(Chemotherapy)

AntiCancer

مادّة أنتجتها نباتات طبيعية بتقضي على الخلايا السرطانية .

Antibiotics

مادة أنتجها كائن حي بقضي على كائن حي آخر

* مثل البنسيلين .

Antibacterial

بتقضي على البكتيريا ، لكنها مُصنّعة مخبريًّا .

لأنه Antibiotics بعرفها أنتجها كائن حي وبتوقي على خلية حيّة .

موضوعنا

حكاية اكتشاف الـ (Sulfonamides):

Anti bacterial agent

- لمّا الناس كان يصير معهم حرارة ← كانوا يعطوهم (Asprin)

↵ NSAIDs ← بنزل الحرارة

قاعدين بوضع صبغة حمراء على الـ (Asprin) اسمها (prolasil) ، شفاءهم بكون أسرع.

لـ جربوا مخبريا خارج جسم الإنسان (in vitro) ما كانت تُجدي نفعًا.

فقط بجسم الإنسان (in vivo) بتكون فعّالة. IMPORTANT

في بكتيريا داخل الأمعاء اسمها (reductase) بتكسر الـ (Azo linkage) N=N بتنتج triamine

+ Sulfanilamide

هاد الـ active

ماكان فعّال بالـ (Vitro) يعني ماكان (prodrug) يتحول لـ (drug) ..

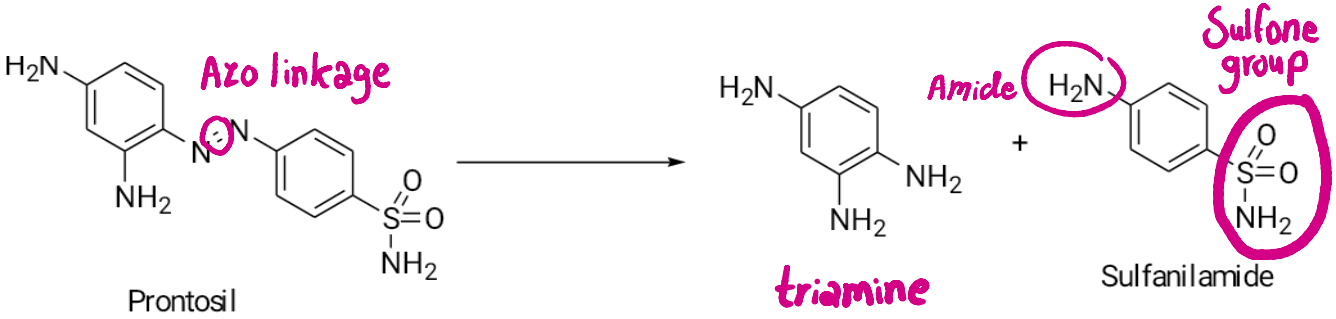
Sulfanilamide بتأثر على الـ (Metabolic pathway) موجودة داخل البكتيريا ، تعتبر آمنة وما إلها آثار جانبية .
(ومش موجودة بجسم الإنسان)

MOA : بتعمل تثبيط لإنزيم اسمه folate reductase اللي بحتاجه البكتيريا على عكس الإنسان .

Sulfonamides antibacterial agents

- In 1932. Domagk began to study a brilliant red dye called prontosil. This dye showed *in-vivo* antibacterial activity while it was *in-vitro* inactive (Pronsasil is inactive on bacterial culture).

- Later it was found that prontosil has to be activated by the in vivo metabolic pathways to give the active form.

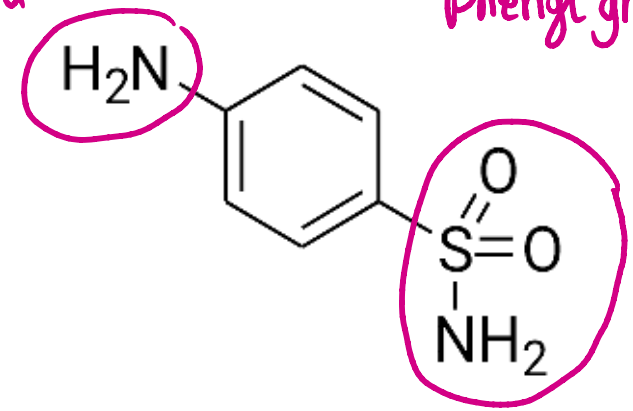


Nomenclature of Sulfonamides (Cont.)

- I. Antibacterials that are anilinesubsitiuited . Sulfonamides (the Sulfanilamides)

Sulfonamide لازم يكونوا para (para)

Phenyl group



Sulfanilamide

مرض مناعي_جهاز المناعة بهاجم الجهاز الهضمي. (Inflammatory bowel Syndrom)

مثل (Ulcerative Colitis) & (Crohn's disease)

المشكلة إنه الأدوية هو المكان اللي بتعبر فيه الـ (feces) والمكان المليء بالبكتيريا

بالتالي مع الإلتهاب رح يصير في تقرحات والتهابات جرثومية.

Sulfasalazine ← Anti-inflammatory, Antibacteria ← # يعني أنا بحاجة إلى نوعين من الدواء

Azo linkage

IMPORTANT

AminoSalicylic acid + Sulfonamides

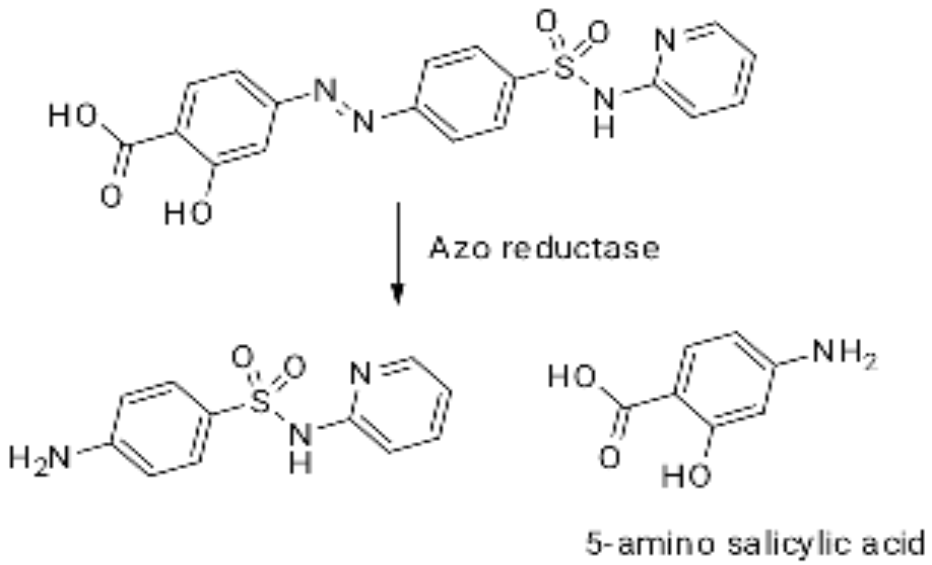
anti-inflammatory — Antibacteria

لمّا المريض اللي معاه الـ (IBS) ياخد هاد الدوا

البكتيريا رح تفرز إنزيم الـ (Azo reductase) ← بتكسر رابطة

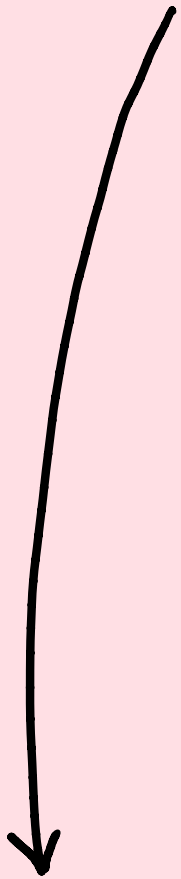
الـ Azo ويتحرروا المُركبين .

- II. Prodrugs that react to generate active Sulfanilamides (i.e Sulfasalazine)

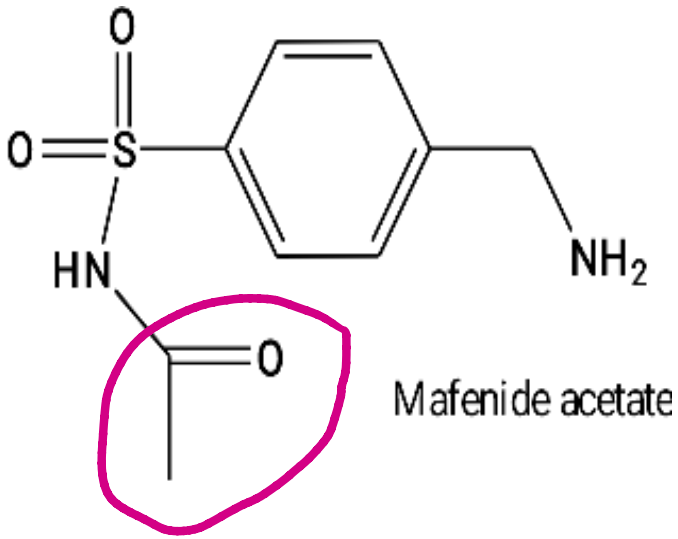


- عادةً الـ Amine مابصير بالـ (SAR) يكون عليها تفرعات مثل الـ Methyl

إلا بحالة وحدة فقط مثل ← Mafenide Acetate



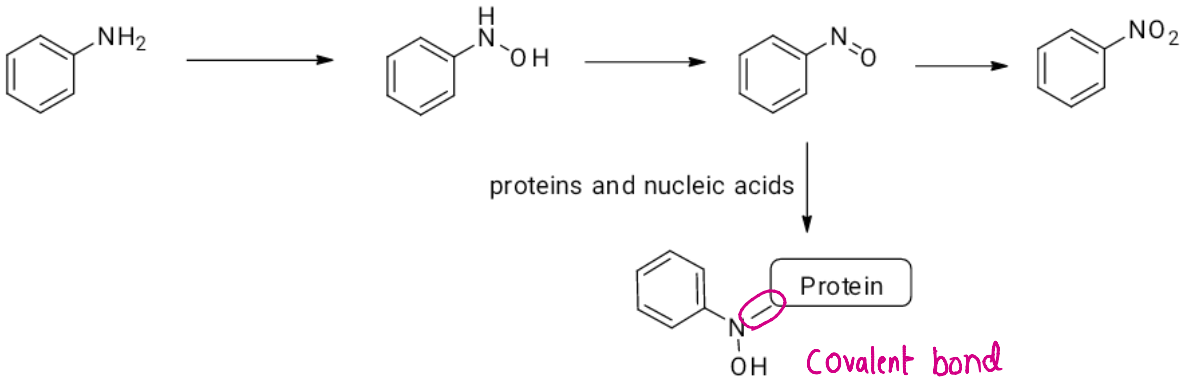
- III. Nonanaline sulfonamides (i.e., mafenide acetate)



