ADME
Distribution

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Distribution

بمجرد ما يصير امتصاص للدواء ح يتوزع عن طريق الدم للخلايا والأنسجة.

- Once a drug is absorbed, it is subsequently distributed around the blood supply and to tissues and cells.
- Distribution is the process by which a drug reversibly leaves the blood stream and enters the interstitial or cellular fluid of the body. Intestinal fluid, intracellular fluid, and transcellular fluid are 16%, 35%, and 2% of the body mass, respectively. Meanwhile, plasma is 5% of body mass and fat is 20%.
- All of the fluid in the body (total body water) in which a drug can be dissolved may be roughly divided into three compartments: (1) intravascular (blood plasma found within blood vessels); (2) interstitial/tissue (fluid surrounding cells), and (3) intracellular (fluid within cells, i.e., cytosol).

extracellular fluid

محيط بالخلايا.

جوا الخلايا

* توزع الدواء بالـ (Compartment) يعتمد على خصائص الدواء نفسه.

- The distribution of a drug into these compartments is dictated by its physical and chemical properties. Compounds distribute differentially within body and PPB may limit distribution.
- Most noticeably, lipophilic compounds may accumulate in fatty tissues. For instance, thiopental, ethers, and minocycline tend to collect in adipose tissues.
- Additional examples of tissue storage include:

أمثلة على توزع الدواء

Iodine in thyroid gland;
Calcium, tetracyclines in bones and teeth;
Digoxin (to muscle proteins) in heart and skeletal muscles;
Chloroquine, tetracyclines, and digoxin in liver;
Tetracyclines and digoxin in kidney;
Chlorpromazine, isoniazid, and acetazolamide in the brain;
(Ephedrine and atropine (to melanin) in iris.)

كل (drug) بروح على مكان مخصص أو بالأحرى بتركز أكثر بهداك المكان.

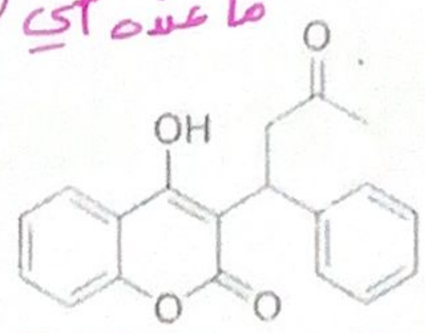
بيرتبطو بالميلانين (Ephedrine & Atropine) اللي بالقزحية (Iris) فالناس اللي عيونهم عشن ملونة (بني فأسود) بتحتاجو (Dose) أقل من هيك الأدوية من الناس اللي عيونهم ملونة لأنه العيون الغير ملونة فيها ميلانين أكثر.

* كلما الدواء صارله توزع أكثر بالخلايا (يعني ماضل موجود بالبلازما/الدم) فبزيد الـ (VD) يعني توزع أكثر بالخلايا.

- Overall, volume of distribution (*V*d) of a drug is determined by its partitioning across various membranes; binding to tissue components; binding to blood components; and physiological volumes. Apparent volume of distribution (*V*d) is a *primary PK parameter* and could be greater than 10,000 L.
- The larger the volume of distribution, the more likely that the drug is found in the tissues of the body. In contrast, the smaller is the volume of distribution, the more likely is the drug confined to the circulatory system. → blood

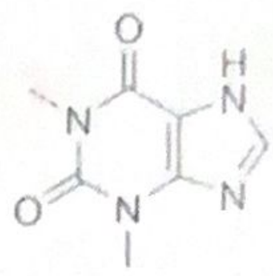
Compounds	*V*d (L/kg)	*V*d (L)
Acidic	<0.4	<28 قليل
Neutral	0.4–1.0	28–70 متوسط
Basic	>1.0	>70 عالي

(Basic group) nuetral to acidic ما عنده أي



Warfarin (60), V_d = 8 L

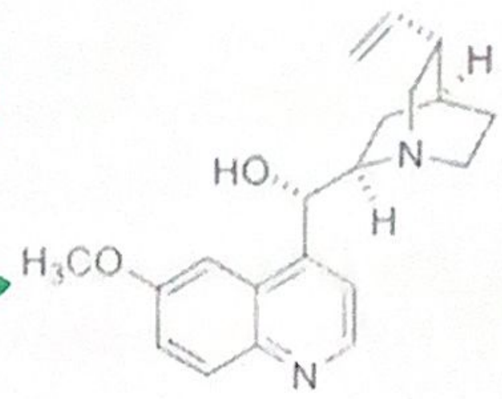
Basic & acidic Properities فيزاد الـ (Vd)



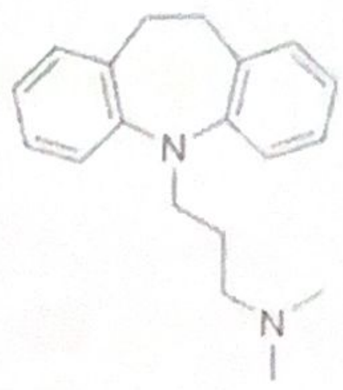
theophylline (61), V_d = 35 L

(quinidine, imiparmine, theophyline)

The presence of basic amines normally leads to increase of tissue affinity, thus boosts the V_d value



quinidine (62), V_d = 150 L

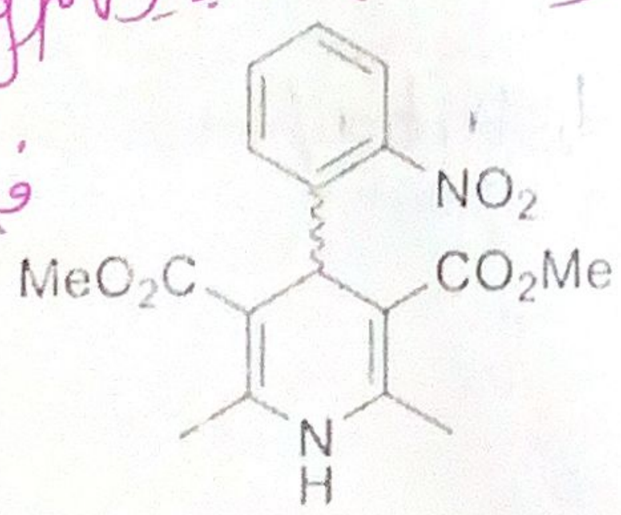


imipramine (63), V_d = 2,100 L

Lysosomotropism:

lipophilic amines (log P >1) and amphiphilic drugs (cationic amphiphilic drugs) with ionizable amines (pK_a >6) can accumulate in lysosomes.

