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:

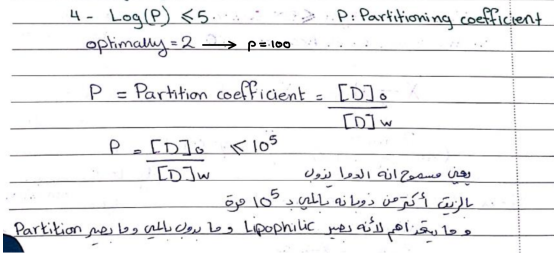
كل تفاعله ما بطابقها الدوا بعنسر ٣٥٪ من الـ bioavi.

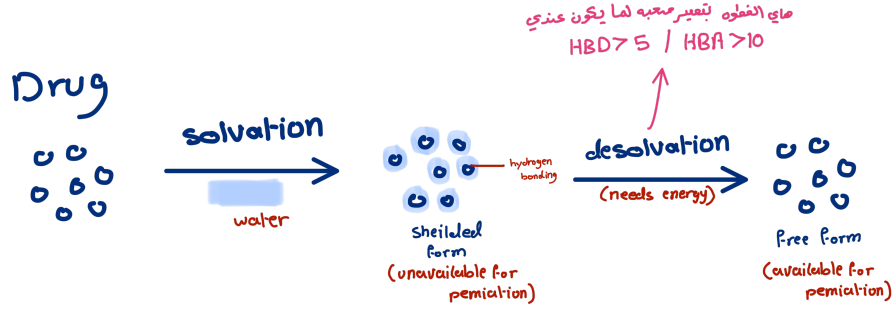
- a molecular weight less than 500; ① MW < 500
- no more than 5 hydrogen bond donor (HBD) groups; ② HBD < 5 (X–H)
- no more than 10 hydrogen bond acceptor groups; ③ HBA < 10 (X–R)

X: N, O, F

* Donner: عندو H وكهروسلبية
* Acceptor: lone-pair عندو
من هيدروجين مثلاً
من حلقة وأمن EWG

- a calculated **log *P*** value less than +5 (log *P* is a measure of a drug's hydrophobicity).





عشان أقرر هل الدوا بصيرلو good abs ولا لا :-

① بتطلع على الـ FG ← is it ionized / unionized

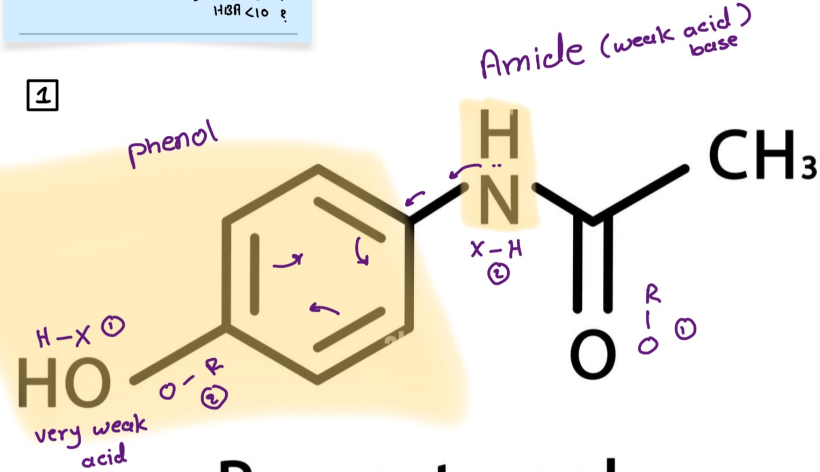
② 5 rules :

a) MW < 500 ؟

b) HBD < 5 ؟
HBA < 10 ؟

Examples:

1



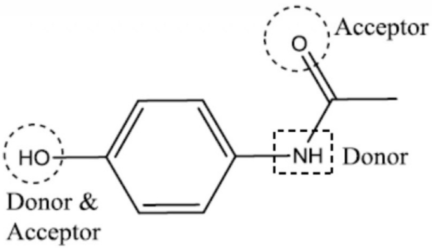
Paracetamol

① weak acids/bases → unionized in GI ✓

② M.w < 500 مبين صغير

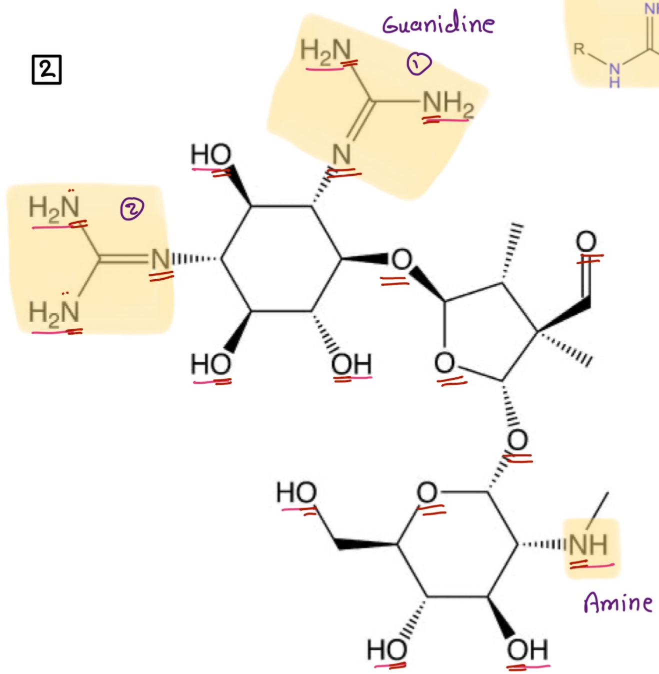
③ HBD = 2 : N–H / O–H < 5 ✓
HBA = 2 : O–R / O=R < 10 ✓

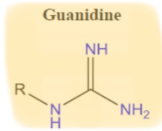
∴ good Abs in SI / IN



Paracetamol

2





STREPTOMYCIN

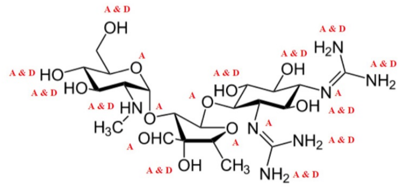
★ strong base → ST : ionized no Abs directly (40% by mucine)

★ MW > 500 → bio. A ↓ 30%

★ HBD = 12 > 5 ✗

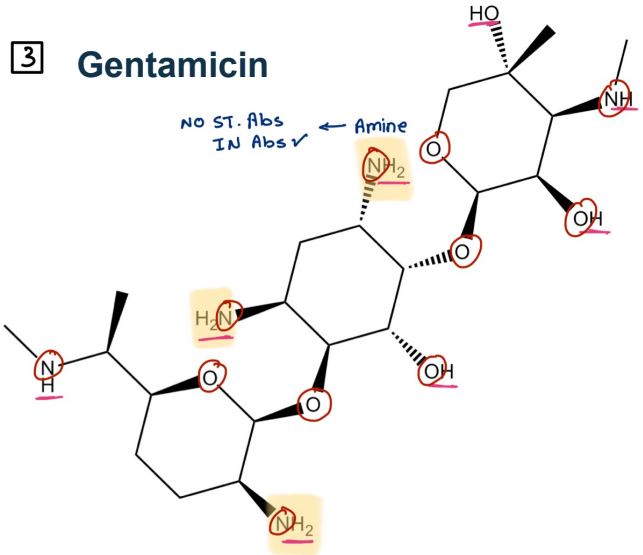
★ HBA = 18 > 10 ✗

∴ zero Abs → ROA : IV



Streptomycin

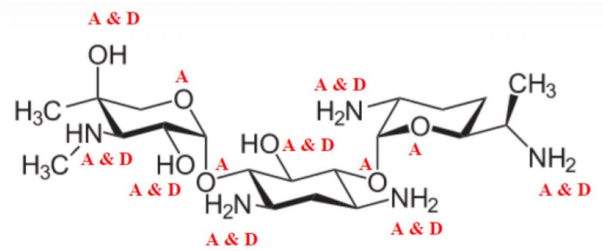
3 Gentamicin



★ MW < 500 صغير

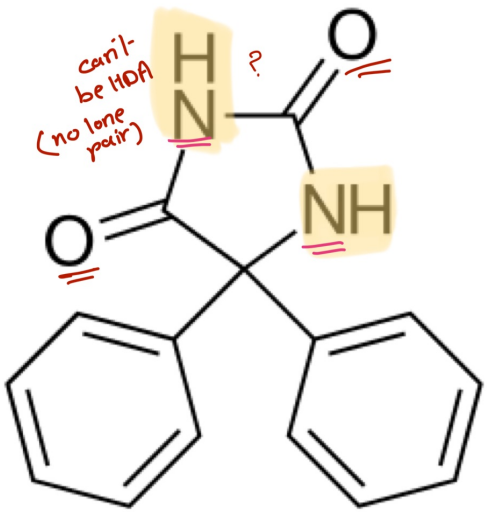
★ HBD = 8 > 5 ✗
HBA = 11 > 10 ✗

∴ orally unavai. ⟶ IV



4 phenytoin

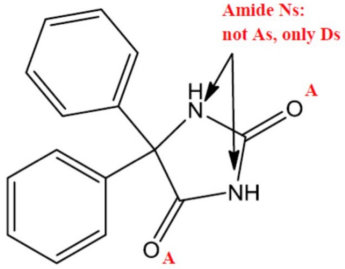
? Amide N-R
Imide R-N-R
] weak acids
bases
↓
unionized ✓



