تفريغ ميديسينال

محاضرة: Distribution

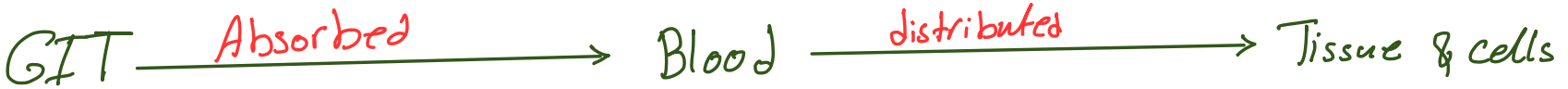
الصيدلاني\ة: _____

لجان الدُّفعات

Soul Academy

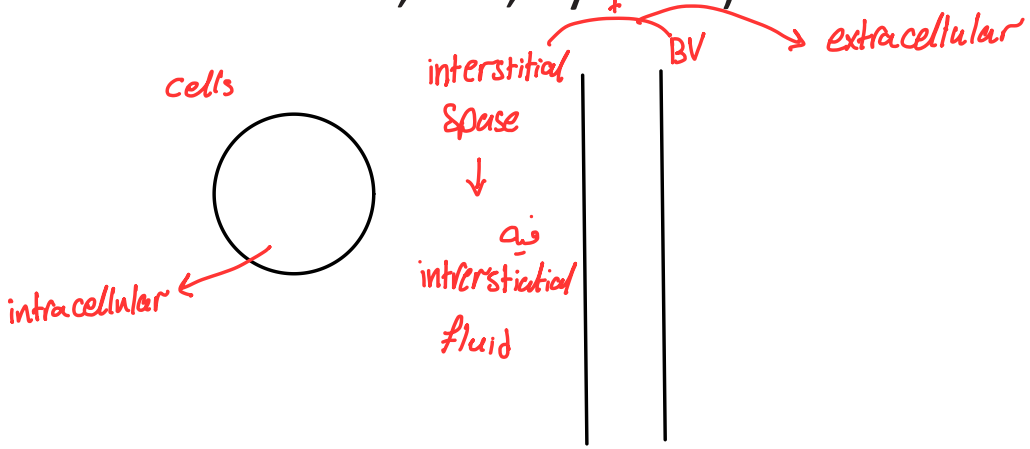
ADME
Distribution

Dr. Asma Fakhoury



Distribution

- 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).



- 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:

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.

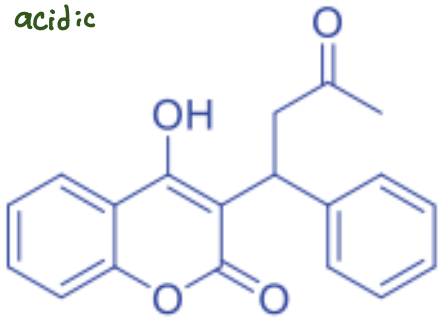
- Overall, volume of distribution (*V*d) of a drug is determined by its partitioning across various membranes; binding to tissue components; binding to blood components; and physiological volumes. Apparent volume of distribution (*V*d) is a *primary PK parameter* and could be greater than 10,000 L.
- 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.

↑Vd ⟶ C_{Tissue} ↑
↓Vd ⟶ C_{plasma} ↑

pH في الـ Distribution

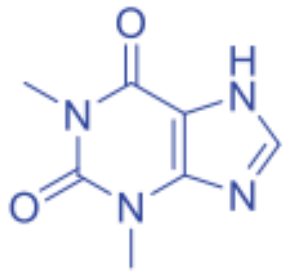
Compounds	*V*d (L/kg)	*V*d (L)
Acidic	<0.4	<28
Neutral	0.4–1.0	28–70
Basic Vd↑	>1.0	>70

