SULFONAMIDES

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Inhibition of synthesis of essential metabolites

Antimicrobials in this class;

- Sulfonamides
- Trimethoprim

Bacteriostatic

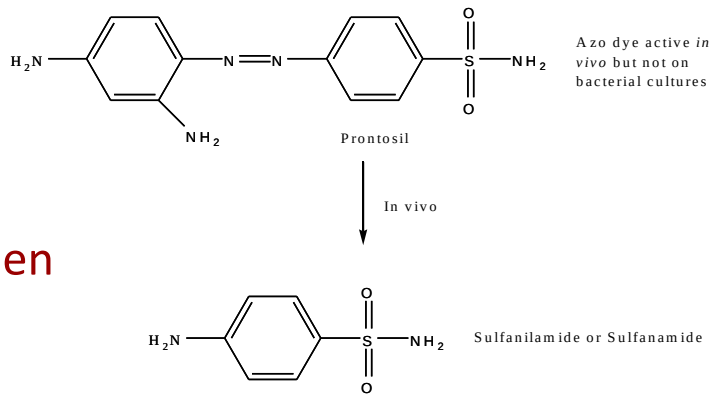
Mode of actions;

- inhibit the production of folic acid required for synthesis of purines and nucleic acid

- does not affect human cells or certain bacteria

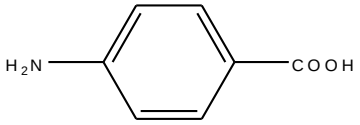
Gerhard Domagk

- German bacteriologist and pathologist who was awarded the 1939 Nobel Prize for Physiology or Medicine for his discovery of the antibacterial effects of Prontosil, the first of the sulfonamide drugs.
- beginning of the concept of prodrug
- used greatly as antibiotic in the 1940's, then replaced by cheaper and less toxic penicillins.
- Sulfa drugs were discovered when a red dye called prontosil has shown *in-vivo* antibacterial activity while it was *in-vitro* inactive.
- This supports the idea that prontosil to exert its action, it has to be activated by the host metabolic pathways to give the active form.

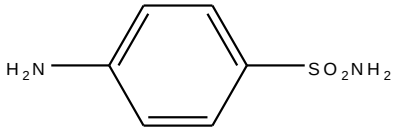


Antibacterial sulfonamides

Mechanism of Action;



P-amino-benzoic acid (PABA)



Sulfanilamide

Step 1;

- Inhibited by Sulfonamides which act by competing with PABA here.

Step 3;

- Inhibited by Trimethoprim

Mechanism of action

- Sulfonamides are a competitive 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.
- Sulfonamide is not recommended in patients with weak or impaired immune system.
- This binding is reversible.
- Because of that sulfonamides have bacteriostatic effect not bactericidal.

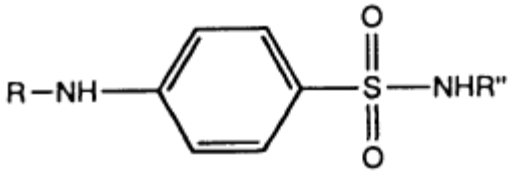
Mechanism of action

- 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:

Mechanism of action

- Because sulfonamides are 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.
- 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 synthetaze enzyme which means sulfonamides have selective antibacterial activity.

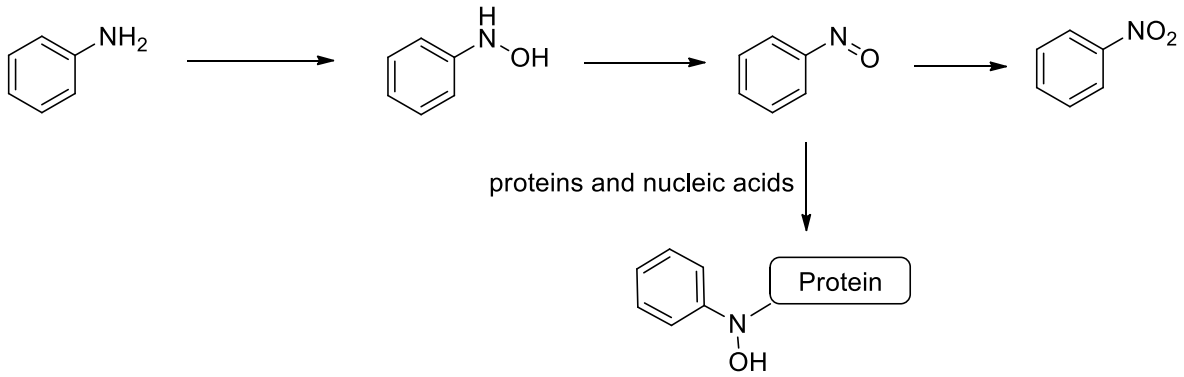
Structure-Activity Relationships (SAR)



