

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

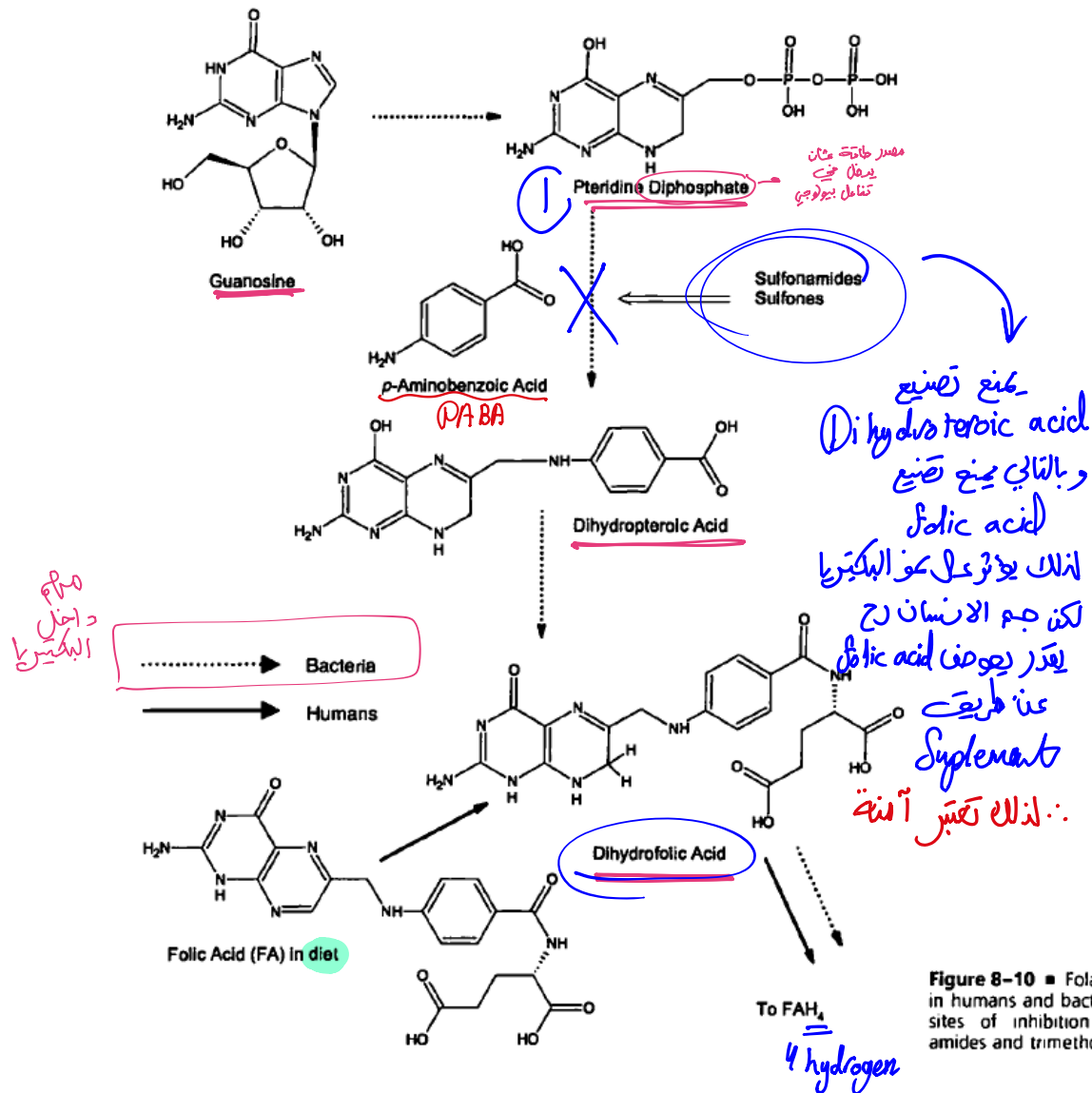
Methyl donor هو Folic acid
هم في صناعة القواعد النيتروجينية
Thymine, Cytosine, Guanine, Adenine
بالتالي فهو مهم في تصنيع DNA
بالتالي فهو مهم في انقسام الخلايا ونموها.

