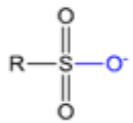
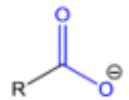
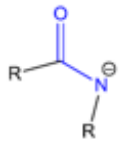
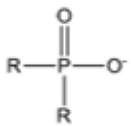
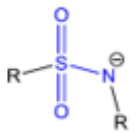
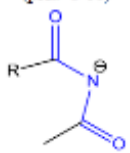
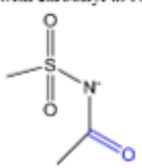
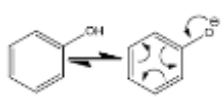
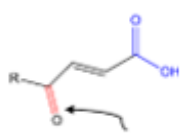
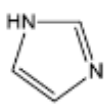
تفريغ ميديسينال

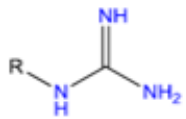
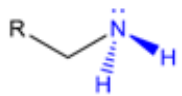
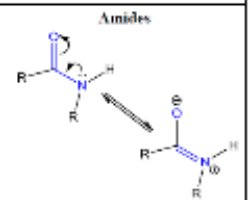
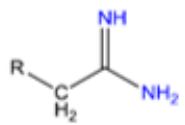
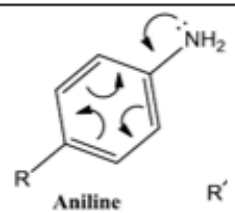
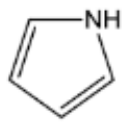
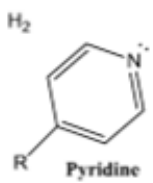
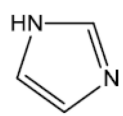
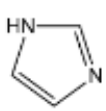
محاضرة: Lec 2

الصيدلاني\ة: Rahaf Zyoud

لجان الدُّفعات

Soul Academy

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 carbonyl at N) 		**Phenols** (pKa=17) 
Carboxylic acid (conjugated to EWD)  EW carbonyl		**Imidazole** 

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

خلينا نتذكر لكم شغله من الشابتر السابق.

الدوا عشان يصير له absorption لازم يكون ① unionize ② optimal hydrophilic hydrophobic

ال strong acid and base بيكونوا ionize بال GI

ال intermediet acid بيكون بالمعدة absorped in stomac اما ال intermediat base بيكونوا absorped

بال intestin

اما ال weak acid , وال weak base بيكونوا unionize

Hydrophilic/Hydrophobic Characters of the Drug

اعطى الدوا الدوا خصائص ليكون optimal hydrophilic hydrophobic

- 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:

الشروط

- a molecular weight less than 500;
- no more than 5 hydrogen bond donor (HBD) groups; (NH, FH, OH) → المركبات اللي تعطي ال H عددهم اقل من 5
- no more than 10 hydrogen bond acceptor groups; (N, F, O)
- a calculated **log *P*** value less than +5 (log *P* is a measure of a drug's hydrophobicity).

→ log P < 5
OR
10^5

→ قديه هذا المركب oilly

شو عمل Lipinski ؟؟

جاب الـ database للأدوية وشافوا الخصائص لكل الأدوية زي الـ

oral bioavailable وشافوا بناءً عليها كيف صار الدوا distribution و absorption

الشروط موجودة بالسلايد السابق • بس في شعلة حلوة لما

نحكي انه optimal log P يعني $\log P = 2$

$$\log P = 2 \text{ (لايزيد)} \quad \frac{\log [D]_{\text{octanol}} \times 10^5}{\log [D]_{\text{body fluid}} \times 1 \text{ (لايزيد)}}$$

لما احكي logP = 2 يعني انه فيه 100 molecule ذائب

بال octanol (cell membrane) مقابل 1 molecule ذائب بال

body fluid او ال GI fluid

anti log 2 = 100

هذا ال degree of hydrophobicity بيأثر على شغلات كثير منها ال (ADME)

وبأثر على Protein binding ال و Vd و clearance وال انزيمات وال Receptor وعلى drug solubility

اذا ماكان عنده degree of hydrophobicity مناسبه مثلا ما يذوب بال body fluid وهيك
ماح استفيد منه