- The p-amino group is essential for activity and must be unsubstituted (i.e. R = H).
- The only exception is when R = acyl (i.e. amides). The amides themselves are inactive but can be metabolized in the body to regenerate the active compound
- The aromatic ring and the sulfonamide functional group are both required.
- The aromatic ring must be para-substituted only.
- The sulfonamide nitrogen must be secondary.
- R" is the only possible site that can be varied in sulfonamides.

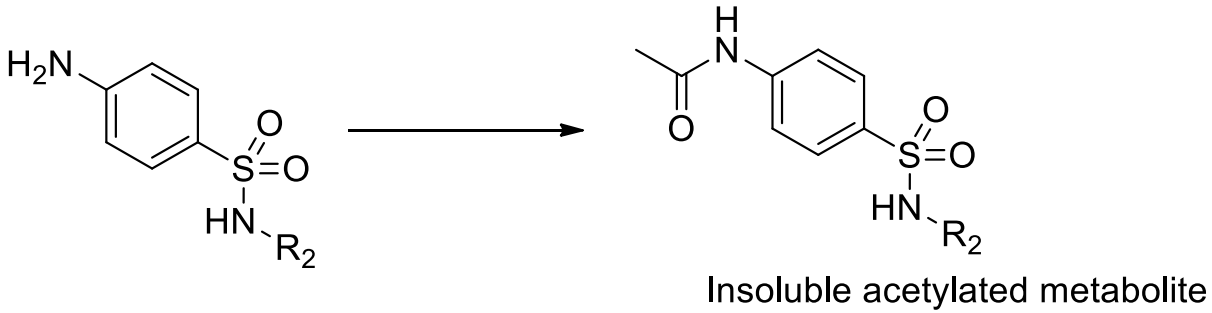
Sulfonamides antibacterial agents

- They are the first synthetic antibacterial agents.
- They have good antibacterial activity mainly on gram +ve bacteria.
- limitation of the sulfa drugs use:
  - Sulfa allergic reactions.
  - The formation of crystalluria.
  - They give toxic metabolites after the oxidation of the aromatic amine:



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.



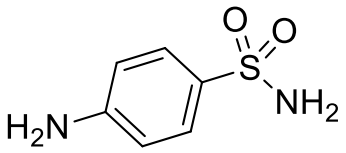
Insoluble acetylated metabolite

- 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)

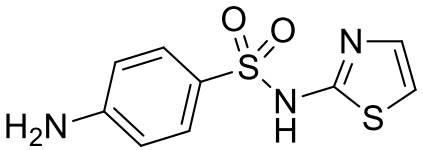
The problem of crystalluria

- 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

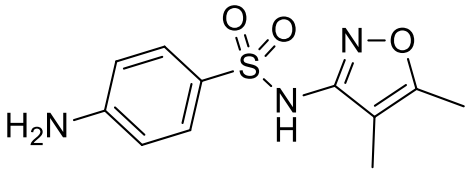
Sulfonamides with reduced crystalluria formation