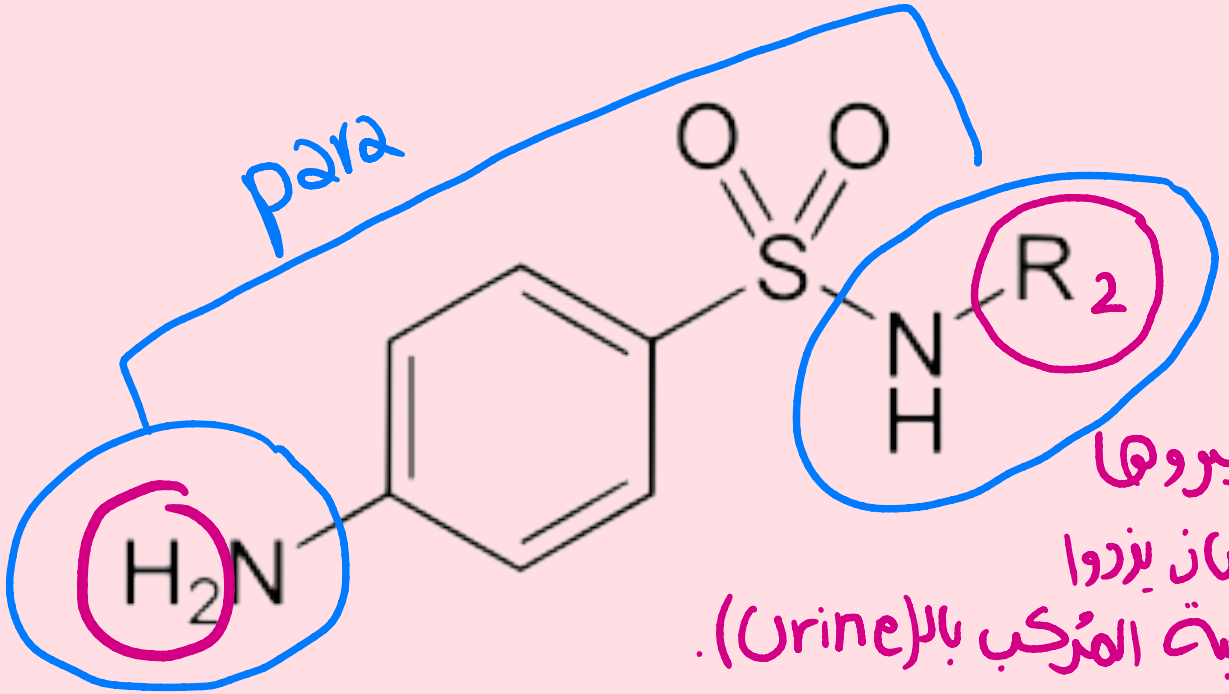
Mafenide acetate

Sulfonamides antibacterial agents

- Their bacterial activity is mainly on gram +ve and -ve bacteria
- limitation of the sulfa drugs use:
  - Sulfa allergic reactions.
  - # The formation of crystalluria.
  - They give toxic metabolites a er the oxidation of the aromatic amine:



remember
الأحماض ذائبتها قليلة بالوسط الحمضي ← تترسب



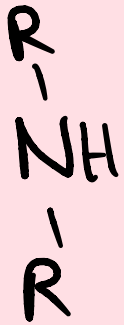
بغيروها
عشان يزدوا
ذائبية المركب بالـ(urine).
وتقلل مشكلة الكريستال.

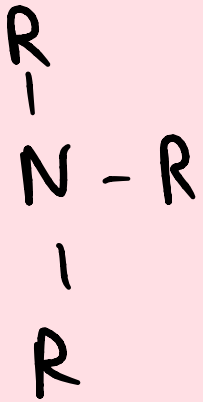
وحدة بس عادي تكون R
بالـ (H)

الـ N لازم تكون يا (pri) أو (sec) بس.

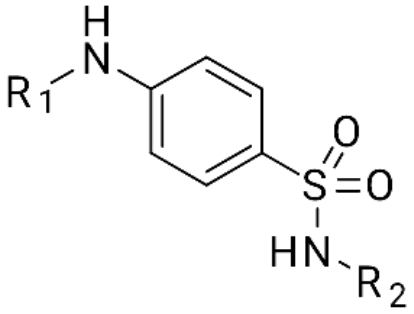
لازم يكون في H عشان تعمل (H-bond) بالـ binding pocket

* primary →  ✓

* Sec →  ✓

* tertiary →  ✗

SAR of sulfonamides



- *P*-amino group is essential for activity and should be free (unsubstituted)
  - The sulfonamide nitrogen must have an attached hydrogen with a pKa similar to that of PABA (~6.5).
- In the case of prodrugs the azo linkage that will be hydrolyzed to give the active free form.
- The aromatic ring and the sulfonamide group are important for activity.
- The sulfonamide and the amino group must be directly attached to the ring and in *P* position to each other.
- Any extra substitution will reduce activity
- sulfonamide nitrogen must be either primary or secondary

MOA : ال (folic acid) ← مهم لنمو الخلايا

مسؤول عن تحول ال (Uracil) لـ (Thymidine)

جزء من ال DNA

خلية الإنسان ← بتقدر تاخد ال folic acid من الأكل

خلية بكتيرية ← ما بتقدر تاخد ال folicacid من الأكل ، لازم تصنّعه.

في بداية الكمل بنعطوا دائمًا إنزيما تاخد (FA) ، عشان مايصير في نقص (شفت أرنبة)

تصنيعه بمرّ بمرحلتين ← para-aminobenzoic acid ← dihydropteroate synthetase

الإنزيم الأول في تصنيع الـ FA بالبكتيريا

إذا وقفنا هاد الإنزيم ← ماني ← tetrahydropteroate ← ماني ← Thymidine ← ما رح تنقسم

(bacteriaStatic)

IMPORTANT

bacteriostatic ← Sulfonamides لهيك الـ ★

penicillin مثل ← not bactericidal

Covalent مش (reversible) يعني

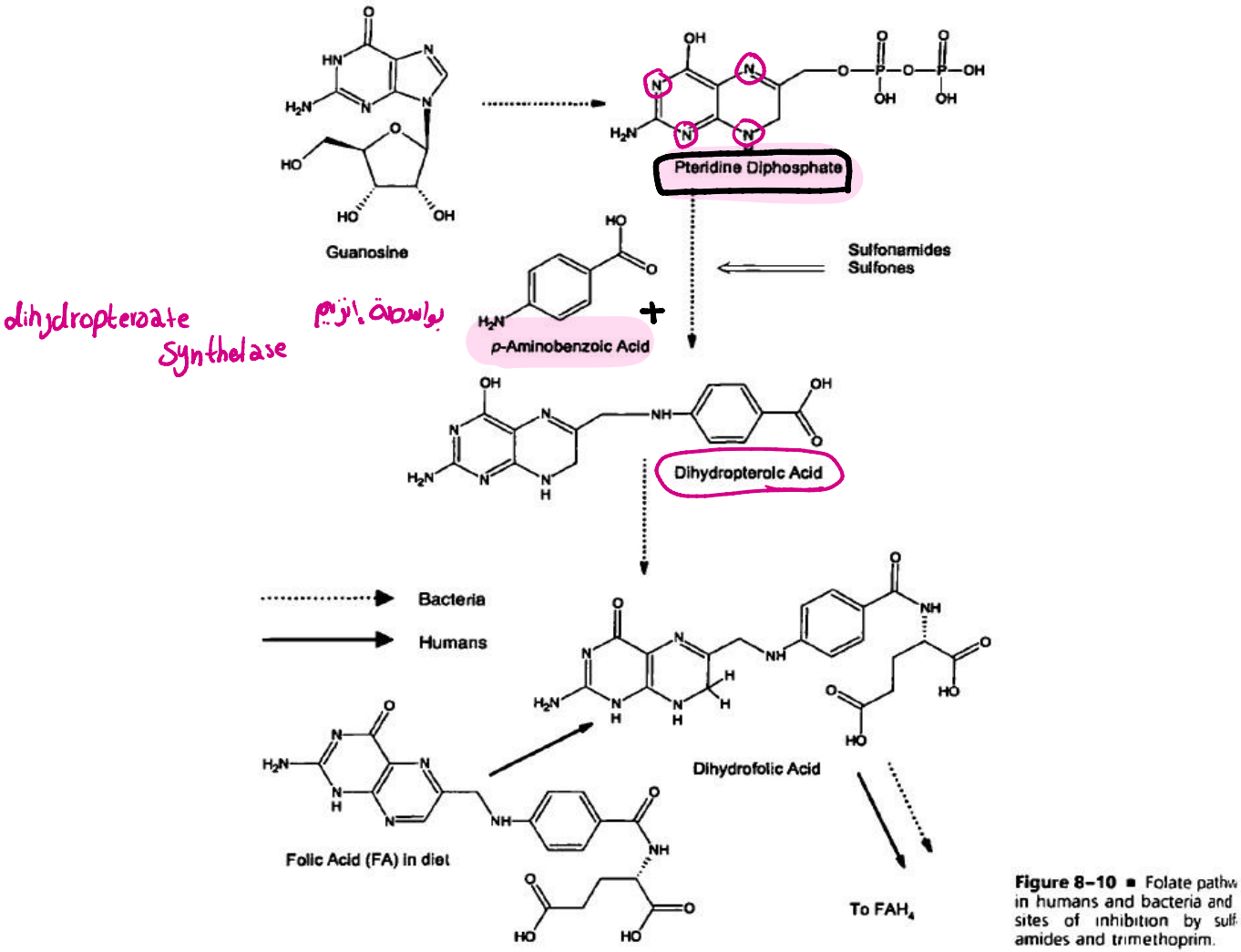
Mechanism of action

- Sulfonamides are a competitive reversible inhibitors of **dihydropteroate synthetase** which is a vital enzyme for the synthesis of tetrahydrofolate (Coenzyme F). Tetrahydrofolate is important for pyrimidine nucleic acid synthesis so the bacteria can no longer grow and divide which gives time for the host immune system to destroy the bacterial cells.