* مابدي أكثر من 1 كما من الـ drug بال oilly phas و/ أكثر من 1 بال aquas phas

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

optimally = 2

P = Partition coefficient = $\frac{[D]_o}{[D]_w}$ → octanol → characteristic ال ال cell membran مشابه لـ

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

يعني مسموح انه الدوا يذوب بالزيت أكثر من ذوبانه بالماي بـ 10^5 مرة

و ما يعتبر مهم لأنه يصير Lipophilic و ما يذوب بالماي وما يصير Partition

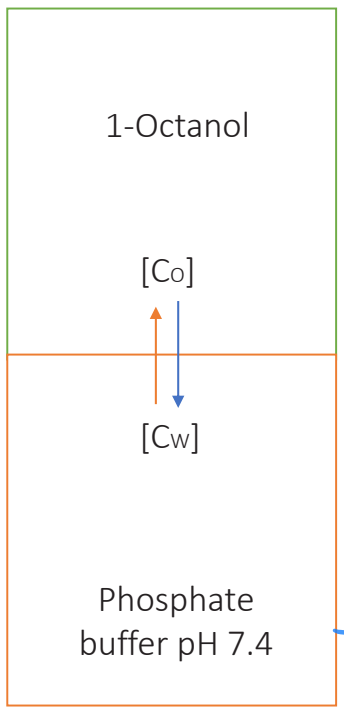
ال Partition co effecnt لا يتأثر بال PH

- 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.

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

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



قريب من pH الدم

لما احط الدوا بال separatory funnle بكون فيه octanol و phosphat buffer

Hydrophilic part بروح لل phosphat buffer و Hydrophobic لل octanol وهيك بحدد كم بدي يذوب بال body fluid وكم بال cell membran

ليش ينتهم بال coeffient Partitioning لانه معروف انه ال larger molecule الها log P

عالي (يعني ال ↑ Lipophilicty) بس اكتشفوا انه ال Potency لحتى يوصلوا ال

target عاليه يعني conc قليل من الدوا رح يعطي تأثير كبير فشو السبب؟!

اكتشفوا انه ال larg molecule الهم multipl functional ① groub وهذول ال groub بخلوا المركب يرتبط

مع ال target enzyme او ال target receptor ب non-specific type يعني مش ضروري بس ال target cell

بخلوهم يروحوا لأكثر من cell او enzyme بس ال bioavalibility الهم قليله لانهم

cant stablize بال GI او blood فال effect ناتج من ال non-specific type

لانه معظم ال biological receptor بكونوا fat فسهل يرتبطوا فيهم

2

وكمان للكلام عن ال Larg molecule بدها طاقة عالية ليذوبوا بال body fluid فعشان

الجسم تتجنب إستهلاك هاي الطاقة بدفع ال larg molecule ليصير الهم permeation بال cell