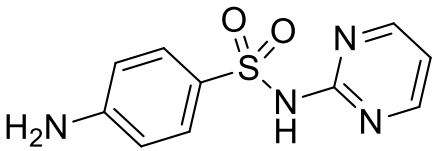
Sulfanilamide pKa = 10.4



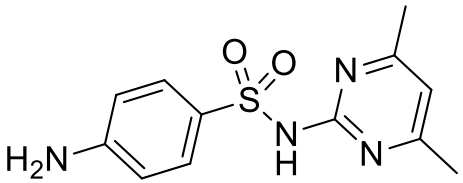
Sulfathiazole pKa = 8.5



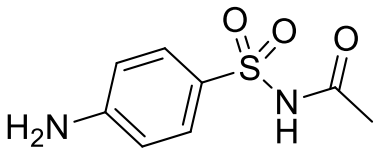
Sulfisoxazole pKa = 5.0



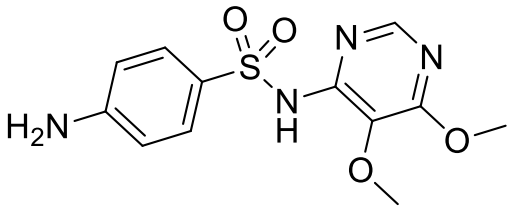
Sulfadiazine pKa = 6.5



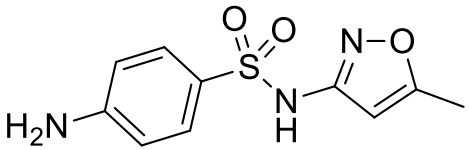
Sulfamethazine pKa = 7.4



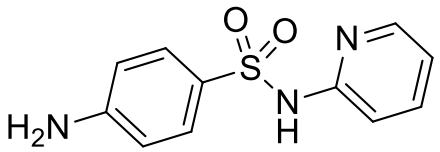
Sulfacetamide pKa = 5.4



Sulfadoxine pKa = 8.1

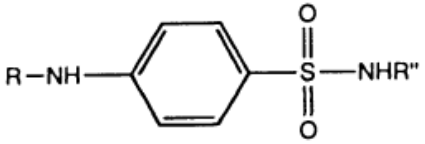


Sulfamethoxazole pKa = 6.1



Sulfapyridine pKa = 8.4

Sulfonamide derivatives

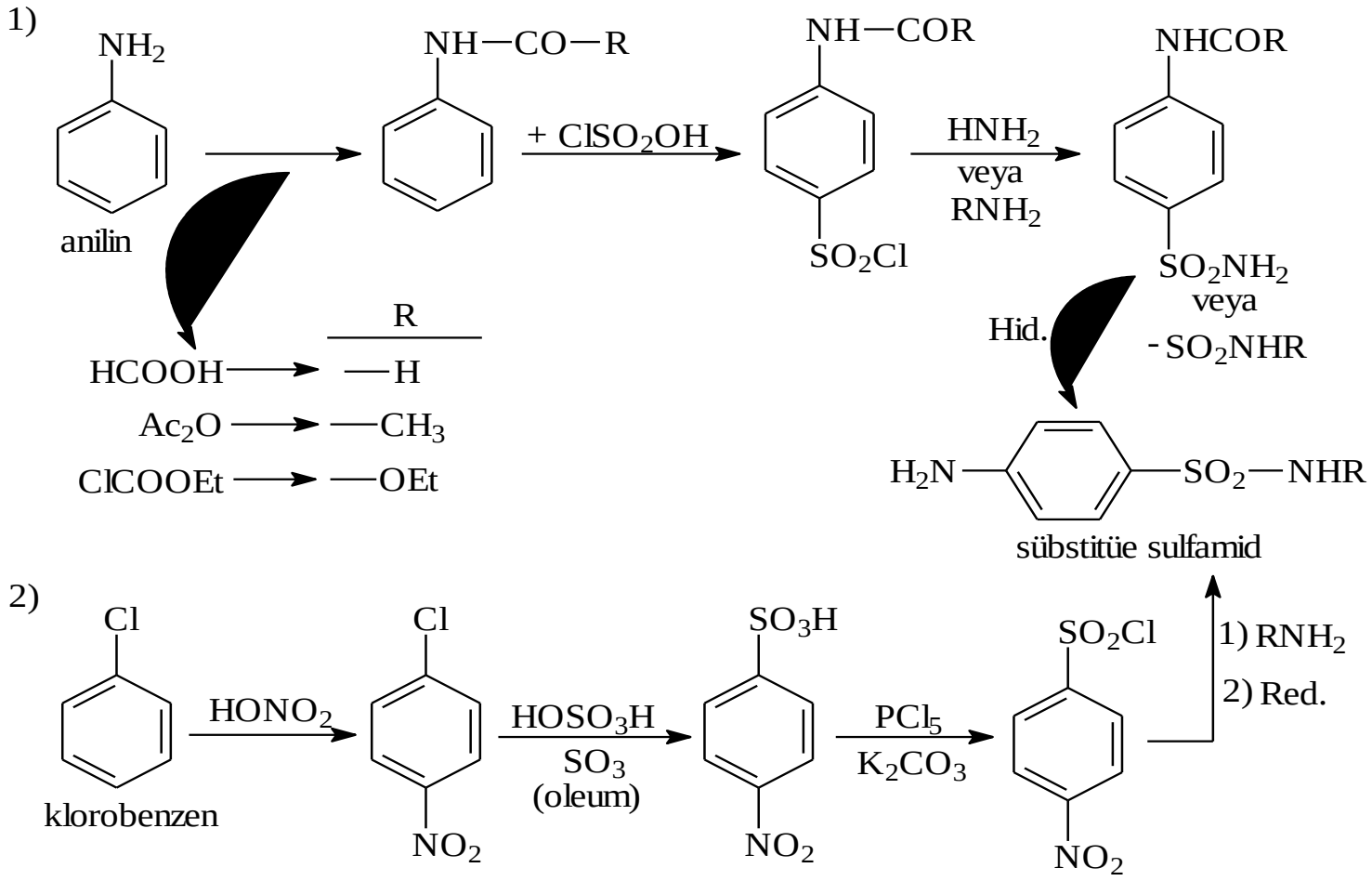


- Differ mainly in the substitution at the sulfonamide side chain… derivatives with heterocyclic or aromatic ring. This was done to:
  - Reduce the pKa of the sulfonamide... Reduce crystalluria.
  - Increase protein binding by adding lipophilic heterocycles…. Long lasting derivatives.
- Few derivatives have the amino group at the *P* position being derivatized except in sulfonamide prodrugs

Nomenclature of sulfonamides

- The sulfonamide termination is used for p-aminobenzene sulfonamide (sulfanilamide) derivatives. The generic nomenclature is made by combining the N1- residue together with the sulphate prefix. such as Sulfapyridine, Sulfaguanidine.

General Synthesis of Sulfonamides



Classification by Therapeutic Effect

*Systemic sulfonamides (used in systemic infections, especially in urinary infections)