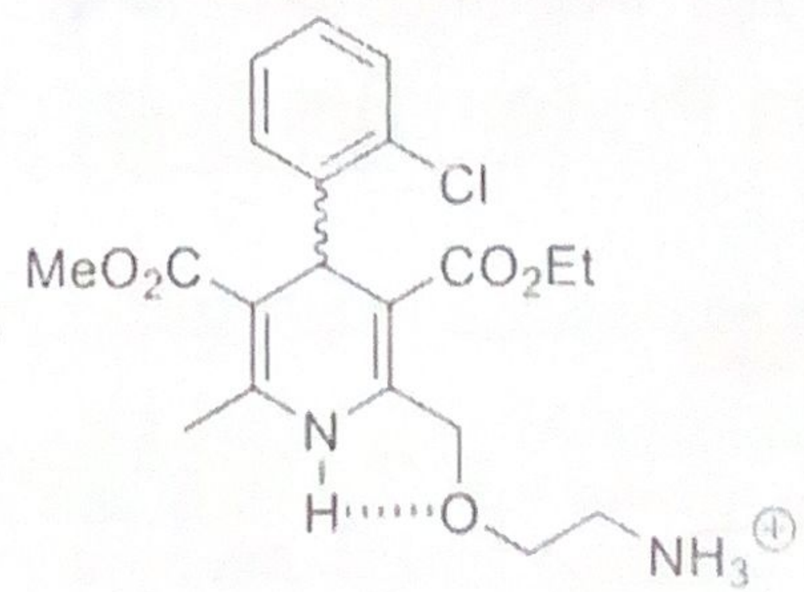
عشان imipramine & quinidine وكمان بعتبرهم (Basic amines) (amphiphilic drug) فبعطوني (Lipophilic) على unionized فالغروض يكونوا الـ Physiological PH لكن لما يدخلو الـ (Lysosome) فبصيرو acidic ← ويكسبو $(H)^+$ وبصيرو Protonated (ionized) وبصير لهم حصر (Trapping) بالـ Lysosomes فبزيد تركيزهم بالخلايا يعني (Vd) على



nifedipine (Adalat, 42)

V_d, 0.75 L/kg

$t_{1/2}$, 2 h



amlodipine (Norvasc, 43)

21 L/kg

35 h!

(Vd) is moderate

- First-generation calcium channel blocker
- Neutral drug with a moderate V_d of 0.75 L/kg
- Has a short half-life of 2 h, thus has to be taken three times a day.

قصير ولهيك كان المريض ياخذه ٣ مرات باليوم ($T_{1/2}$)

3rd

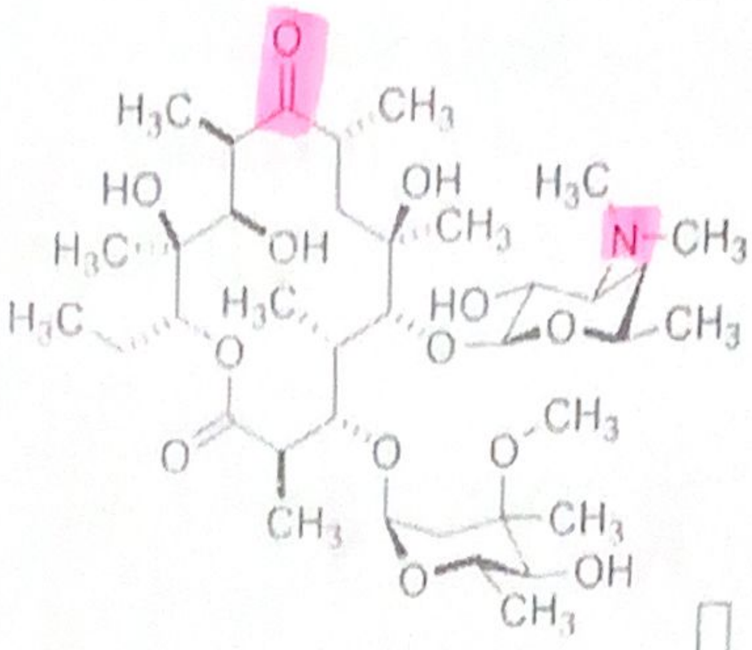
- Third-generation calcium channel blocker
- Has a basic primary amine sidechain (lysosomotropism)
- Has a very high V_d of 21 L/kg
- Has a half-life of 35 h (once daily regimen).