membran عشان هيك الهم potency ↑

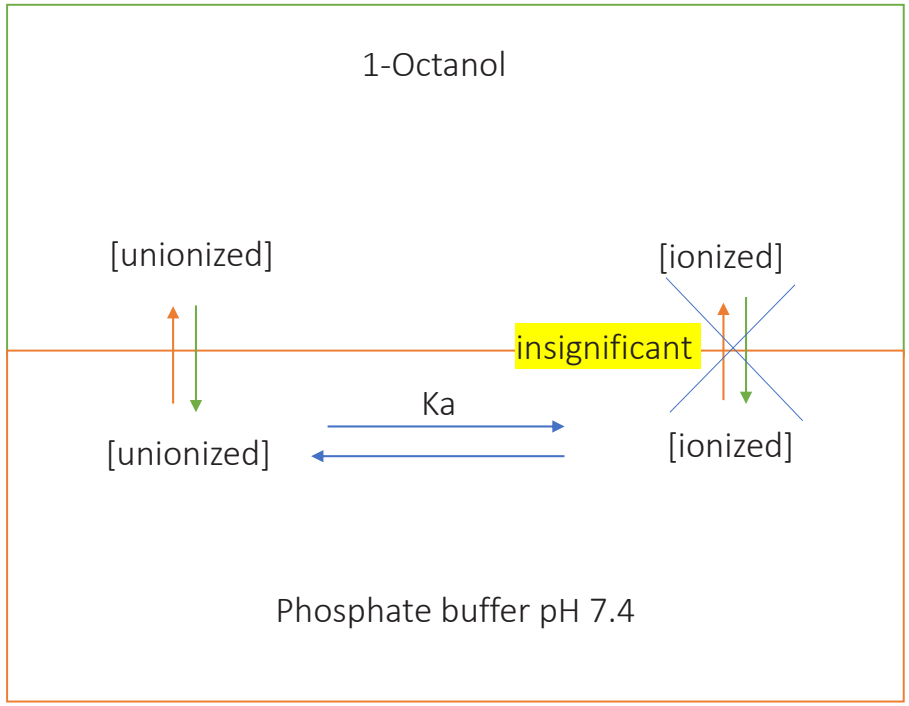
Effect of Log P

- 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.**



Distribution Coefficient (D)

بقيس ال Lipophilicty

وبقيس ال ionization بال body fluid

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

- For an acid:

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

$$D = [HA]_o / \{[HA]_w + [A^-]_w\}$$

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

- For a base:

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

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

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

Example

لما ال pH = 9.5 ال pH > pKa بمقدار أكبر من 3. اذا رح يكون 99.99% ionize و 0.001 unionize. اذا ما رح يصير اله absorption

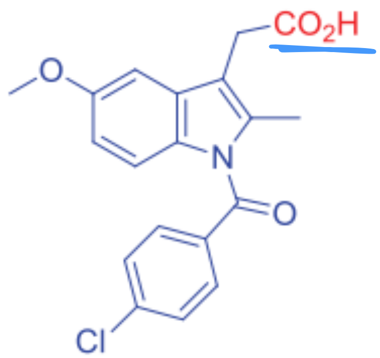
بما انه ال pH اقل من ال pKa بمقدار 2.5
وهو يعتبر acid intermediat اذا رح يكون تقريبا 99.9% unionize اذا logD = logp لانه كله unionize بالمعدة

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.

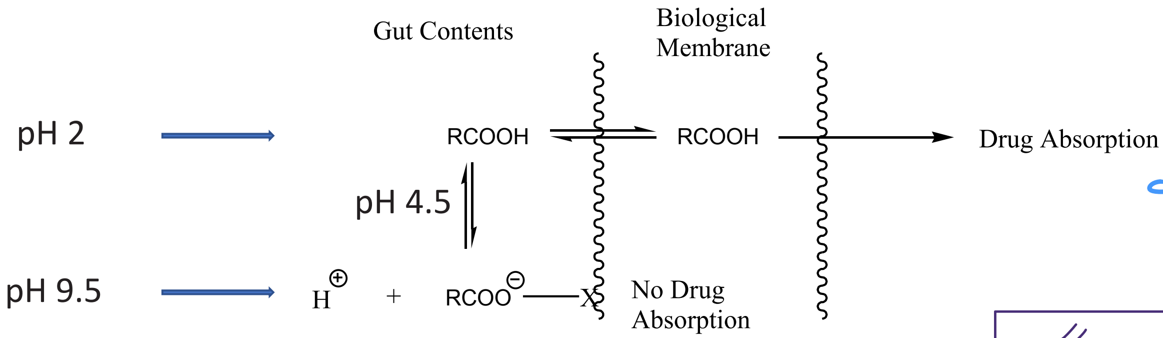
- At pH 4.5, 50% of the drug remains unionized and its log *D* is 3.95.

- 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.



indomethacin (Indocin, 1)

عند carboxlic acid يعني intermediat acid اذا ممكن يكون بأماكن ionize و بأماكن unionize حسب ال pH



اذا كانت ال pH = 4.5 ال pKa تقريبا تساوي ال pH اذا 50% unionize، رح ما احسبها على الآله الحاسبة logD = 3.95 لانه ما يتأثر ب pH

.اذا بنلاحظ انه معظم المركبات تحتوي على N ليش؟

الـ خاصية انه يكون مرة hydrophobic ومرة hydrophilic لما يكون بال ionize form تكون

hydrophobic تكون ionize form ولما يكون بال hydrophilic عشان هيك انا بضيفه للمركبات

