ADME
Distribution

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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: intravascular (blood plasma found within blood vessels); interstitial/tissue (fluid surrounding cells); and 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;

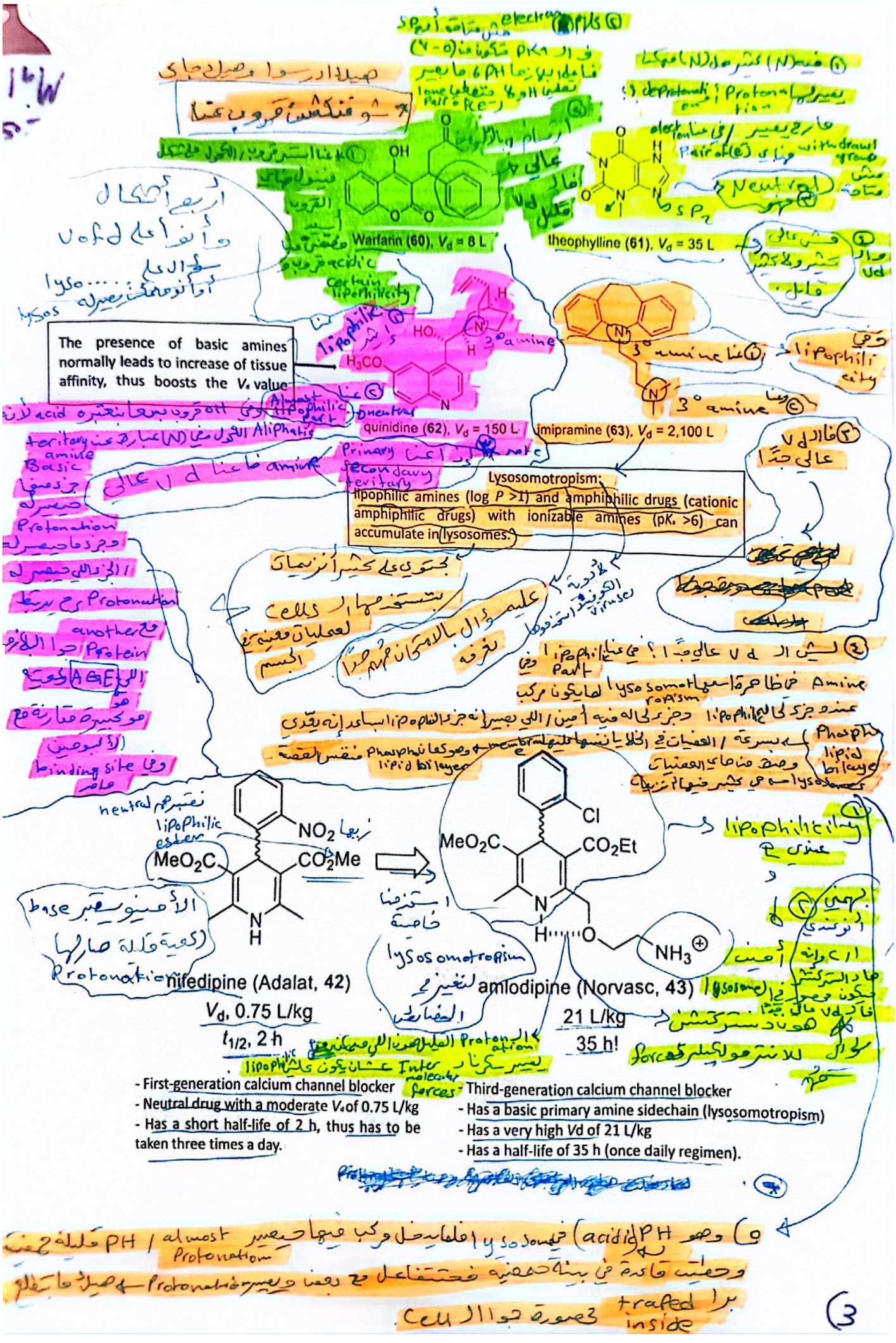
Tetracyclines and digoxin in kidney;

Chlorpromazine, isoniazid, and acetazolamide in the brain;

Ephedrine and atropine (to melanin) in iris.