Nutral - acidic



Warfarin (**60**), V_d = 8 L

مش لحشي عالي



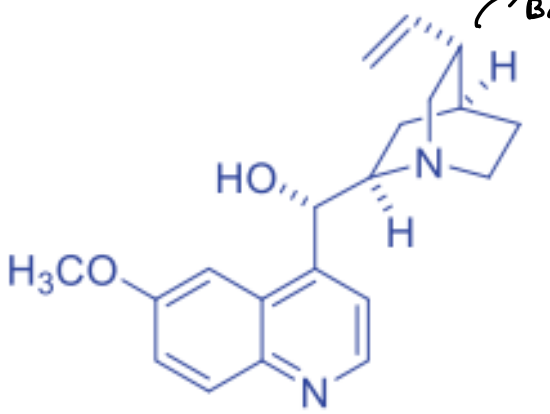
theophylline (**61**), V_d = 35 L

اعلى بكانه

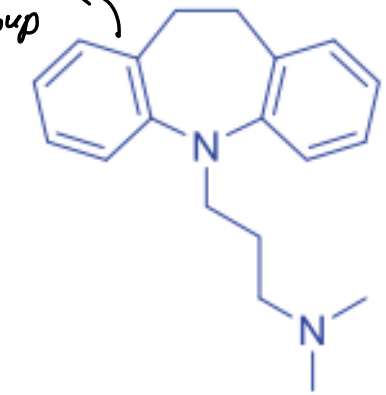
Basic properties عنده

المركبات عندها

Basc amin Group



quinidine (**62**), V_d = 150 L



imipramine (**63**), V_d = 2,100 L

Lipophilic عنده Part

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

+ طيب ليه هاي الميزة موجودة عند الأدوية الـ Basic

السبب

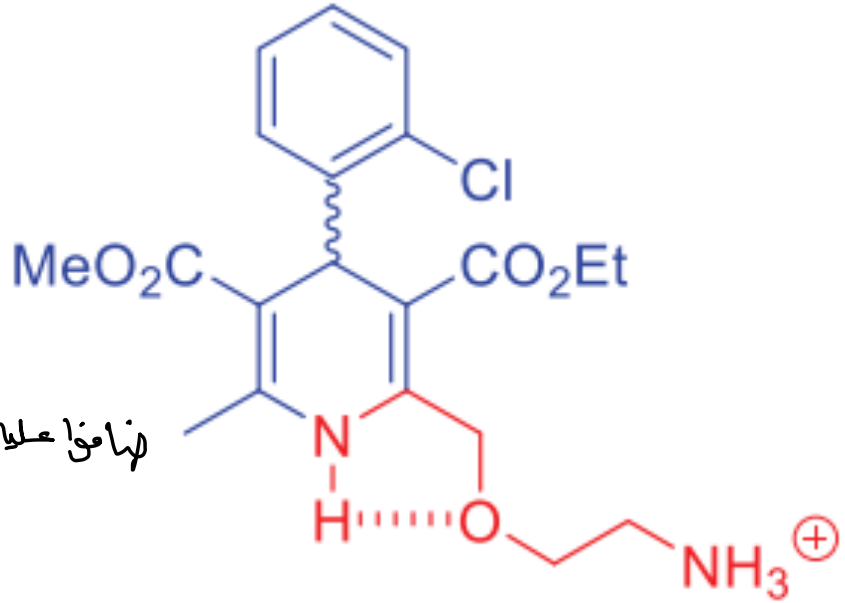
Lysosomotropism:

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

↳ physiological pH الـ على unionized بكونوا

لبس لما يفوتوا على الـ lysosoms والـ pH جوا acidic فيصيروا protonated لينحشروا جوا (Trapping) وبزيد الـ Conc اللعم جوا الـ Cells

Primary Amin
side chain



nifedipine (Adalat, **42**)

V_d, 0.75 L/kg

$t_{1/2}$, 2 h

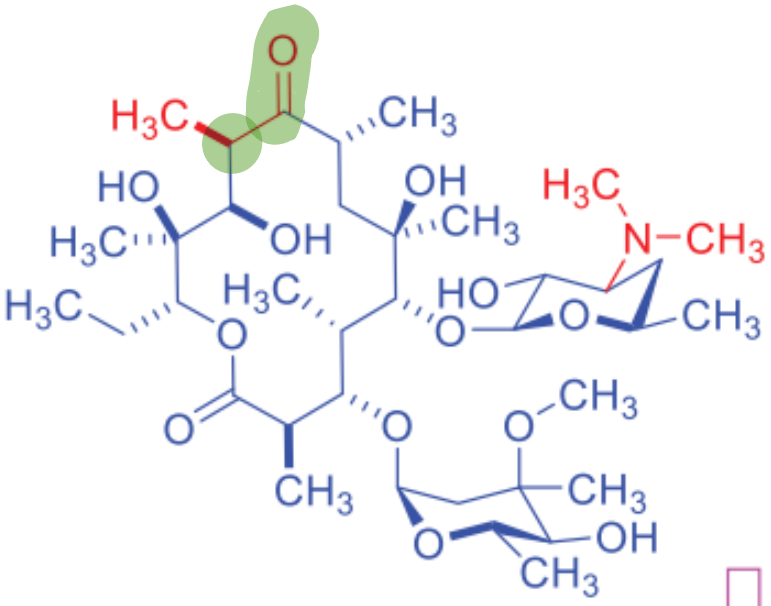
amlodipine (Norvasc, **43**)

21 L/kg

35 h!

- 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.

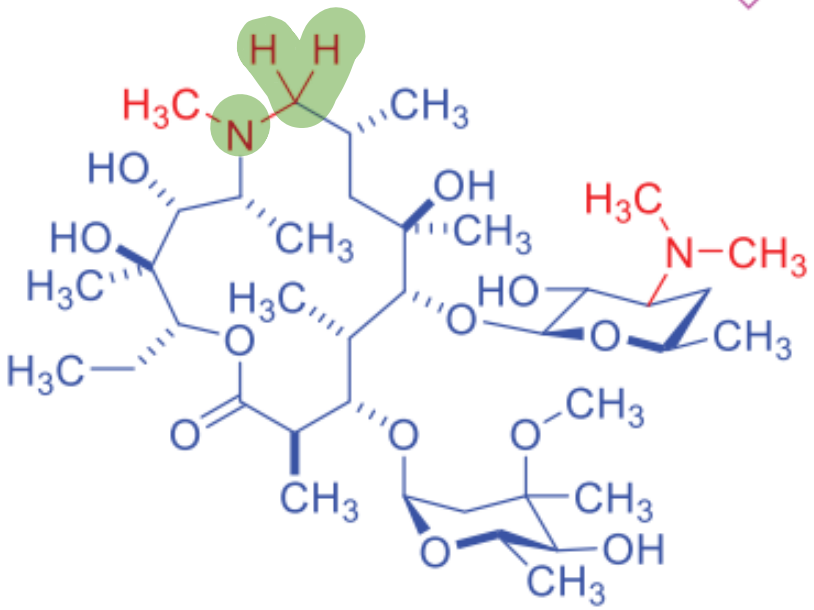
- Third-generation calcium channel blocker
- Has a basic primary amine sidechain (lysosomotropism)
- Has a very high *V*d of 21 L/kg
- Has a half-life of 35 h (once daily regimen).



