“SULPHONAMIDES"

Presented By

MR.GHULE A.V.
Assistant Professor,
Department Of Chemistry,
MES’S,College Of Pharmacy,Sonai.

Description

- One of the oldest antibacterial agents used to combat infection
- Used for coccal infection in 1935
- They are bacteriostatic because it inhibits bacterial synthesis of folic acid
- Clinical usefulness has decreased because of the effectiveness of other antibiotics and penicillin

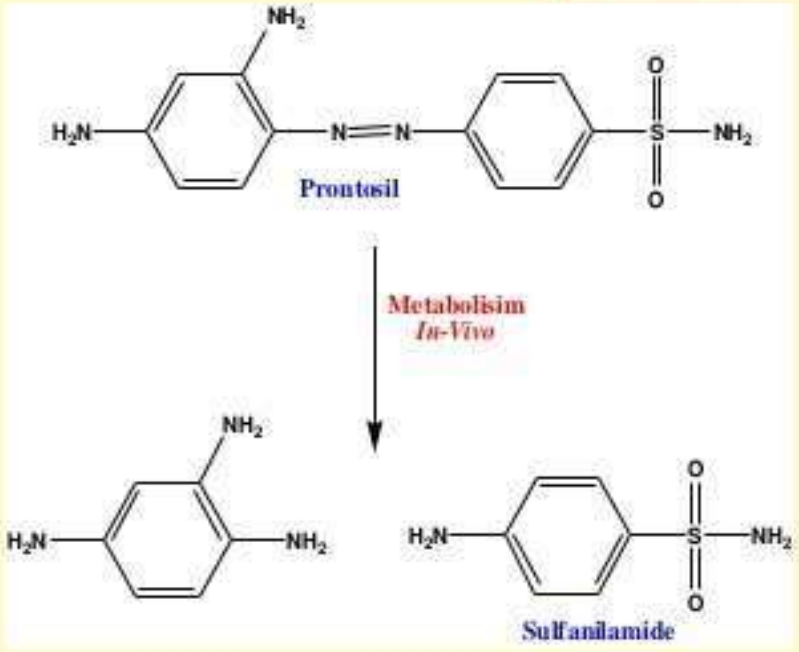
Antimicrobial activity

1) Sulfonamides have a wide range of antimicrobial activity.

- G+,G- bacteria, Nocardia,Chlamydia trachomatis, etc.
- Enteric bacteria etc. less effective

2) Sulfonamides exert only bacteriostatic effect.

PRONTOSIL



Building on Ehrlich's early work, **Gerhard Domagk**, a medical doctor employed by a German dye manufacturer made a breakthrough discovery by finding that a dye known as prontosil, dosed orally, was effective in curing life threatening streptococci infections in humans. He made the discovery in a desperate, but successful attempt to save his daughter who was dying of a streptococci infection.

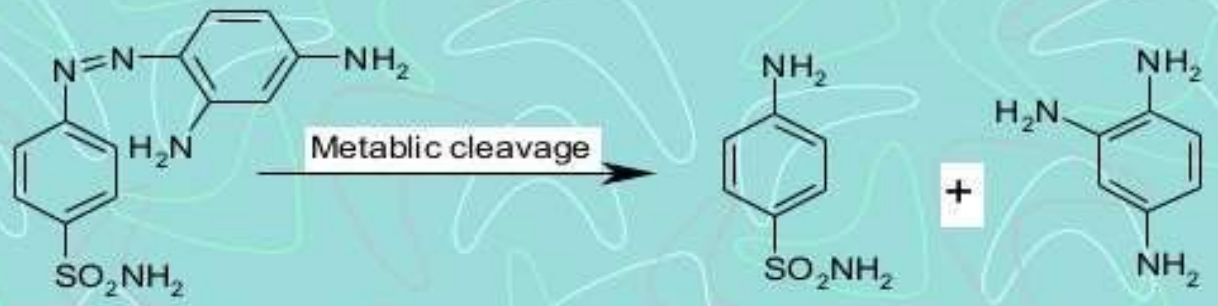
German bacteriologist and pathologist who was awarded the 1939 Nobel Prize for Physiology or Medicine for his discovery (announced in 1932) of the antibacterial effects of Prontosil, the first of the sulfonamide drugs.

- ✓ Presence of free amino group

⇩

Antibacterial action

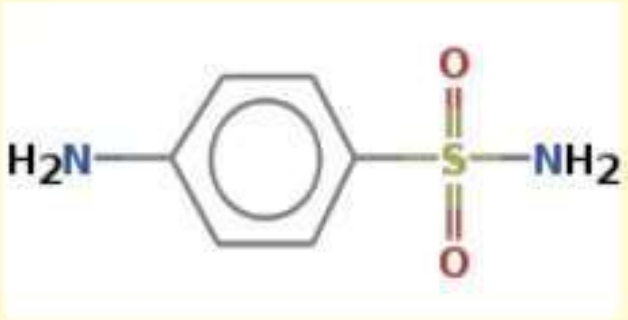
- ✓ Prontosil red ⟹ Prodrug
- ✓ In vitro ⟹ Inactive
- ✓ In vivo ⟹ Active



Prontosil Red

Sulphonamide

Chemistry of Sulfonamide



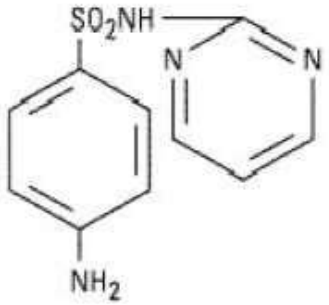
- Recognized since 1932.
- In clinical usage since 1935.
- First compounds found to be effective antibacterial agents in safe dose ranges.
- Chemically, it is a molecule containing the sulfonamido (sulfanilamide, SO_2NH_2) functional group attached to an aniline.
- Structurally related to p-amino benzoic acid (PABA).
- This group is also present in other non-antibacterial compounds like

-Sulphonureas
-Benzothiazids
-Furosemide
-Acetazolamide

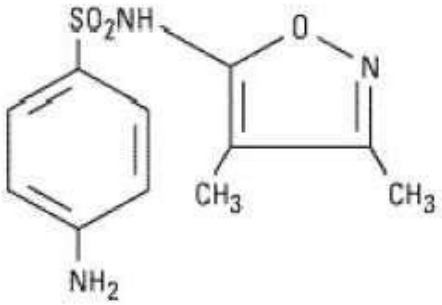
They act as antimicrobial agents by inhibiting bacterial growth and activity and commonly *called sulfa drugs*.

Chemistry

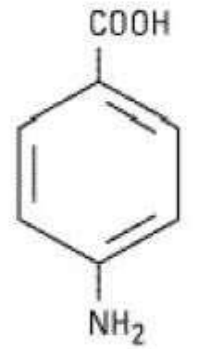
Sulfanilamide



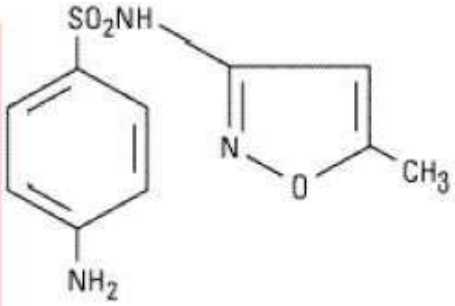
Sulfadiazine



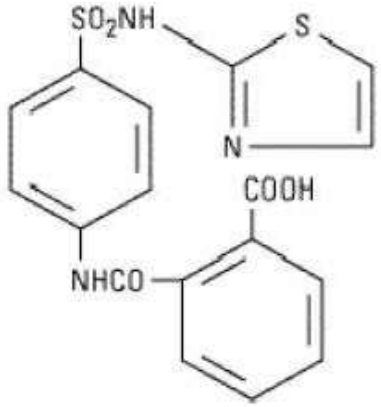
Sulfisoxazole



p-Aminobenzoic acid (PABA)



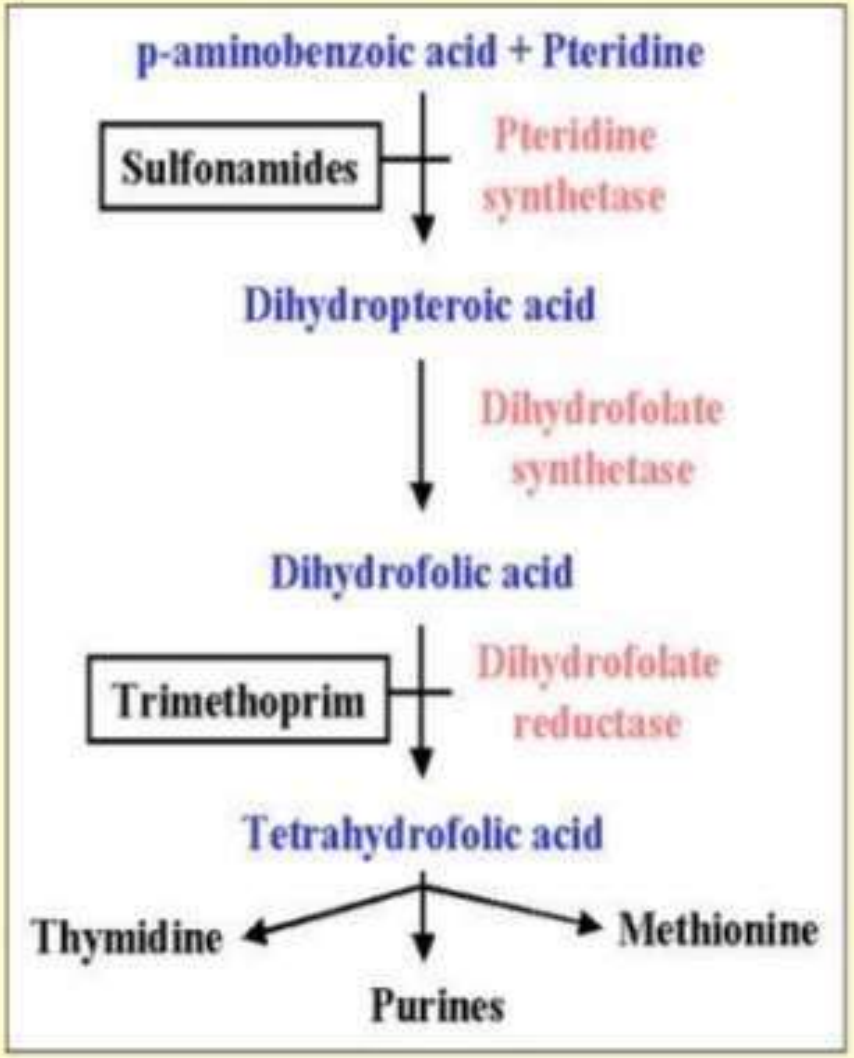
Sulfamethoxazole



Sulfathalidine
(phthalylsulfathiazole)

Mechanism of Sulfonamide

- Sulfonamide molecular structure is similar to p-Amino benzoic acid (PABA) which is needed in bacteria organisms as a substrate of the enzyme dihydro pteroate synthetase for the synthesis of Tetra Hydro Folic acid (THF).
- Folic acid - synthesized from PABA, pteridine and glutamate.
- All sulfonamides are analogs of PABA.
- All sulfa drugs are bacteriostatic.



