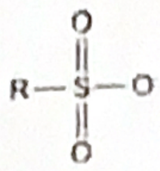
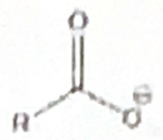
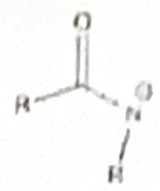
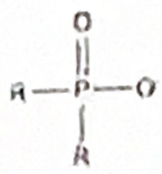
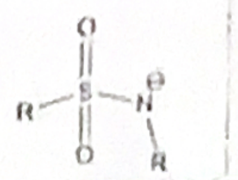
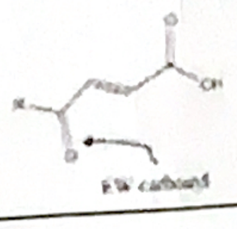
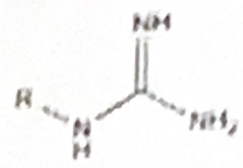
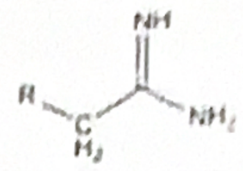
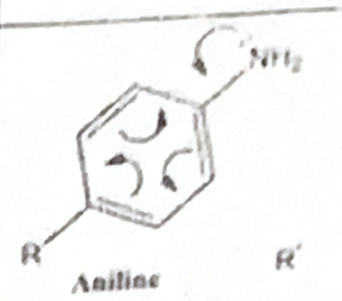
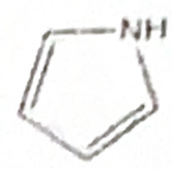
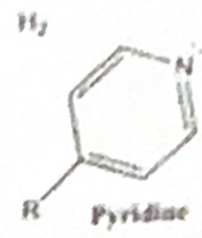
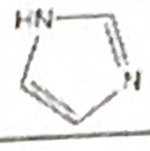
* الجدول هاد ملخص للكل الي انشرح قبل للمجموعات (Categories).

Strong acids	Intermediate acids	Weak acids
Sulfonic acid 	**Carboxylic acid** (conjugated to EWD) 	**Amides** (pKa ≈ 12) 
Phosphoric acid 	**Sulfonamides** (without EWD) 	**Imides** (pKa ≈ 8-10) 
Sulfonamides (with carboxylic acid) 		**Phenols** (pKa ≈ 7) 
Carboxylic acid (conjugated to EWD) 		**Imidazole** 

Strong bases	Intermediate bases	Weak bases
Guanidine 	 **Amine**	
Amidine 	 **Aniline**	 **Pyrrole**
	 **Pyridine**	
	Imidazole 	

Hydrophilic/Hydrophobic Characters of the Drug

- As a rule of thumb, orally absorbed drugs tend to obey what is known as **Lipinski's 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 five: قواعد كل وحدة فيها رقم (5) أو مضاعفاته ٤

M.w

- a molecular weight less than 500;
- no more than 5 hydrogen bond donor (HBD) groups;
- no more than 10 hydrogen bond acceptor groups;
- a calculated **log *P*** value less than +5 (log *P* is a measure of a drug's hydrophobicity). Optimum around (2)

4 - $Log(P) \leq 5$ ← P: Partitioning coefficient

optimally = 2

$$P = \text{Partition coefficient} = \frac{[D]_o}{[D]_w}$$

$$P = \frac{[D]_o}{[D]_w} \leq 10^5$$

يعني مسموح انه الدوا يذوب

بالزيت أكتر من ذوبانه بالماي بـ 10^5 مرة

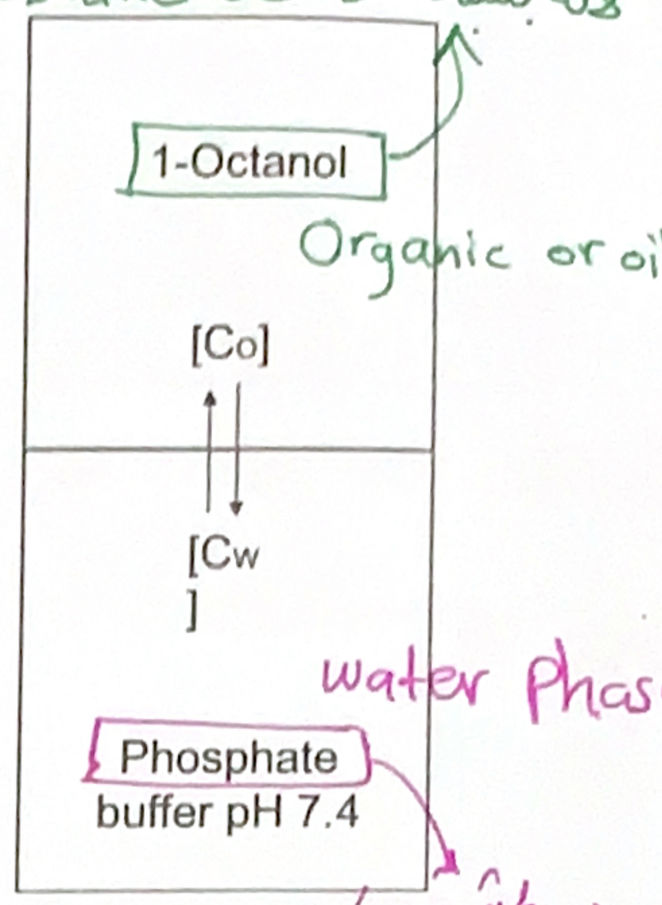
وما يتعداهم لأنه يصير Lipophilic وما يذوب بالماي وما يصير Partition