- Because of that sulfonamides have **bacteriostatic** effect not bactericidal so is not recommended in patients with weak or impaired immune system

Mechanism of actions

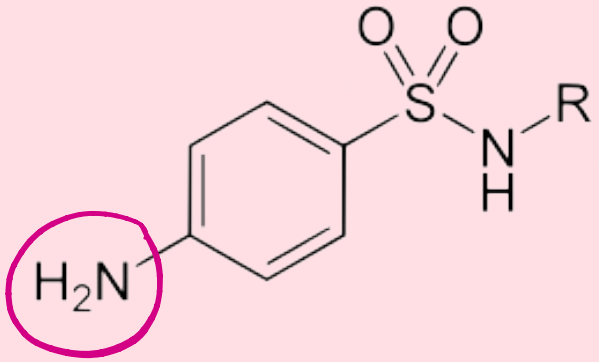
* خطوات تصنيع الـ tetrahydrofolate داخل البكتيريا



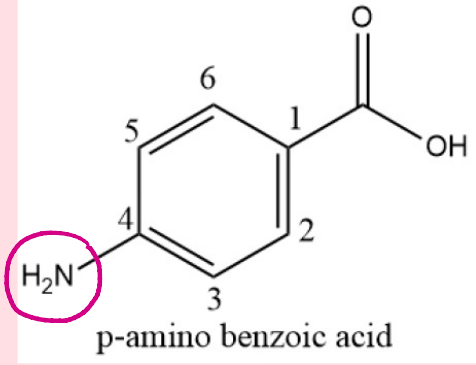
dihydropteroate Synthetase بواسطة انزيم

Figure 8–10 ■ Folate pathw in humans and bacteria and sites of inhibition by sulf amides and trimethoprim.

بشبهوا بعض كتير بال Structure



Sulfonamides



PABA

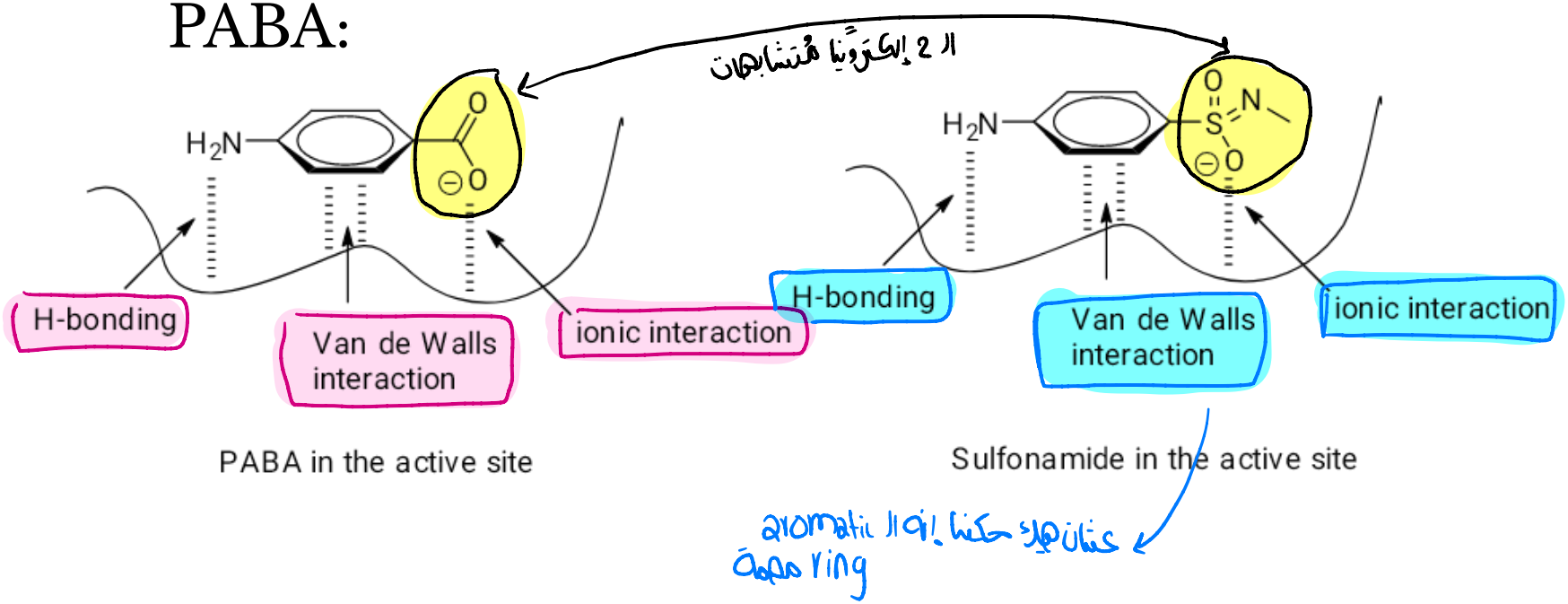
Sulfonamide زي بنافس مع PABA على سطح الإنزيم

* عشان كمبيك هو ← reversible Competitive inhibitor

* حسب مين الـ (Conc.) إله أعلى

Mechanism of action

- Sulfonamides mimic *P*-aminobenzoic acid (PABA) which is the normal substrate for dihydropteroate synthetase. This means that sulfonamide will bind in the same manner as PABA:



folic acid ⟶ tetrahydrofolic acid

هوالشكل النشط

+ $4H_2$ اختزال

reductase Enzyme

Sulfonamide ال بيعطوه مع مُركب (Trimethoprim) عشان أقلل من ال resistance

Trimethoprim ← inhibition dihydro-folate reductase

+Sulfonamide ← inhibition dihydro-pteroate Synthelase

Synergistic Effect

IMPORTANT

Mechanism of action

- Because sulfonamides are reversible competitive inhibitors for the enzyme, the bacteria can increase the production of PABA to compete with sulfonamide at the active site and become resistant to sulfa drugs.
- In such case, the dose of sulfonamide agents should be increased to overcome this resistant mechanism. But this high dose is accompanied with an increase in side effects especially the crystalluria.
- N4 acetylation reduces drug solubility, which may result in precipitation in the urine leading to crystalluria. Increasing the pH of urine with a systemic alkalizer along with increased water intake will decrease the risk of this potential adverse effect.

Mechanism of action

- In human, the cell synthesized tetrahydrofolate from folic acid that obtained from food sources. This folic acid is normally transported to inside the cell by special transport system.
- Bacterial cell does not have such transport system and they should synthesize tetrahydrofolate using PABA.
- For that reason, human cells do not need dihydropteroate synthetase enzyme which means sulfonamides have selective antibacterial activity.

Mammalian Folate biosynthesis

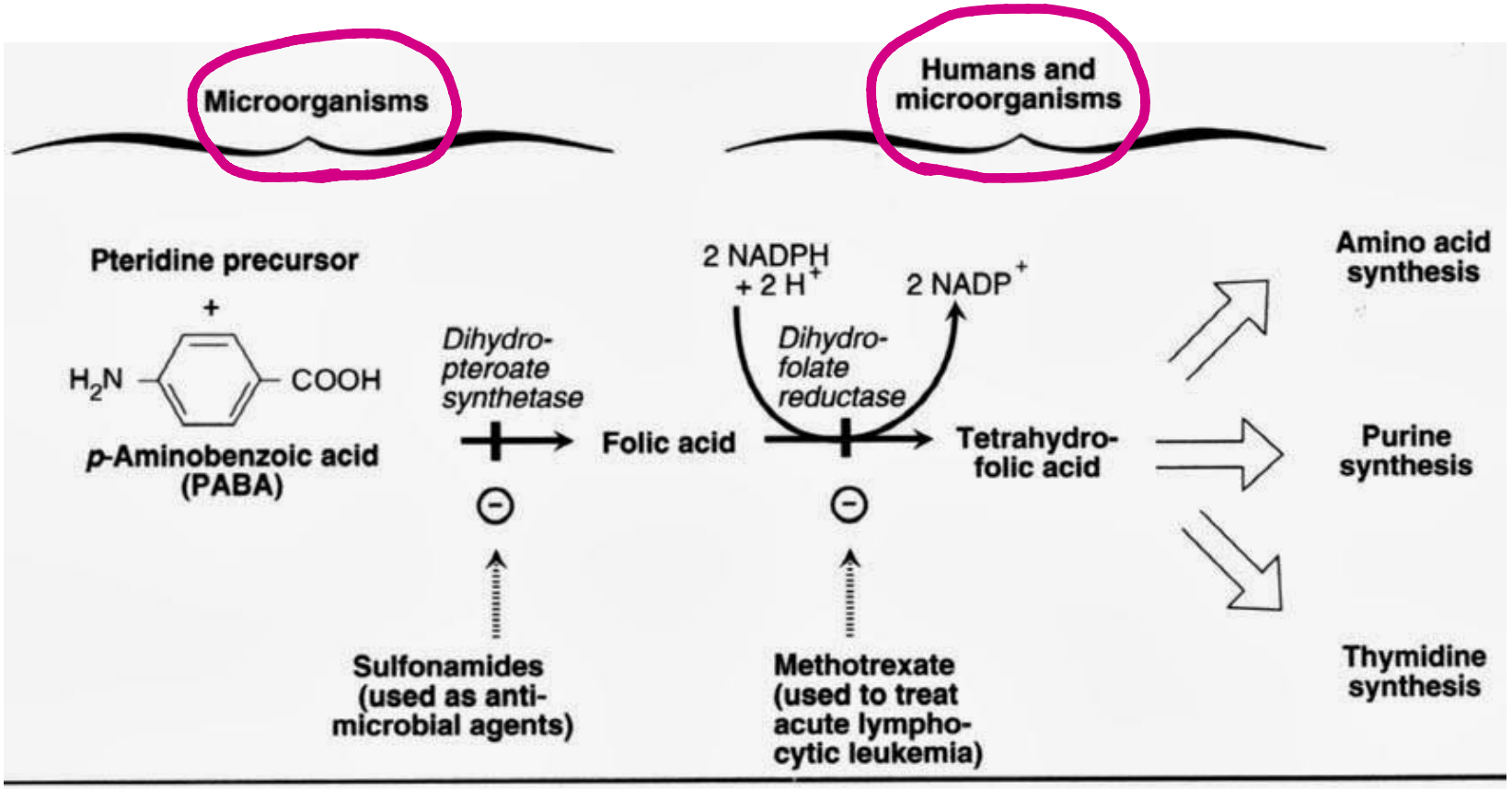
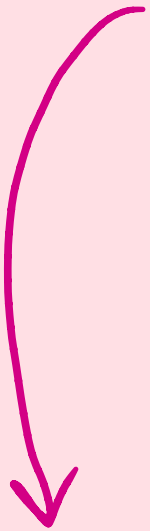