-Short-acting sulfonamides
-Moderately active sulfonamides
-Long acting sulfonamides

*Sulfonamides used in GI infections

*Sulfonamides used in ophthalmic infections

*Sulfonamides used in urinary infections

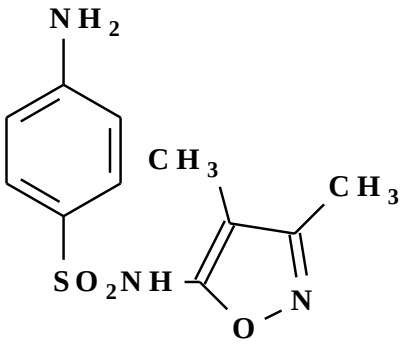
*Sulfonamides used in burn treatment

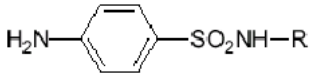
*Sulfonamides used in the treatment of vaginal infections

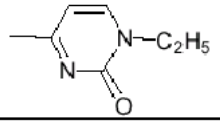
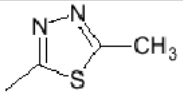
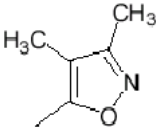
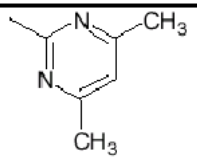
A- Short-Acting Sulfonamides

They are absorbed fast. Their half-lives are 4-7 hours. They are preferred for systemic infections

Sulfisoxazole



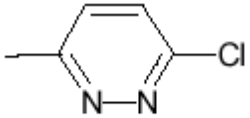
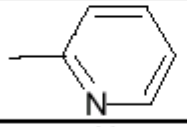
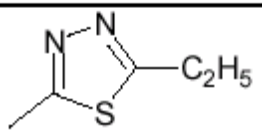
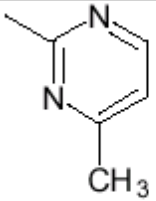
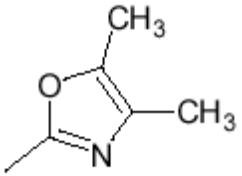
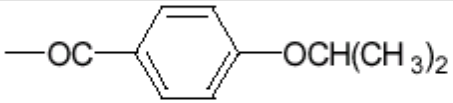
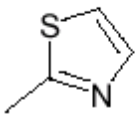


Bilesik	R
Sülfasitin N[1]-(1-Etil-1,2-dihidro-2-okso-4-pirimidinil)sülfanilamit	
Sülfametizol N[1]-(5-Metil-1,3,4-tiyadiazol-2-il)sülfanilamit	
Sülfisoksazol (Azo-Gantrisin, Gansol) N[1]-(3,4-Dimetil-5-izoksazolil)sülfanilamit	
Sülfametazin N[1]-(3,4-Dimetil-2-pirimidinil)sülfanilamit	
Sülfasetamit (Optamid, Suprenil) N[1]-Asetilsülfanilamit	-COCH$_3$