- Lipinski's Ro5 predicts that a drug may have poor solubility and permeability (marked as an "*Alert*") if the compound exceeds two or more of the four limits.
- However, it is neither quantitative nor reliable. For example, orally active drugs, such as **atorvastatin**, **rosuvastatin**, **ciclosporin**, and **vinorelbine**, do not obey the Ro5.
- It has also been demonstrated that a high molecular weight does not in itself cause poor oral bioavailability (larger molecules invariably have too many functional groups capable of forming hydrogen bonds. Another source of debate concerns the calculation of the number of hydrogen bond acceptors (HBAs)).

- Lipophilicity is a measure of how greasy a molecule is. It has a profound impact on a drug's ADME because it is closely associated with drug's solubility, plasma protein binding (PPB), metabolic clearance, volume of distribution, enzyme/receptor binding.
- A quantitative measure of a molecule's lipophilicity is its *partition coefficient, P*, which is the ratio of the equilibrium concentrations of a dissolved solute in a two phase system containing two largely immiscible solvents.

$$P = P_{o/w} = [Co]/[Cw]$$

$$\text{Log } P = \log([Co]/[Cw])$$



Effect of Log P

- **increase** in log *P* **increases binding** to targets such as receptors and enzymes with **larger molecules** the potency grow.
- Reasons: lipophilicity enhances a drug's binding as a nonspecific driving force for the partition of the drug into the binding site by raising its free energy in water.
- However, larger molecules (high log p) are associated with **lower bioavailability**.
  As the log *P* value increases, the aqueous solubility decreases, although absorption through the membrane increases.

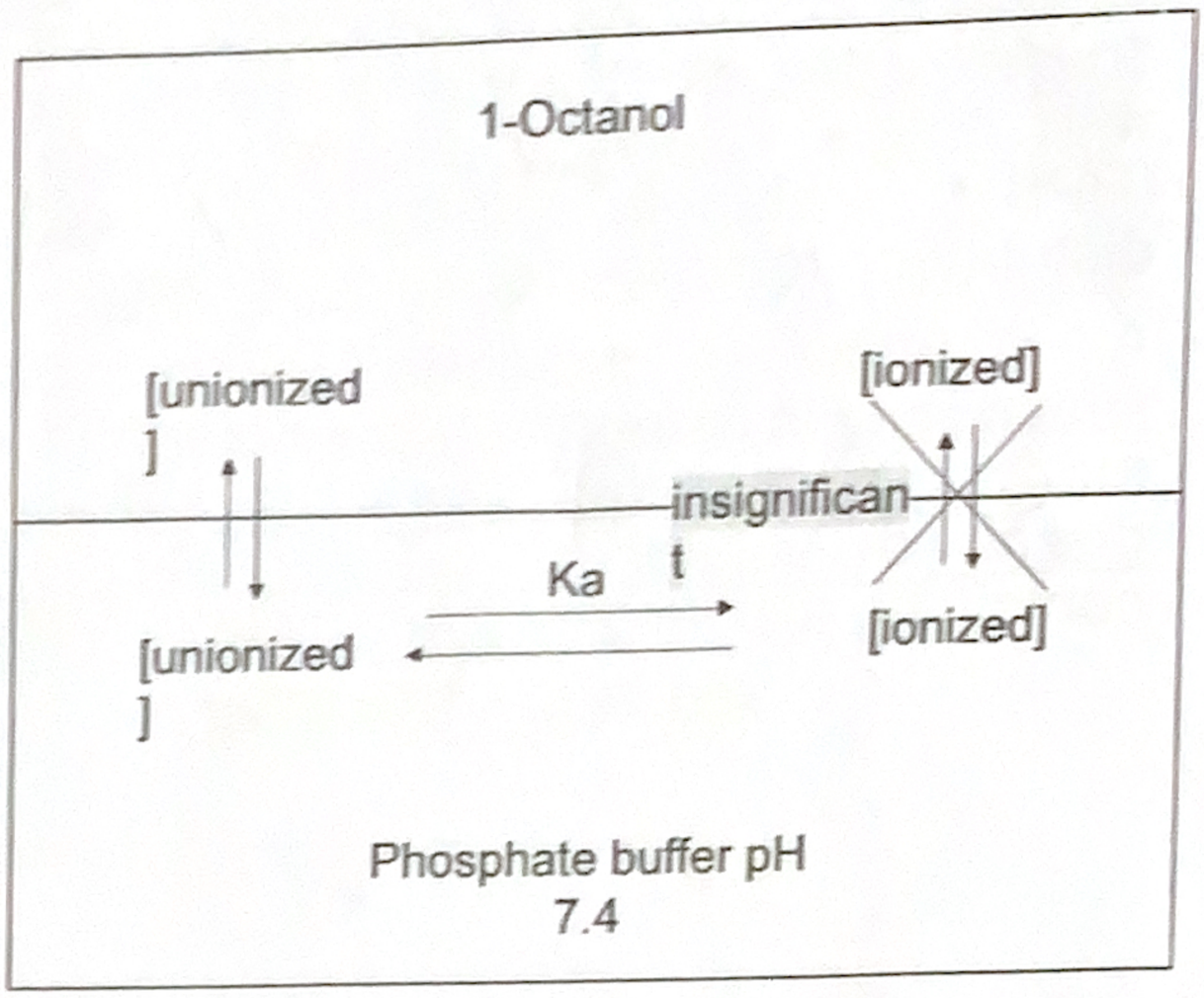
Partition Coefficient and Distribution Coefficient