Figure 28.9
Inhibition of tetrahydrofolate synthesis by sulfonamides and methotrexate.

TAKE IT EASY

المحاضرة (2)



rev
مراجع

Sulfonamide → weak acid

لـ مادة قادرة على إعطاء $(H)^+$ بروتون

negative charge ← بتأين داخل جسم الإنسان

↓

ionic interaction

مصنوع أبدل الـ H بـ C لازم تضل موجودة

عشان يصير عندي ionization

حمض ضعيف بوسطا حتى راح تنرسب وما تذوب (ماحي تأين)

(reversabile reaction)

↓

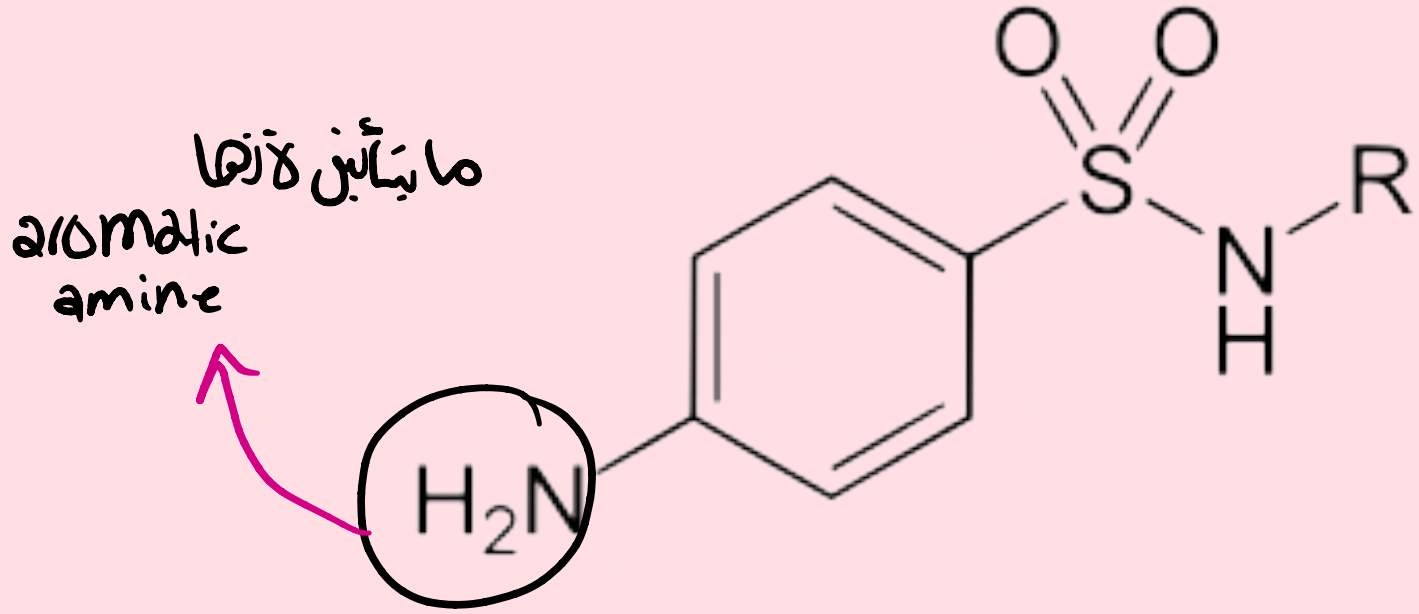
باتجاه ال unprotonated

بال (urine) يعلق ← Crystal urea

① اكل: (Keep hydrated)

② ممكن نحوّل الوسط لوسط قاعدي !!

* Na^{+2} bicarbonate
* K^{+} Citrate



ما بتأثير لأنها aromatic amine

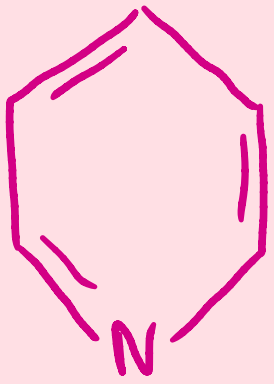
بالتأثير ↓ يفقد H أسرع

إذا كانت الرابطة أضعف ← حمض أقوى

الرابطة عبارة عن إلكترونين

إذا بدل الـ R electron with drawing group بحط

مثال



دوامة من الـ C سحب الروابط إلها وبتصير أضعف وفقدان الـ H أسهل لـ ionization أفضل

Strong acid

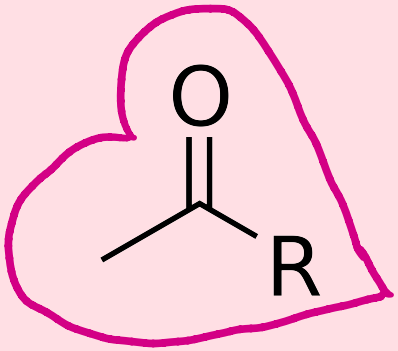
More water Soluble

ionization ↑

less Crystal ures

يعني الكل: Variation on R group

Phase two Metabolism



acyl group

↓

acylation on aromatic Ring

(aromatic amine)

↓

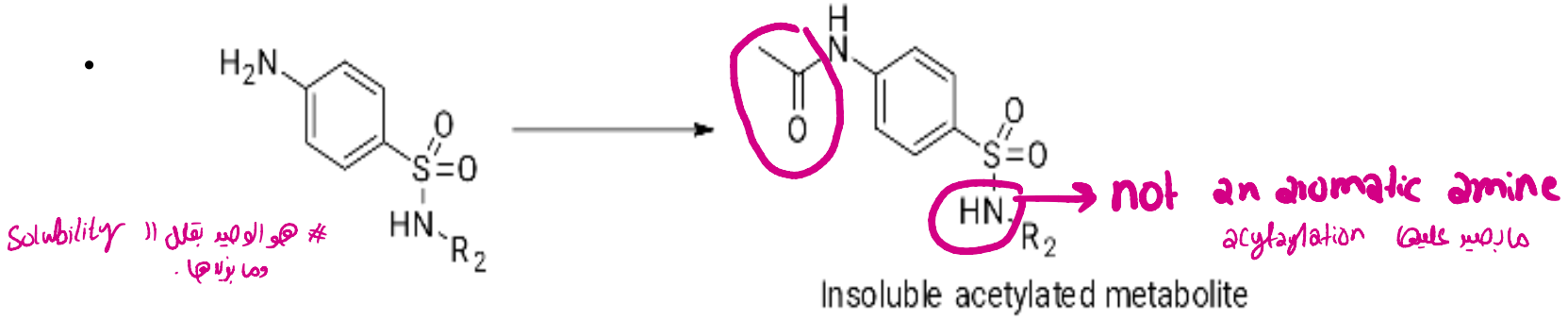
less Soluble

↓

Crystal urea بتزيد مشكلة الـ #

The problem of crystalluria

- Sulfonamides are mostly excreted in urine as acetylated metabolite.
- They are relatively water insoluble mainly due to the formation of the acetylated metabolites



- The acetylated metabolite is non-ionizable under the pH conditions of the urine (≈ 7) that increase the possibility of precipitation and the formation of crystals in the urine (crystalluria)

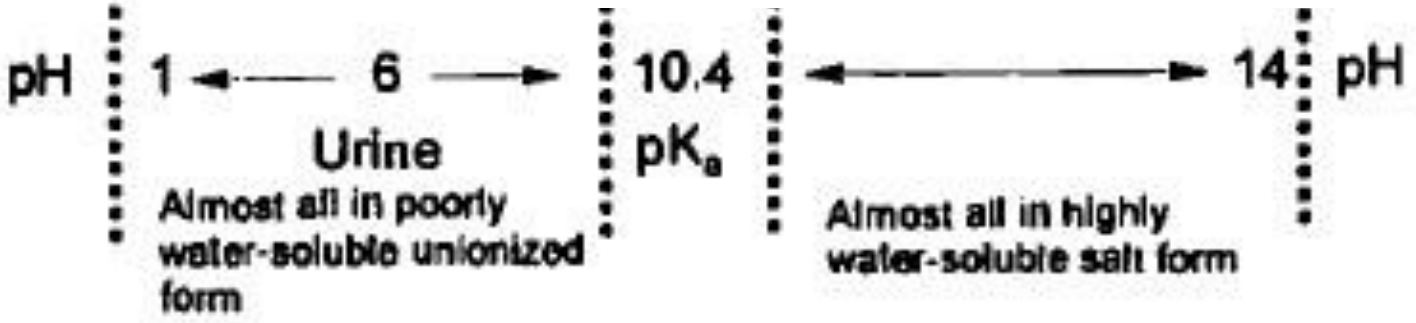
The problem of crystalluria

- How to minimize the possibility of crystalluria formation with sulfonamides:

- ✓ Increase the urine flow. → يشرب ماء أكتر
- ✓ Increase the pH of the urine to increase the ionization of sulfonamides and the formation of water soluble salts (this can be done by taking sodium bicarbonate or potassium citrate. → وسط قاعدي
- Lowering the pKa of the sulfonamide group which will help to increase the ionization under the acidic conditions. This can be done by adding electron withdrawing group on the sulfonamide side chain. → النزع بعد → Stronger acid

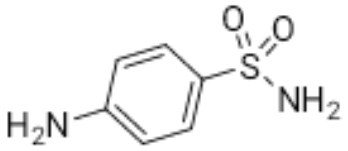
TABLE 8–8 pK_a Values for Clinically Useful Sulfonamides

Sulfonamide	pK_a
Sulfadiazine	6.5
Sulfamerazine	7.1
Sulfamethazine	7.4
Sulfisoxazole	5.0
Sulfamethoxazole	6.1



pKa → وصف لقوة الحمض ← ↑ pKa → قاعدي أكثر → حمض أضعف → قدرته على إعطاء H^+ أقل

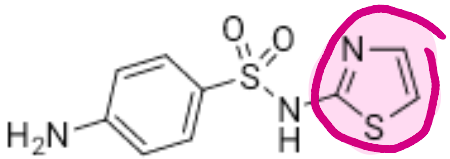
Sulfonamides with reduced crystalluria formation



Sulfanilamide pKa = 10.4

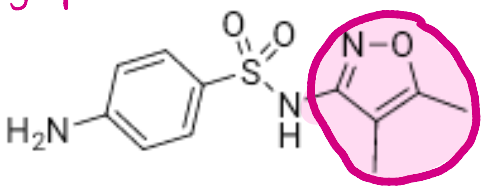
very weak acid

thiazine group

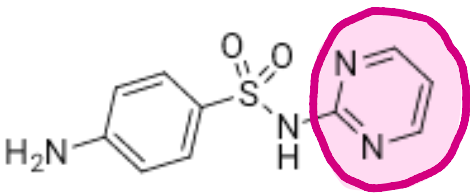


Sulfathiazole pKa = 8.5

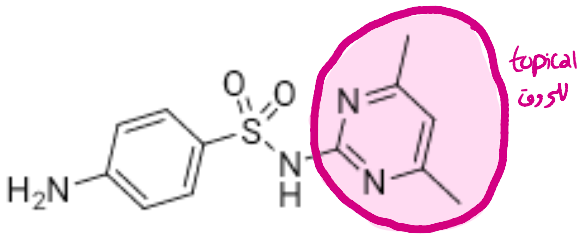
قدرته على إعطاء H^+ أكثر



Sulfisoxazole pKa = 5.0

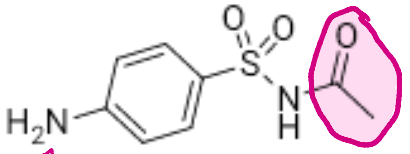


Sulfadiazine pKa = 6.5



topical للجروح

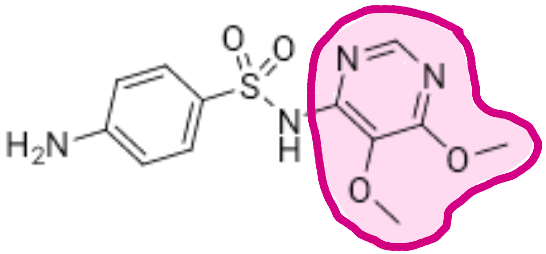
Sulfamethazine pKa = 7.4



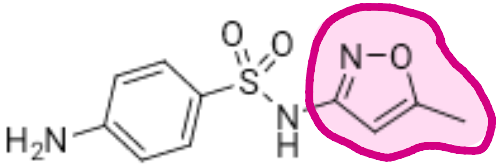
قطرة للعين لما التهاب

Sulfacetamide pKa = 5.4

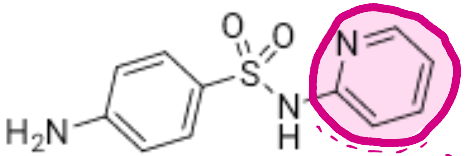
هون ← مش acyfel لأن جديد بتصير



Sulfadoxine pKa = 8.1



Sulfamethoxazole pKa = 6.1



Sulfapyridine pKa = 8.4

anti-inflammatory / antibacterial

prodrug

$$pH = pK_a + pK_b$$

toxoplazma parazide

تحوصل داخل رحم المرأة.

↓

* لعلاجها

Sulfadiazine with antiprotozoal.

(Clinical Application)

more

The drugs are effective against both gram-positive and gram-negative organisms, but bacterial resistance and newer more effective drugs have replaced the majority of the previously available sulfonamides.

Today, many of the sulfonamides have been discontinued, but some are still available and are primarily limited to treatment of susceptible gram-negative organisms.

resistance ← مقاومة

Products containing sulfonamides are shown in Table 23.1.

Sulfisoxazole, in the form of the prodrug N1-acetylsulfisoxazole, is used in combination with erythromycin ethylsuccinate (EES) and indicated for the treatment of **otitis media.**

prodrug

Cotrimoxazole

لـ علاج الالتهابات البولية

Crystal urea من يقلل

resestance sulfer يقلل

وكمية ال Sulfer بالجسم.

Static

Sulfamethoxazole in combination with trimethoprim (see below) is used to treat **uncomplicated urinary tract infections**, while sulfadiazine when combined with the antiprotozoal agent pyrimethamine is used to treat ***Toxoplasma gondii* infections.**

Silver sulfadiazine is used topically to treat burns, with both the sulfa drug and the silver ion having antibacterial activity.

Sodium sulfacetamide is a water-soluble preparation used to treat ophthalmic infections, while sulfasalazine is effective in the treatment of **ulcerative colitis.** It is only poorly absorbed from the GI tract where it is hydrolyzed by intestinal

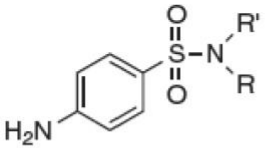
وسط قاعدي

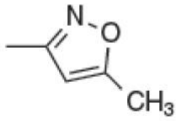
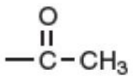
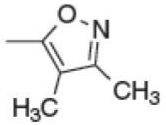
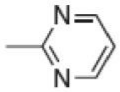
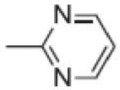
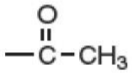
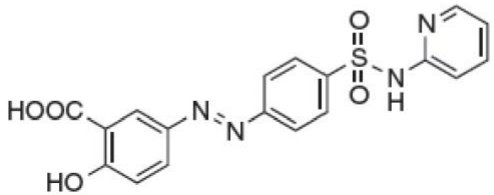
أدوية العين ← Completly water Soluble

ملخص

Clinically relevant sulfonamides

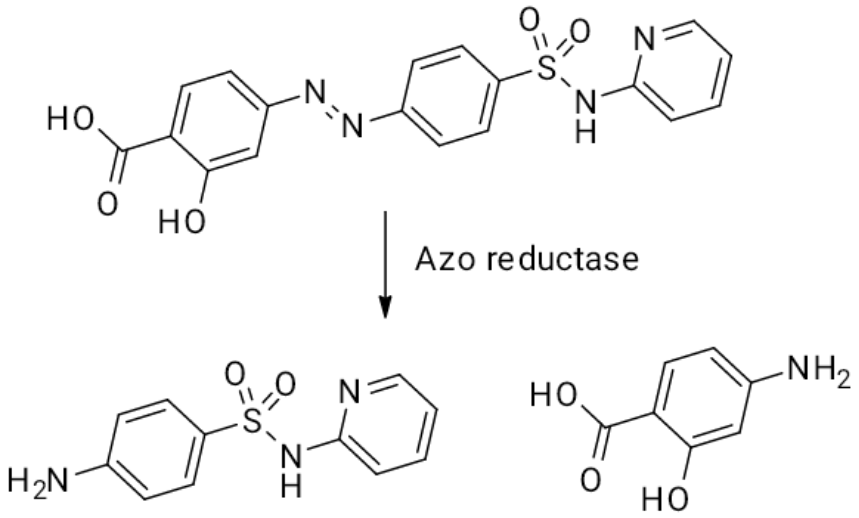
Clinically Relevant Sulfonamides



Drug: Generic Name	Product	R	R′	pKa
Sulfisoxazole acetyl (prodrug)	In combination with erythromycin ethylsuccinate			5.6 after hydrolysis
Sulfamethoxazole	In combination with trimethoprim		—H	5.0
Sulfadiazine	Oral dosage form		—H	6.52
Silver sulfadiazine	Topical dosage form			
Sulfacetamide sodium	Ophthalmic dosage form			5.4 free acid
Sulfasalazine	Gastrointestinal oral dosage form			

Sulfonamide prodrugs

- Sulfasalazine:
  - Used in local intestinal infections.
  - Gives sulfapyridine and 5-aminosalicylic acid upon the breakdown of the azo bond.
  - Used mainly in ulcerative colitis.