صار يعطى مرة واحدة يوميا.

modification على (1st) generation على

وكانوا الـ Compound من (amine) فيها خاصية (Lysosomotropism)

يعني صار (Vd) أعلى بالأنسجة وزادت $T_{1/2}$



erythromycin (Erythrocin, 64)

V_d, 4.8 L/kg

Cl, 55 mL/kg

$t_{1/2}$, 3 h

tissue/serum ratio, 0.5–5x

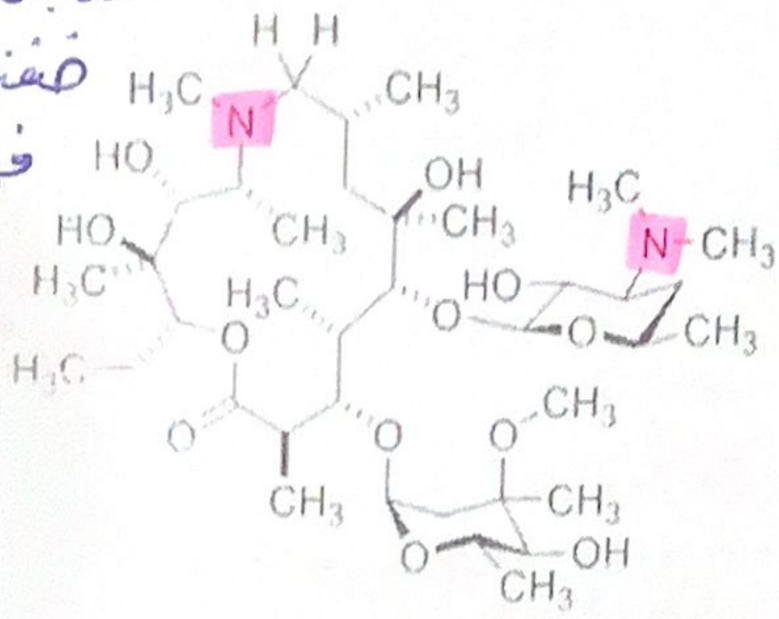
F%, 25%

4x daily

1

One basic nitrogen atom

صعون بيل الكاربونيل
amine صفنا
فزاد الـ(Vd)



azithromycin (Zithromax, 65)

V_d, 62 L/kg

Cl, 15 mL/kg

$t_{1/2}$, 18 h

tissue/serum ratio, 10–100x

F%, 37%

qd

2

Two basic nitrogen atoms

Lysosomotropism زادت

* من الشغلات اللي بتأثر على (Vd)

Plasma Protein Binding

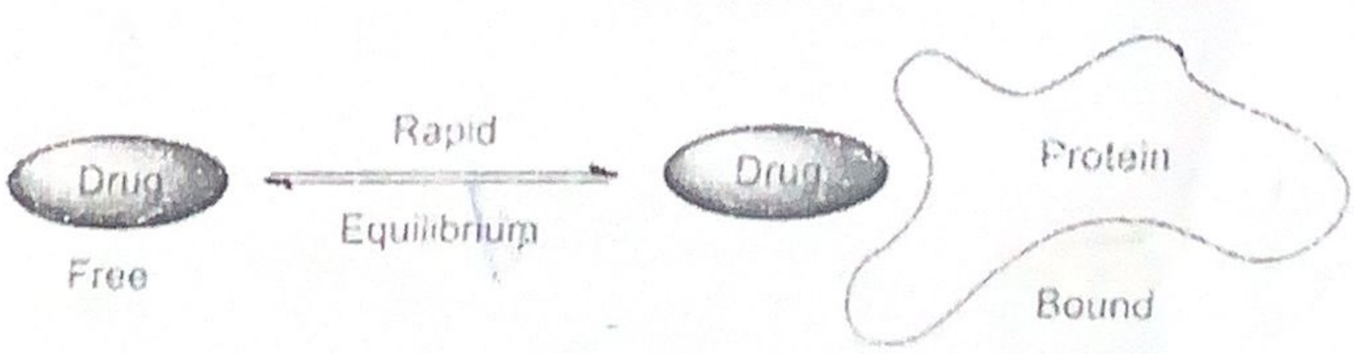
ممكن الدواء يرتبط مع البروتينات اللي بالدم
بالتالي يصير الدواء not available for ~~distribution~~ distribution / metabolism / elimination

- Drugs can bind to protein macromolecules in the blood, a phenomenon known as *plasma–protein binding* (PPB).
- The protein-bound form of the drug must dissociate from the protein in order to be useful because only unbound compound is available for distribution into tissues. There are three types of plasma proteins: human serum albumin (HSA) and α-1 acid glycoprotein (AAG) are the two more abundant proteins; whereas the third plasma protein, lipoprotein, is of less importance for PPB.

(1) (2) (3)

تعميم ←

NOTE:
Drug bound to albumin is also not available for metabolism in hepatocytes nor for renal elimination. The complex is large and cannot penetrate the cell membrane of hepatocytes.



Clinical implications of drugs' PPB

1. There is an equilibration between the PPB fraction of the drug and the free molecules of the drug. The PPB fraction is not available for action.
2. The drugs with high physicochemical affinity for plasma proteins (e.g., aspirin, sulfonamides, chloramphenicol) can replace the other drugs (e.g., warfarin) or endogenous compounds (bilirubin) with lower affinity.
3. High degree of protein binding makes the drug long-acting, because bound fraction is not available for metabolism, unless it is actively excreted by the liver or kidney tubules.
4. Generally expressed plasma concentrations of the drug refer to bound as well as free drug.
5. In hypoalbuminemia, binding may be reduced and high concentration of free drug may be attained.

Human serum albumin (HSA)

- Human serum albumin ((HAS): 6700 Dalton) , the most abundant protein in human blood plasma, has more than six distinctive binding sites including two for long-chain fatty acids; one for bilirubin; and two for acidic drugs
- On the other hand, AAG has only one selective site for basic drugs.
- Acidic drugs, in particular, bind to serum albumin and tend to have higher PPB than neutral/basic drugs (low Vd).
- Meanwhile, bases bind to AAG.
- Serum albumin binding increases as log *P* increases. In other words, hydrophobic drugs bind more strongly to serum albumin than hydrophilic drugs