$$\text{Log } P = \log([Co]/[Cw])$$

Only adequate in quantifying a drug's lipophilicity for *neutral* molecules.

Not suitable for ionizable acids or bases because their concentrations in octanol and water vary depending upon the degree of ionization.

For acids and bases, *distribution coefficient D* is a more appropriate measurement of lipophilicity at a given pH. **It is a function of both lipophilicity of the un-ionized compound and degree of ionization.**



Organic Phase ما بصير فيه ionized الـ
Phase [aqeous] وممكن بال Organic بال] ممكن فيه unionized لكن الـ
(Distribution Coefficient) فيه الـ
اللي بتختلف حسب الـ PH الموجودة
. ثابت Partition Coefficient أما

Distribution Coefficient (D)

- used to predict the behaviour of a compound at all pH values, as long as we know P.
- For an acid:

$$HA_{aq} \rightleftharpoons H^+_w + A^-_w$$

$$D = [HA]_o/\{[HA]_w + [A^-]_w\}$$ → ionized form of acid

$$\longrightarrow \quad \log D = \log P - \log [1 + 10^{(pH - pKa)}]$$

- For a base:

$$BH^+_w \rightleftharpoons B_w + H^+_w$$

$$D = [B]_o/\{[BH^+]_w + [B]_w\}$$

$$\longrightarrow \quad \log D = \log P - \log [1 + 10^{(pKa - pH)}]$$

PH و Pka لبنتج
(أول مبارة فيها Pka)

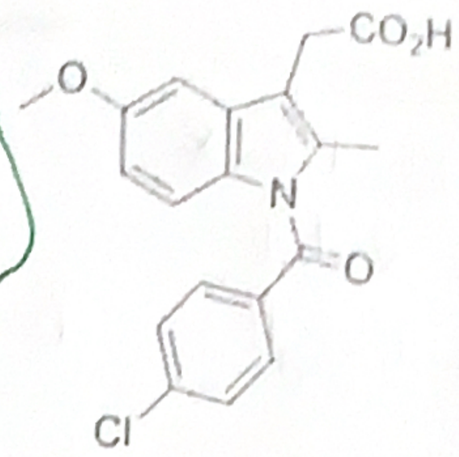
Example

Carboxyl group عنده
indomethacin has a p*K*a value of 4.5:

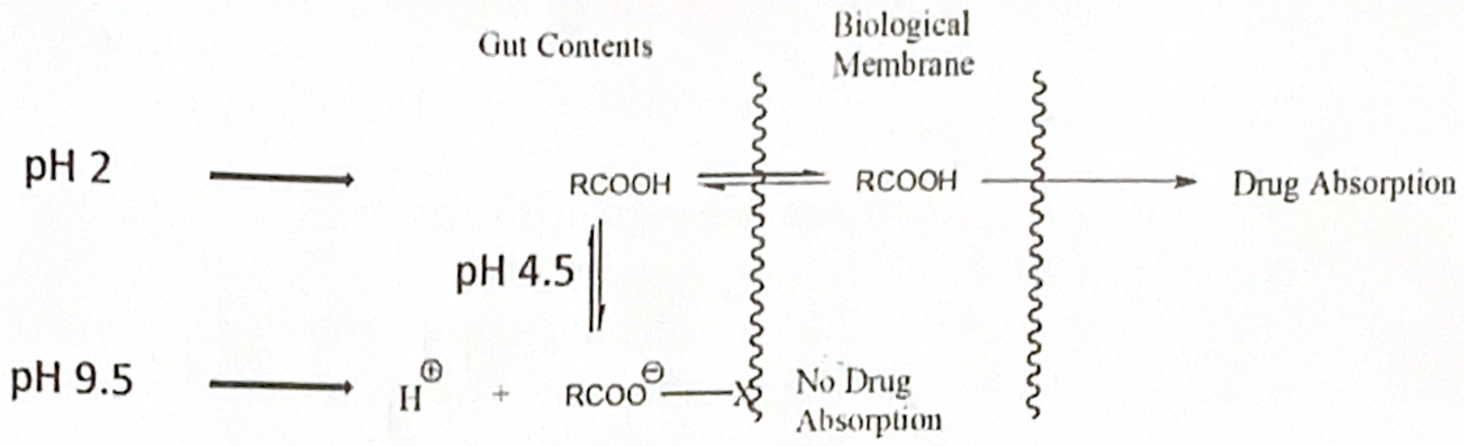
- In a very acidic environment, pH 2.0 for instance, the log *D* is the same as log *P*: 4.25 since 100% of the molecules are unionized. Totally
PH = Pka
- At pH 4.5, 50% of the drug remains unionized and its log *D* is 3.95. عالفانون
(50% ionized)
- Under very basic conditions, pH 9.5 for example, merely 0.001% of the drug remains un-ionized since essentially all drug molecules are ionized and its log *D* is –0.75. $LogD = 4,25 - \log(1+10^{9,5-4,5})$

عكس

توضيح:
$LogD = LogP - \log(1+10^{Ph-Pka})$
$LogD = 4,25 - \log 2$
$= 3,95$



indomethacin (Indocin, 1)



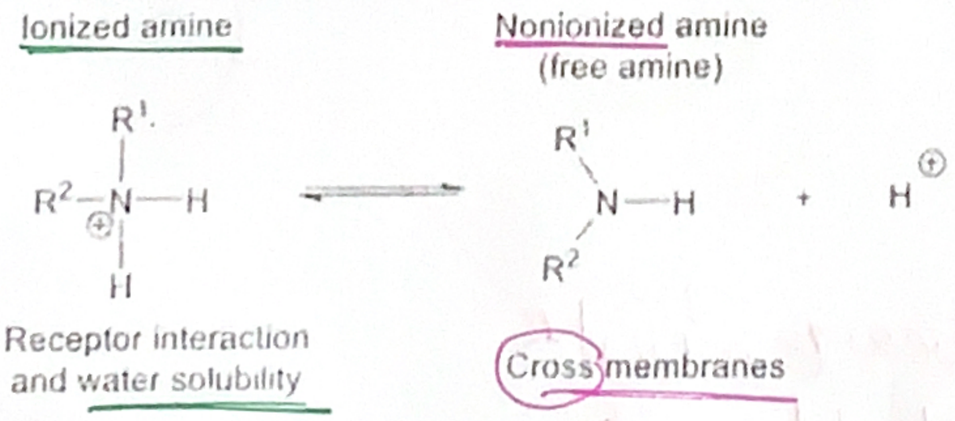
Log P = Log D
أي أنه لا يوجد أيونة
(Ionization)
PKa > PH of حيث

Good to Relate with Previous Lecture

- Why the prevalence of nitrogen atoms in so many drugs?

(ionized & unionized) بمنح هاي الخصائص للمركب (amine) و وجود الـ (N) (Slightly hydrophilic) بمعنى بالماء يكون و (Slightly lipophilic)

In order for a drug to pass through cell membranes, a dichotomy is at play. On one hand, the drug should be slightly hydrophilic so that it can dissolve in water. On the other hand, it should be somewhat lipophilic so that it may cross the cell membranes. **Amines fit the bill well**. Amines' p*K*a values are in the range of 6 to 8, thus they are partially ionized at blood pH 7.45. They can easily equilibrate between their ionized and nonionized forms with a good balance of the dual requirements of water and fat solubility. They can cross cell membrane in the nonionized form, while the ionized form gives good water solubility and permits good binding interactions with its target's binding sites. Striking a balance of lipophilicity is one of the drug design challenges.