* الانسان يمكن تصنيع Folic acid
رغم ان يحصل عليه من الغذاء Supplement
* البكتيريا لا بد من تصنيعه حتى
تقدر تنقسم ما يقدر تحصل عليه من مصدر خارجي

بشيط انزيم
في تصنيع صناعة
Folic acid

* بالتالي أي حاد مناعه ضعيفه
سولفوناميد اعطاه

Mechanism of action



Reference: Wilson and Gisvold's Textbook of Organic

DHP synthase
حل على الانزيم
PABA

Sulfonamide يحل محل PABA
على الانزيم وبالتالي يثبط تصنيع Folic acid
*** (أي تركيزه أعلى هو الجي يرتبط بالانزيم)

إذا زادت كمية PABA
أعلى من Sulfonamide
بالتالي تحسن resistance Sulfonamide
عن طريقه

Figure 8-10 ■ Folate path in humans and bacteria and sites of inhibition by sulfonamides and trimethoprim.

To FAH₄
4 hydrogen

Mammalian Folate biosynthesis

التي كمن inhibition sequential

(Sulfonamide + Trimethoprim)
 لجفت

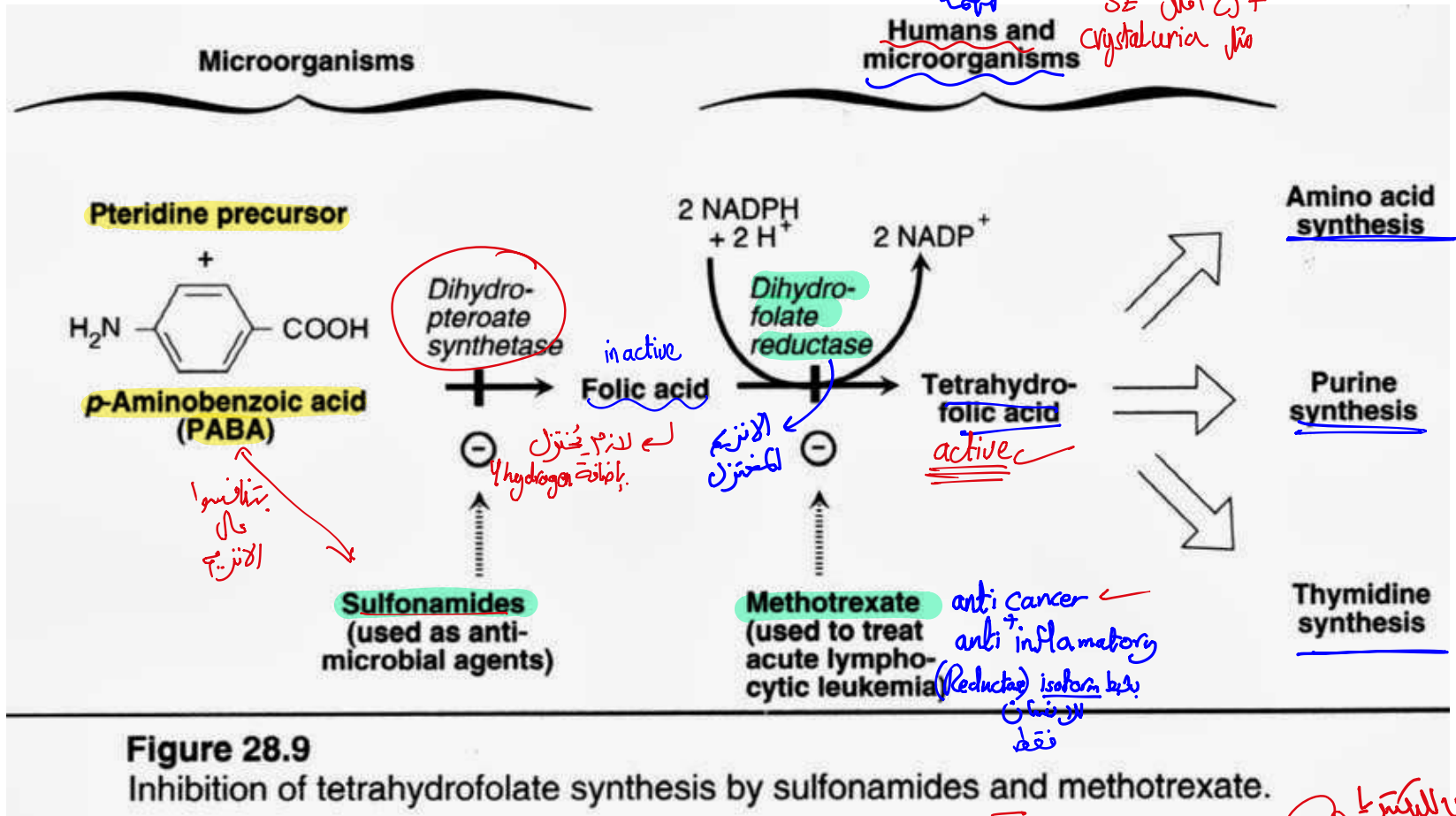
Cotrimoxazole

هذا مازح اقل اعلي

حجات كبيرة من Sulfon.