كيف يرتبط الأسبرين بالalbumin

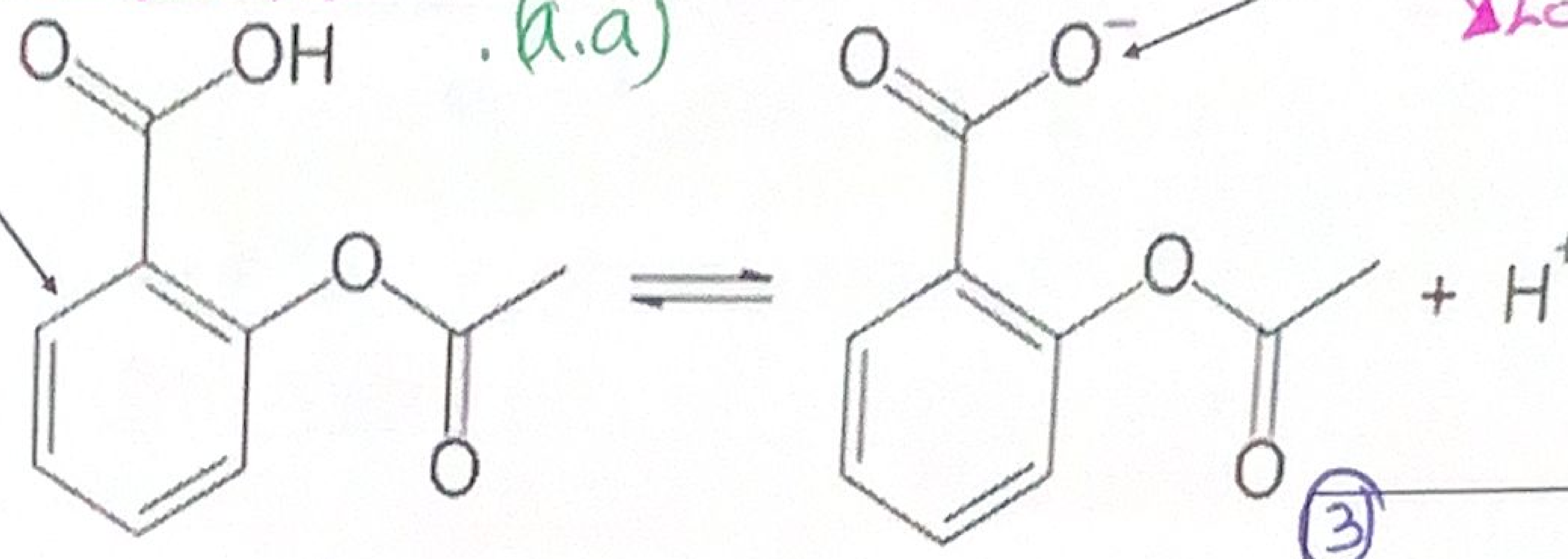
Example1: Aspirin

(حدود 554)
الalbumin كثير فيه (amino acids) منها arginine & Lysine وهدول شحنتهم بالبلازما موجبة (+) لكن الnet charge للalbumin هي (-) بالتالي الأسبرين فقط ح يرتبط على المواقع الموجبة (a.a).

① Aromatic ring will bind to other aromatic rings found in aromatic amino acids in albumin (by π stacking) van der val

② >80% will bind to the positively charged arginine and lysine in albumin

→ Loss of 20% from aspirin



الأسبرين عنده Carboxyl group (acidic group) يعني فهو جوا البلازما عليه شحنة سالبة (-)

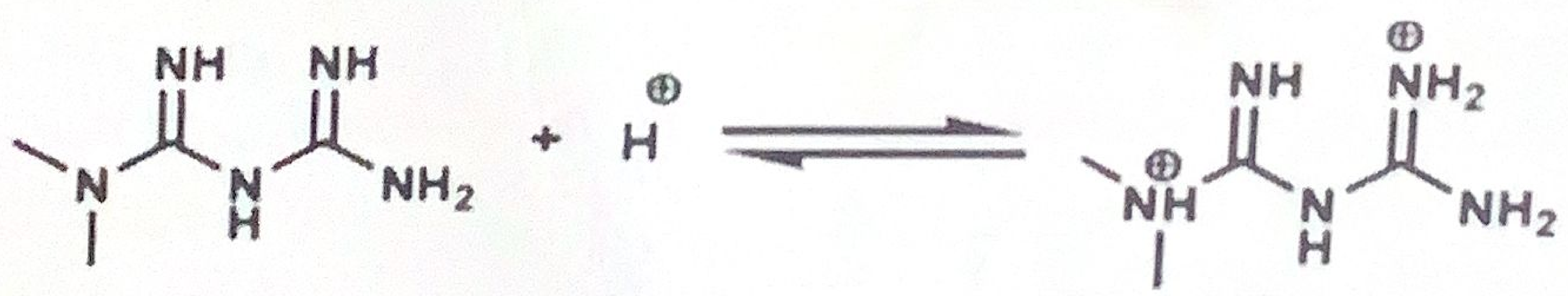
③ ← H-bond forming groups

وممكن يصير ارتباط بين الـ(Hydrogen Bond) الي بالأسبرين وبالـ(a.a) ويزيد نسبة ارتباط الأسبرين حوالي (5%)

Aspirin at pH 7.4 will be in the ionized form (negatively charged) ⊖
→ 95% is bound to albumin

Basic compound يعني صعب يصير (Negatively charge)

Example2: Metformin



weak binding of metformin to BSA was **governed by hydrogen bonds and van der Waals forces**

الBinding للـ(metformin) مع الـ serum albumin قليل جداً
ممكن يصير شوي (5-10)%
بسبب الـ(forces) لهيك الـ Vd
لهذا الدواء عالي جداً (270) لتر تقريباً