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

One basic nitrogen atom

one Basic اعطانا
⇓
رفعت الـ Vd كثير



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

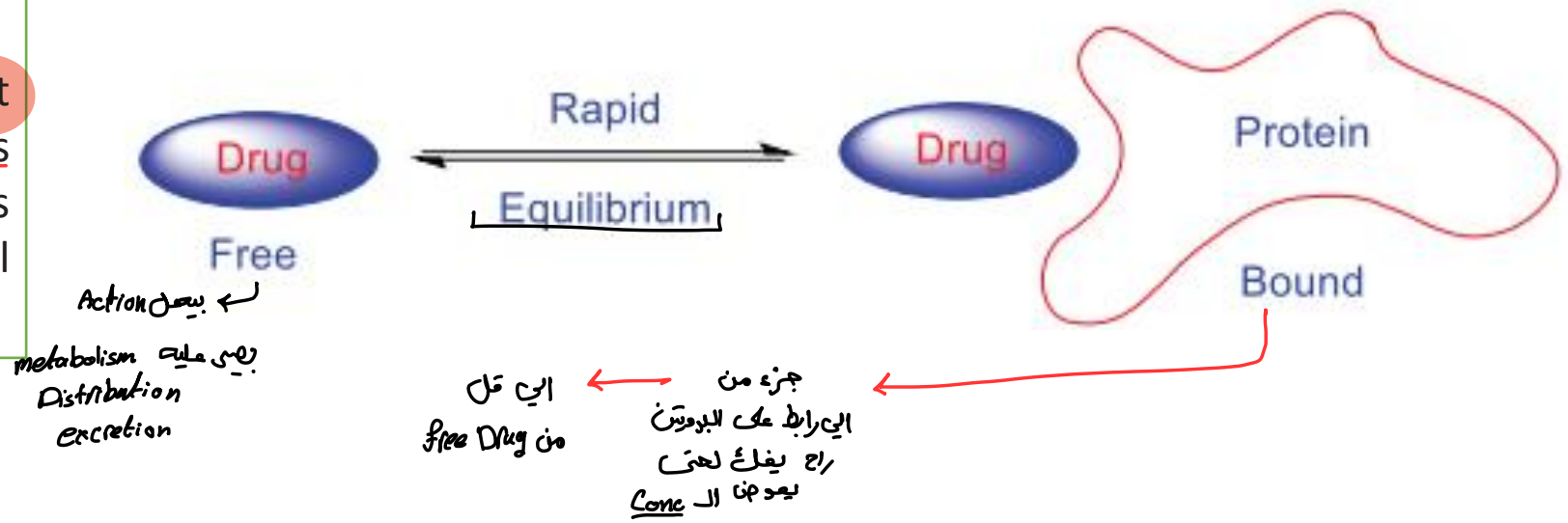
& Hydroxychloroquine ⇒ استخدموهم بكورونا لتخفيف اعراضها
اعراضها لانها مبدأ Lysosomotropism
Two basic nitrogen atoms

كيف Lysosom فيها enzyms مجمين في
عملية انقسام الفايروس لما يصير Trapping
لعمول الأدوية بتتثل فعالية الأنزيمات وبتطل عد الفايروس

Plasma Protein Binding

- 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.

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.

موجبات داخل الجسم ←

بزيد تركيزه بالدم ↓ Toxic ←

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.

الدوا مرتبط مع البروتين ← ماقيا metabolism ← بفل منتج دوائية
ممكن يصل Replacment الأدوية ومركبات أخرى

4. Generally expressed plasma concentrations of the drug refer to bound as well as free drug.

← بشرح: لما أعمل تحليل دم بيبين انه عندي تركيز الدوا عالي
لأنه ما بعتبر امين ال Bound Drug وال free drug
التأثير راح يكون قليل لكن التركيز عالي ←
ومنها بعرف انه الدوا الخاص رابط مع بروتين

ألبومين عندهم قليل

5. In hypoalbuminemia, binding may be reduced and high concentration of free drug may be attained.

← لما اكون حاسب انه الدوا X يربط بـ 55% مع ال Albumin
ويكون الألبومين قليل ويربط الدوا بنسبة 30% يكون عندي زيادة 25% ممكن تصير Toxic side effect