SE + ز اقل
 crystaluria
 فول

Synergistic effect (1+1=10)

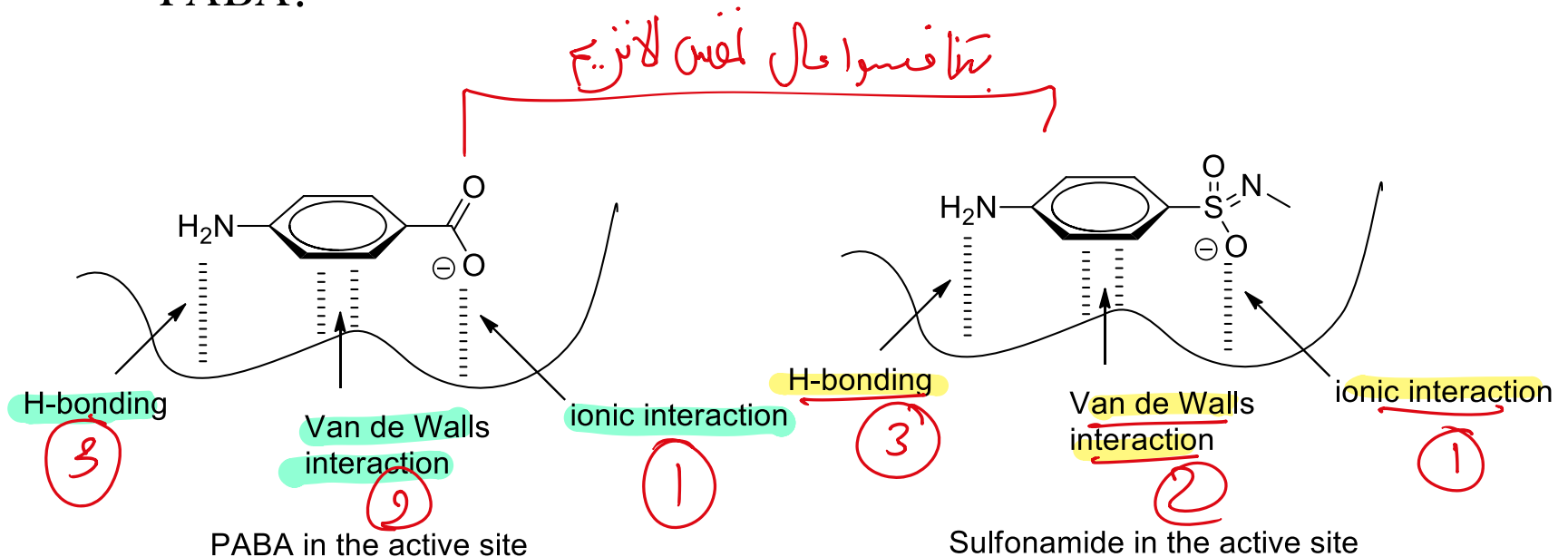


folate reductase inhibitors

← [Trimethoprim ①
 Methotrexate ②]

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:



كيف يعبر resistance
ببساطة البكتيريا راح تزيد انتاج PABA
وراح يعبر Sulfon. على قادر عال الارتباط
بالانزيم.

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. لازم فعلي Sulfon. بالحماكة تصوف PABA وهاداشي غير ممكن
- 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. لانه راح تزيد SE

- 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.