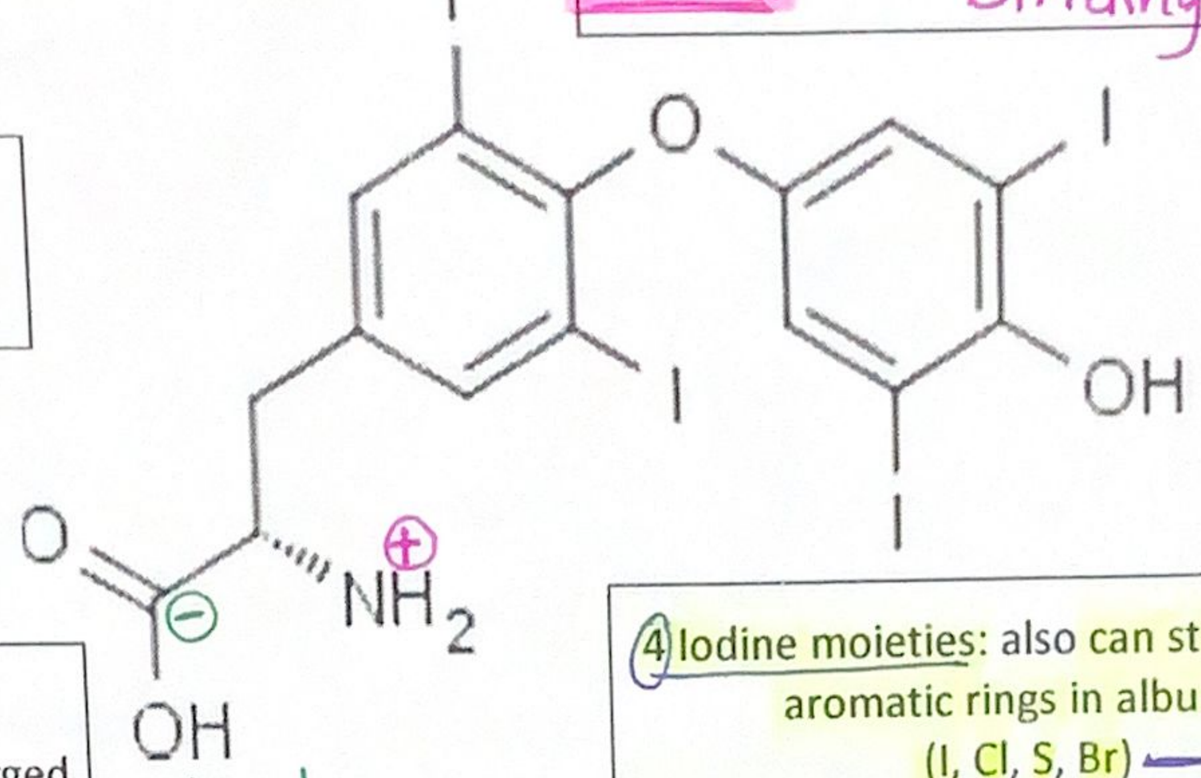
Example 3: Thyroxine

Aromatic ring will bind to aromatic rings found in in albumin (by π stacking)

binding بزيبو ال

H-bond forming groups

NH_3, OH, O, ...



witterion at pH 7.4

e charge will bind to +vely charged nding pocket in albumin

albumin بـ (a.a) مع بترتبط

Carboxyl ⊖

4 Iodine moieties: also can stack against aromatic rings in albumin

(I, Cl, S, Br) → aromatic يرتبطوا بال

(albumin) بال ring

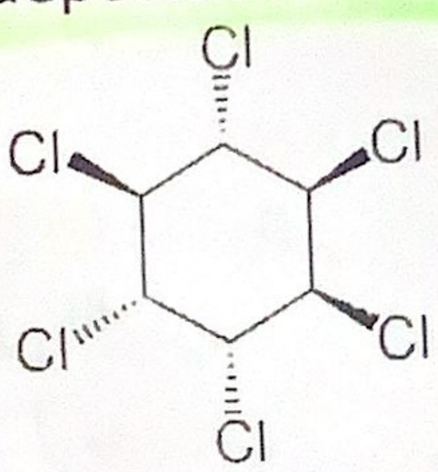
Thyroxine is more than 98% bound to albumin

So (Vd) is very Low for thyroxine.

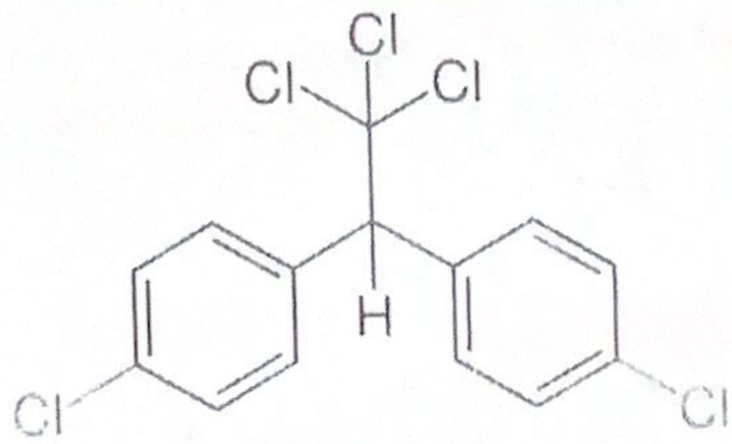
عامل آخر بأثر على (Vd)

Fat Deposition

- Lipophilic drugs and multi-halogenated drugs tend to deposit in fats (adipose Tissue)
- 20-30% of human weight is fat
- Drugs deposit in fat are biologically inactive, neither metabolised nor renally eliminated.
- Fat deposition caused sustained release of the drug.