← عشان انجنب الموقف هاد
بقلل ال Dose لجدول التاسي

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

Example1: Aspirin

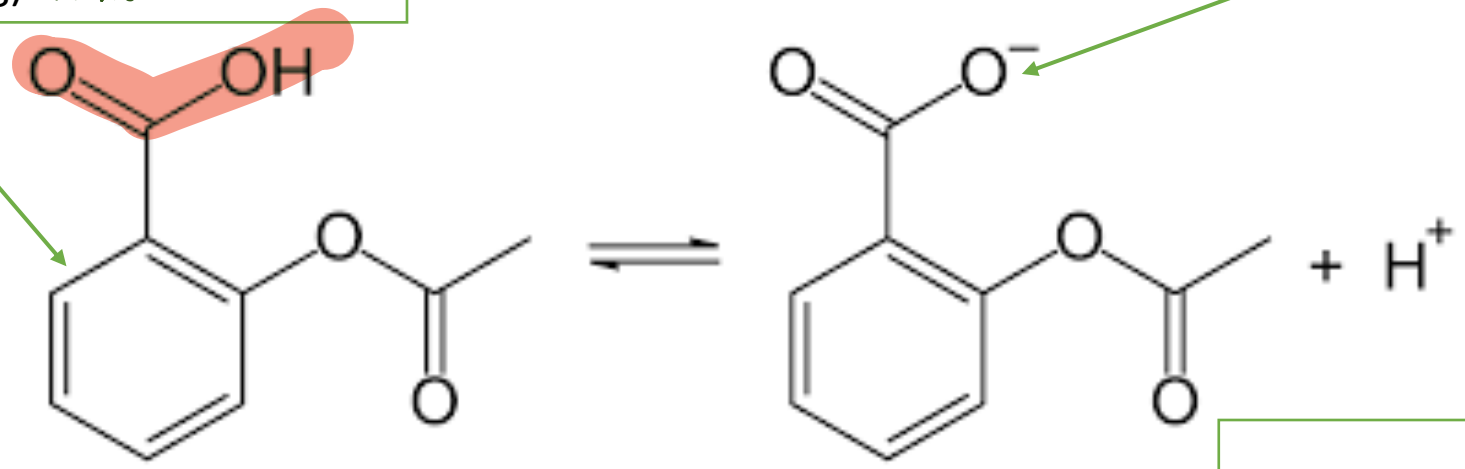
3 Forces

aspirin بتزيد ارتباط الـ

Albumin على الـ

③ Aromatic ring will bind to other aromatic rings found in aromatic amino acids in albumin (by π stacking) → Van der Waals

① >80% will bind to the positively charged arginine and lysine in albumin



Albumin → (-ve) عليه physiological على الـ pH

جزيئة 554 a.a فيه arginine + lysine (+ve) عشان يرتبط الـ acidic drug

Physiological pH على

بتكون (-ve) Charge

② H-bond forming groups

+ 5% من الارتباط

Aspirin at pH 7.4 will be in the ionized form (negatively charged)

→ 95% is bound to albumin

Example2: Metformin (Basic compund)

-ve charged لـ جذب يعني

فال Binding مع ال Albumin قليل

weak binding of metformin to BSA was **governed by hydrogen bonds and van der Waals forces** (5-10 %) only