5-amino salicylic acid

folate reductase inhibitor
- Cancer
- RA
- Anti protozoal
- Anti-bacterial

منع تحويل "folic acid" إلى (tetrahydrofolic acid)

إنزيمات reductase عبارة عن protein ← تسلسل (amino acid)

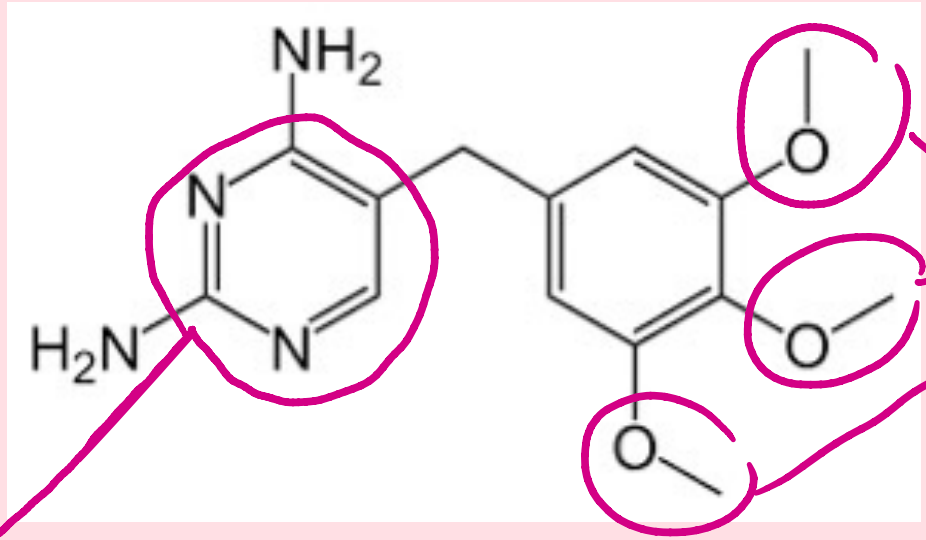
لـ مختلف عن الحيوان والإنسان و البكتيريا .

- * Homologous Enzyme
- * Homologous isomers

bacterial isomer ← عنده affinity كتير لـ Trimethoprim ← anti-bacterial

Human isomer ← عنده affinity كتير لـ Methotrexate ← anti-Cancer / anti-rheumatoid

parasite isomer ← عنده affinity كتير لـ Pyrimethamine ← anti parasitic agent



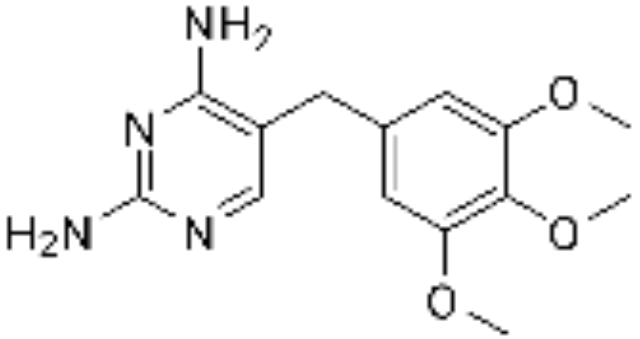
trimethoxy

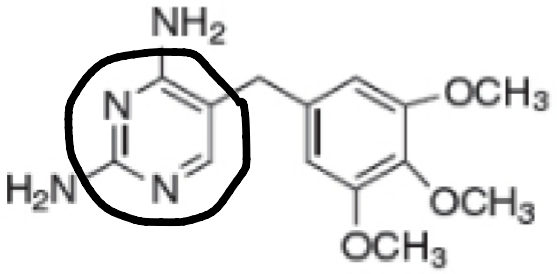
pyrimidines

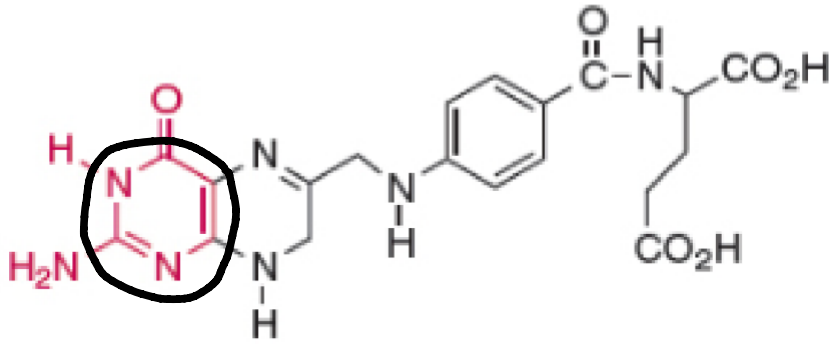
* يرتبط بال reductase ويمنع ارتباط ال Substrate الأصلي للإنزيم ← dihydrofolic acid

Other folate reductase inhibitors

- Trimethoprim:
  - Inhibits dihydrofolate reductase: this enzyme has human homologue but they do not have that much similarity in structure…. Therefore trimethoprim is 1000 more active on the bacterial copy of this enzyme..
  - Normally used in combination with sulfamethoxazole (cotrimoxazole):
    - Lower dose from both drugs means less side effects.
  - More effective than the monotherapy since they are targeting two different enzymes in the same metabolic pathway… this is what is called sequential blocking.





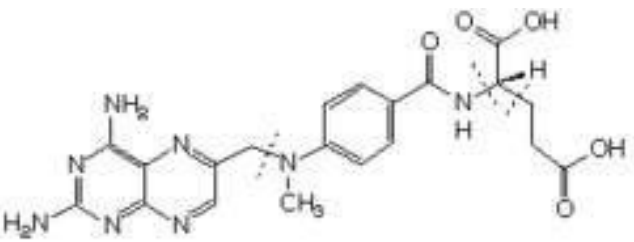


Trimethoprim (Proloprim, Trimpex)
Trimethoprim + ~~sulfisoxazole~~ (Co-Trimoxazole)
Trimethoprim + sulfamethoxazole (Bactrim, Septra)

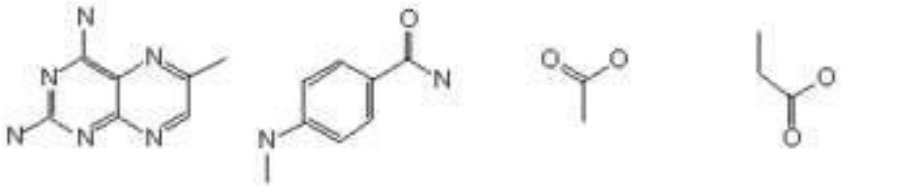
Dihydrofolic acid

SulfaMethoxazole

- There is another dihydrofolate reductase
- inhibitor –for Human enzymes (**Methotrexate**)
- which is used as anticancer drug .
- There is another one too, (**pyrimethamine**), as a malarial dihydrofolate reductase inhibitor



Methotrexate

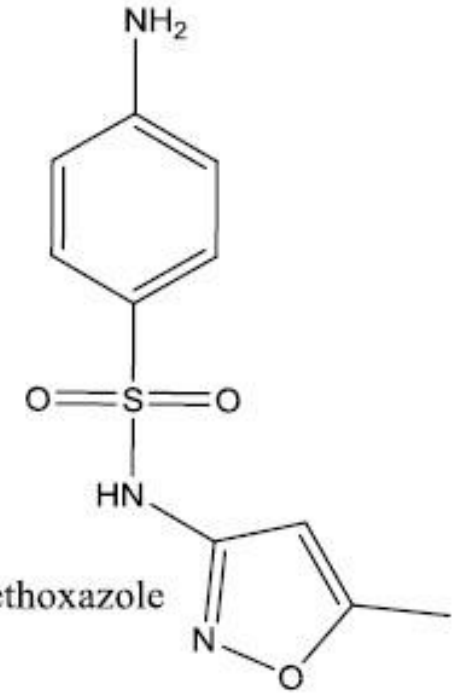


fragment1 fragment2 fragment3 fragment4

- Sulfonamide + Trimethoprim are :
- Septra®
- Balkatrin® .
- Another use of Sulfadrug is for Protozoa (eukaryotic cells) like Amoeba & Malaria, and the most important use is to treat **Pneumocystis carinii** (Pneumonia) in AIDS patients, (Sulfamethoxazole + Trimethoprim).

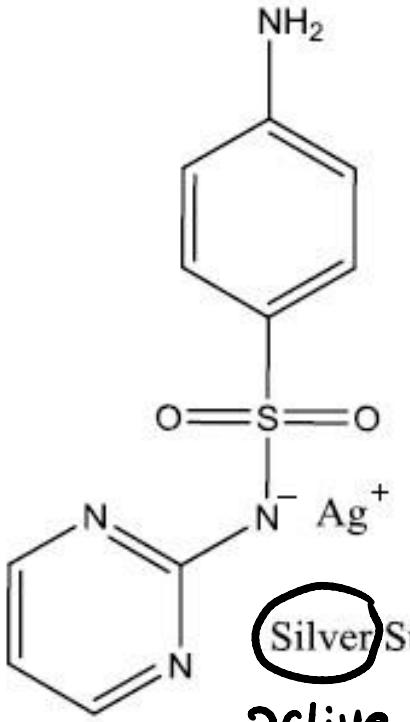
*Sulfadugs are divided to : Short(Sulfacetamide), Moderate, Long acting.

UP



Sulfamethoxazole

DOWN



Silver Sulfadiazine

active

لعلاج الحروق

- topically

protein binding of Sulfonamide

↓

توزّع الدواء بالجسم

في بروتينات بالدم قد ترتبط ببعض الأدوية.

↓

من ال Albumin ← basic

Alfaglycoprotein ← acidic

لأن ال Sulfonamide negatively charge

رح ترتبط بال

اللي مرتبط بال Albumine هو مش Active هو بس حافظ عليه عشان يزيد ال half-life ← That

لمّا يخلص الدوا بالدم ، بصير يطلع من Abumine للدم

↓

not Clear

لأنه ممكن يكون أصلًا ال half-life عالية

بس هو مرتبط ببروتينات الدم

Protein binding of sulfonamides

- Vary in plasma protein binding:
  Sulfaisoxazole.. 76%, Sulfamethoxazole... 60%, sulfadiazine.... 38%.

  # الفرق بين Methyl

- The fraction that is protein bound is not available for enzyme inhibition, therefore this fraction is inactive.
- The protein binding is a reversible process, so there will be a gradual release of sulfonamide which will become available.
- Factors affecting protein binding of sulfonamides:
  - Lipophilicity of the structure.

    # زاد الـ Lipophilicity زاد يزيد الارتباط
  - Substitution on the free amine will increase protein binding (such as the acetylayed metabolite is more protein bound than the parent sulfonamide).