Mechanism of action

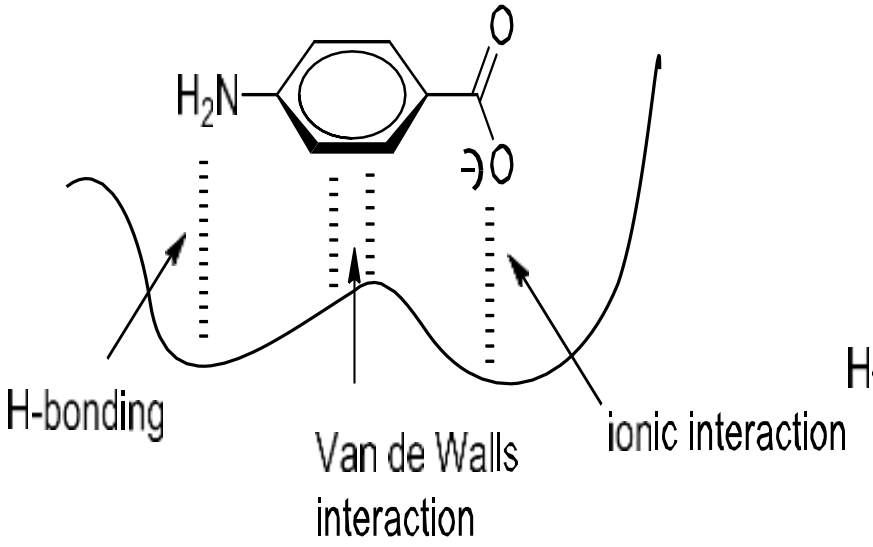
- Structural analogs of para-aminobenzoic acid (PABA)
- Inhibit dihydropteroate synthase - needed for folic acid synthesis
- Prevent normal bacterial utilization of PABA for the synthesis of folic acid

Mechanism of action

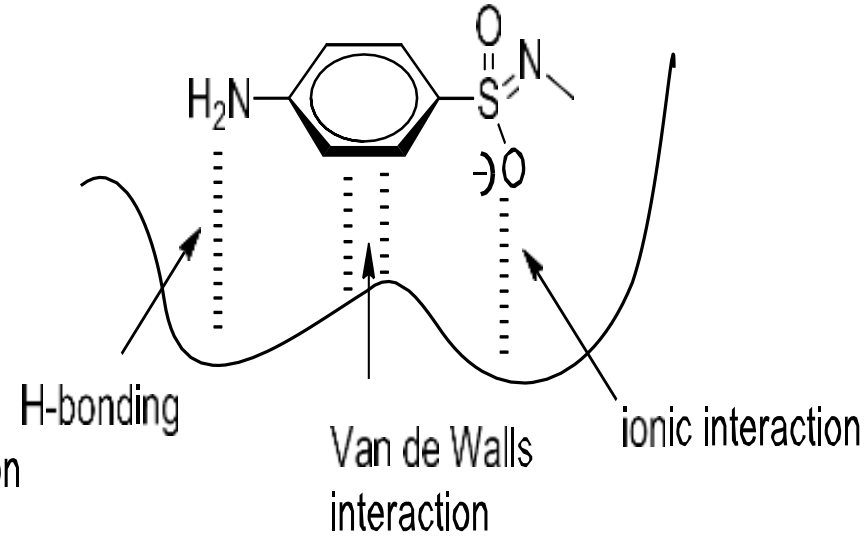
- Sulfonamides are a competitive inhibitors of dihydropteroate synthetase which is a vital enzyme for the synthesis of tetrahydrofolate (Coenzyme F).
- Tetrahydrofolate is important for pyrimidine nucleic acid synthesis so the bacteria can no longer grow and divide which gives time for the host immune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



PABA in the active site



Sulfonamide in the active site

Mechanism of action

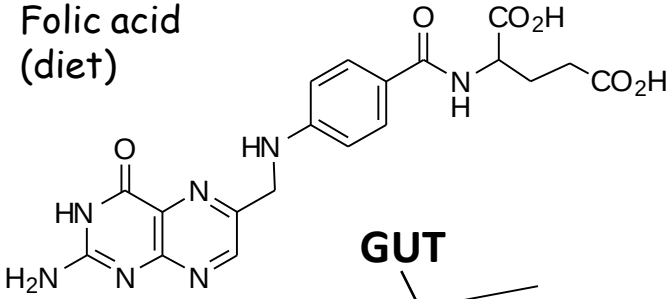
- Because sulfonamides are competitive inhibitors for the enzyme, the bacteria can increase the production of PABA to compete with sulfonamide at the active site and become resistant to sulfa drugs.
- In such case, the dose of sulfonamide agents should be increased to overcome this resistant mechanism. But this high dose is accompanied with an increase in side effects especially the crystalluria.

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 synthetaze enzyme which means sulfonamides have selective antibacterial activity.

Mammalian Folate biosynthesis

Folic acid (diet)



GUT

Dihydrofolate synthetase

Dihydrofolate

Dihydrofolate reductase

Tetrahydrofolate

Methylenetetrahydrofolate

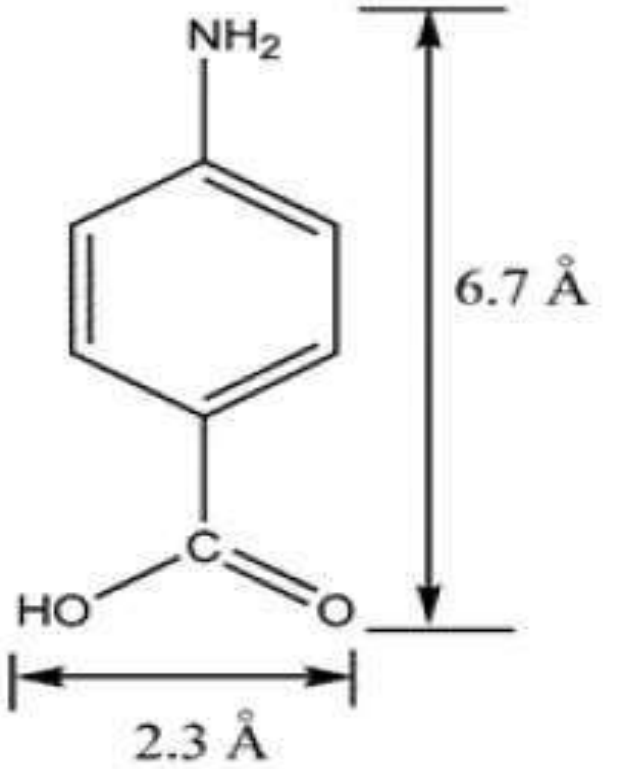
Thymidylate synthetase

dTMP (Thymidine)

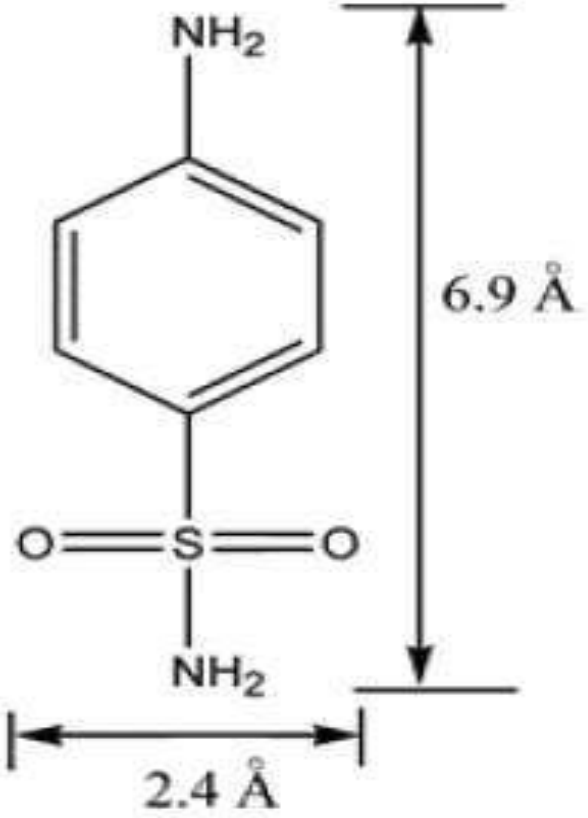
dUMP (uridine)