لتحسين خصائصها. الـ N إلها pKa من 6-8 وبهيك الـ mostly absorbed

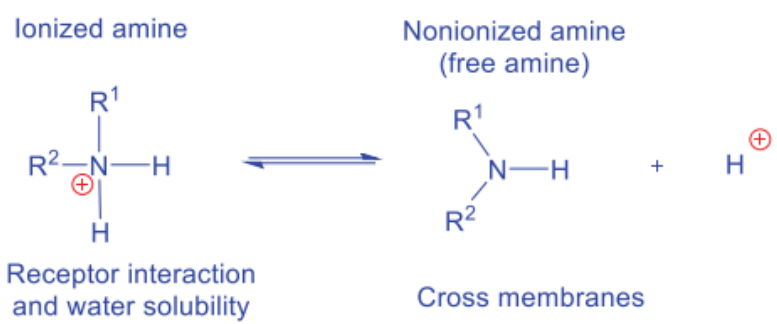
بال intestine عشان هيك بعطي good absorption و good permeation ، اذا تكون

optimal hydrophilic hydrophobic الـ N للذلك ال

Good to Relate with Previous Lecture

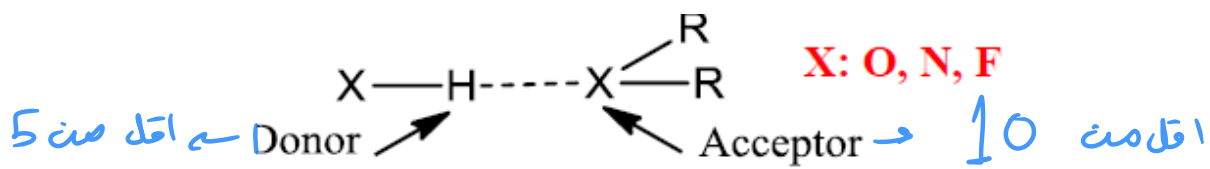
- Why the prevalence of nitrogen atoms in so many drugs?

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.



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.



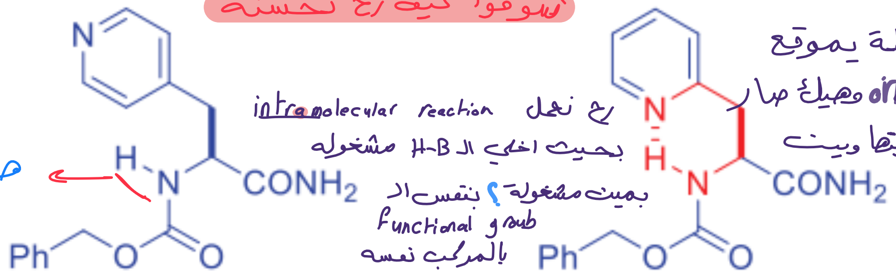
- hydrogen bonding in a drug contributes significantly to its physicochemical properties. For a drug dissolved in water, intermolecular hydrogen bonds with each other are virtually non-existent between drug molecules themselves, which are surrounded by water molecules. To form a hydrogen bond between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

بديل ال H-B بالمركب تكون مشغوله يعني مرتبطه ع اشي عشان ما تتفكك ويرتبط ال drug بال H_2O.

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.
- 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%**.

شوفوا كيف رح نحسنه



هون تفك ال H-B ورح يرتبط فيه water وصليك صار Less soluble ورح تمتع انه يصير اله Permeation

رح نعمل intramolecular reaction بحيث اخلي ال H-B مشغوله بصيت مشغولة؟ بنفس ال functional group بالمركب نفسه

حركنا ال ring ← ال N كانت مرتبطة بموقع Para واحنا خليناها ortho وصليك صار في H-B بين ال N الي حركتها وبين ال H وصليك رح تزيد ال solubility

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

→ لازم يكون بالمركب Limited number of H-B donor, H-B acceptor

Polar Surface Area → Polar atom ال surface يقيس

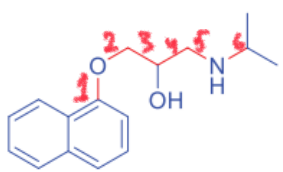
- Polar surfacer area (PSA) is a simple measure of total hydrogen bonding capacity. It is defined as a sum of surface of polar atoms (usually oxygen and nitrogen atoms).
- Orally active drugs transported passively by the transcellular route should not exceed a PSA of 120 Å. For CNS drugs, their PSA values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