N1- (3,4-dimethyl-5-isoxazolyl) sulfanilamide

5- (4-aminobenzensülfonamido) -2,3-dimethyl-isoxazole

A- Short-Acting Sulfonamides

Sülfakloropiridazin N^1-(6-kloro-3-piridazinil)sülfanilamit	
Sülfapiridin N^1-(2-Piridil)sülfanilamit	
Sülfaetidol N^1-(5-Etil-1,3,4-tiyadiazol-2-il)sülfanilamit	
Sülfamerazin N^1-(4-Metil-2-pirimidinil)sülfanilamit	
Sülfamoksol N^1-(4,5-Dimetil-2-oksazolil)sülfanilamit	
Sülfaproksilin N^1-(4-Izopropoksibenzil)sülfanilamit	
Sülfatiyazol N^1-(2-Tiyazolil)sülfanilamit	

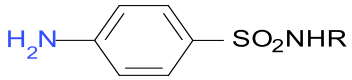
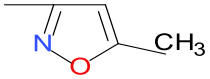
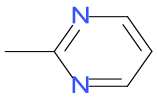
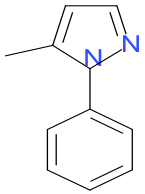
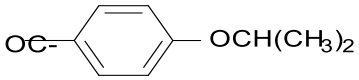
B- Moderate Effect Sulfonamides

They are absorbed and discarded more slowly than short-acting sulfonamides.

Their half-lives are 10-12 hours.

They are given twice a day.

Use for long-term treatment and especially for urinary infections.

orta etki süreliler		
		
Bileşik	**R**	**Müstahzarlar**
Sülfametoksazol N1-(5-metil-3-izoksazolil)sülfanilamit		Gantanol(roche)
Sülfadiazin N1-(2-primidinil)sülfanilamit		Silvadiazin,Sulfatrim,Silvadene Silverdin,Sulfadiazin,Ultradiazin Pedidiyazin
Sülfafenazol N1-(1-fenil-1H-1-pirazol-5-il)sülfanilamit		
Sülfamoksol N1-(4,5-dimetil-1,3-oksazol-2-il)sülfanilamit		

C- Long Acting Sulfonamides

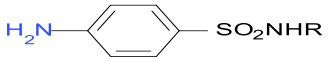
- Absorption of these derivatives is fast and their breakthrough is slow (More lipophilic).
- Their half-lives are 35-40 hours
- Long-acting sulfonamides are given once or twice a day.
- These compounds are used only in special cases. Because;

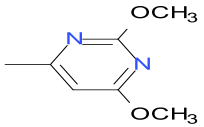
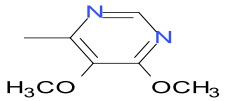
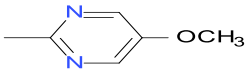
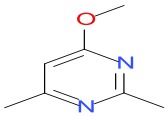
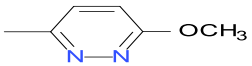
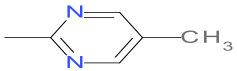
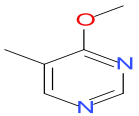
  -They do not have a clinical advantage over short acting sulfonamides.

  -They can not pass blood-brain barrier as easily as short-acting sulfonamides
- They can reach dangerous concentration because they are slowly taken away.
- Therefore, attention should be paid especially to patients with poor renal function.
- Due to these reasons and some side effects such as Stevens-Johnson syndrome, it has been removed from U.S. therapy today.

Stevens-Johnson syndrome *is a rare serious complaint in which the skin and mucous membrane reacts severely to the drug or infection*

C- Long Acting Sulfonamides



Uzun etki süreliler		
Bileşik	**R**	**Müstahzarlar**
Sülfadimetoksin N1-(2,6-dimetoksi-4-primidinil)sülfanilamit		Duramid(Deva)
Sülfadoksin N1-(5,6-dimetoksi-4-primidinil)sülfanilamit		Fanasil(roche)
Sülfametoksidiazin N1-(5-metoksi-2-primidinil)sülfanilamit		
Sülfametomidin N1-(6-metoksi-2-metil-4-primidinil)sülfanilamit		
Sülfametoksipiridazin N1-(6-metoksi-3-pridizanil)sülfanilamit		Depo-sulfon(Öztürk) Metamit(Yavuz)
Sülfaperin N1-(5-metil2-primidinil)sülfanilamit		
Sülfalen N1-(4-metoksiprimidin-5-il)sülfanilamit		

Sulfonamides Used in Gastrointestinal Infection

- Hydrophilic groups are attached to the free amino group to increase water solubility of these drugs.
- Due to the presence of hydrophilic groups such as maleyl, succinyl, it is less absorbed from the gastrointestinal tract.
- This leads to a high concentration in the colon lumen. Bacterial hydrolysis occurs in the colon lumen resulting in active sulphonamide structure.