DNA synthesis

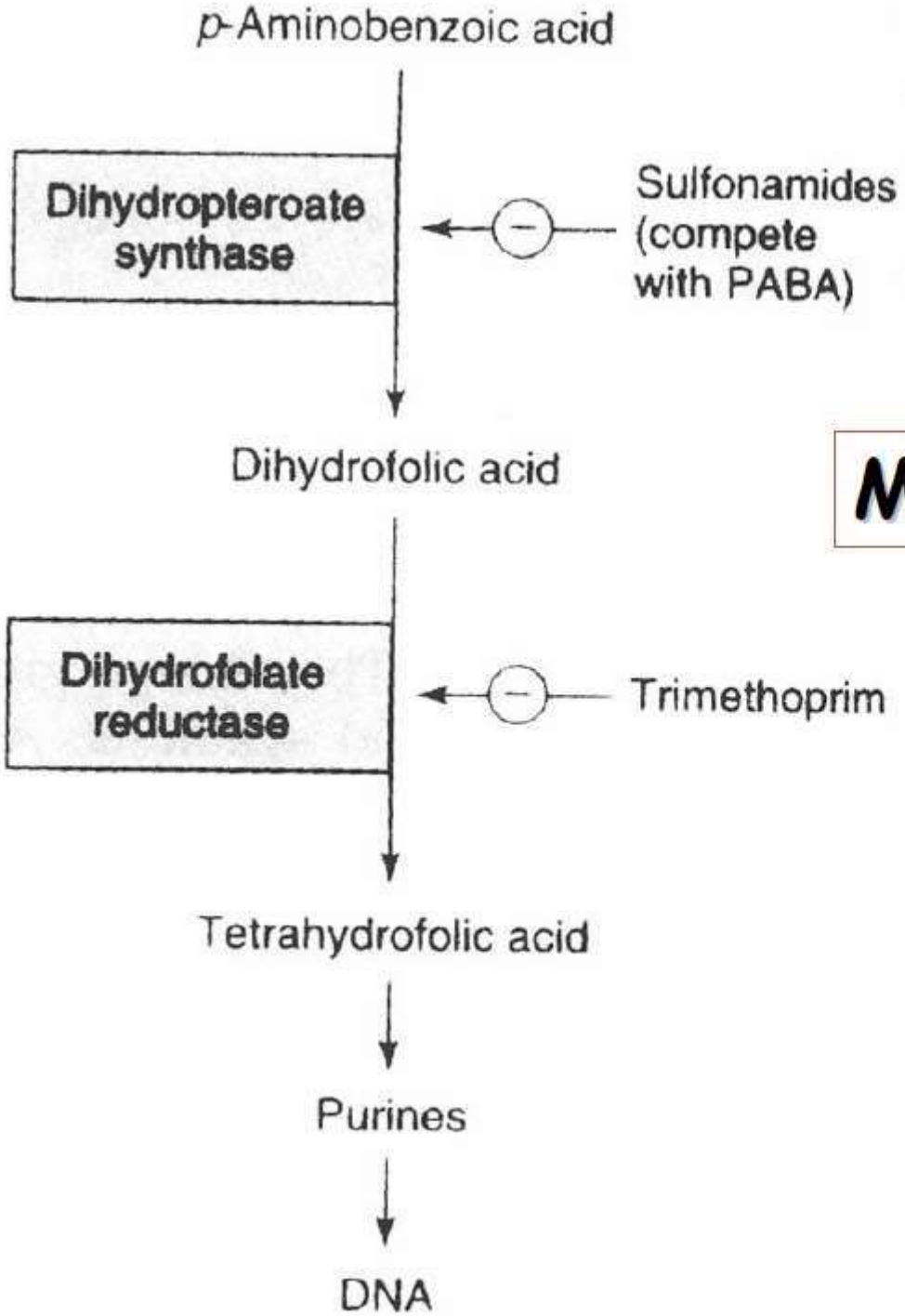
Structural Similarity :



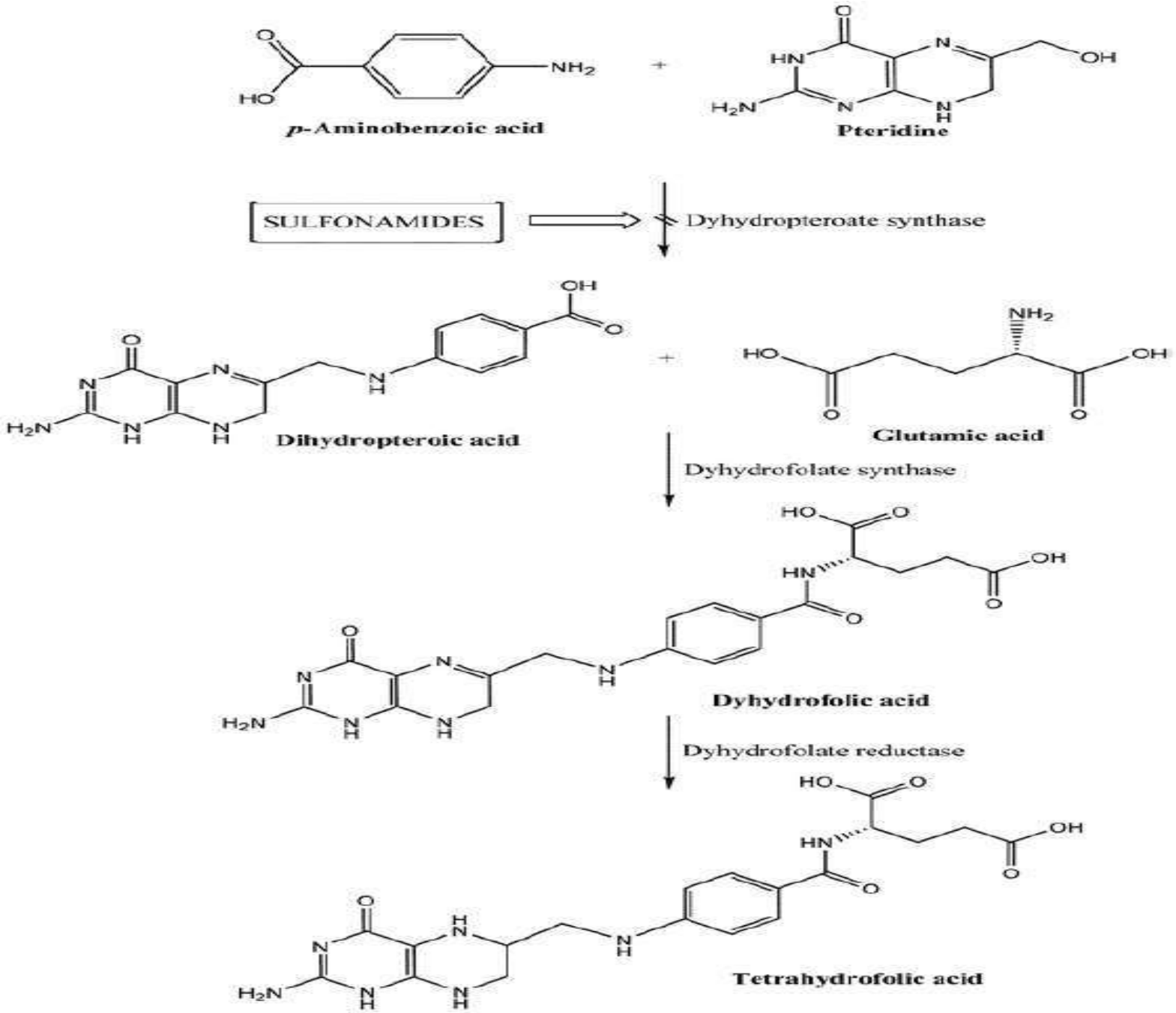
p-Aminobenzoic acid (PABA)



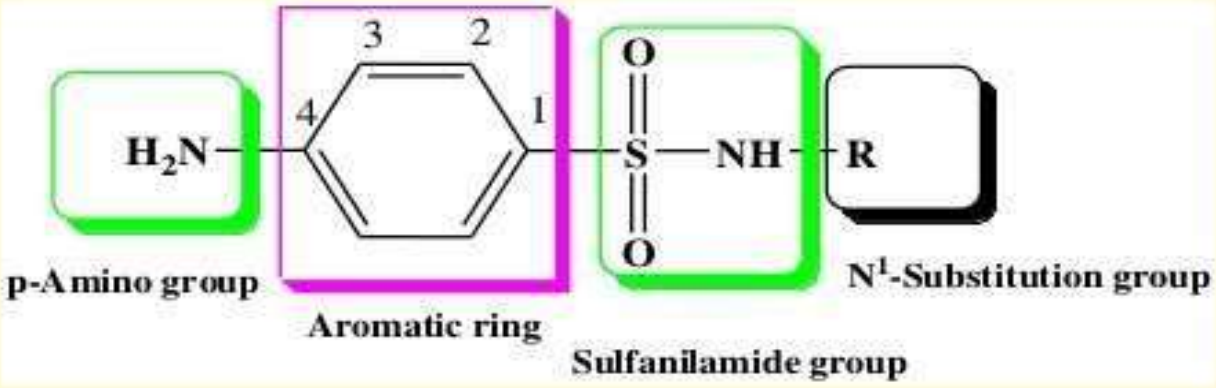
Sulfanilamide



Mechanism of action


p-Aminobenzoic acid
Pteridine
SULFONAMIDES
Dyhydropteroate synthase
Dihydropteroic acid
Glutamic acid
Dyhydrofolate synthase
Dyhydrofolic acid
Dyhydrofolate reductase
Tetrahydrofolic acid

SAR of Sulfonamide



- The amino & Sulphonyl groups on the benzene ring are essential & should be in 1,4-position

- Replacement of Aromatic ring by other ring systems or the introduction of additional substituents on it decreases or abolish activity.

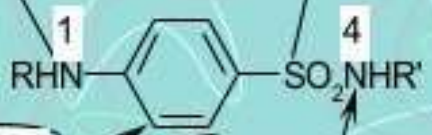
- Exchange of the -SO_2NH group by –CO-NH reduce the activity.

- Substitution of Aromatic Heterocyclic nuclei at N^1 - yields highly potent compounds.

- N^1 –Di substitution in general leads to inactive.

The free aromatic amino group should reside para to the sulphonamide group

Sulphur atom should be directly linked to the benzene ring



Substituents at these positions results in devoid of antibacterial activity

Substitution at this position activity varies with the nature of substituents.

1) Electron donating substituents to SO2 leads to increase in antibacterial activity.
2) Heterocyclic substituents leads to highly potent derivatives.
3) Substitution of free Sulphonic acid (-SO3H) group for sulphonamide function destroys activity.
4) Replacement by a sulfinic acid group (-SO2H) an acetylation of N1 positio retains activity.

