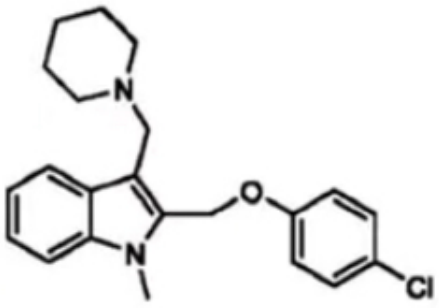
Doxorubicin

veber rules تتجاوز كل

!!

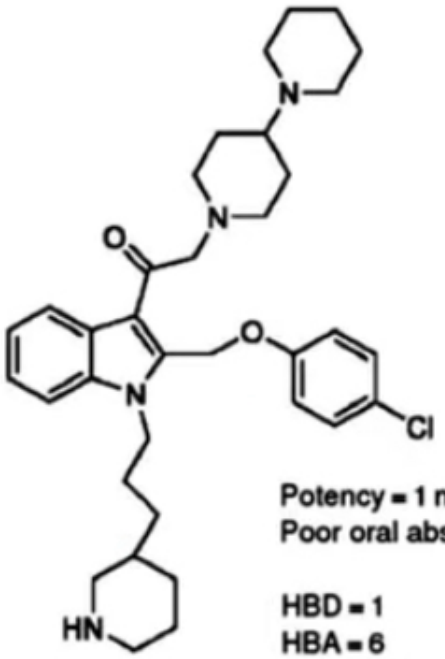
لذلك

has v. low oral bioavailability



Potency = 2 µM

HBD = 0
HBA = 3
MW = 369 ✓
Log P = 5.7 ✗
PSA = 17
Rotatable bonds = 6



Potency = 1 nM
Poor oral absorption

HBD = 1
HBA = 6
MW = 591
Log P = 7.3
PSA = 50
Rotatable bonds = 14
Total HB = 6

Structural modification for the compound on the left were made to enhance activity, however, the new compound has better potency but poor bioavailability, a pitfall that could be avoided if lipinski and veber rules were predicted prior to synthesis.

• كان الهدف من التّعديل لحتّى أحسّن الفعاليّة والتعديل فعلاً زادها لكن قلّل من bioavailability !

⇒ After modification { * better potency ✓ poor bioavailability
very low absorbion ✓