Rotatable Bonds → singl bond يعني rotatable لما نشوف

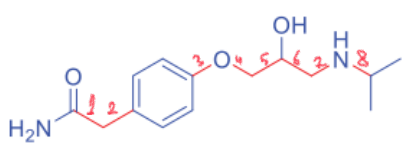
كل ما قل ال rotatable bond
راح يزيد ال absorption

- 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**)
6 rotatable bond



Atenolol (Tenormin, **15**)
8 rotatable bond

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%.

absorption صيني اله احسن
Propranolol يعني ال rotatable bond اي اله اقل

شروط الـ Rotatable bond

① Singl Bond

② ما يكون فيه aromatic ring وما يكون فيه ring من الأساس

③ الـ bond ما تكون مرتبطة بـ H

بس في exception الـ Amid

كم عدد الـ Rotatable bond

Atenolol (Tenormin 15)

لأنحسب بسبب الـ with drawing group

- 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.

احسن absorption لأ يكون

لكل السلايدات اللي قبل بتشرح عن permeability

هسا رح نبلش بال solubility

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:

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

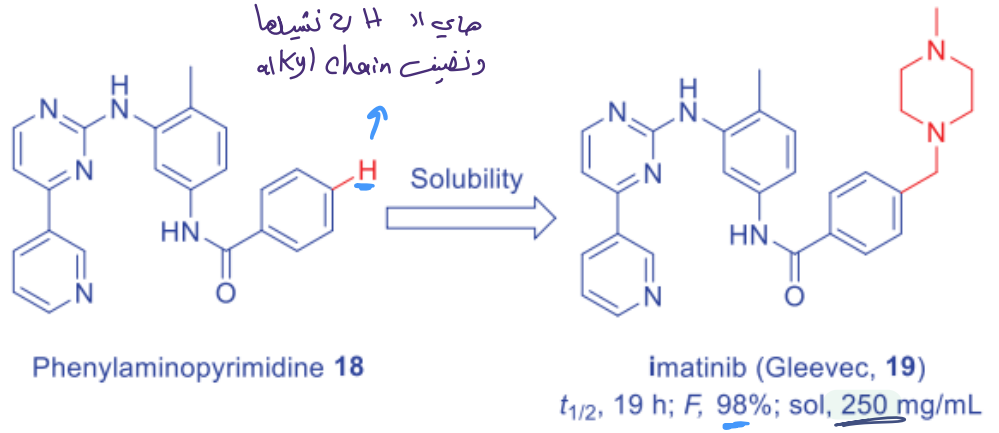
FDA's Biopharmaceutical Classification System (BCS)

Attaching a basic side-chain

Examples:

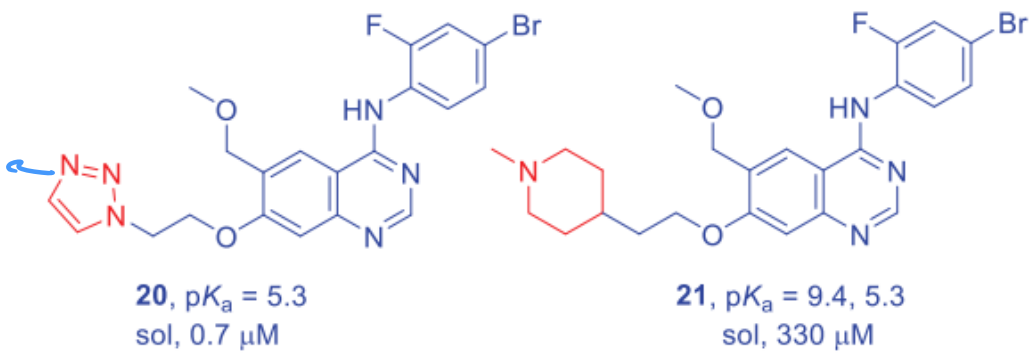
- Piperazine Ring

add alkyl chin



thridine Ring

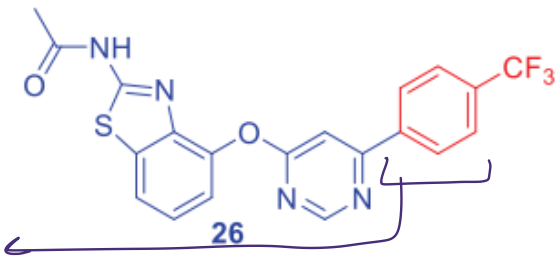
- Piperidine Ring



Replacment the Thridine Ring by Piperidine Ring

2. Disruption of Aromaticity

hydration like
two double bond



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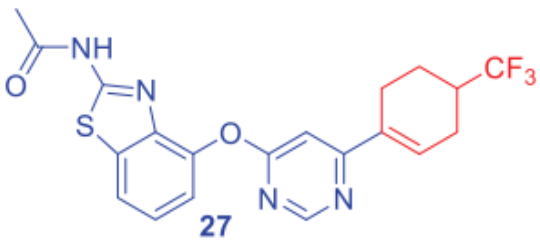
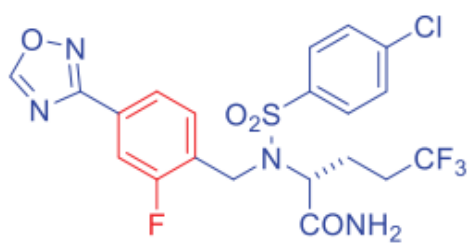
solubility (0.01 M HCl) <1 μg/mL

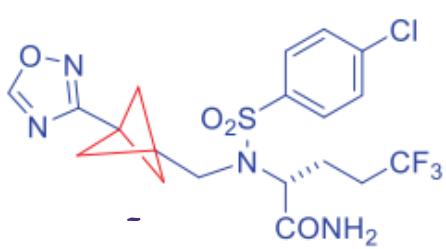


27

13 μg/mL



sol pH 7.4 = 0.9 μM

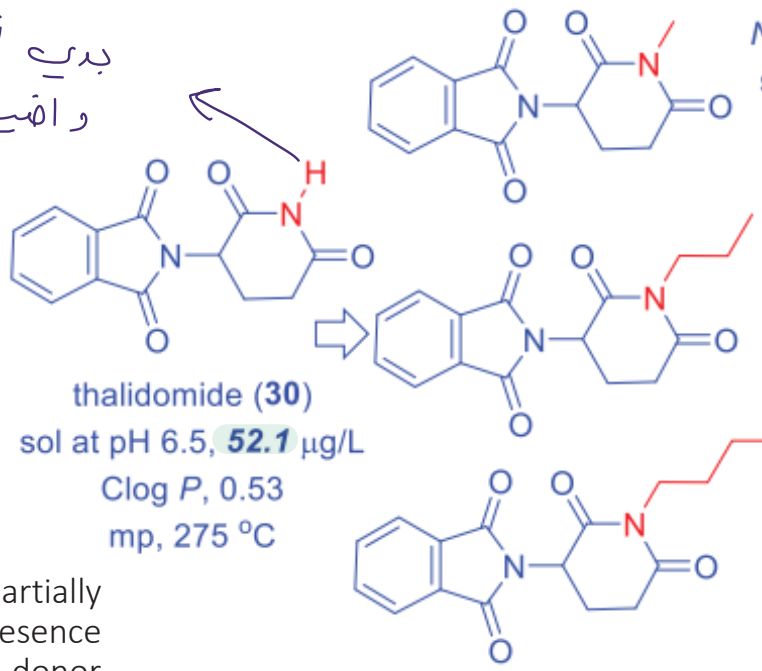


sol pH 7.4 = 29.4 μM

3-

Disrupting Hydrogen Bonding

بدي أشيل ال H-B
وأضيف ال alkyl group



thalidomide (**30**)
sol at pH 6.5, ***52.1*** µg/L
Clog *P*, 0.53
mp, 275 °C

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

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

N-propyl-thalidomide (**32**)
sol at pH 6.5, ***57.3*** µg/L
Clog *P*, 2.24
mp, 136 °C

⇒ زدت ال lipophilicity

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

⇒ زدت ال lipophilicity لدرجة صار لحبيب

لما بدي اضيف alkyl chain
لازم انتبه انها ما تكون كثير lipophilic

إن شاء الله هذا الشابتر يكون خفيف لطيف عليكم .

أتوقع كلكم سمعتوا بحملة عطاء صيدلية مهاي حملة

انطلقت من كلية الصيدلة بالجامعة الهاشمية لتوفير أبسط الإحتياجات

بهذا الشهر الكريم لناس همة بأمس الحاجة إلها

إلي بحب يبدي رأي صبلغ يتواصل معي