Structure activity relationship of sulphonamide

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

BACTERIAL SPECTRUM

- Staphylococcus pneumonia
- S. Pyogenes
- H. Influenzae
- H. Ducrey
- Nocardia
- Actinomycin

Classification According To Duration of Action

Orally absorbable agents

Short acting (6-9hrs.)-

- Sulfadiazine
- Sulfacytine
- Sulfamethizole
- Sulfisoxazole

Intermediate acting (10-12hrs.)-

- Sulfamethaxazole
- Sulfamoxole

Long acting(7days)-

- Sulfadoxine
- Sulfamethopyrazine

Orally non absorbable agents

- Sulfasalazine
- Olsalazine

Topical agents

- Silver sulfadiazine
- Sulfacetamide
- Mafenide

Classification According To Therapeutic Use

- **Topically applied sulfonamides**

for eye infection-
Sulfacetamide(10%,20%&30%)
for skin infection-
Silver sulfadiazine
Mefanide acetate

- **GIT Infections**

Succinyl sulfathaizole,
Phthalyl sulfathiazole,
Sulfaguanidine

- **Meningitis**

Sulfadiazine,
Sulfadimidine

- **UTI Infections**

Sulfioxazole,
Sulfamethopyrazine

- **Respiratory tract infections**

Sulfaphenazine,
Cotrimoxazole

- **Leprosy**

Dapsone,
Solapsone

- **Drugs for bowel disinfection**

Sulfasalazine,
Pthalylsulfathiazole

- **Malaria**

Sulfadoxine + Pyrimethamine

- **Nocardiosis**

Sulfadiazine,
Sulfisoxazole

- **Children's antibacterial drugs**

Sulfafurazole (in Pediazole)

Antimicrobials

Short-acting
Sulfacetamide
Sulfadiazine
Sulfadimidine
Sulfafurazole (sulfisoxazole)
Sulfisomidine (sulfaisodimidine)

Intermediate-acting
Sulfadoxine
Sulfamethoxazole
Sulfamoxole
Sulfanitran

Long-acting
Sulfadimethoxine
Sulfamethoxypyridazine
Sulfametoxydiazine

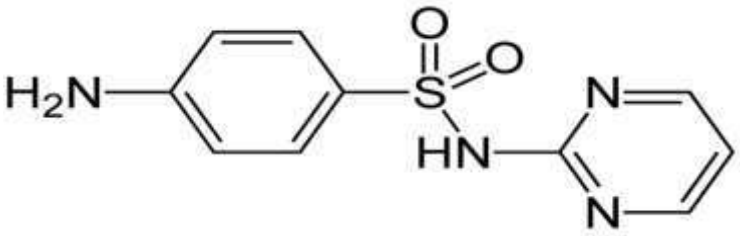
Ultra long-acting

Sulfadoxine
Sulfametopyrazine
Terephtyl

Orally Absorbable Sulphonamides

- Short acting (6-9hrs)
- Sulfadiazine
- Sulfacytine
- Sulfamethizole
- Sulfisoxazole

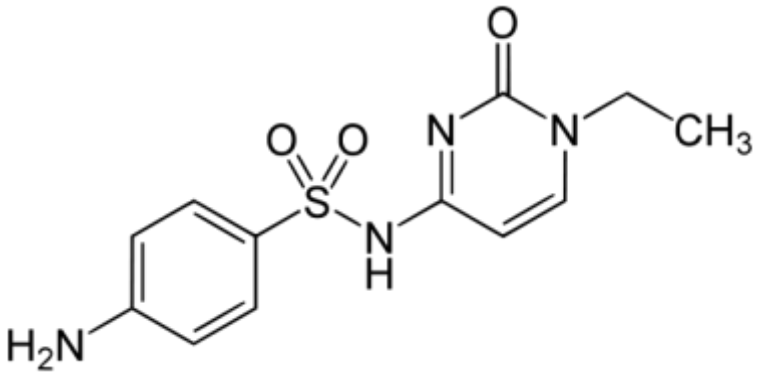
Sulfadiazine



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

- **Sulfadiazine** is antibacterial. Used together with pyrimethamine, it is the treatment of choice for toxoplasmosis. It is a second line treatment for otitis media, prevention of rheumatic fever, chancroid, chlamydia and infections by *Haemophilus influenzae*. It is taken by mouth.
- Common side effects include nausea, diarrhea, headache, fever, rash, depression, and pancreatitis.It should not be used in people who have severe liver problems, kidney problems, or porphyria. If used during pregnancy it may increase the risk of kernicterus in the baby.While the company that makes it does not recommend use during breastfeeding, use is believed to be safe if the baby is otherwise healthy. It is in the sulfonamide class of medications.

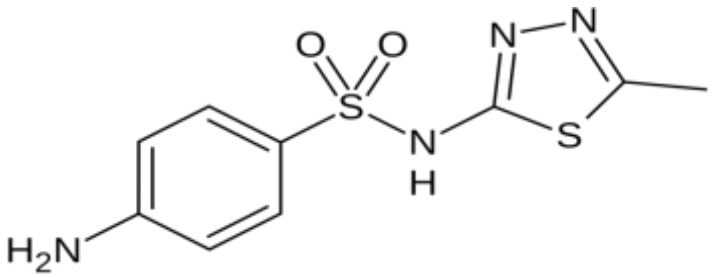
Sulfacytine



4-amino-N-(1-ethyl-2-oxopyrimidin-4-yl)benzenesulfonamide

Sulfacytine is a short-acting sulfonamide antibiotic, taken orally for treatment against bacterial infections. Sulfonamides, as a group of antibiotics, work by inhibiting the bacterial synthesis of folate. In 2006 the drug was discontinued.

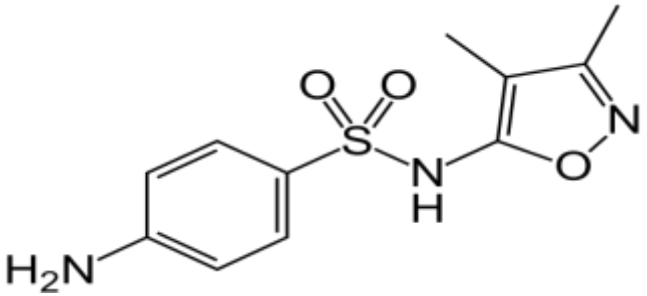
Sulfamethizole



4-amino-N-(5-methyl-1,3,4-thiadiazol-2-yl)benzenesulfonamide

Sulfamethizole is a competitive inhibitor of bacterial enzyme dihydropteroate synthetase. The normal para-aminobenzoic acid (PABA) substrate is prevented from binding. The inhibited reaction is necessary in these organisms for the synthesis of folic acid.

Sulfisoxazole (Sulfafurazole)



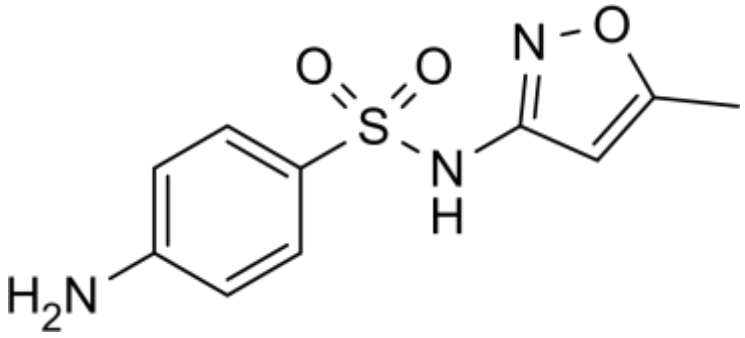
4-Amino-N-(3,4-dimethyl-5-isoxazolyl)benzenesulphonamide

Sulfisoxazole is a **sulfonamide** ("**sulfa**") **antibiotic** that helps keep bacteria from growing in your body. Sulfisoxazole is used to treat or prevent many different types of **infections** caused by bacteria, such as **bladder infections**, **ear infections**, or**meningitis**.

Orally Absorbable Sulphonamides

- Intermediate acting (10-12hrs)
- Sulfamethoxazole
- Sulfamoxole

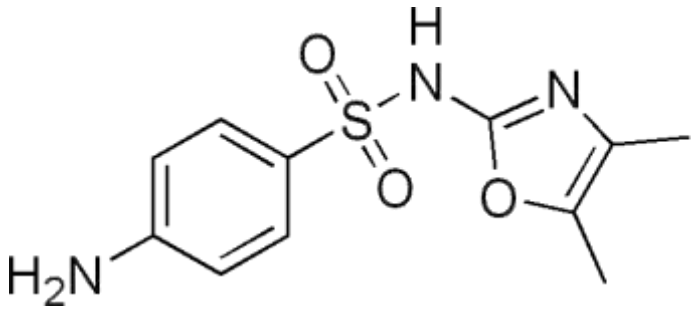
Sulfamethoxazole



4-Amino-N-(5-methyl-3-isoxazolyl)benzenesulfonamide

- Sulfamethoxazole is a sulfonamide drug that inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid (PABA) for binding to dihydropteroate synthetase (dihydrofolate synthetase). Sulfamethoxazole is bacteriostatic in nature. Inhibition of dihydrofolic acid synthesis decreases the synthesis of bacterial nucleotides and DNA. Sulfamethoxazole is normally given in combination with Trimethoprim, a dihydrofolate reductase inhibitor, which inhibits the reduction of dihydrofolic acid to tetrahydrofolic acid. Studies have shown that bacterial resistance develops more slowly with the combination of the two drugs than with either Trimethoprim or Sulfamethoxazole alone.