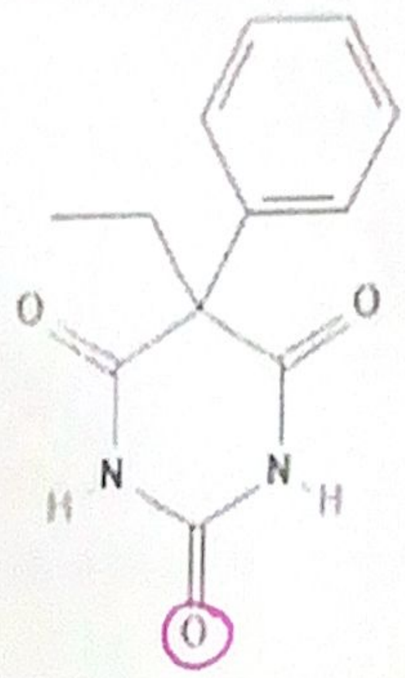
Hexachlorohexane



dichlorodiphenyltrichloroethane

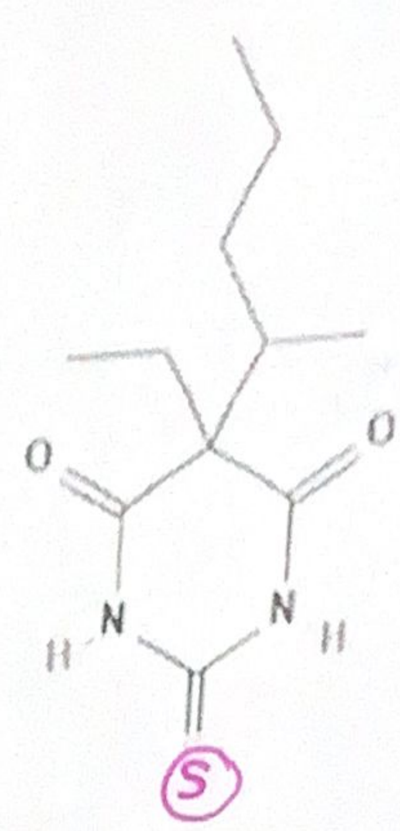
هدول المركبين بصير لهم deposition يعني ممكن يضلو بالجسم طلة فترة حياة for Life Long of human ← للإنسان

Example



Phenobarbital
Onset of action: 1.5hr
t1/2= 8 hr

Fats تركيزه أقل بال
وأعلى بالبلازما
(LiPoPhiLicity) لأنه أقل



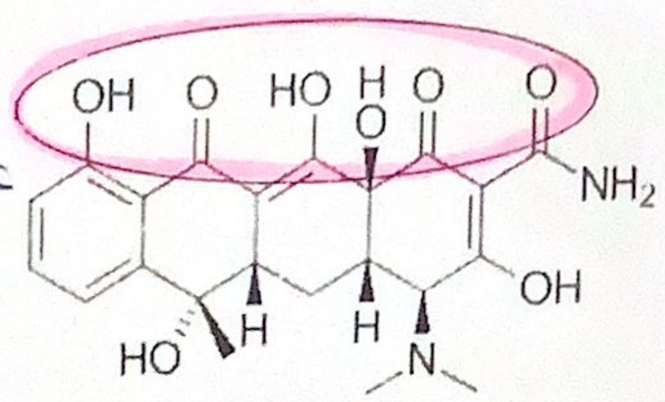
Thiopental
Onset of action: 5 min ← صار أعلى لما بدلنا O بـ S لأنه زادت الـ (LiPoPhiLicity)
t1/2 :2 days
Quickly cross the BBB and deposit in the body fat

لكن تأثيره راح يضل لفترة أعلى
لأنه تراكيزه أكثر بال fat
وراح ينطلع شوي شوي منهم (بطيء)
(Sustained release)

عامل آخر بأثر عالـ Vd :

Bone Adsorption (Celation) في أدوية بتفضل تروح عالـ (Bone) وتعمل

- Any drug contains acetoacetic acid or acetoacetone group will form a complex with metals in bones (Celation) ← inactive
- Bone deposits remain for a long time (sometimes for a life time)
- Drugs chelate to bones are biologically inactive, neither metabolised nor renally eliminated.

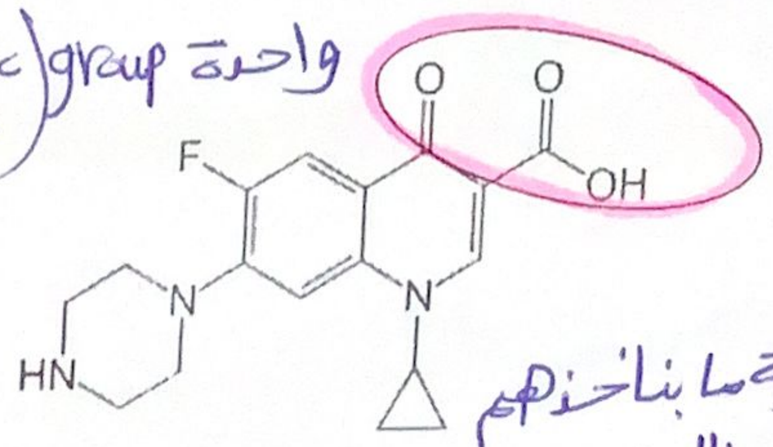


٤-acetoacidic groups

(Tetra) ٤ حلقات ← Tetracycline
4 acetoacetic acid groups

(Tetra) بتعمل صبغة/تلون للعظم والأسنان

(aceto acetic acid) group واحدة



Ciprofloxacin

هاي الأدوية ما بناخذهم مع الأكل اللي فيه كالسيوم أو مغنيسيوم مثل الحليب مثلاً... فلازم ننتبه لهاي الشغلات.