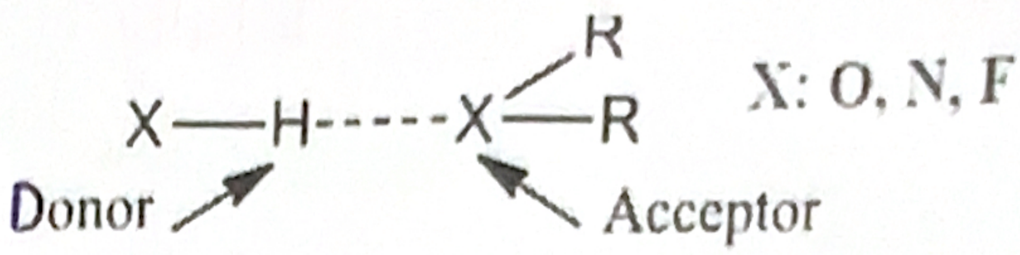


* حكينا قبل بانه حسب القاعدة ولو كان أكبر من 5 (LogP ≤ 5) بالتالي ما بيكون بيكون ذائب كثير بالـ (Organic Phase) ذائب وما بيصير (absorption)

Hydrogen bonding and permeation

- In hydrogen bonds oxygen and nitrogen atoms on the drug serve as hydrogen bond acceptors, while the OH, NH, and FH groups act as hydrogen bond donors.

* عشان يصير Solubility للمركب بالماء لازم المركب يكسر intracellular hydrogen Bond الداخلية



- hydrogen bonding in a drug contributes significantly to its physicochemical properties. For a drug dissolved in water, intermolecular hydrogen bonds with each other are virtually non-existent between drug molecules themselves, which are surrounded by water molecules. To form a hydrogen bond between a donor and an acceptor, both must first break their hydrogen bonds with surrounding water molecules.

Bond يعمل غير كامل مع الماء وهاي عملية مش سهلة وبدها طاقة كبيرة خصوصاً لو كان المركب hydrated form

- Because most oral drugs are absorbed by transcellular absorption (permeation), neutral molecules are favoured over solvated molecules. However, desolvation and formation of a bare molecule is not favoured thermodynamically if the compound forms many hydrogen and/or ionic bonds with water. As a consequence, drugs with too many hydrogen bond donors and/or acceptors experience difficulty getting from the gut into the blood

hydrated (hydrogen-bond) عنده أكثر من الـ Anhydrous أكثر في الـ Solubility الهيك الـ Anhydrous

Transcellular absorption حتى يصير لازم الـ molecule يكون neutral ولازم يصير له desolvation يعني مش محاط بأي شيء وهاد بده طاقة كبيرة لهيك المركب اللي عنده كثير hydrogen Bond

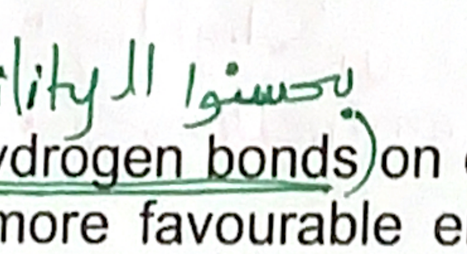
Intramolecular H-bonding and permeation

- (Intramolecular hydrogen bonds) on drugs are more readily formed in water since they are much more favourable entropically. Intramolecular hydrogen bonding frequently boosts cell membrane penetration.

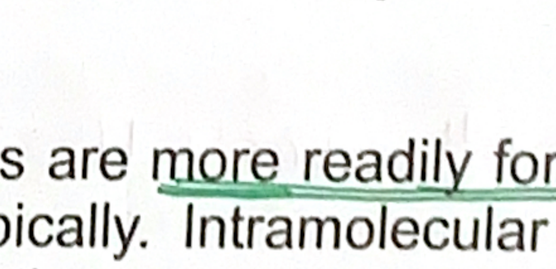
وبحسنوا الـ Solubility بالـ (water) وبحسنوا الـ Permeation لأنهم مرتبطة مع نفسها بالماء (water)

- It is hypothesized that formation of (intramolecular) hydrogen bonds in drug molecules **shields polarity**, thus offering improved membrane permeability and intestinal absorption. Statistically, the **chance that intramolecular hydrogen bonding improves biological activities is 50%**

فبتقلل عندي عدد الـ Hydrogen Bond فبصير أنها desolvation أسرع.



اربطوه مع بعض (NH-NH) كأنهم عاملوا Sheild (حماية) وفش مجال تعمل Bond مع الـ water فزاد الـ Permeability (الاختراق)



four-times more cell-permeable by virtue of the intramolecular hydrogen bond.