- Overall, volume of distribution (*Vd*) 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 (*Vd*) 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.

	Compounds	*Vd* (L/kg)	*Vd* (L)
1	Acidic	<0.4	<28
2	Neutral	0.4–1.0	28–70
3	Basic	>1.0	>70



Warfarin (60), V_d = 8 L

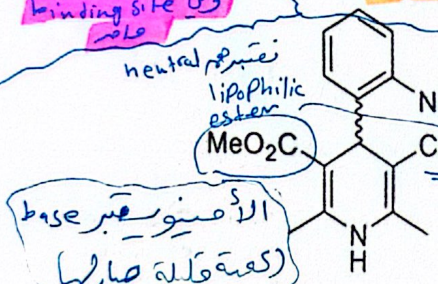
Theophylline (61), V_d = 35 L

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.

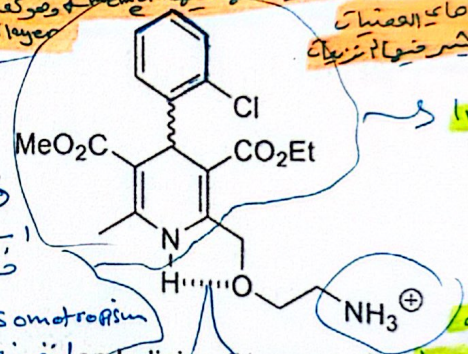


nifedipine (Adalat, 42)

V_d, 0.75 L/kg

$t_{1/2}$, 2 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.



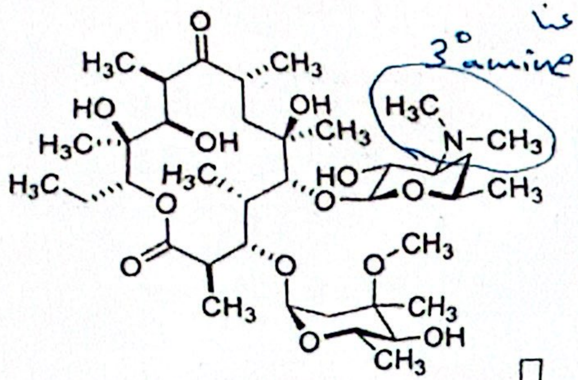
amlodipine (Norvasc, 43)

21 L/kg

35 h!

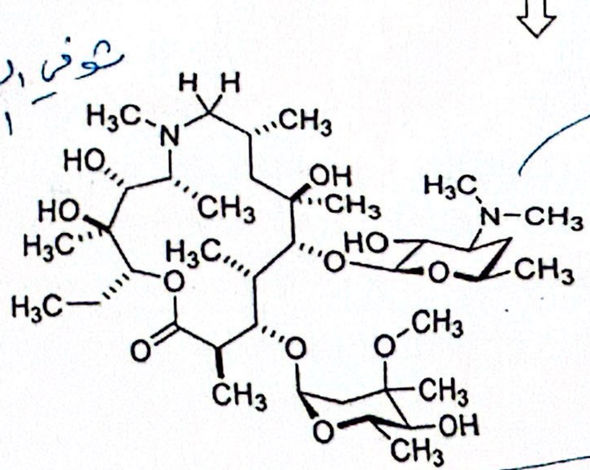
- Third-generation calcium channel blocker
- Has a basic primary amine sidechain (lysosomotropism)
- Has a very high Vd of 21 L/kg
- Has a half-life of 35 h (once daily regimen).

* عارح يجي ستركتشر كبير هالقد.