USE:

- The original Sulfanilamide was used against most of the infections, Upper and Lower respiratory tract infections (Pneumonia mainly), it was the only treatment available.
- Their use was mainly for UTI (because it's eliminated quickly & their spectrum covers G-ve bacteria), it's still used until now.

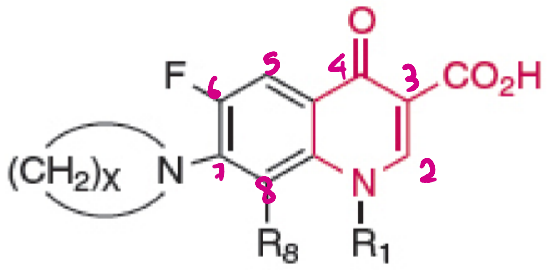
Spectrum:

- Broad spectrum (G+ve & G-ve) bacteria , with time, development of resistant happen.

Protein binding of sulfonamides

- Since albumin is basic, acidic and neutral drugs will primarily bind to albumin.
- If albumin becomes saturated, then these drugs will bind to lipoprotein.
- Basic drugs will bind to the acidic alpha-1 acid glycoprotein.
- Protein binding can influence the drug's biological half-life in the body but this relationship still not clear since some drugs with low protein binding have long duration of action (sulfisoxazole: protein binding ~~37~~ 76% and half life is 17 hours).

4-Quinolones → # يُصنّع بالمختبر



4-Quinolone
(pharmacophore shown in red)

The fluoroquinolones have been found to be effective in treatment of various bacterial infections depending on the nature of the substitution on the 4-quinolone pharmacophore. → # رسم بين المجموعات الأساسية المهمة بارتباط الدواء بالإنزيم

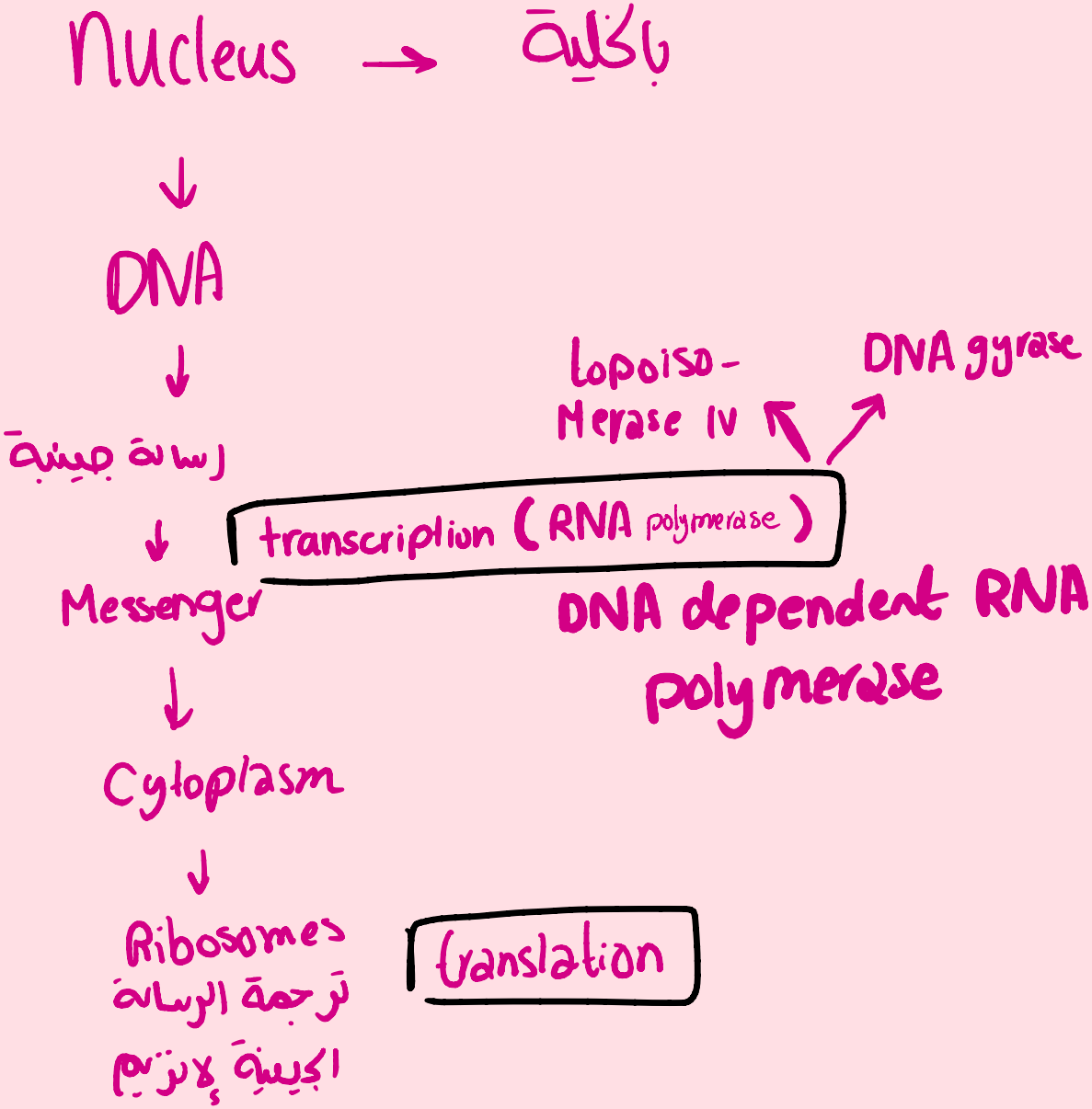
MOA

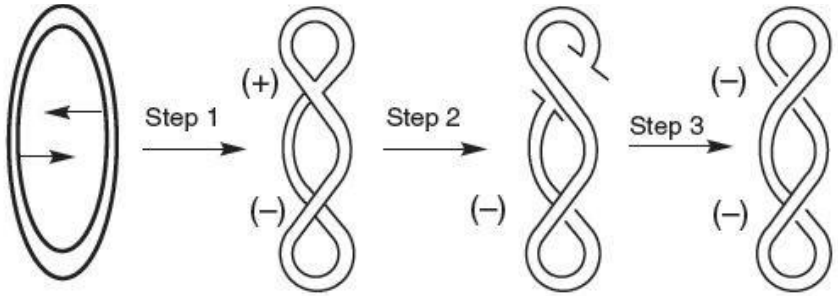
- Irreversible inhibitors of DNA gyrase and topoisomerase IV, key enzymes involved in DNA-dependent RNA polymerase (DDRP).

bactericidal ←

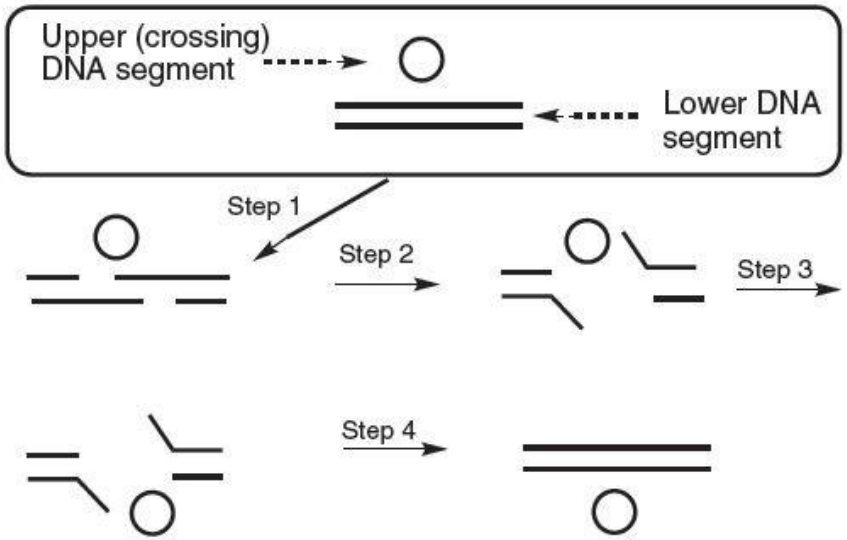
← # لهدول الإنزيمين ✓

← inhibit لهاد الإنزيم ✗


Nucleus → باكلية
DNA
رسالة جينية
Messenger
transcription (RNA polymerase)
Topoiso-Merase IV
DNA gyrase
DNA dependent RNA polymerase
Cytoplasm
Ribosomes
ترجمة الرسالة الجينية لإنزيم
translation

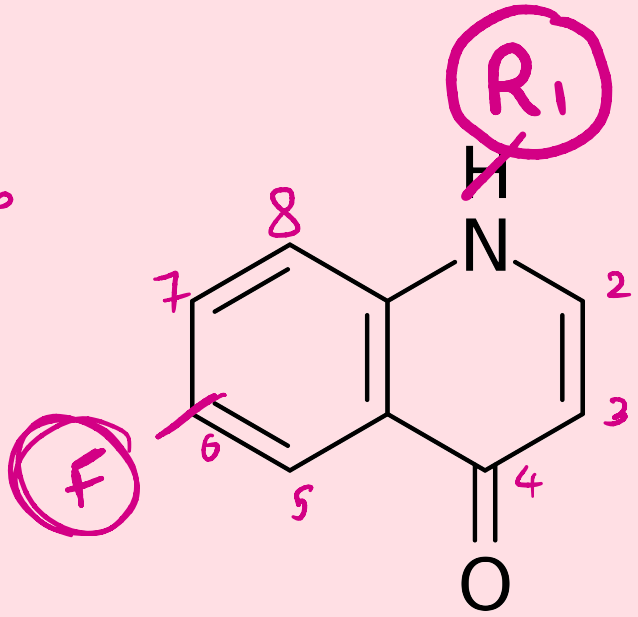


A. View from the top: Step 1. Stabilize positive node. Step 2. Break both strands of the back segment. Step 3. Pass unbroken segment through the break and reseal on the front side.