Sulfamoxole



4-amino-N-(4,5-dimethyl-1,3-oxazol-2-yl)benzenesulfonamide

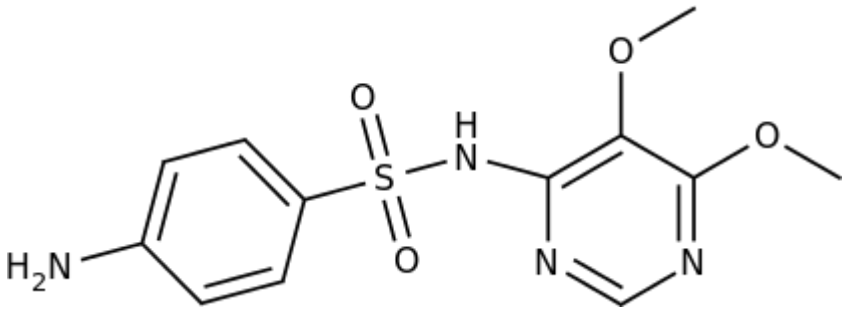
Sulfamoxole And Trimethoprim is used in the treatment of:
AIDS-Related Opportunistic Infections
Bronchitis
Escherichia coli Infections
Eye Infections, Bacterial
Pneumonia, Pneumocystis
Proteus Infections
Staphylococcal Infections
Toxoplasmosis
Urinary Tract Infections

Orally Absorable Sulphonamides

Long Acting Sulfonamides (7 days)

- Sulfadoxine
- Sulphamethopyrazine

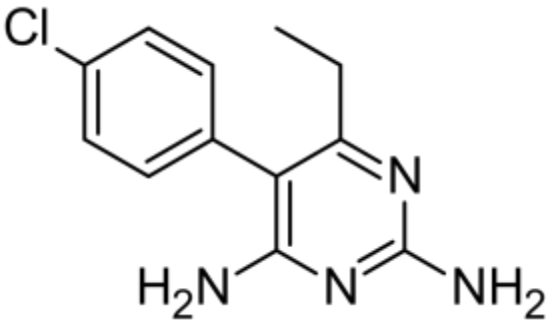
Sulfadoxine



4-amino-N-(5,6-dimethoxypyrimidin-4-yl)benzenesulfonamide

- **Sulfadoxine** (also spelled **sulphadoxine**) is an ultra-long-lasting sulfonamide used in combination with pyrimethamine to treat malaria.
- It was previously used to prevent malaria but due to high levels of resistance, this use is no longer recommended routinely.
- It is also used, usually in combination with other drugs, to treat or prevent various infections in livestock

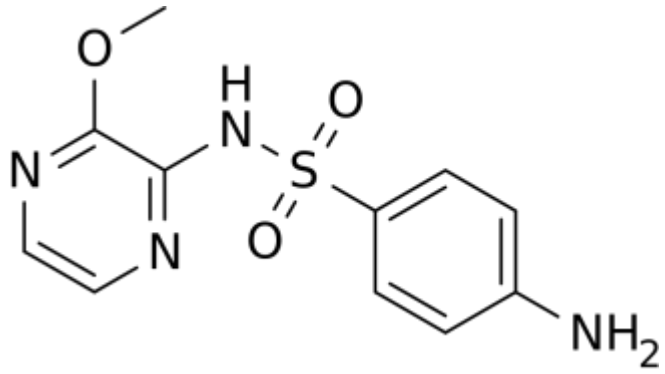
Sulfadoxine/Pyrimethamine



- **Sulfadoxine/pyrimethamine**, sold under the brandname **Fansidar**, is a combination medication used to treat malaria. It contains sulfadoxine (a sulfonamide) and pyrimethamine (an antiprotozoal). For the treatment of malaria it is typically used along with other antimalarial medication such as artesunate.

- Side effects include diarrhea, rash, itchiness, headache, and hair loss. Rarely a severe allergic reaction or rash such as toxic epidermal necrolysis, may occur. It is not generally recommended in people with a sulfonamide allergy or significant liver or kidney disease. It is unclear if use during pregnancy is safe for the baby. It works by blocking malaria's ability to use folinic acid

Sulfamethopyrazine (Sulfasalene)



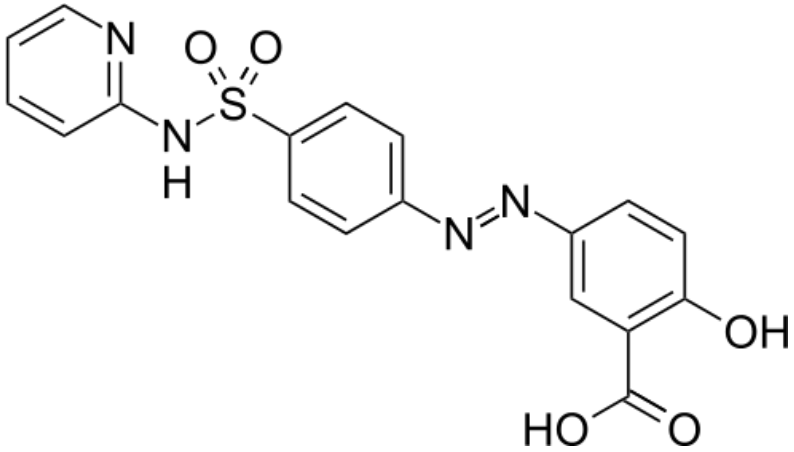
4-amino-N-(3-methoxypyrazin-2-yl)benzenesulfonamide

Sulfalene or **sulfametopyrazine** is a long-acting sulfonamide antibacterial used for the treatment of chronic bronchitis, urinary tract infections and malaria. As of 2014 there were only two countries in which it is currently still marketed: Thailand and Ireland.

Orally Non Absorbable Sulfonamides

- Sulfasalazine
- Olsalazine

Sulfasalazine

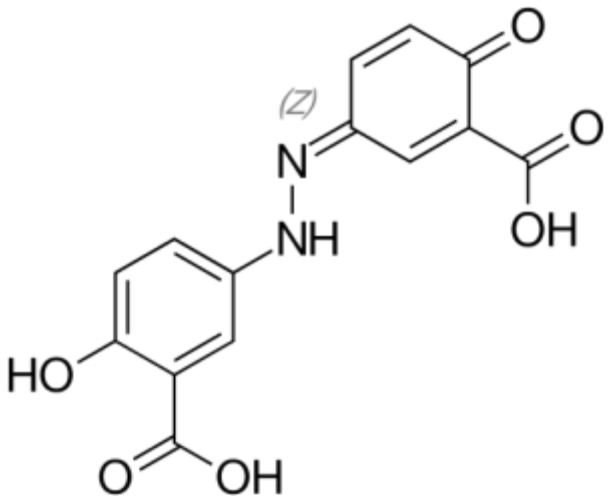


5-((P-(2-Pyridylsulfamoyl)phenyl)azo)salicylic acid

- Sulfasalazine is used to treat a certain type of bowel disease called ulcerative colitis. This medication does not cure this condition, but it helps decrease symptoms such as fever, stomach pain, diarrhea, and rectal bleeding. After an attack is treated, sulfasalazine is also used to increase the amount of time between attacks. This medication works by reducing irritation and swelling in the large intestines.
- In addition, delayed-release tablets of sulfasalazine are used to treat rheumatoid arthritis. Sulfasalazine helps to reduce joint pain, swelling, and stiffness. Early treatment of rheumatoid arthritis with sulfasalazine helps to reduce/prevent further joint damage so you can do more of your normal daily activities. This medication is used with other drugs, rest, and physical therapy in patients who have not responded to other medications (salicylates, nonsteroidal anti-inflammatory drugs-NSAIDs).

Olsalazine

Not a Sulfonamide



5-[(2Z)-2-(3-carboxy-4-oxocyclohexa-2,5-dien-1-ylidene)hydrazinyl]-2-hydroxybenzoic acid

Sulfonamide and Trimethoprim Combinations

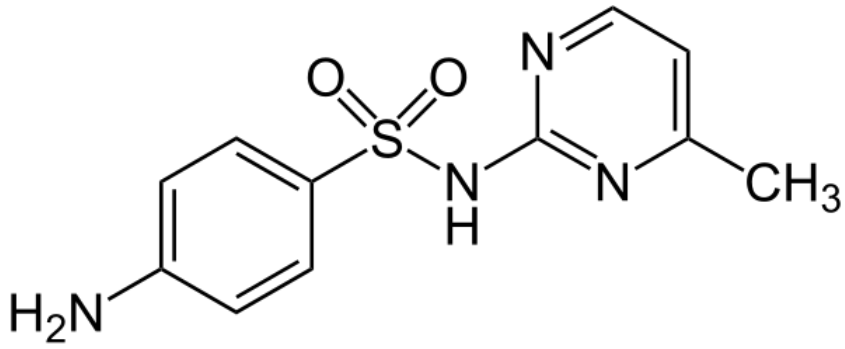
- Sulfadiazine And Tetroxoprim
- Sulfadiazine And Trimethoprim
- Sulfamerazine And Trimethoprim
- Sulfamethoxazole & Trimethoprim
- Sulfametrole And Trimethoprim
- Sulfamoxole And Trimethoprim

Sulfamoxole And Trimethoprim

Uses of Sulfamoxole And Trimethoprim

AIDS-Related Opportunistic Infections
Bronchitis
Escherichia coli Infections
Eye Infections, Bacterial
Pneumonia, Pneumocystis
Proteus Infections
Staphylococcal Infections
Toxoplasmosis
Urinary Tract Infections

Sulfamerazine And Trimethoprim



Sulfamerazine And Trimethoprim is used in the treatment of:

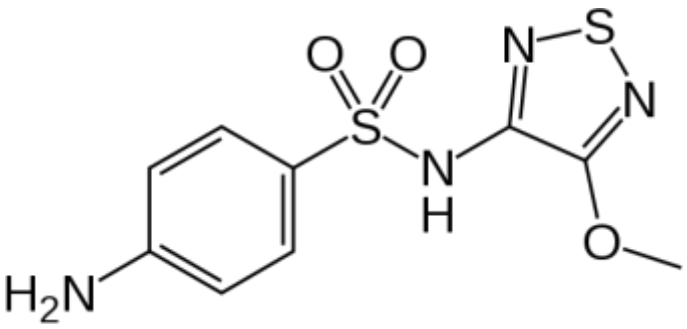
AIDS-Related Opportunistic Infections
Bronchitis
Escherichia coli Infections
Eye Infections, Bacterial
Pneumonia, Pneumocystis
Proteus Infections
Staphylococcal Infections
Toxoplasmosis
Urinary Tract Infections

Sulfamethoxazole & Trimethoprim

Sulfamethoxazole/trimethoprim is a prescription medication used to treat bacterial infections of the urinary tract, lungs, intestines, and ears. It also treats infections that cause traveler's diarrhea. This medication is a single formulation containing 2 drugs, sulfamethoxazole and trimethoprim.

G6PD is an enzyme in your body that is responsible for helping red blood cells to work properly. Some patients are born with less of this enzyme in their bodies, leading to the destruction of red blood cells.
When sulfamethoxazole/trimethoprim is used in patients with G6PD deficiency, they have a higher chance of experiencing hemolytic anemia (a condition in which the body does not have enough red blood cells to deliver oxygen to your tissues).
G6PD testing may be done to determine whether you are at a higher risk of experiencing hemolytic anemia if you are to be treated with sulfamethoxazole/trimethoprim.