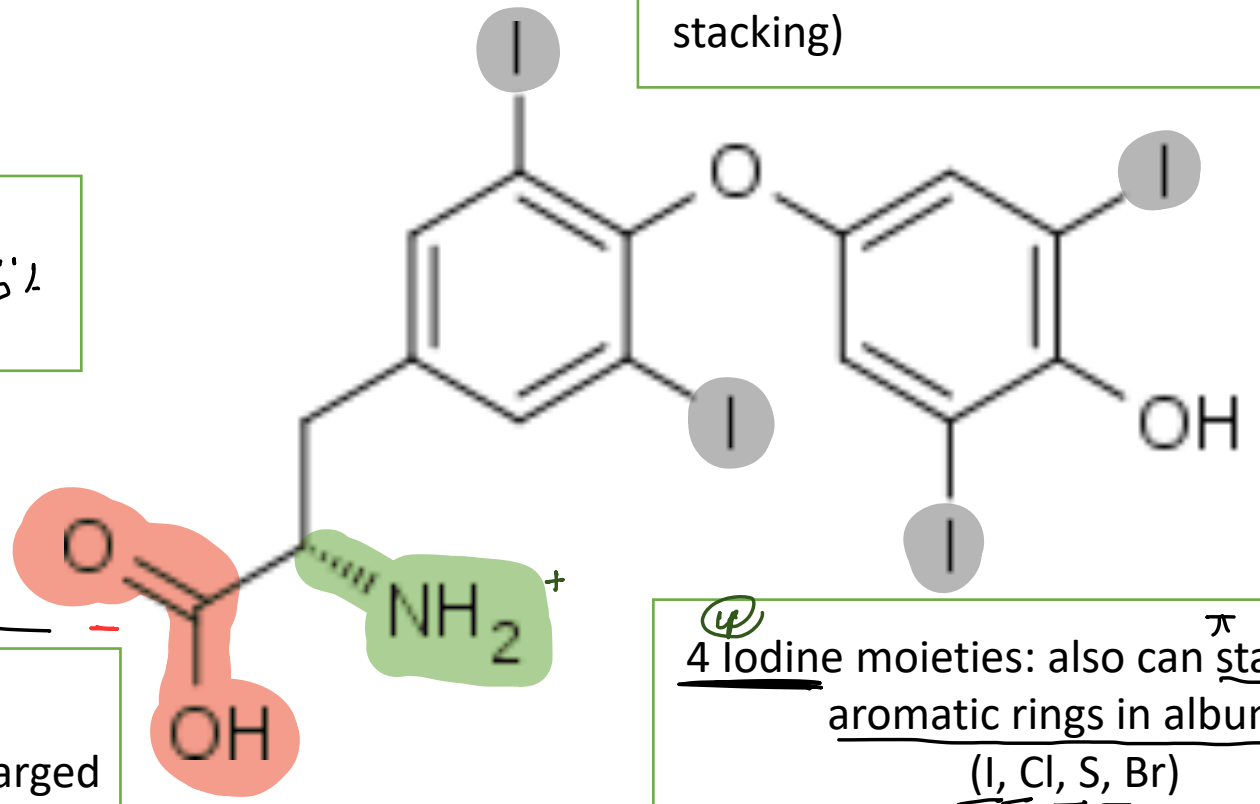
Vd ↑

Example 3: Thyroxine

4 Forces
Thyroxine بتزيد ارتباط الـ
Albumin على الـ

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

2. H-bond forming groups + 5'ل



3. Zwitterion at pH 7.4
-ve charge will bind to +vely charged binding pocket in albumin

Arg & lys مع راح تربط ← + 80٪

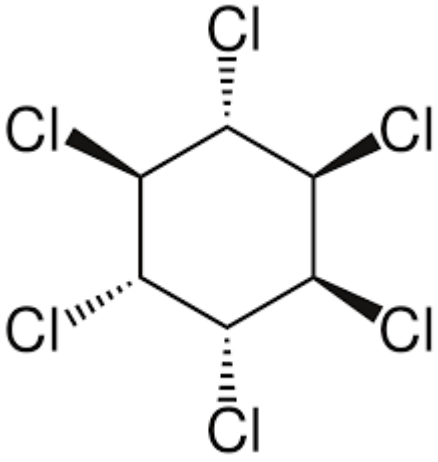
4. 4 Iodine moieties: also can stack against aromatic rings in albumin (I, Cl, S, Br)

π

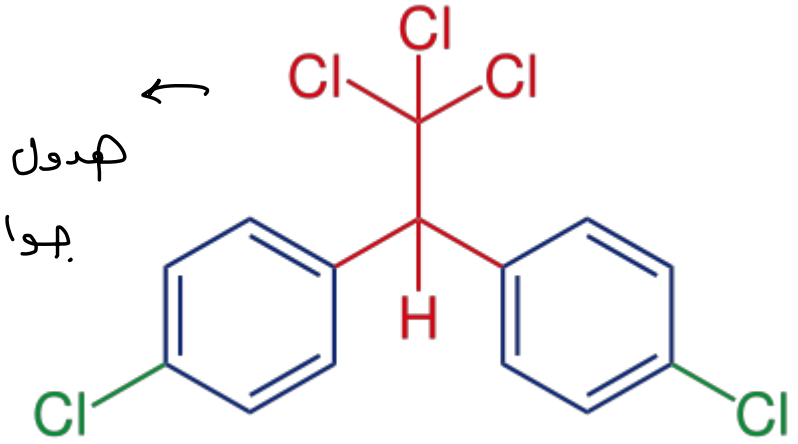
Thyroxine is more than 98% bound to albumin ٧٨↓↓

Fat Deposition

- Lipophilic drugs and multi-halogenated drugs tend to deposit in fats
- 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.