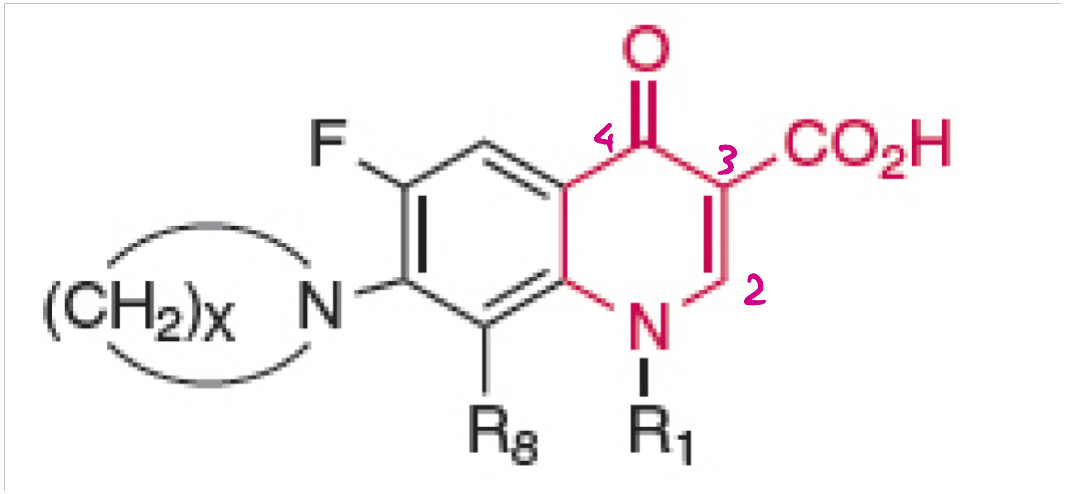


B. View from the side: Step 1. Staggered cuts in each strand. Step 2. Gate opens. Step 3. Transverse segment passed through the break. Step 4. Reseal cut segment.

الهالوجينات بتكبر الـ
hydrophobic
electron-withdrawing group
حجم صغير
↓
good pentration
for cell wall



Quinolone



SAR

- The quinolone pharmacophore is essential for activity through binding tothe DNA gyrase (Table 23.2).
- R_1 is important for potency and commonly consists of an ethyl or cyclopropyl.
- **Fluoro at C6** improves penetration of the bacterial cell wall through improved hydrophobicity.
- Heterocyclic substitution at C7 affects the spectrum of activity againstgram-negative bacteria.
- R_8 affects spectrum of activity as does R_1/R_8 linked forming a third ring in the molecule (finafloxacin).

Empty orbital ← Metal ← Co-ordinate #

الغنية بالـ e

Complex activity

* إنزيم gyrase في مغنيوسيوم بتركيبته برتصير الإلكترونات تدخل وتعمل Co-ordinate

↓

رابطة قوية

↓

irreversible

↓

bactericidal

* عشان هيك الكربونيل برقم (4) مُهمّات كبيروها بقدر استغني عنها.

Physicochemical and Pharmacokinetic Properties

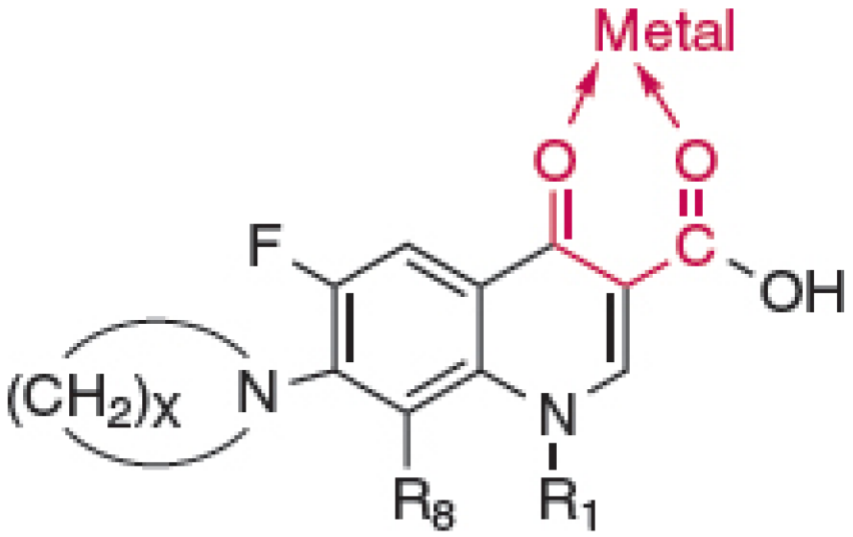
- • 4-Quinolones are incompatible with heavy metals (e.g., Ca^{2+}, Mg^{2+}, Zn^{2+}, Fe^{2+}, Al^{3+}) due to an insoluble chelate resulting from bonding between the metal and the C3 carboxyl and C4 ketone.
- • 4-Quinolones may cause skin phototoxicity upon exposure to the sun (UV A radiation).

ADVERSE EFFECTS

4-Quinolones: GI disturbance: nausea, vomiting, and abdominal discomfort. CNS effects: headache and dizziness, but may also include hallucinations, insomnia, and visual disturbances due to binding of lipophilic drugs to GABA receptors. Several analogs caused QT prolongation leading to their removal from the market.

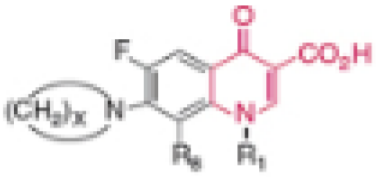
* عضلة القلب

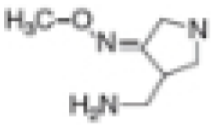
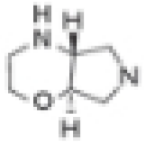
Binding of the drug to DNA gyrase involves the carboxyl and the ketone.



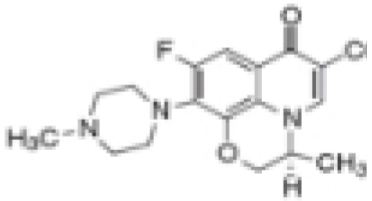
Metal chelation

* ما بصير أكلهم مع الأكل لأنه في معادن بالأكل ، رح ترتبط معه ويقل الامتصاص.



Drug: Generic Name	Trade Name	R_1		R_8
Norfloxacin	Noroxin	C_2H_5		H
Ciprofloxacin	Cipro	△		H
Gatifloxacin	Tequin	△		CH_3O
Moxifloxacin	Avelox	△		CH_3O
Gemifloxacin	Factive	△		
Besifloxacin	Besivance	△		Cl
Finafloxacin[a]	Xtoro	△		N≡C

بس هاد



Ofloxacin (Racemic)(Floxin)
Levofloxacin (1-*S*)(Levaquin)

Clinical Application

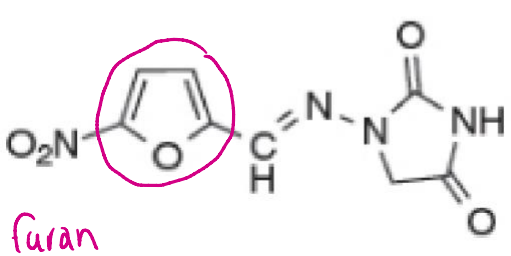
- The fluoroquinolones represent a potent class of
  - ✓ **bactericidal** agents with utility in a variety of infectious conditions. **The most common** indications include **UTIs** caused by sensitive organisms; prostatitis; some sexually transmitted infections; respiratory infections; and bone, joint, and soft tissue infections.

* صعب علاجهم مابتوصلهم التروية الدموية

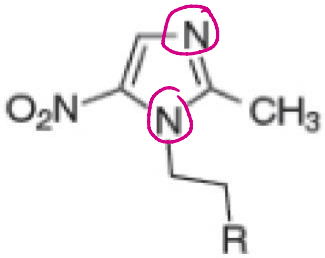
(3) Nitroheteroaromatic Compounds

Nitrofurantoin

Nitro : NO_2



furan



imidazole

① Nitrofurantoin (Furadantin, Macrodantin)

② Metronidazole, R = OH (Flagyl)

③ Tinidazole R = $SO_2C_2H_5$ (Fasigyn)

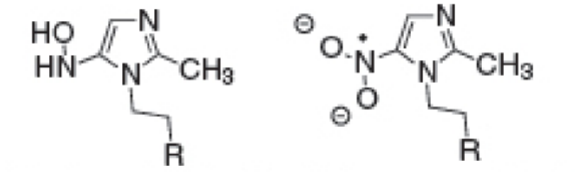
- Nitrofurantoin is the only nitrofuran which remains available and is used for treatment of uncomplicated UTIs.

* الباقي كلهم سامين

Metronidazole

- Metronidazole and tinidazole are used to treat some bacterial infections (e.g., GI tract peptic ulcer, pseudomembranous colitis) and protozoal infections (e.g., giardiasis, trichomoniasis).

CHEMICAL NOTE



"Hydroxylamine" "Nitrogen radical"

Possible active form of nitro aryls

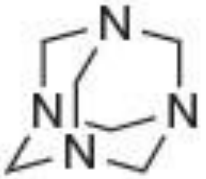
MOA

- Most likely, the nitroheteroaromatic compounds are prodrugs in which **the nitro group is reduced** to the active hydroxylamine or nitrogen radical which interferes with DNA and or RNA.

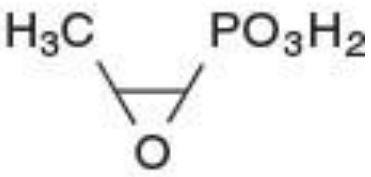
1) reduction
2) Hydrogenation

Methenamine and Phosphomycin

4 Ammonia group ← بتحلل بالبول
6 form Aldehyde ← (وسط حمضي)



Methenamine
(Prosed, Urimax, Urised, Uroqid-Acid)



Phosphomycin
(Monurol)

limited values and are used in uncomplicated UTIs.

MOA

- Methenamine is a prodrug, which in acidic urine generatesammonia and formaldehyde. The latter forms a Schiff's base with bacterial protein resulting in antibacterial action.
- Phosphomycin, through alkylation of a key sulfhydryl group in abacterial transferase essential in cell wall glycoprotein synthesis, inhibits bacterial growth.

Covalent bond"

Saja Dwaikat

Artery academy