الحل لـ Crystalluria هو زيادة pH البول + شرب الماء

عن طريق اعطاء ملح قاعدي (citrate K) more basic

الجمع حتى
يتخلص من
Sulfon

راح يعمل اضافية
acetyl

ف يصير اقل
ذوبانية

تربس في البول

Mechanism of action

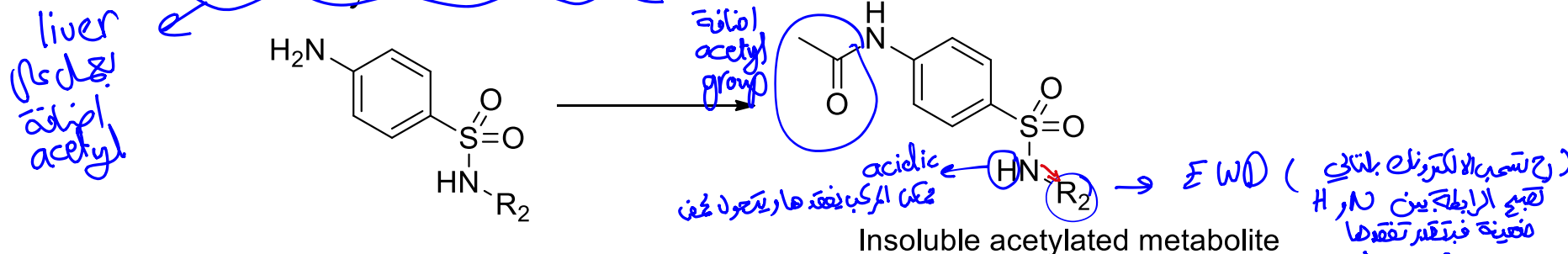
- In human, the cell synthesized tetrahydrofolate from folic acid that obtained from food sources. This folic acid is normally transported to inside the cell by special transport system.
- Bacterial cell does not have such transport system and they should synthesize tetrahydrofolate using PABA.
- For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

The problem of crystalluria

حرب الماء
 اكلون
 make urin more basic
 إضافة (R₂) group
 تكون EWD

Crystal

- 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.

✓ 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).

✓ 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

لما نقتل pKa ← معناها زيادة قوة الحمض

بذا طريق اضافة EWG

عشان يكون ionization أعلى

زيادة قوة الحمض
 $K_a \uparrow$
 $K_a = \frac{[\text{نواتج}]}{[\text{مفاعلات}]}$

كيف K_a تزداد ؟
 كما تزداد النواتج

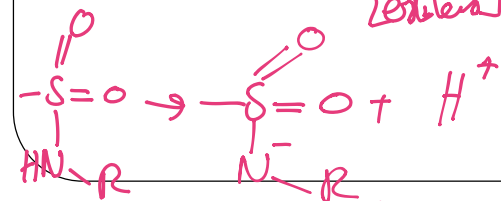
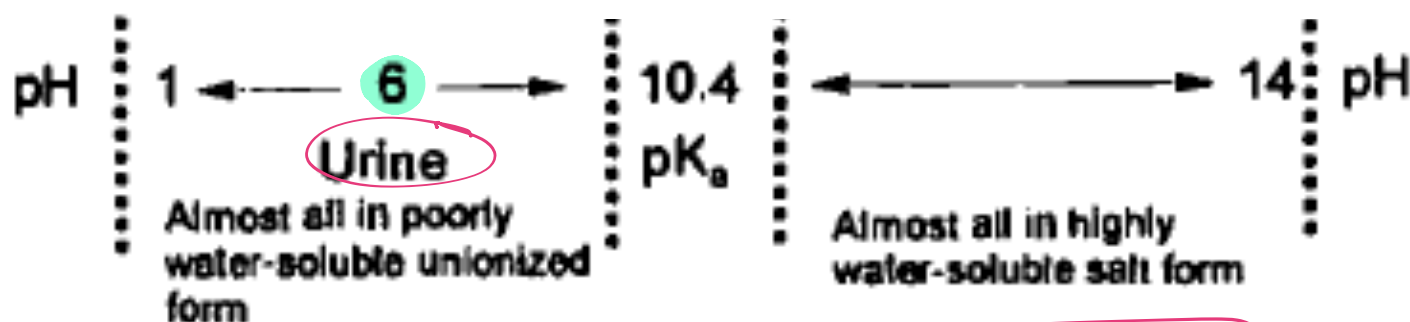


TABLE 8-8 pK_a Values for Clinically Useful Sulfonamides

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

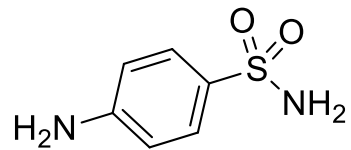


pK_a لا ٥٠٠٠ اقل من ٤

Sulfonamides with reduced crystalluria formation

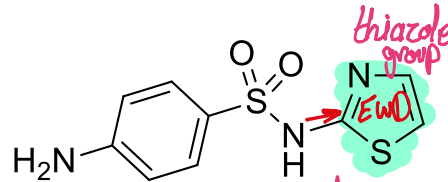
الملاحظة: زيادة قوة الحف: زيادة القدرة على فقدان H $\leftarrow$ more soluble