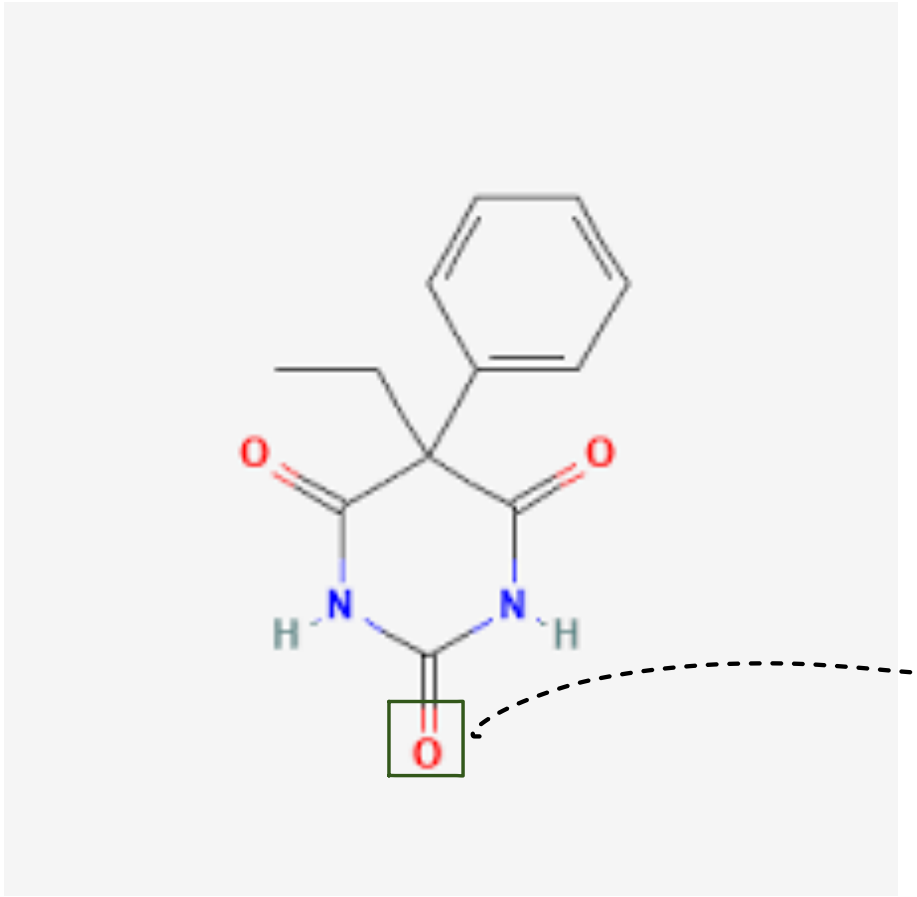
Hexachlorohexane



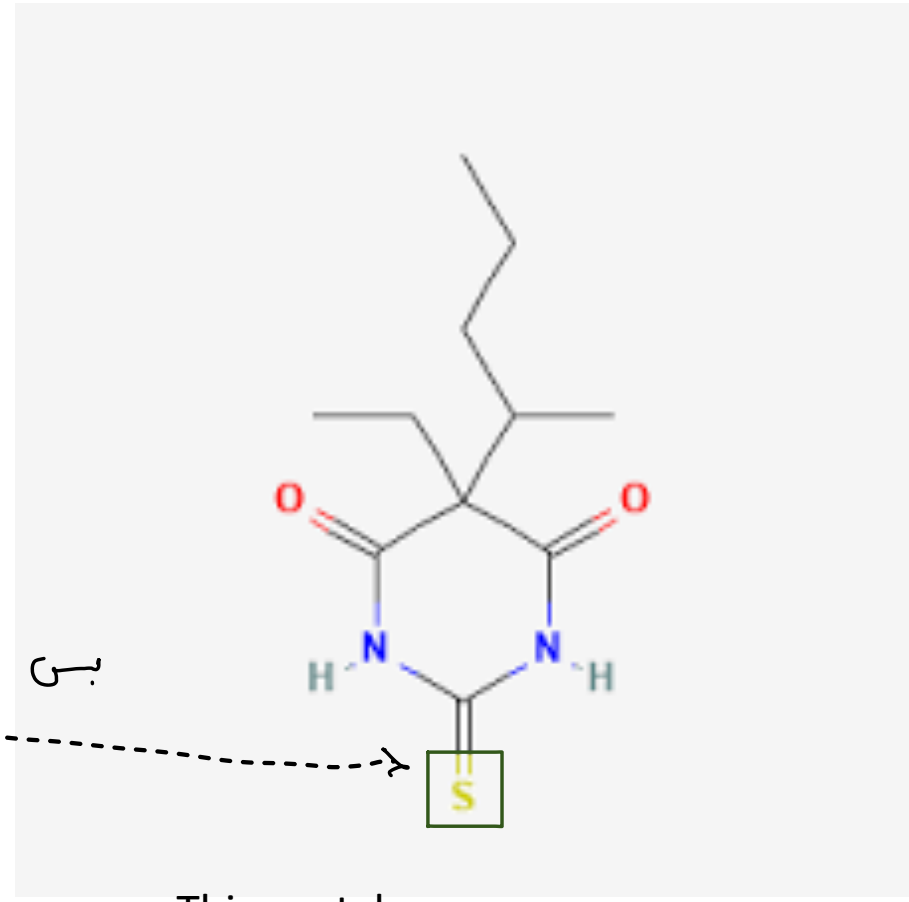
dichlorodiphenyltrichloroethane

Example

* بستخدمه بالتخدير



بس فيها الـ S بدل O



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

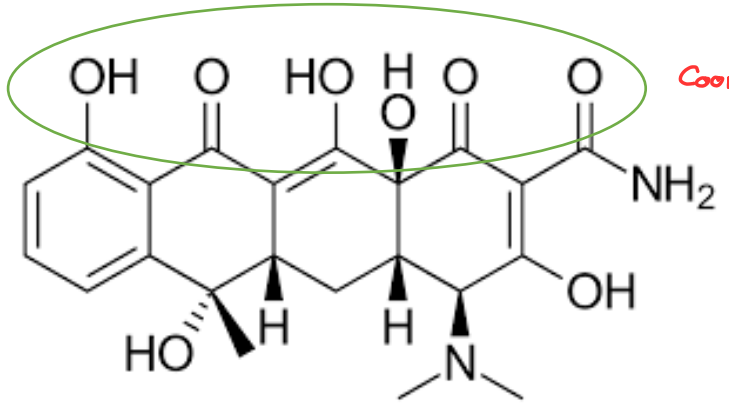
تغير التأثير والـ t½

Thiopental
Onset of action: 5 min
t1/2 :2 days
Quickly cross the BBB and deposit in the body fat

بظل لفترة اطول داخل الجسم

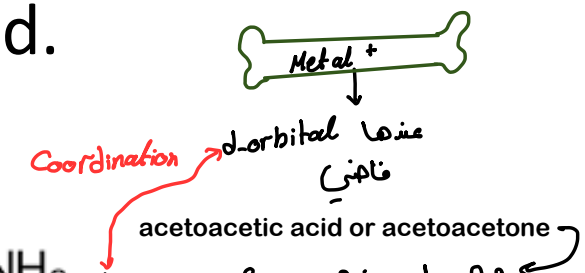
Bone Adsorption

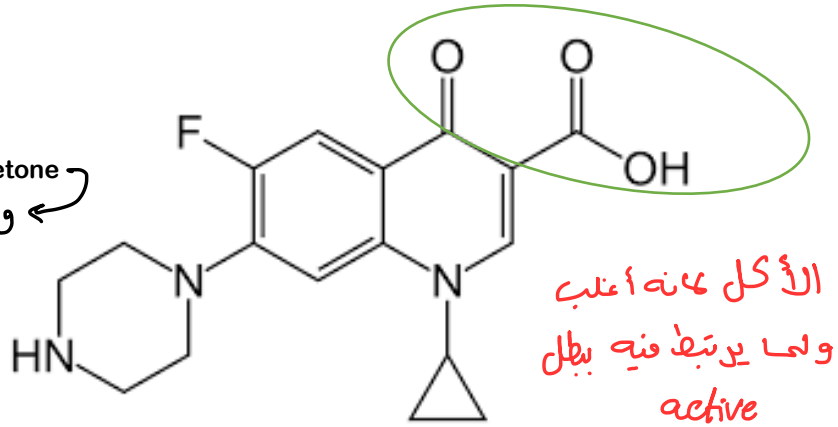
- Any drug contains acetoacetic acid or acetoacetone group will form a complex with metals in bones
- Bone deposits remain for a long time (sometimes for a life time)
- Drugs chelate to bones are biologically inactive, neither metabolised nor renally eliminated.