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



شوفي الأحمر في السلايد

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

زدنا ال lipophilicity وجبنا كمان (N) ثانية

هادتم استخدامه للكوفيد ١٩

القاعدي فيزداد فيصير له lysosomotropism

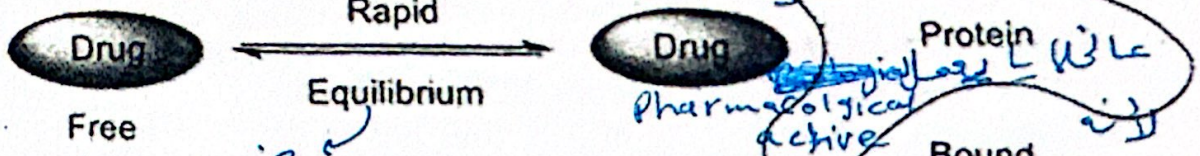
Two basic nitrogen atoms

ستركتشر في lipophilicity بحكم انه فيه alkyl chain، هالوجينيشن، methyl، aromatic ring، كربونيل / carboxylic acid، sulfuric acid بعرفا انه acid، الستركتشر.

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.
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)

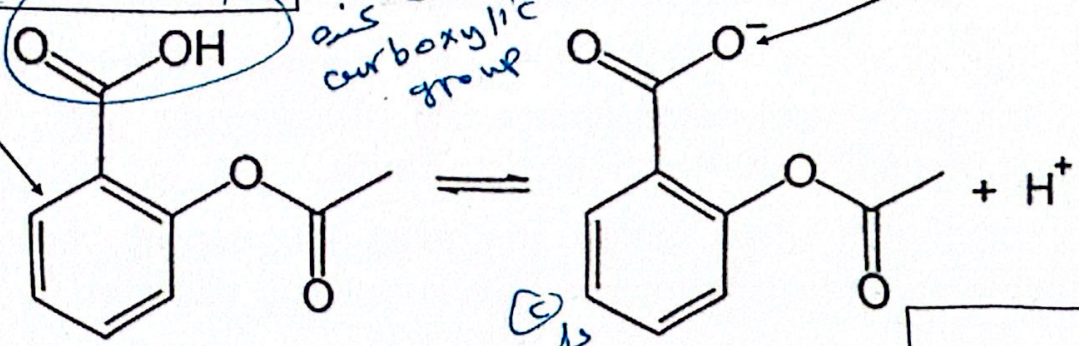
- Human serum albumin ((HAS): 6700 Dalton) , the most abundant protein in human blood plasma, has more than six distinctive binding sites including two for long-chain fatty acids, one for bilirubin; and two for acidic drugs
- On the other hand, AAG has only one selective site for basic drugs.
- Acidic 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