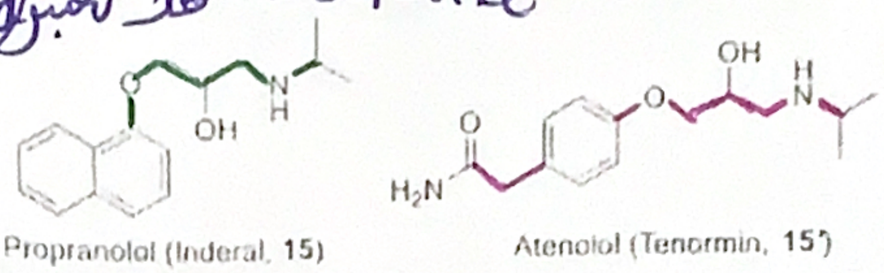
لما كانت الـ (N) اللي على الـ (aromatic ring) بموقع (Para) بعيدة ولما نقلنا الـ (N) على ortho position اربطوه مع بعض وزادت الـ Permeability by (3-4) times.

Polar Surface Area

- Polar surfacer area (PSA) is a simple measure of total hydrogen bonding capacity. It is defined as a sum of surface of polar atoms (usually oxygen and nitrogen atoms).
- Orally active drugs transported passively by the transcellular route should not exceed a PSA of 120 Å. For CNS drugs, their PSA values should not exceed 70 Å.

Rotatable Bonds

- A rotatable bond is defined as any single bond, not in a ring, bound to a nonterminal heavy (nonhydrogen) atom. Amide C-N bonds are not rotatable because of their high barrier to rotation, thus possessing a partial double bond character.
- The number of rotatable bonds influences both **bioavailability** and **binding potency**. Generally speaking, when all is equal or similar for two drugs, the one with **fewer rotatable bonds has higher absorption**.
- Example



Propranolol (Inderal, 15) Atenolol (Tenormin, 15')

The rotatable bond count for propranolol is 6 and that of atenolol is 8 since the C-N bond does not count as one. The *absorption* for propranolol is 90% and that of atenolol is 50%.

- In general, two criteria for drugs to be orally bioavailable , either:
  - a polar surface area ≤140 Å and ≤10 rotatable bonds or
  - ≤12 HBDs and acceptors in total and ≤10 rotatable bonds
- Some researchers set the limit of rotatable bonds to ≤7 as analysis shows a marked improvement in oral bioavailability for such molecules.

Improvement of solubility: medicinal point of view

- For a drug to be absorbed, it has to be dissolved first. Not surprisingly, aqueous solubility is a key factor to influence a drug's bioavailability. A superb review by Walker on improving solubility via structural modification was published in 2015.

- Tactics to improve a compound's solubility include: (4) classes of Drugs

سو ممكن نعمل حتى نحسن Solubility

1- Attaching a basic side-chain
2- Disruption of aromaticity
3- Disrupting hydrogen bonding
4- Certain subtle changes.

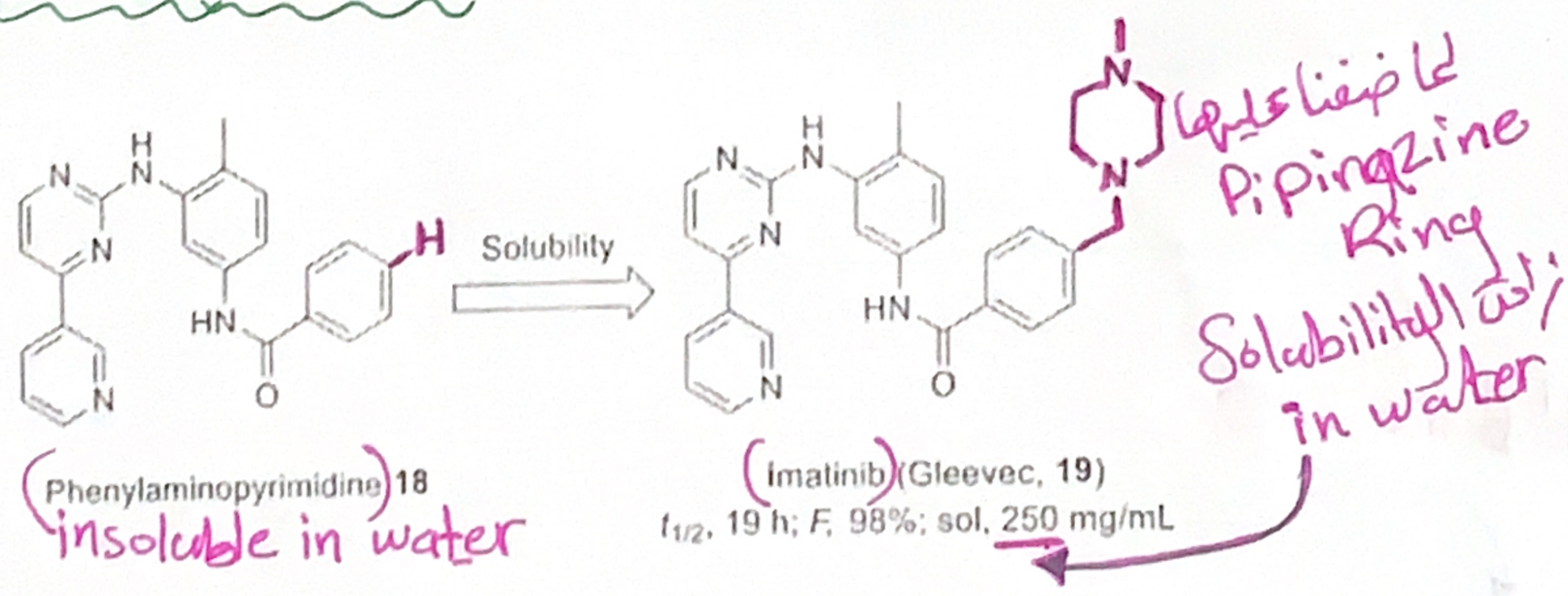
Class I High solubility High permeability	Class II Low solubility High permeability
Class III High solubility Low permeability	**Class IV** Low solubility Low permeability