Sulfonamides Used in Gastrointestinal Infection

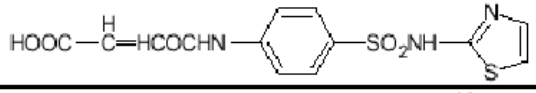
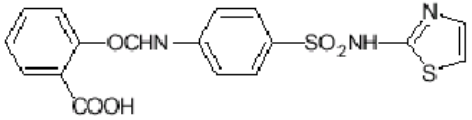
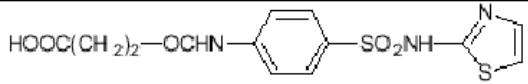
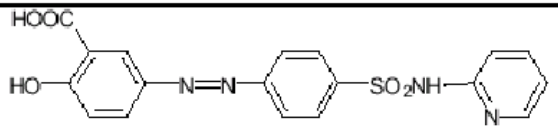
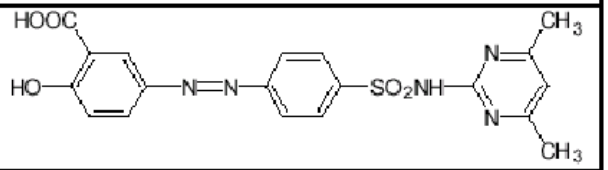
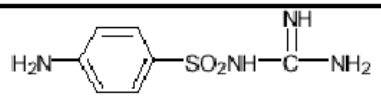
Sulfasalazine

Composed of salicylic acid and sulpyridine.

In the intestine, sulphapyridine and 5-aminosalicylic acid are separated.

Therefore, both anti-inflammatory and antibacterial effects occur.

Use for thick intestinal inflammation.

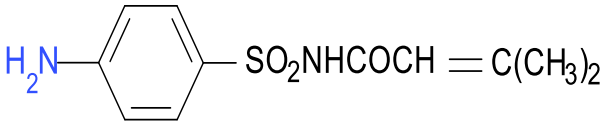
Bilesik	Formül
Maleil sülfatiyazol 2-(N^4-Maleilsülfanilamido)tiyazol	
Ftalil sülfatiyazol 2-(N^4-Ftalilsülfanilamido)tiyazol	
Süksinil sülfatiyazol 2-(N^4-Süksinilsülfanilamido)tiyazol	
Sülfasalazin (Salazopyrin) 5-[4-(2-Piridilsülfamoil)fenilazo]salisilik asit	
Salazosülfadimidin 5-[4-[(4,6-Dimetil-2-pirimidinil)sülfamoil]fenilazo]salisilik asit	
Sülfaguanidin N^1-Amidinosülfanilamit	

Sulfonamides Used in Ophthalmic Infections

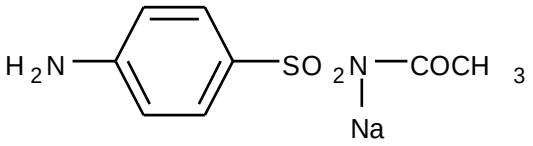
They are used topically in conjunctivitis and similar ocular infections.

Sülfadikramit

3-Metil-N-sülfanililkrotonamit



Sulfacetamide Sodium:



N1-Asetilsülfanilamit sodyum

Sodium salt is used in ophthalmic infections as it is in good solubility at physiological pH (7.4)

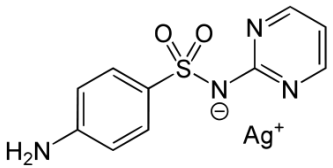
Sulfonamides Used in Burn Treatment

Mafenit

4- (aminomethyl) benzenesulfonamide

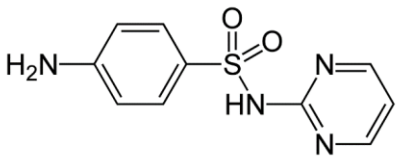
Since it is not a true sulfonamide type, it is not inhibited by PABA. Therefore, the mechanism of antibacterial action differs from the others. It is not used orally. It is used alone or in combination with antibiotics in the treatment of infected burns.