Tetracycline

4 acetoacetic acid groups





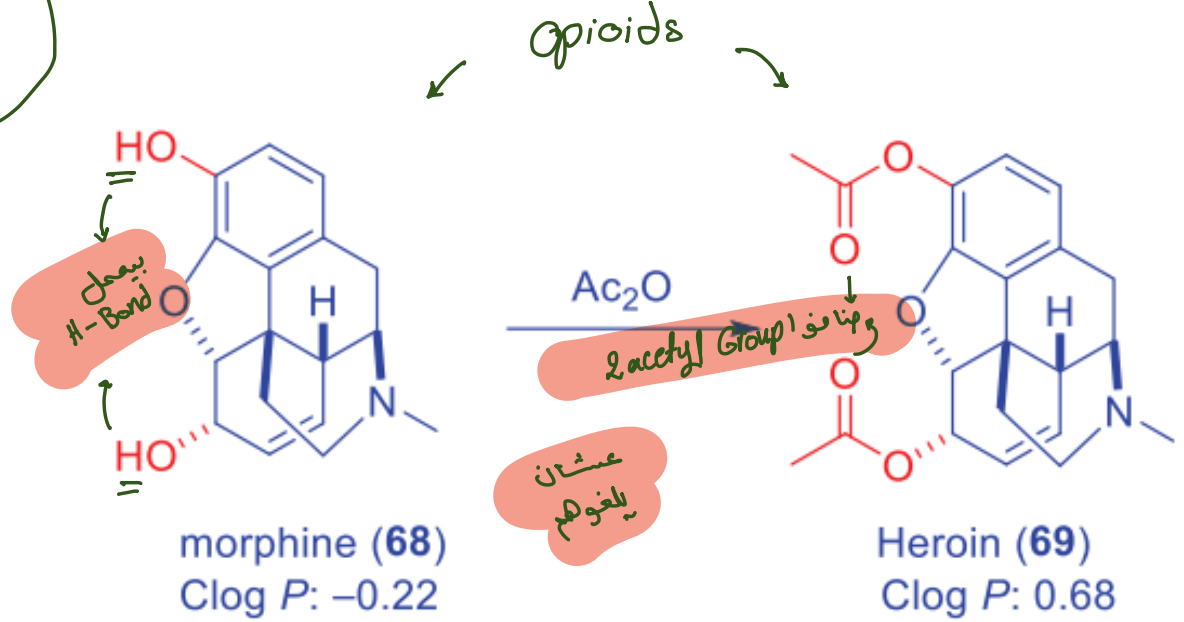
Ciprofloxacin

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 ⇒

من اسباب الـ Resistance لـ Some Drugs

ناقلة، عبّارة

- 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.

موجود بكثرة

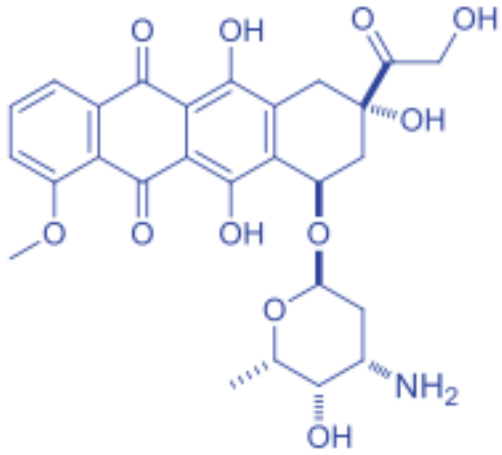
- Pgp can transport drugs back out of the gut wall and into the gut lumen, thus reducing absorption. It transports drugs out of the kidney and into the urine. Pgp is mainly expressed in cells of large/small intestines, liver, kidney, pancreas, and the BBB and plays an important role in pumping foreign substance/toxins out of the cells in the gut and/or the brain, etc.

مش دائمًا شغله سلبي هو برضوله دور بحماية الجسم من السموم والأجسام الغريبة

Why is it important to study about Pgp?

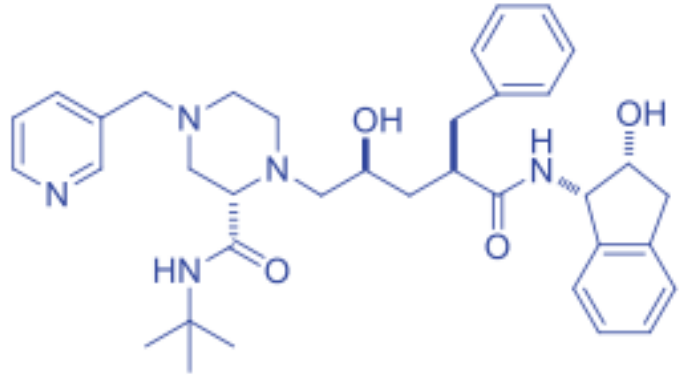
- Half of the marketed drugs are Pgp substrates. *Pgp substrates* are defined as compounds transported by the Pgp, whereas *Pgp inhibitors* are compounds that have been shown to inhibit Pgp.
- Pgp is characterized by having a binding pocket that allows for hydrophobic and aromatic interactions which 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.