بمعني pK_a تكون اقل من $pH(wrin)$ δ حتى ينوب تماماً



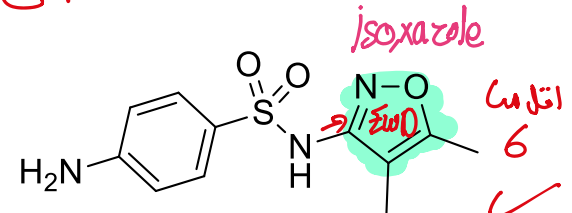
Sulfanilamide $pK_a = 10.4$

week acid



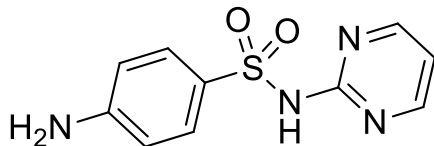
Sulfathiazole $pK_a = 8.5$

معناها قوة الحفز زادت
ف ر ج تقل Crystal uria

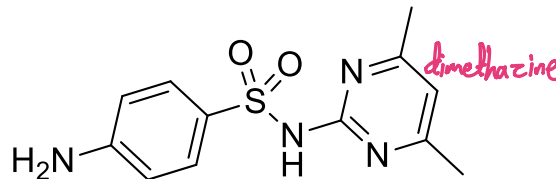


Sulfisoxazole $pK_a = 5.0$

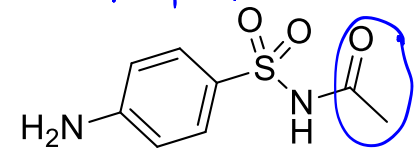
more acids



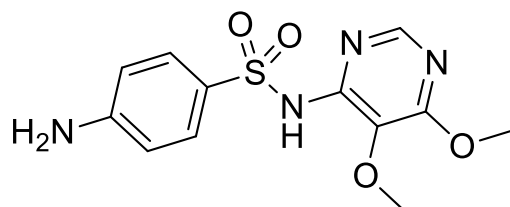
Sulfadiazine $pK_a = 6.5$



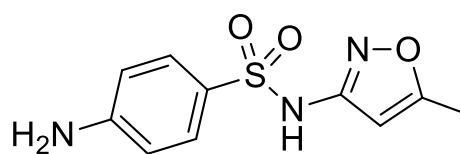
Sulfamethazine $pK_a = 7.4$



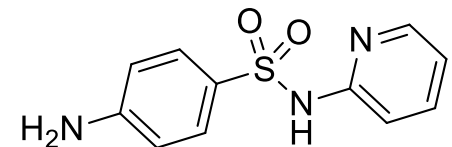
Sulfacetamide $pK_a = 5.4$



Sulfadoxine $pK_a = 8.1$



Sulfamethoxazole (pKa = 6.1)



Sulfapyridine ($pK_a = 8.4$)

Clinical Application

علاج UTI (الخطأ الثاني بعد الخط الأول) Ciprofloxacin

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.

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.

التهابات الأذن الوسطى

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.

anti malaria

مرض القمل
في مآل الأنثى

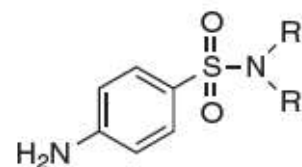
Silver sulfadiazine is used topically to treat burns, with both the sulfa drug and the silver ion having antibacterial activity.