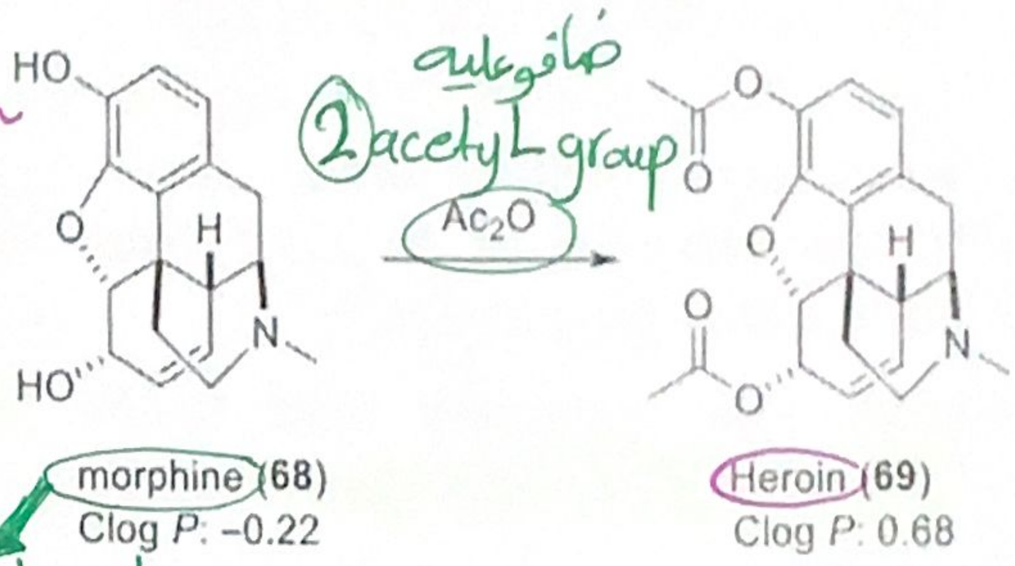
* الرابطة تحدث عندما يرتبط الـ Lone Pair اللي بالـ acetoacidic acid/acetoacetone مع الـ D orbitals اللي بالـ (metals) وبعملو رابطة تناسقية (Coordination)

Distribution to Blood Brain Barrier

- Normally, high potential for hydrogen bonding generally results in decreased BBB permeability, thus highly polar molecules (nominally defined as drugs with log *P* <0) with strong hydrogen bonding capacity do not traverse BBB readily.
- Lipinski rule for CNS penetration:

1. Molecular weight ≤400
2. log *P* ≤5
3. Hydrogen bond donor ≤3
4. Hydrogen bond acceptor ≤7

multiple-drug resistance (MDR) value:
A measure of *P-glycoprotein (Pgp)* 1-mediated efflux
The smaller the number, the less likely the drug is pumped out of BBB.



Heroin's brain penetration is 100-fold greater than that of morphine

Efflux Transporters

- Contrary to active drug transports, which ferry drugs across the cell membrane from outside the cell to cytoplasm, *efflux transporters* shuttle drug *outside* the cell membranes.
- Pgp belongs to a class of ATP-binding cassette (ABC) transporters. exist in various tissues such as liver, intestine, kidney, and BBB.
- Pgp can transport drugs back out of the gut wall and into the gut lumen, thus reducing absorption. It transports drugs out of the kidney and into the urine. Pgp is mainly expressed in cells of large/small intestines, liver, kidney, pancreas, and the BBB and plays an important role in pumping foreign substance/toxins out of the cells in the gut and/or the brain, etc.

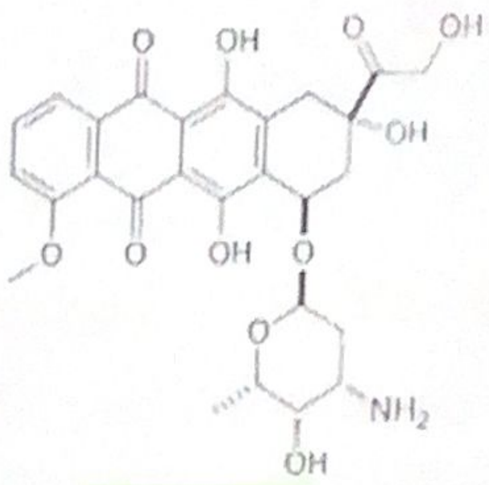
Why is it important to study about Pgp?

- Half of the marketed drugs are Pgp substrates. *Pgp substrates* are defined as compounds transported by the Pgp, whereas *Pgp inhibitors* are compounds that have been shown to inhibit Pgp.
- Pgp is characterized by having a binding pocket that allows for hydrophobic and aromatic interactions which allow for a variety of structurally diverse drugs to be transported out of the cell from the plasma membrane, resulting in low intracellular drug levels.
- Most Pgp substrates tend to be amphipathic in nature, containing both hydrophobic and hydrophilic moieties that are spatially separated.

يكونو بعاد عن بعض

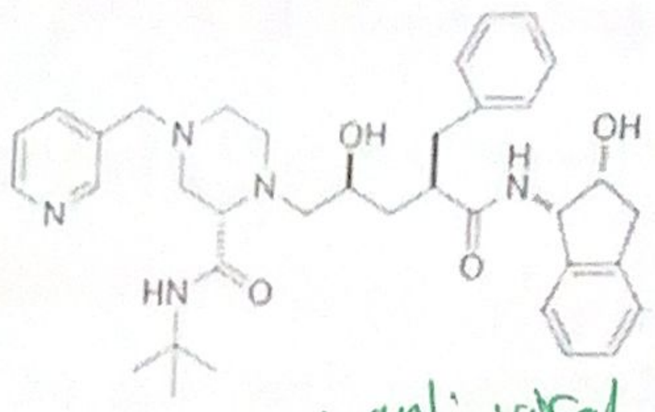
Examples of Pgp substrates and inhibitors