★ MW < 500 ✓

★ HBD = 2 < 5 ✓
HBA = 2 < 10 ✓

∴ 100% absorbed



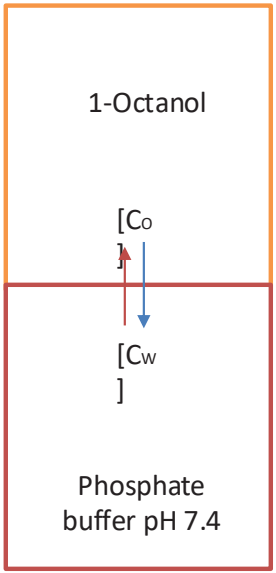
Phenytoin

- 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 (oilly) 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.

$$P = P_{o/w} = [C_o]/[C_w]$$

$$\text{Log } P = \log([C_o]/[C_w])$$



Log *P*

high

- ↑permiation
- ↑ potency
- bio. Ava in GI = Zero solubility

كيف دخ يتصرفو بالـ GI ؟ وسط كلومي :-

① بتجمعو على بعض — water molecules (order arrgment = low entropy = not favorable)

② cage-like strsure

③ unstable الوضع هاد

④ عندي هون receptors و enzymes ذات :
hydrophobic binding site

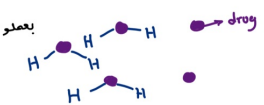
⑤ بعربو لهون بـ:
(non-specific forces)
بسميها
" hydrophobic effect "

side-effect بعمل non-specific binding الو مش اسي منيح

Low

- ↓permiation , no oral availability
- ↓potency
- ↑ solubility

بعملو H-bonding ذا بقين بالماء



water molecules not in order arrgment
(high entropy = favorable)

هاد الوضع stable بس الـ permiation صعب

هاد كان توضيح ليه لازم الدواء يكون نص نص لا hydrophilic عالآخر ولا hydrophobic عالآخر

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.

تزيد **محبة الدهون (lipophilicity)** من قدرة الدواء على الارتباط، لأنها تعمل **كقوة دافعة غير نوعية** تساعد على **انتقال الدواء إلى موقع الارتباط (binding site)**، وذلك عن طريق **رفع طاقته الحرة في الماء**.

بمعنى آخر: عندما يكون الدواء **محبًا للدهون أكثر** فإنه **يفضّل مغادرة الوسط المائي والدخول إلى الموقع الكاره للماء في البروتين**، مما يعزز عملية الارتباط.

log P ← لما نكون ضاعطين انو الدوا unionized مبه بالعبه

log D ← لما احتمال يصير ionization

Partition Coefficient and Distribution Coefficient

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

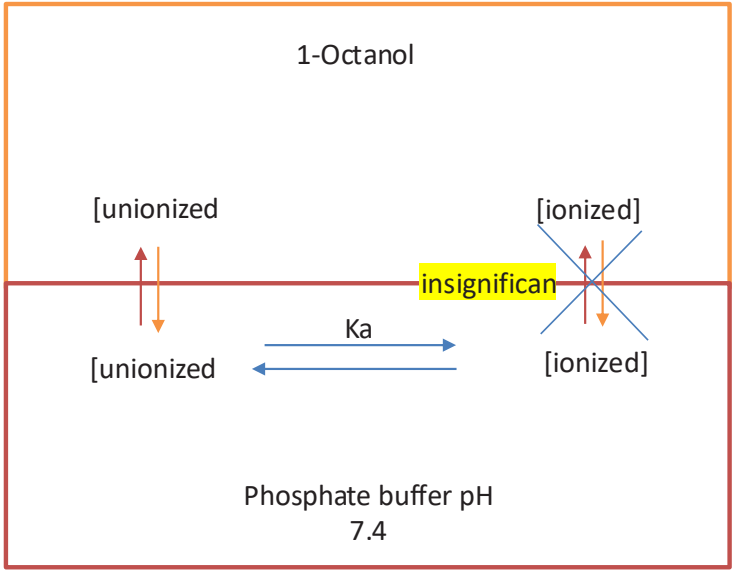
Only adequate in quantifying a drug's lipophilicity for ***neutral molecules.***

•مناسب فقط لقياس محبة الدهن (lipophilicity) للدواء عندما يكون الجزيء متعادلًا (غير متأين).