Silver Sulphadiazine



Silver [(4-aminophenyl) sulfonyl] (pyrimidin-2-yl) azanide

It is used topically in the form of water-miscible cream, especially for the treatment of infections caused by pseudomonas species. This is very important in the treatment of burns because, if it fails, pesudomonas infection is often developing.



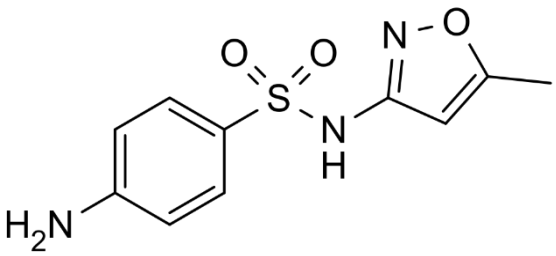
•4-amino-N-pyrimidin-2-yl-benzenesulfonamide

Sulfonamides Used in Urinary Infection

- The sulfonamides in this group are preferred because of their rapid absorption and slow release from the kidneys, which leads to high concentrations in the kidneys.

- Sulfacytin, sulfamethoxazole, sulfamethisole, sulfisoxazole are preferred because they are relatively reliable, well tolerated, highly concentrated in urine, and therefore low in crystallinity risk.

Sulphamethoxazole



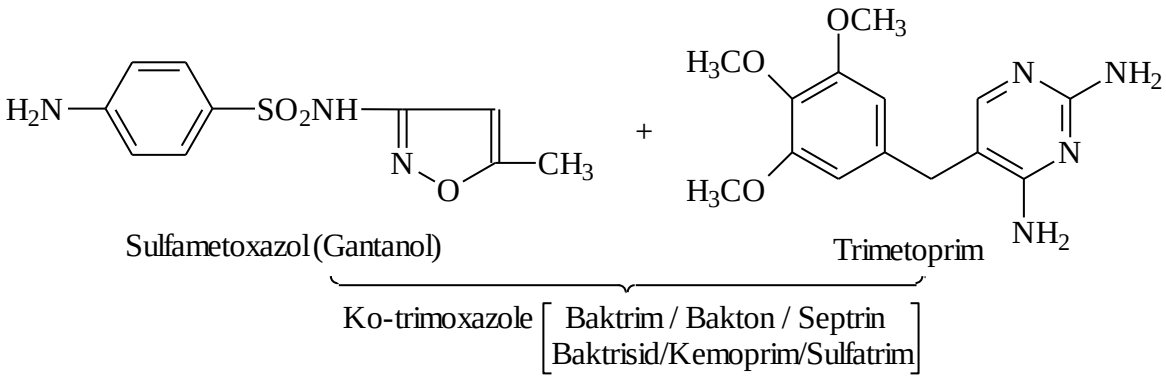
4-Amino-N- (5-methylisoxazole-3-yl) -benzenesulfonamide

CO-TRİMOXAZOLE

Sulfamethoxazole with trimethoprim in 5: 1

Tablets contain 400 mg of sulfamethoxazole plus 80 mg of trimethoprim.

Trimetoprim inhibits the enzyme dihydrofolic acid reductase and exhibits bacteriostatic activity.



Sulfametoxazol (Gantanol) + Trimetoprim

Ko-trimoxazole [Baktrim / Bakton / Septrin Baktrisid/Kemoprim/Sulfatrim]

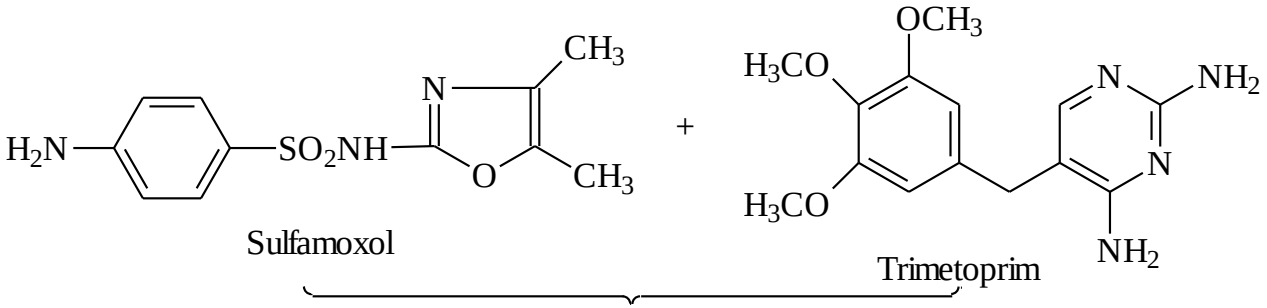
5- (3,4,5-trimethoxybenzyl)
-2,4-diaminopyrimidine

CO-TRİMOXAZOLE

Since the biochemical event necessary for the bacteria is blocked from two separate points, the synthesis of purine in the bacteria is disrupted. This results in a bactericidal effect.