FDA's Biopharmaceutical Classification System (BCS)

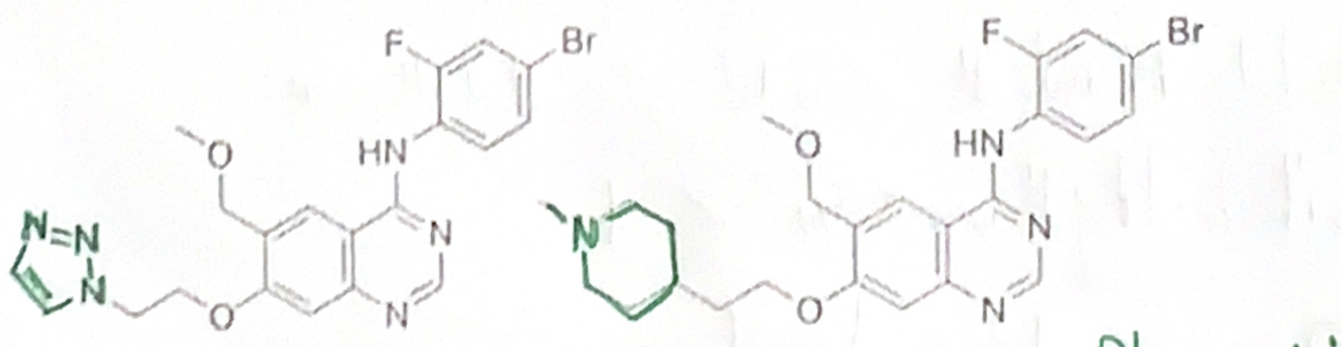
Attaching a basic side-chain

Examples:

- Piperazine Ring

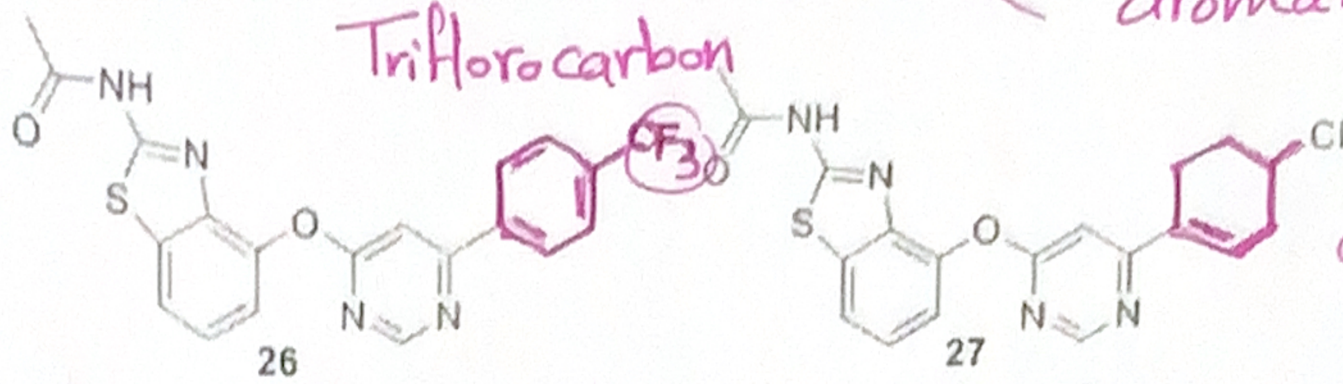


- Piperidine Ring



Disruption of Aromaticity

(distribution - of aromaticity) ← لهيك صار



Trifloro carbon

2 double bond لهيك

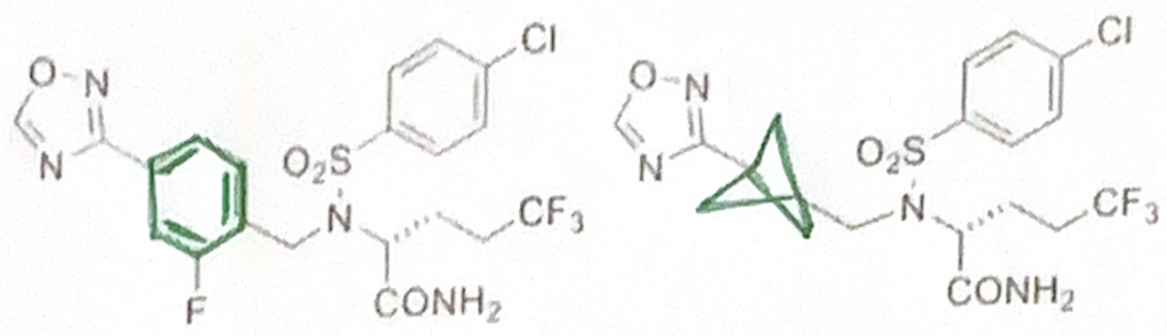
Solubility ↓ نزلت

26

solubility (0.01 M HCl) <1 μg/mL

27

13 μg/mL



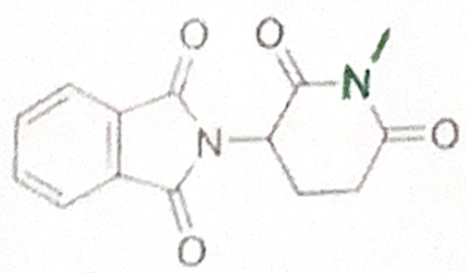
sol pH 7.4 = 0.9 μM

sol pH 7.4 = 29.4 μM

هون غيرنا الحلقة كاملة وشلنا الـ F اللي ممكن يعطي H. Bond فزادت الـ Solubility

Disrupting Hydrogen Bonding

زادت الذائبية صفر (5) أضعاف



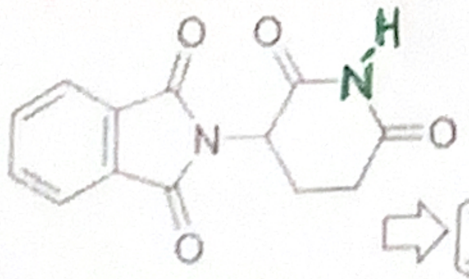
N-methyl-thalidomide (31)

sol at pH 6.5, 275.9 μg/L

Clog *P*, 1.19

mp, 159 °C

reduced crystallinity of the compound



thalidomide (30)

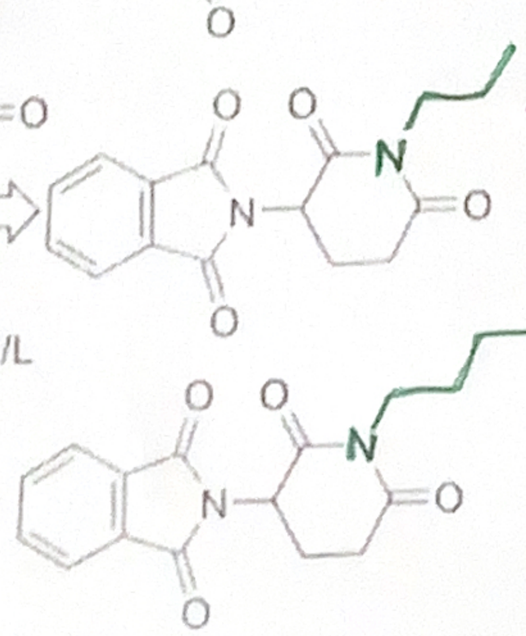
sol at pH 6.5, 52.1 μg/L

Clog *P*, 0.53

mp, 275 °C

Low solubility

highly crystalline partially because of the presence of a hydrogen bond donor on the imide ring



N-propyl-thalidomide (32)

sol at pH 6.5, 57.3 μg/L

Clog *P*, 2.24

mp, 136 °C

قلت الـ Solubility لأنه (LogP) ارتفع فقلت الذائبية سبب زيادة الـ liphphilicity

reduced crystallinity of the compound but increased lipophilicity

N-pentyl-thalidomide (33)

sol at pH 6.5, 6.5 μg/L

Clog *P*, 3.30

mp, 105 °C