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

•غير مناسب للأحماض أو القواعد القابلة للتأين لأن تركيزها في الأوكتانول والماء يتغير اعتمادًا على درجة التأين.

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.**



في **Octanol-1**:

•تركيز الشكل **غير المتأين (unionized)** يكون هو الغالب.

•أما الشكل **المتأين (ionized)** فوجوده **ضئيل جدًا (insignificant)**.

لذلك بالنسبة **للأحماض والقواعد** يكون **معامل التوزيع D** أكثر ملاءمة لقياس **محبة الدهن عند pH معين**، لأنه يعتمد على عاملين:

1. **محبة الدهن للشكل غير المتأين من المركب.**
2. **درجة تأين المركب** عند ذلك الـ pH.

Distribution Coefficient (D)

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

- For an acid:

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

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

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

- For a base:

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

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

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

يختار حسب
pH الـ

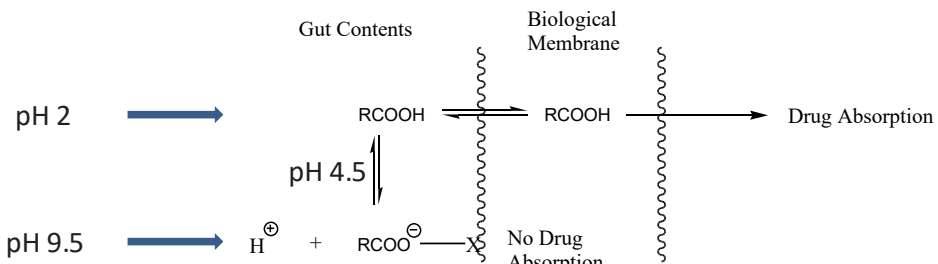
Example

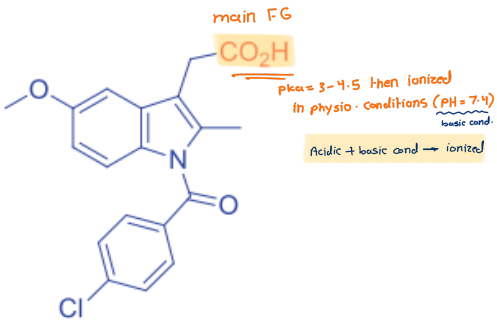
indomethacin has a p*K*a value of 4.5:

a - 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.

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

c - 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)

pka = 4.5
log P = 4.25
معطيات
Find log D when :-

a) pH = 2
pH = 2 very acidic + Drug acidic too
= unionized
∴ log P = log D = 4.25

b) pH = 4.5
$\log D = 4.25 - \log(1+10^{(4.5-4.5)}) = 4.25 - \log 2 = 3.95$

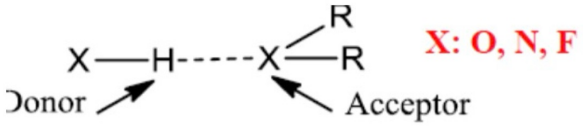
c) pH = 9.5 (basic)
$\log D = 4.25 - \log(1+10^{9.5-4.5}) = 4.25 - 5 = -0.75$
كتر حب للماء

خلاصة الفكرة

- **Neutral (unionized)** → عبور أسهل للغشاء → ارتباط أضعف بالماء.
- **Ionized** → عبور أصعب للغشاء → ارتباط قوي بالماء.

Hydrogen bonding and permeation

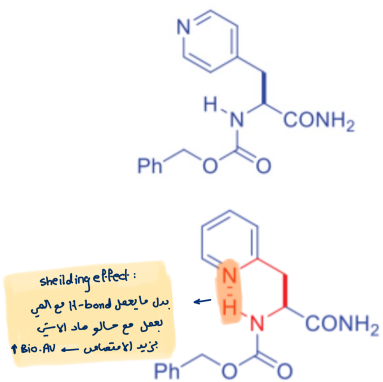
- In hydrogen bonds **oxygen and nitrogen** atoms on the drug serve as hydrogen bond acceptors, while the **OH, NH, and FH** groups act as hydrogen bond donors.



- 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.

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%**.