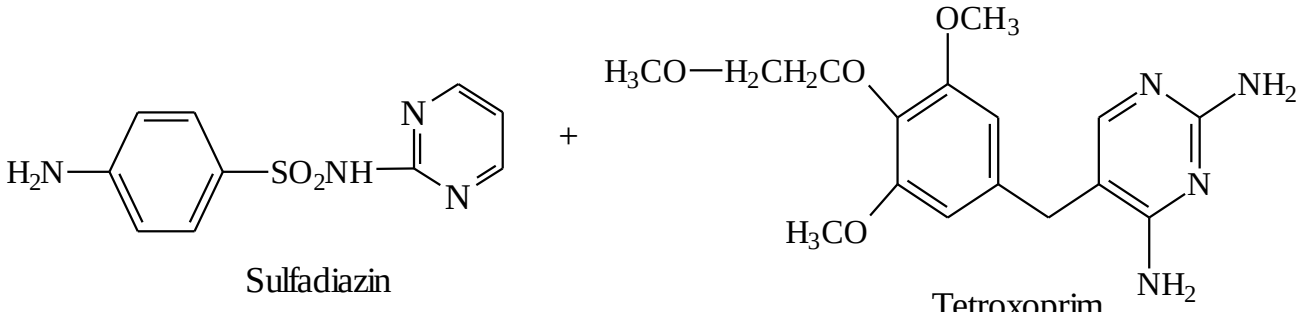
This compound is used in urinary tract, respiratory tract and prostate infections.

Ca-trimoxazole users should not be given sodium bicarbonate (Sulfametoxazole is acidic, Trimetoprim is basic) because urine chalevilization changes the outcome of the compound in the opposite direction.



Sulfamoxol + Trimetoprim

Ko-trifamole [Supristol]

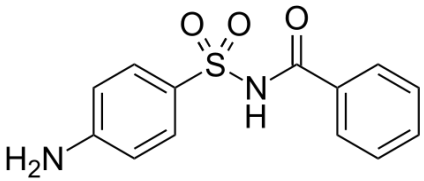


Sulfadiazin + Tetroxoprim

Ko-tetroxazin [Sterinor / Tibirox]

Sulfonamides Used in the Treatment of Vaginal Infections

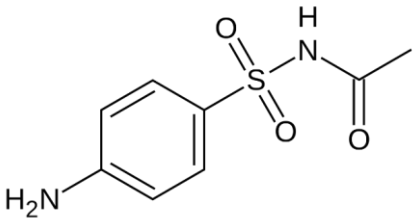
- Sulfabenzamide + Sulfacetamide + Sulfathiazole used in mixture.



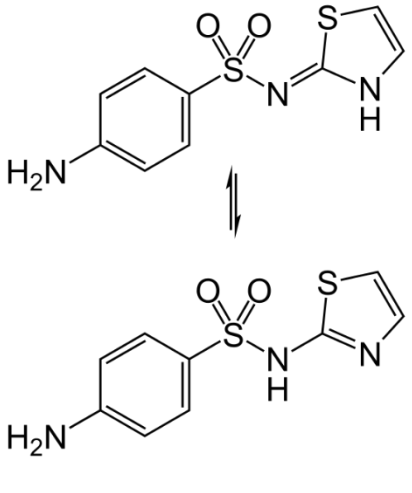
Sulfabenzamide

N^1-Benzoilsülfanilamit

4-Amino-N-benzoyl-benzenesulphonamide



Sulfacetamide



Sulfathiazole

Trimetoprim-Sülfonamid Kombinasyon

- -Bactrim Tablet®: 80/400 mg'lik.
- -Bactrim Fort Tablet®: 160/800 mg'lık.
- -Bactrim Süspansiyon®: 40/200 mg/5 ml'lik pediatrik süspansiyon
- -Septrin Tablet®:
- Septrin Fort Tablet®:
- Septrin Pediyatrik Süspansiyon®:
- Bacton Tablet Fort Tablet Süspansiyon®

ve Kemoprim Fort Tablet®:

- Oftalmix®, Polyciline®,

Sukfatrim®, Kemoprim®, Metoprim®

Mikrosid®, Trimoks®.