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

Clinically relevant sulfonamides

Clinically Relevant Sulfonamides

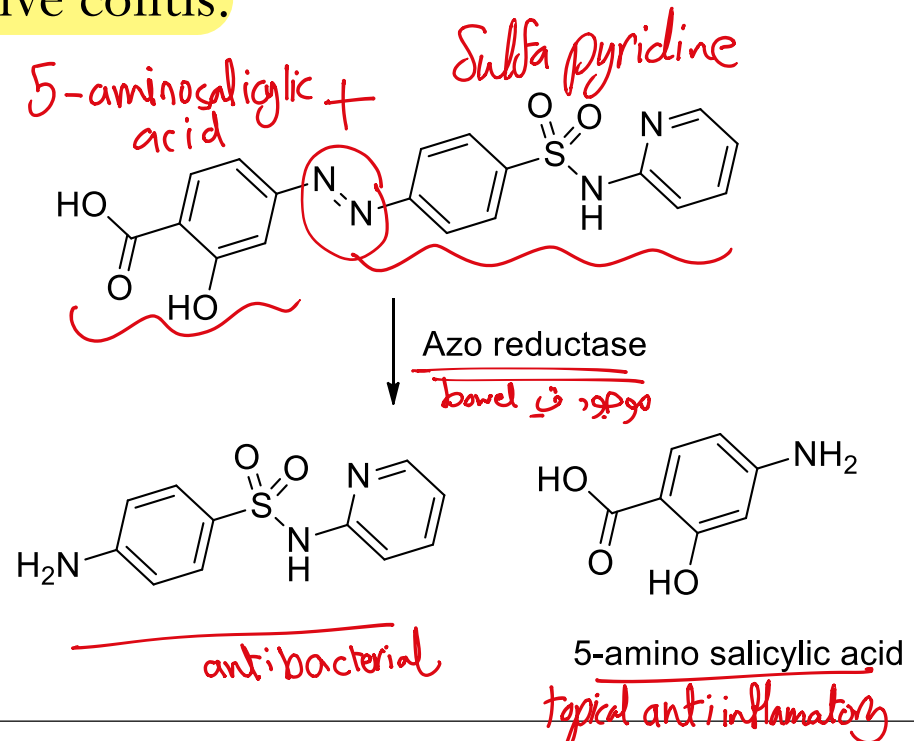


Drug: Generic Name	Product	R	R'	pKa
Sulfisoxazole acetyl (prodrug)	In combination with erythromycin ethylsuccinate			5.6 after hydrolysis
<u>Sulfamethoxazole</u>	In combination with trimethoprim		-H	5.0
Sulfadiazine	✓ Oral dosage form		-H	6.52
Silver sulfadiazine	✓ Topical dosage form لعلاج الحروق			
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.



دihydrofolate reductase
لعمل على تحويل folic acid
لشكله الفعال في الخلية تستخدمه.

Other folate reductase inhibitors

• Trimethoprim:

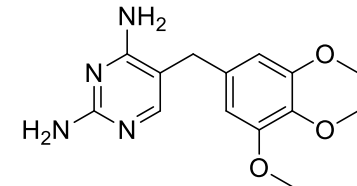
- Inhibits (dihydrofolate reductase) this enzyme has human homologue but they do not have that much similarity in structure.... Therefore trimethoprim is 1000 more active on the bacterial copy of this enzyme..

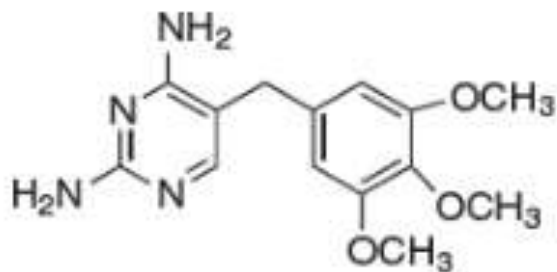
- Normally used in combination with sulfamethoxazole (cotrimoxazole):

لأنه PKa
أقل من 6
فيما يلي راجع
مزيد من
معلومات

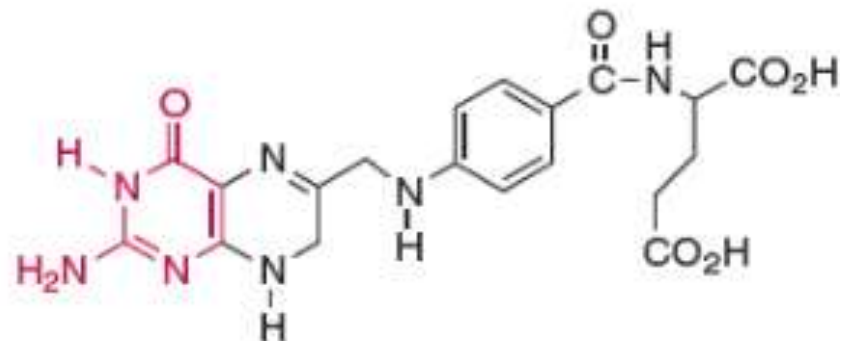
- ✓ • Lower dose from both drugs means less side effects.
- ✓ • More effective than the monotherapy since they are targeting two different enzymes in the same metabolic pathway... this is what is called sequential blocking.

أقل كمية + أقل سعر





Trimethoprim (Proloprim, Trimpex)
 Trimethoprim + sulfisoxazole (Co-Trimoxazole) ✓
 Trimethoprim + sulfamethoxazole (Bactrim, Septa) ✓



Dihydrofolic acid