Examples of Pgp substrates and inhibitors



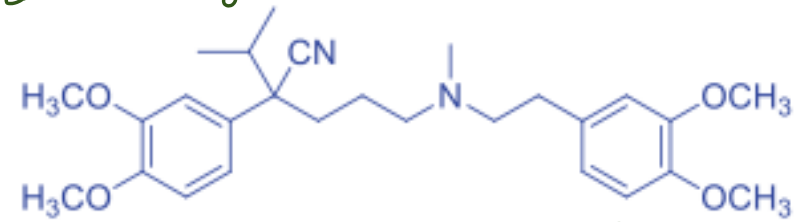
doxorubicin (**77**)
Pgp substrate

Anticancer Drug ← Resistance صار عندها

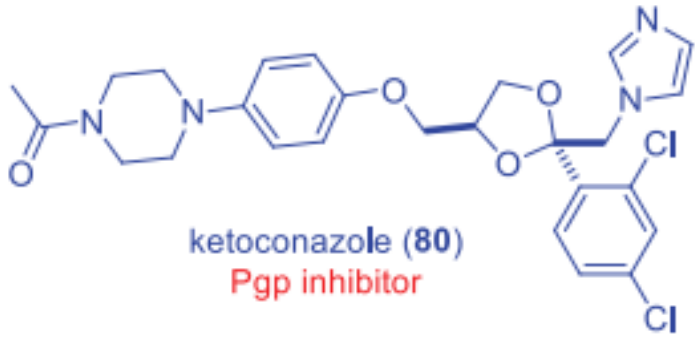


indinavir (Crixivan, **78**)
Pgp substrate

Antiviral → بستخدموه لـ AIDS



verapamil (**79**) CCB
Pgp inhibitor



ketoconazole (**80**)
Pgp inhibitor

- **Strategies to control the Pgp issue include:**

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

ممكن اني اتهرب منه وابدل على structure

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

اسم العالم

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:

مجموعهم

N + O ≥ 8;

MW > 400; and

p*K*a > 4

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

✓ N + O ≤ 8;

✓ MW > 400; and

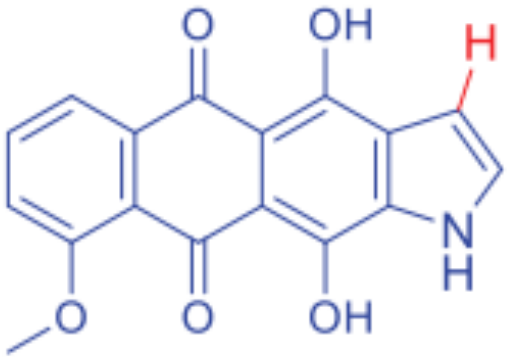
✓ p*K*a < 8 (acids and neutrals).

اذا الـ ٣ شروط تواجدوا بالدوا معناته Pgp ما بأثر على الدوا

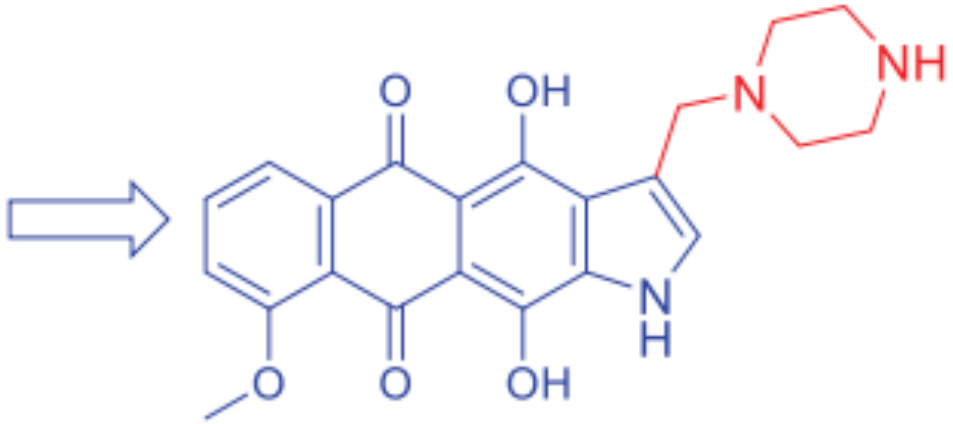
Tactics to Reverse the Pgp Issue

- introduce steric hindrance to the hydrogen bond-donating atoms by attaching a bulky group
- methylate the nitrogen atom
- decrease hydrogen bond acceptor potential by adding an adjacent electron withdrawing group
- replace or removing the hydrogen bonding group, e.g., amide
- modify structural features to interfere with Pgp binding, e.g., adding a strong acid
- modify log *P* to reduce penetration into the lipid bilayer where binding to Pgp occurs.

Example

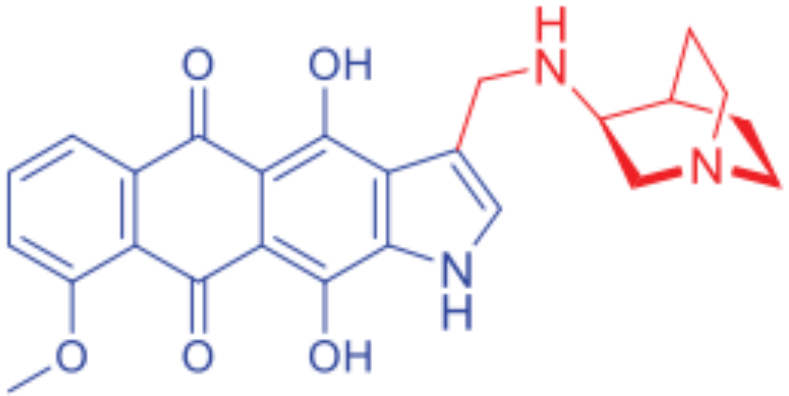


81, Pgp substrate



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