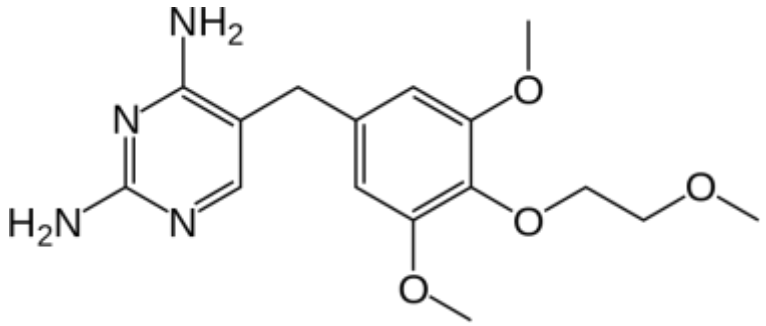
Sulfametrole And Trimethoprim



Sulfametrole And Trimethoprim is used in the treatment of:

AIDS-Related Opportunistic Infections
Bronchitis
Escherichia coli Infections
Eye Infections, Bacterial
Pneumonia, Pneumocystis
Proteus Infections
Staphylococcal Infections
Toxoplasmosis
Urinary Tract Infections

Tetroxoprim



Uses of Sulfadiazine +Tetroxoprim:
Sulfadiazine And Tetroxoprim is used in the treatment of:

AIDS-Related Opportunistic Infections
Chlamydiaceae Infections
Enterobacteriaceae Infections
Malaria
Nocardia Infections
Toxoplasmosis
Urinary Tract Infections
Sulfadiazine And Tetroxoprim is used in the prevention of:
Rheumatic Fever

Sulfadiazine And Tetroxoprim

Uses of Sulfadiazine And Tetroxoprim

Sulfadiazine And Tetroxoprim is used in the treatment of:

AIDS-Related Opportunistic Infections

Chlamydiaceae Infections

Enterobacteriaceae Infections

Malaria

Nocardia Infections

Toxoplasmosis

Urinary Tract Infections

Sulfadiazine And Tetroxoprim is used in the prevention of:

Rheumatic Fever

Sulfadiazine And Trimethoprim

. **Uses of Sulfadiazine And Trimethoprim**

AIDS-Related Opportunistic Infections
Chlamydiaceae Infections
Enterobacteriaceae Infections
Malaria
Nocardia Infections
Toxoplasmosis
Urinary Tract Infections
Bronchitis
Escherichia coli Infections
Eye Infections, Bacterial
Pneumonia, Pneumocystis
Proteus Infections
Staphylococcal Infections

Sulfadiazine And Trimethoprim is used in the prevention of:
Rheumatic Fever

Interactions of Sulfonamide/ Trimethoprim Combinations

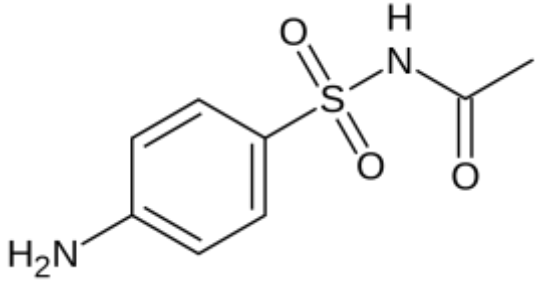
- CYCLOSPORINE/TRIMETHOPRIM
- DOFETILIDE/TRIMETHOPRIM
- EPLERENONE/TRIMETHOPRIM
- ERYTHROMYCIN/TRIMETHOPRIM
- FOSPHENYTOIN SODIUM/TRIMETHOPRIM
- MEPHENYTOIN/TRIMETHOPRIM
- METHOTREXATE/TRIMETHOPRIM
- PHENYTOIN/TRIMETHOPRIM
- PRALATREXATE/TRIMETHOPRIM
- PROCAINAMIDE/TRIMETHOPRIM
- SPIRONOLACTONE/TRIMETHOPRIM
- SULFAMETHOXAZOLE/TRIMETHOPRIM

Topically Used Sulfonamides

For Eye Infections:

Sulfacetamide (10%, 20%, 30%)

Sulfacetamide



N-(4-aminophenyl)sulfonylacetamide

Sulfacetamide 10% topical lotion, is approved for the treatment of acne and seborrheic dermatitis. When combined with sulfur, it is sold, which contain 10% sulfacetamide and 5% sulfur.

Sulfacetamide has been investigated for use in the treatment of pityriasis versicolor and rosacea. It also has anti-inflammatory properties when used to treat blepharitis or conjunctivitis (in eye-drop solution).

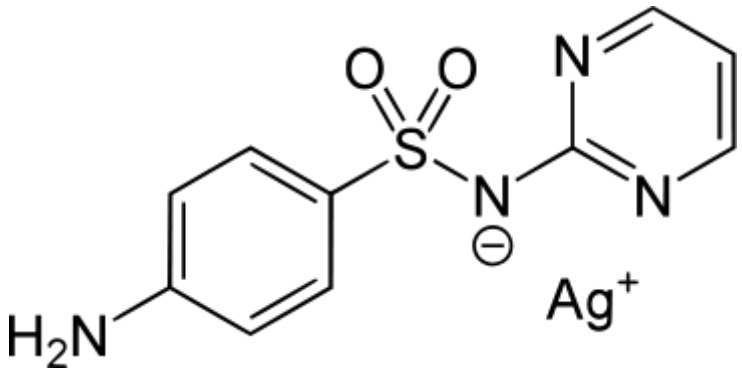
It is believed to work by limiting the presence of folic acid which bacteria need to survive. Sulfacetamide has antibacterial activity and is used to control acne. Products containing sulfacetamide and sulfur (a keratolytic) are commonly promoted for the treatment of acne rosacea (rosacea with papules, pustules, or both). There are several prescription topical products containing sulfacetamide, such as foams, shampoos, cream and washes.

Topically Used Sulfonamides

- **For Skin Infections**

- **Silver Sufadiazine**
- **Mefanide Acetate**

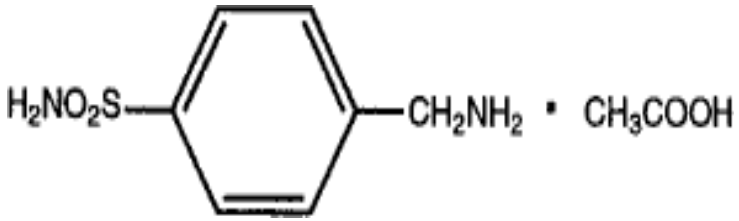
Silver Sufadiazine



4-amino-N-(2-pyrimidinyl)benzenesulfonamide silver salt

- **Silver sulfadiazine**, sold under the brand **Silvadene** among others, is a topical antibiotic used in partial thickness and full thickness burns to prevent infection. Tentative evidence has found other antibiotics to be more effective and therefore it is no longer generally recommended.
- Common side effects include itching and pain at the site of use.
- Other side effects include low white blood cell levels, allergic reactions, bluish grey discoloration of the skin, red blood cell breakdown, or liver inflammation. Caution should be used in those allergic to other sulfonamides. It should not be used in pregnant women who are close to delivery. Silver sulfadiazine is not recommended in children less than two months.

Mefanide Acetate



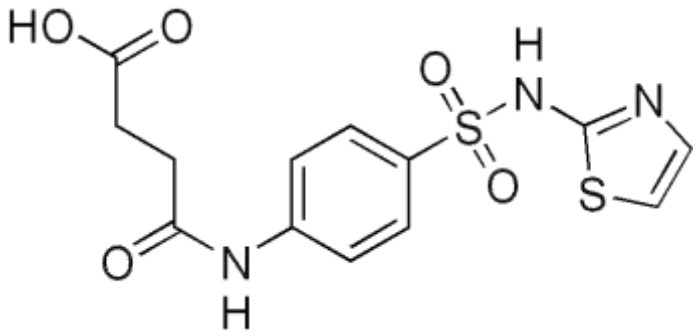
α-amino-p- toluenesulfonamide monoacetate

•

Sulfonamides Used for GIT Infections

- Succinylsulfathiazole
- Pthalylsulfathiazole
- Sulfaguanidine

Succinylsulfathiazole

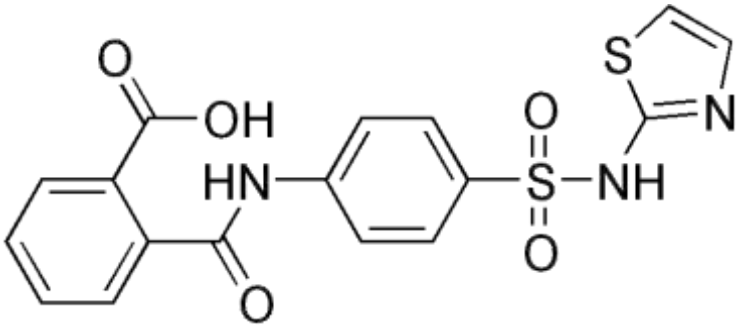


4-oxo-4-[4-(1,3-thiazol-2-ylsulfamoyl)anilino]butanoic acid

Succinylsulfathiazole is a sulfonamide. It is also spelled as succinylsulphathiazole. It is a white or yellow-white crystalline powder. It dissolves in aqueous solutions of alkali hydroxides and carbonates but is very slightly soluble in water.

- It is classified as ultra long acting drug. About 95% of the drug remains in the intestine and only 5% is hydrolyzed, slowly, to Sulfathiazole and is absorbed.
- The drug is used for its antibacterial activity in the GIT. The dose is 10g - 20g daily in divided doses.

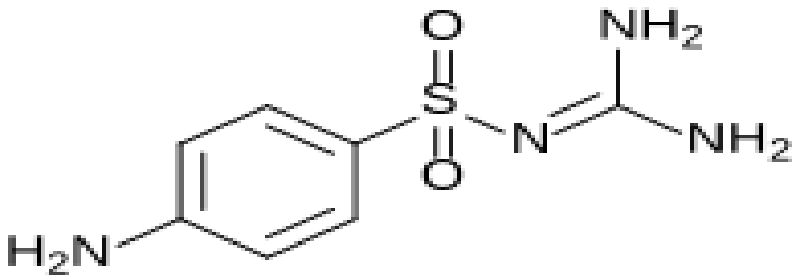
Phthalylsulfathiazole



2-[[4-(1,3-thiazol-2-ylsulfamoyl)phenyl]carbamoyl]benzoic acid

- **Uses**
- Phthalylsulfathiazole is used for the treatment, control, prevention, & improvement of the following diseases, conditions and symptoms:
- Bacillary dysentery
- Dysentery
- Colitis
- Gastroenteritis.