الأمثلة حفظ



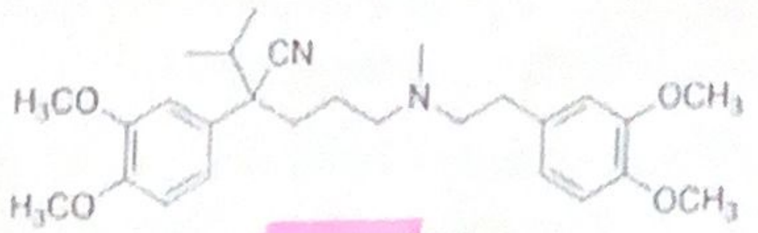
doxorubicin (77)
Pgp substrate

anti cancer agent



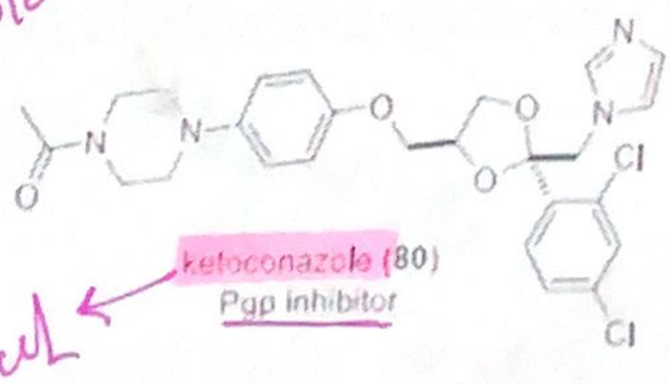
indinavir (Crixivan, 78)
Pgp substrate

anti-viral



verapamil (79)
Pgp inhibitor

Calcium chanel Blocker



ketoconazole (80)
Pgp inhibitor

antifungal

- **Strategies to control the Pgp issue include:** (Pgp substrate عشان الدواء يطلع)

(i). Co-administer an effective/selective Pgp inhibitor that does not cause cytotoxic effects and is reversible with the drug

(ii). Evade Pgp by optimizing physicochemical properties to make the drug's permeability higher going into the cell than going out.

(Petrauskas and colleagues) proposed a rule of 4 (Ro4) regarding Pgp substrates. It states that a compound is more likely to be a Pgp substrate if its:

* N + O ≥ 8;
* MW > 400; and
* pKa > 4

} Pgp substrate خصائص المركب اللي

In contrast, a compound is more likely to be a non-Pgp substrate if its:

* N + O ≤ 8;
* MW > 400; and
* pKa < 8 (acids and neutrals).

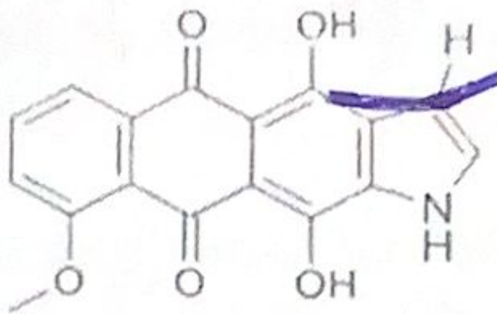
} Pgp substrate. خصائص المركب اللي مش

Tactics to Reverse the Pgp Issue

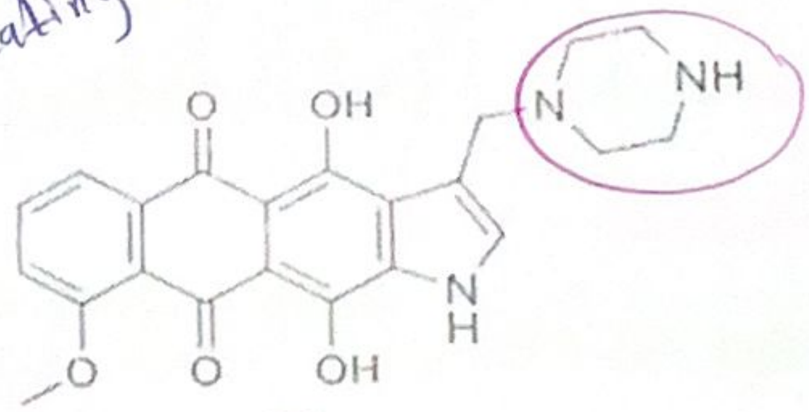
Structural modification طيب شو ممكن أعمل على الـ drug ليصير (not Pgp substrate)

1. introduce steric hindrance to the hydrogen bond-donating atoms by attaching a bulky group (hydrogen Bond الـ بالتالي بقلل (O, N) نقلل)
2. methylate the nitrogen atom (methylation)
3. decrease hydrogen bond acceptor potential by adding an adjacent electron withdrawing group
4. replace or removing the hydrogen bonding group, e.g., amide
5. modify structural features to interfere with Pgp binding, e.g., adding a strong acid
6. modify log *P* to reduce penetration into the lipid bilayer where binding to Pgp occurs.

Example

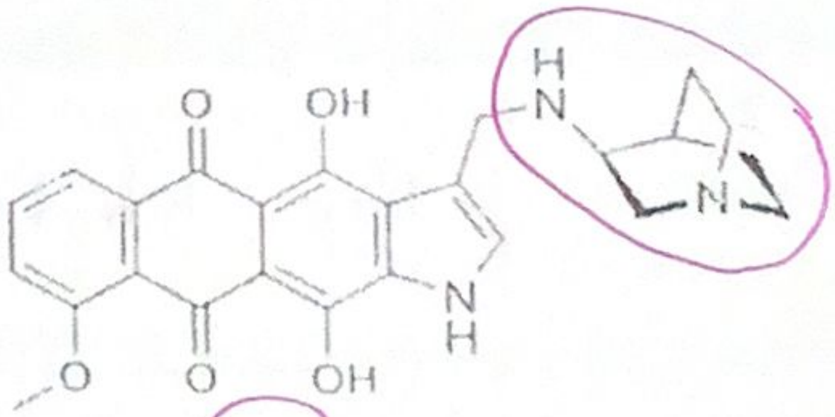


81. Pgp substrate



82. NOT a Pgp substrate

The (steric hindrance) of cyclic amines (piperazine and quinuclidine) minimized the hydrogen bonding-donating potential of the adjacent phenol group.



83. NOT a Pgp substrate

Done By Ruaa Kh

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