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

- **الروابط الهيدروجينية داخل الجزيء (Intramolecular hydrogen bonds)** في الأدوية تتكوّن بسهولة أكبر في الماء لأنها **مفضلة أكثر من ناحية الإنتروبيا (entropically favorable)**. وغالبًا ما يؤدي تكوّن هذه الروابط داخل الجزيء إلى **زيادة قدرة الدواء على اختراق غشاء الخلية**.
- يُفترض أن تكوّن **روابط هيدروجينية داخلية** داخل جزيئات الدواء يمكن أن **يُخفي أو يقلّل من قطبية الجزيء (shields polarity)**، وبالتالي يمنح **نفاذية أفضل عبر غشاء الخلية وامتصاصًا أفضل في الأمعاء**.
- إحصائيًا، احتمال أن يؤدي **تكوّن الروابط الهيدروجينية داخل الجزيء** إلى **تحسين النشاطات البيولوجية للدواء** يقارب 50%.

الفكرة الأساسية:
عندما تتكوّن رابطة هيدروجينية **داخل نفس الجزيء** بدل أن تتكوّن مع الماء، فإن المجموعات القطبية تصبح **"مخفية" جزئيًا** داخل الجزيء، فيبدو الجزيء **أقل قطبية بالنسبة للوسط**، مما يساعده على **عبور الغشاء الدهني للخلايا بسهولة أكبر**.

Lipinski's rule of five طريقه اخرى غير

A Polar Surface Area

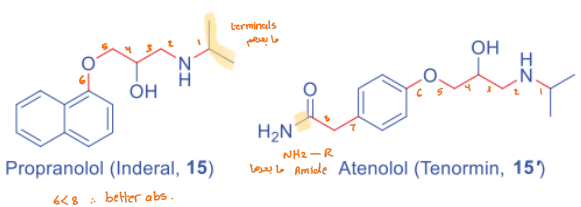
- Polar surfacer area (PSA) is a simple measure of total hydrogen bonding capacity. It is defined as a sum of surface of polar atoms (usually oxygen and nitrogen atoms).
- Orally active drugs transported passively by the transcellular route should not exceed a PSA of 120 Å. For CNS drugs, their PSA values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

B 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. C–N ⟶ C=N : bond = لانو معكي تتحول لـ *
- 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**.

Abs & No. rotatable bonds

- Example



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

<8 ∴ better abs.

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
a polar surface area ≤140 Å and ≤10 rotatable bonds or
B
≤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

لبعض الادوية الحكي حتى شرحا ينطبق على كل الادوية .

- 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.

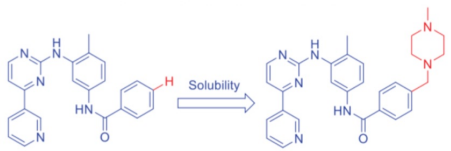
Non- polar

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

FDA's Biopharmaceutical Classification System (BCS)

Improvement of solubility

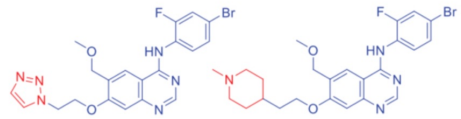
Attaching a basic side-chain



Phenylaminopyrimidine **18**

imatinib (Gleevec, **19**)
$t_{1/2}$, 19 h; *F*, 98%; sol, 250 mg/mL

Piperazine

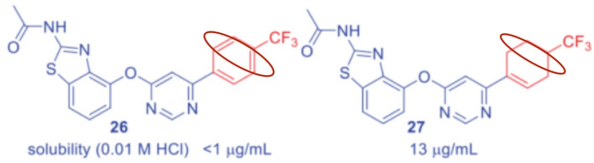


20, pK_a = 5.3
sol, 0.7 μM

21, pK_a = 9.4, 5.3
sol, 330 μM

Piperidine

Disruption of Aromaticity



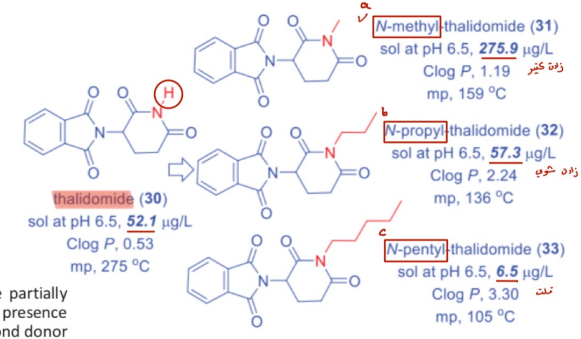
26
solubility (0.01 M HCl) <1 μg/mL

27
13 μg/mL

sol pH 7.4 = 0.9 μM

sol pH 7.4 = 29.4 μM

Disrupting Hydrogen Bonding



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

reduced crystallinity of the compound but increased lipophilicity

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-pentyl-thalidomide (**33**)
sol at pH 6.5, ***6.5*** μg/L
Clog *P*, 3.30
mp, 105 °C