Sulfaguanidine



2-(4-aminophenyl)sulfonylguanidine

Uses

- **Sulfaguanidine** is used for the treatment, control, prevention, & improvement of the following diseases, conditions and symptoms:
- Bacillary dysentery
- **Sulfaguanidine** may also be used for purposes not listed here.

Classification According To Therapeutic Use

- **Topically applied sulfonamides**

for eye infection-
Sulfacetamide(10%,20%&30%)
for skin infection-
Silver sulfadiazine
Mefanide acetate

- **GIT Infections**

Succinyl sulfathaizole,
Phthalyl sulfathiazole,
Sulfaguanidine

- **Meningitis**

Sulfadiazine,
Sulfadimidine

- **UTI Infections**

Sulfioxazole,
Sulfamethopyrazine

- **Respiratory tract infections**

Sulfaphenazine,
Cotrimoxazole

- **Leprosy**

Dapsone,
Solapsone

- **Drugs for bowel disinfection**

Sulfasalazine,
Pthalylsulfathiazole

- **Malaria**

Sulfadoxine + Pyrimethamine

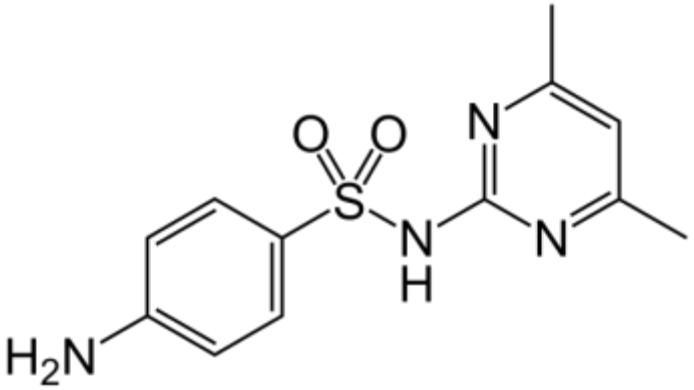
- **Nocardiosis**

Sulfadiazine,
Sulfisoxazole

Sulfonamides Used in Meningitis

- Sulfadiazine (Discussed Earlier)
- Sulfadimidine

Sulfadimidine (Sulfamethazine)



4-amino-N-(4,6-dimetyl-2-pyrimidinyl)- benzenesulfonamide,

Uses

Sulfadimidine is used for the treatment, control, prevention, & improvement of the following diseases, conditions and symptoms:

Chlamydia

Toxoplasma

Coccidia

Sulfonamides Used In UTI Infections

- Sulfioxazole
- Sulfamethopyrazine (Discussed Earlier)

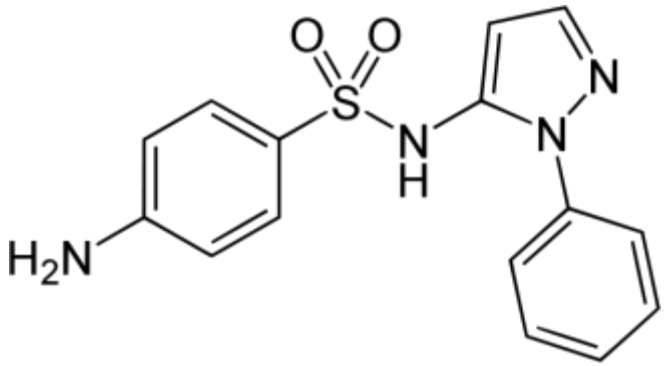
Sulfisoxazole

- Sulfisoxazole is a **sulfonamide** ("**sulfa**") **antibiotic** that helps keep bacteria from growing in your body. Sulfisoxazole is used to treat or prevent many different types of **infections** caused by bacteria, such as **bladder infections**, **ear infections**, or **meningitis**.
- The sulfonamides are widely distributed throughout all tissues. High levels are achieved in pleural, peritoneal, synovial, and ocular fluids. Although these drugs are no longer used to treat meningitis, CSF levels are high in meningeal infections. Their antibacterial action is inhibited by pus.

Sulfonamides Used For RTIs

- Sulfaphenazine
- Cotrimoxazole

Sulfaphenazole



Benzenesulfonamide, 4-amino-N-(1-phenyl-1H-pyrazol-5-yl)-

- **Sulfaphenazole** is used for the treatment, control, prevention, & improvement of the following diseases, conditions and symptoms:
- Leprosy
- Bacterial infections

Co-trimoxazole (Trimethoprim-sulfamethoxazole) (DHFR Inihibitor)

Treatment of urinary tract infections due to E. coli Klebsiella and Enterobacter sp, M. morganii P. mirabilis and P. vulgaris; acute otitis media; acute exacerbations of chronic bronchitis due to susceptible strains of H. influenzae or S. pneumoniae; treatment and prophylaxis of Pneumocystis jirovecii pneumonia (PCP); traveler's diarrhea due to enterotoxigenic E. coli; treatment of enteritis caused by Shigella flexneri or Shigella sonnei

Cotrimoxazole - Uses

- Uncomplicated infection of the lower urinary tract infection
  - Cystitis (5 tablet dose)
  - chronic and recurrent urinary tract infections (including enterobacteriaceae) – 3-10 days
- Respiratory tract infection – lower and upper, chronic bronchitis, facio-maxillary infections, otitis media due to gm+ve cocci and H influenzae etc
- Typhoid
- Bacterial diarrhoeas & dysentery: due to campylobacter, E coli, Shigella etc.
- Pneumocystis jiroveci: Severe pneumonia - Prophylactic use in AIDS patients with neutropenia. Dose – DS tablet 4-6 times 2-3 weeks
- Chancroid – H. ducreyi
- Alternative to penicillin in agrannulocytosis patients, scepticaemia etc.

Trimethoprim

- **Trimethoprim** (trimethyl benzyl pyrimidine) is a diaminopyrimidine, chemically related to Pyrimethamine
- **Do not confuse: Clotrimazole (antiungal) - Cotrimoxazole** is TMP –SMZ, but Sulfadoxine + Pyrimethamine is **antimalarial**
- **MOA:** Sequential block of folate metabolism
- Trimethoprim is 50,000 or more times more active against bacterial DHFRase enzyme than mammalian
- So, no harm to human folate metabolism

Cotrimoxazole – general points

- Individually, both are bacteriostatic, but combination is – bactericidal
- Both drugs have almost similar half lives (10 Hrs)
- Maximum synergism if the organism is sensitive to both the agents
- Optimal synergism is obtained at 20 (S) : 1 (T) concentration (MIC of both is reduced by 3 - 6 times)
  - This ratio is obtained at 5:1 dose ratio (e.g. 800 mg:160 mg)
  - Because TMP has large Vd and enters many tissues – plasma conc. is low
- But, TMP crosses BBB and placenta and SMZ not
- TMP is more rapidly absorbed than SMZ
- TMP is 45% plasma protein bound but SMZ is 65% bound
- TMP is partly metabolized in liver

Spectrum

- **G + VE**
- *S. pneumoniae* [susceptible, there has been a disturbing increase in resistance]
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *S. pyogenes*
- *S. viridans*
- MRSA

- **G –VE**
- *E. coli*
- *Proteus mirabilis*
- *Proteus morganii*
- *Proteus rettgeri*
- *Enterobacter* spp
- *Salmonella*
- *Shigella*
- *Pseudomonas pseudomallei*
- *Serratia*
- *Klebsiella* spp.
- *Brucella abortus*
- *Pasteurella haemolytica*
- *Yersinia pseudotuberculosis*
- *Yersinia enterocolitica*

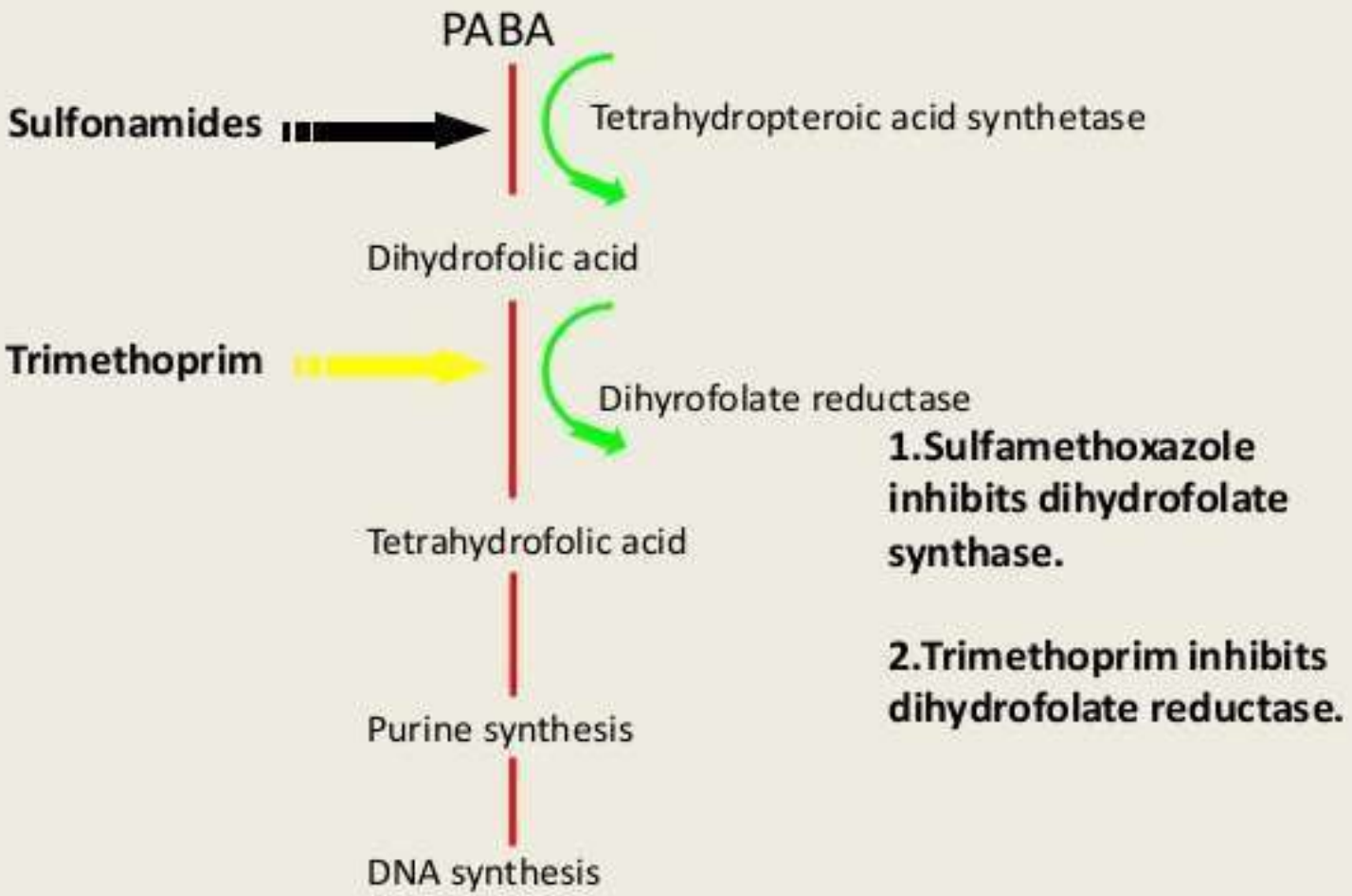
Adverse reactions

- Similar to that of sulphonamides

Therapeutic uses

- Uncomplicated lower urinary tract infections
- *Bacterial Respiratory Tract Infections*
- *Infection by Pneumocystis jiroveci*
- *In G-VE rods infection's*
- *Gastrointestinal Infections*
- *MRSA infections –skin and soft tissue infections*