Example1: Aspirin

أهم اشيين بعيره ارتباط HSA

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

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



aic carboxylic group

H-bond forming groups

deprotonation بعيره ph physiological pH

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

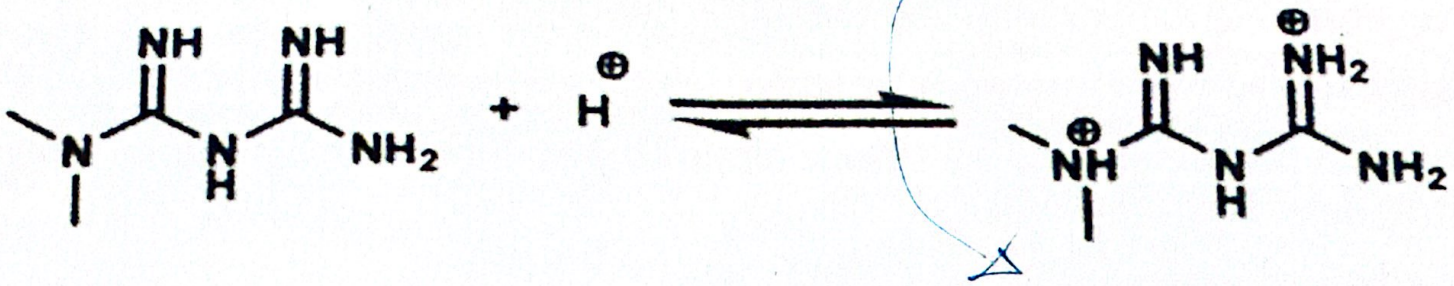
→ 95% is bound to albumin

٪5 Free للسيل حيوا

% Free
للسيل حيدوا

Example2: Metformin

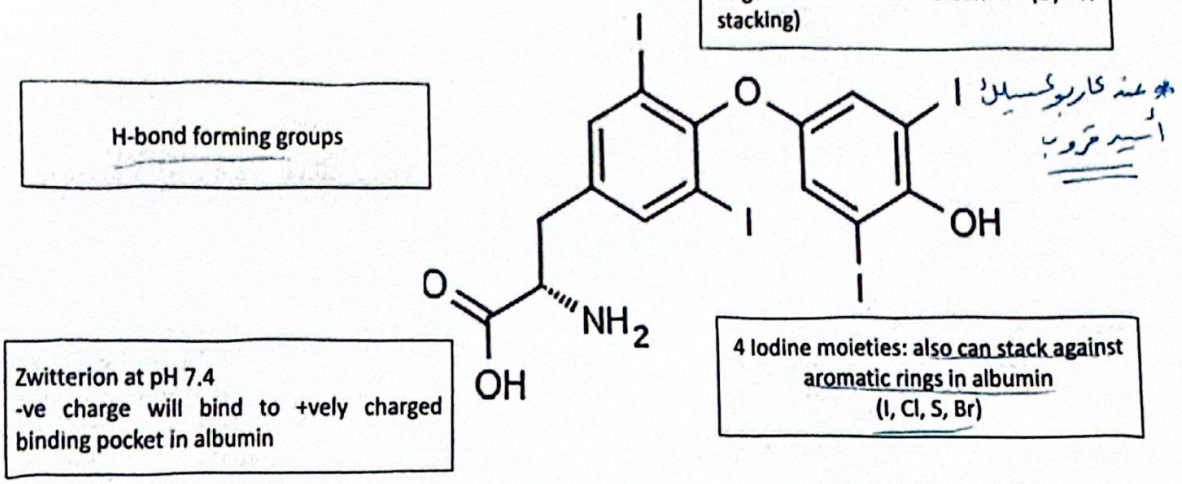
basic drug
معكن يرتبط بال HSA الكن الارتباط حيكون
كتير ضعيف



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

فالقوى
عالي لالا

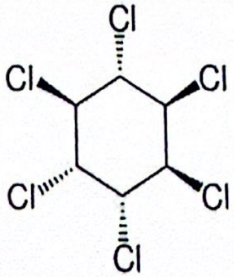
Example 3: Thyroxine



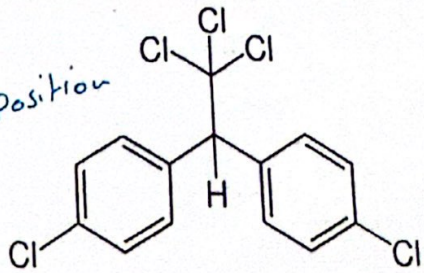
Thyroxine is more than 98% bound to albumin

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.

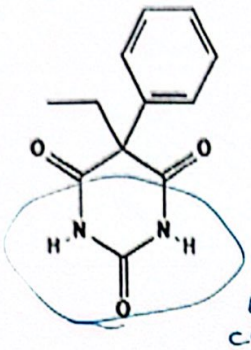


Hexachlorohexane

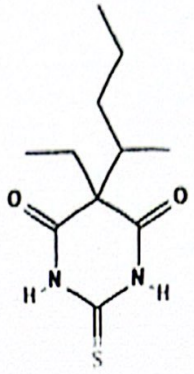


dichlorodiphenyltrichloroethane

Example



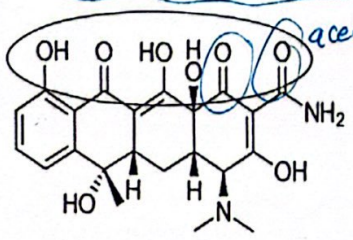
Phenobarbital
Onset of action: 1.5hr
t1/2= 8 hr



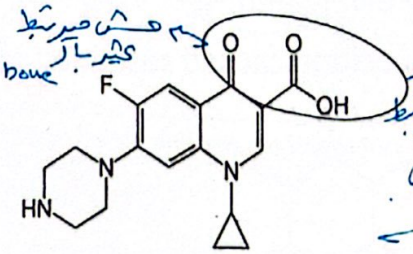
Thiopental
Onset of action: 5 min
t1/2 :2 days
Quickly cross the BBB and deposit in the body fat

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