MOA OF TRIMETHOPRIM-SULFAMETHOXAZOLE



1.Sulfamethoxazole inhibits dihydrofolate synthase.

2.Trimethoprim inhibits dihydrofolate reductase.

Sulfonamides Used For Bowel Disinfection

- Sulfasalazine (Discussed Earlier)
- Phthalylsulfathiazole (Discussed Earlier)

- **Sulfonamides Used in Malaria**
- Sulfadoxine + Pyrimethamine (Discussed Earlier)

- **Sulfonamides Used in Nocardiosis**
- Sulfisoxazole (Discussed Earlier)
- Sulfadiazine (Discussed Earlier)

Metabolism of Sulphonamides

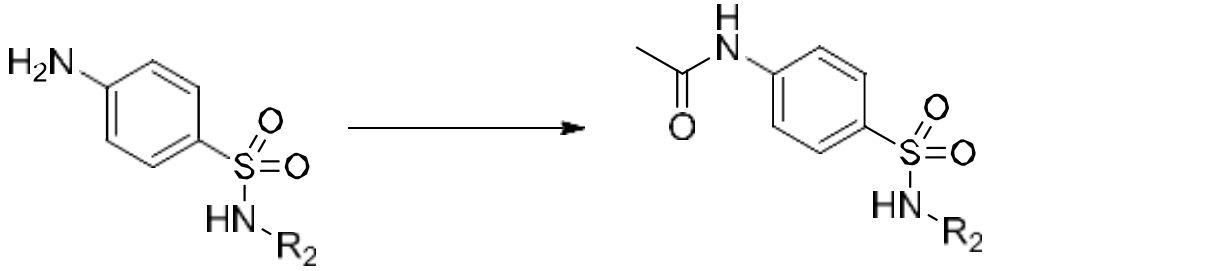
- In humans, metabolic transformation of sulfonamides takes place mainly in the liver by acetylation of amino group.
- The resulting *N*-acetyl metabolites are inactive and can be excreted in the urine together with the unchanged sulfonamides.
- However, in humans the cytochrome P450 catalyzed *N*-oxidation is also possible, which produces reactive hydroxylamine metabolites.
- This metabolic reaction is particularly present in slow acetylators with deficiency of polymorphic enzyme *N*acetyltransferase.
- Once formed, hydroxylamino metabolites can undergo auto-oxidation to the corresponding nitrozo intermediates.
- Nitrozo metabolites are unstable in body fluids and can be reduced using glutathione and excreted.
- However, when the capacity for conjugation with glutathione is exceeded, the reactive metabolites show a direct cytotoxic activity or can be bound to proteins and participate in the immune reactions

Metabolism of Sulphonamides

- Most of sulfonamides can be rapidly excreted through kidneys. The exceptions are depot sulfonamides which can be reabsorbed in the renal tubules and very slowly excreted from the body .
- The rate and mode of sulfonamide excretion depend on the applied compound, administered dose, treated species and route of administration

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.



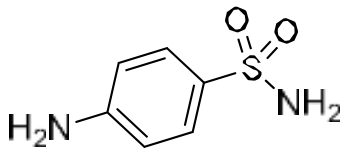
Insoluble acetylated metabolite

- 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)

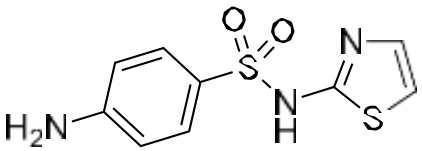
The problem of crystalluria

- 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

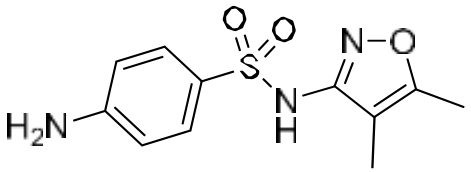
Sulfonamides with reduced crystalluria formation



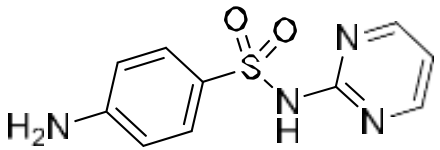
Sulfanilamide pKa = 10.4



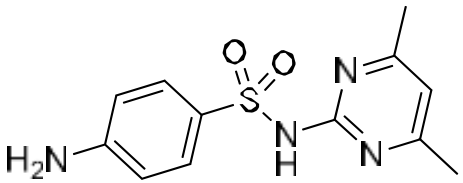
Sulfathiazole pKa = 8.5



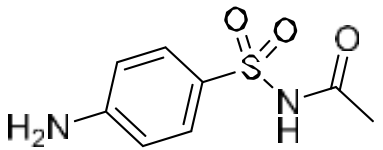
Sulfisoxazole pKa = 5.0



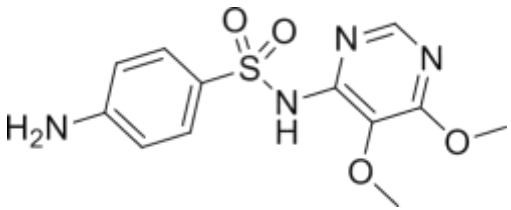
Sulfadiazine pKa = 6.5



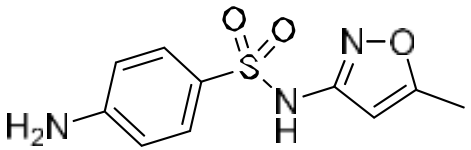
Sulfamethazine pKa = 7.4



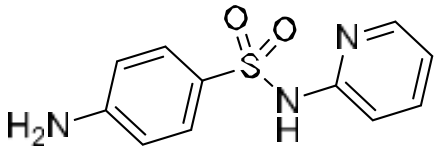
Sulfacetamide pKa = 5.4



Sulfadoxine pKa = 8.1



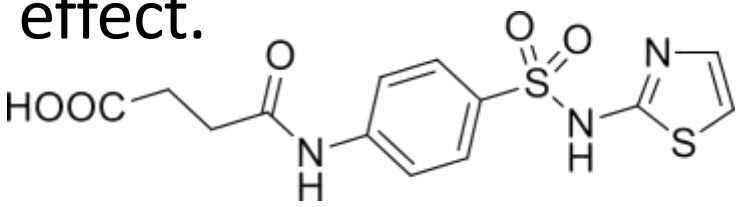
Sulfamethoxazole pKa = 6.1



Sulfapyridine pKa = 8.4

Sulfonamide prodrugs

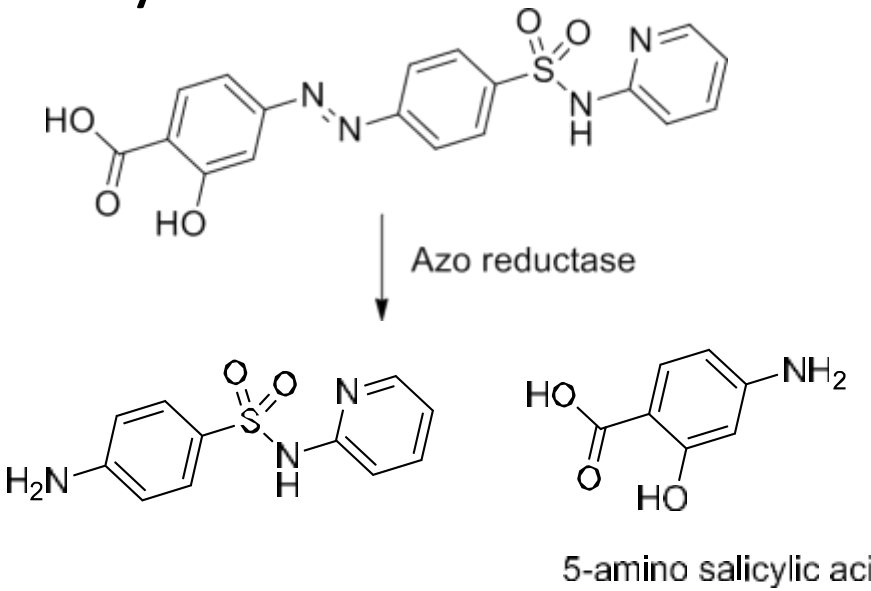
- Succinyl sulfathiazole:
  - Mainly used for intestinal infections.
  - It has a carboxylic acid at the amine side chain… ionized in intestine… will not be absorbed…. So it has only local effect.



  - The gradual hydrolysis of the amide will liberate the active form; sulfathiazole.

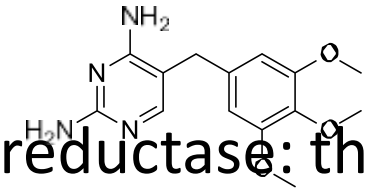
Sulfonamide prodrugs

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



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.

Protein binding of sulfonamides

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

- 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.
  - Substitution on the free amine will increase protein binding (such as the acetylayed metabolite is more protein bound than the parent sulfonamide).

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% and half life is 17 hours).