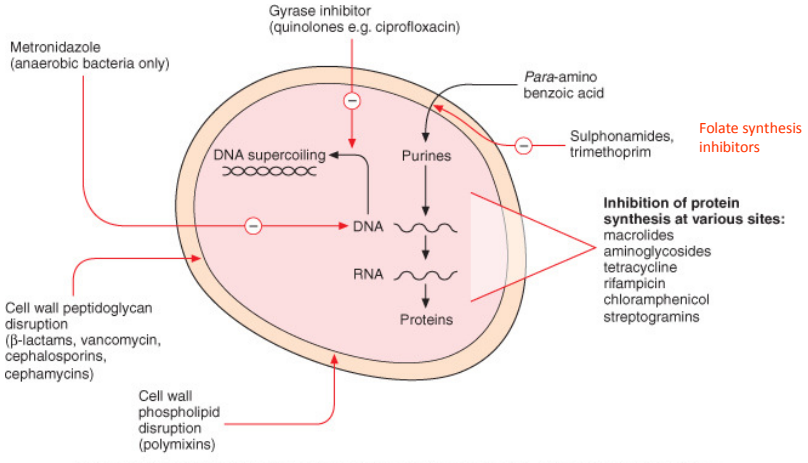
ANTIFOLATE DRUGS

FOLIC ACID SYNTHESIS INHIBITORS

SULFONAMIDES and TRIMETHOPRIM

MECHANISM OF ACTION OF VARIOUS ANTIMICROBIALS



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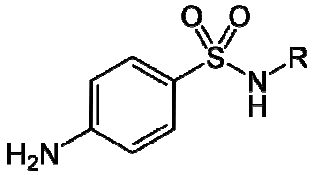
Sulfonamides-Sulfa drugs



Sulfonamides derived from p-aminobeneznesulfonamide are commonly referred to as Sulfa drugs.

They are synthetic antibacterial agents wherein all sorts of drug design strategies have been applied successfully.

In 1930s it was developed as life saving drugs called era of sulfa drugs with an illustrious history.

History of Sulfonamides

The discovery of sulfonamides is a significant milestone event in the human chemotherapeutic history.

Sulfonamides are synthetic compounds that have activity against both gram-positive and gram- negative bacteria.

Originally sulfonamides were synthesized in Germany as azodyes as antibacterial agents by a man named DOMAGK who later received nobel prize for his pioneering work.

ANTIMETOBOLITE ANTIBIOTICS

CLINICAL USE

1. Sulfonamides (now rarely used by themselves)

- They are active against gr(-) and gr(+) organisms
- They are used for the condition that:

simple urinary tract→sulfisoxasole
ocular infections → sulfacetamide
burn infections → silver sulfadiazine
ulcerative colitis
rheumatoid arthritis → sulfasalazine
toxoplasmosis → oral sulfasalazine plus pyrimethamine (a dihdyrofolate reductase inhibitor) plus folic acid

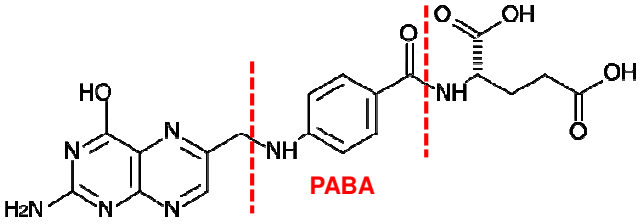
ANTIFOLATE DRUGS

MECHANISMS OF ACTION

1. Sulfonamides

- The sulfonamides are bacteriostatic inhibitors of folic acid synthesis.
- As antimetabolites of PABA, they are competitive inhibitors of dihydropteroate synthase.
- The selective toxicity of sulfonamides results from the inability of mammalian cells to synthesize folic acid; they must use preformed folic acid that is present in the diet.

Mechanism of action (Wood-Fields Theory)



The structure of Folic acid

Folic acid, another form of which is known as **folate**, is one of the B vitamins. Folate is essential for the body to make DNA, RNA, and metabolise amino acids which are required for cell division.

Humans cannot make folic acid, it is required from the diet.

Sulfonamides inhibit the folic acid synthesis IN BACTERIA Mechanism of action

p-Aminobenzoic acid (PABA)

Dihydropteroate synthase — Sulfonamides (compete with PABA)

Dihydrofolic acid

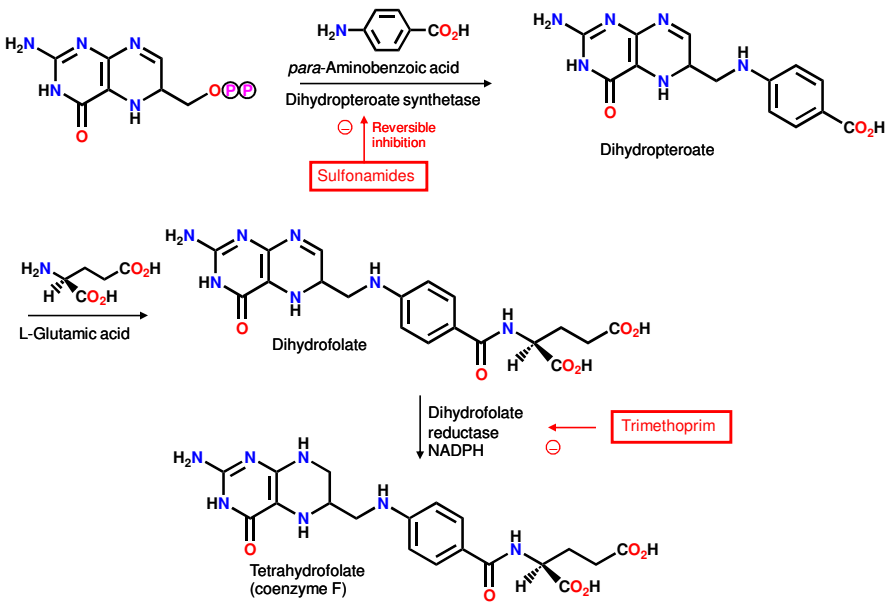
Dihydrofolate reductase — Trimethoprim, pyrimethamine

Tetrahydrofolic acid

Purines

DNA

Mechanism of action



Mechanism of action

Target enzyme

- Dihydropteroate synthetase - bacterial enzyme
- Not present in human cells
- Important in the biosynthesis of the tetrahydrofolate cofactor
- Cofactor is crucial to pyrimidine and DNA biosynthesis
- Crucial to cell growth and division

Sulfonamides

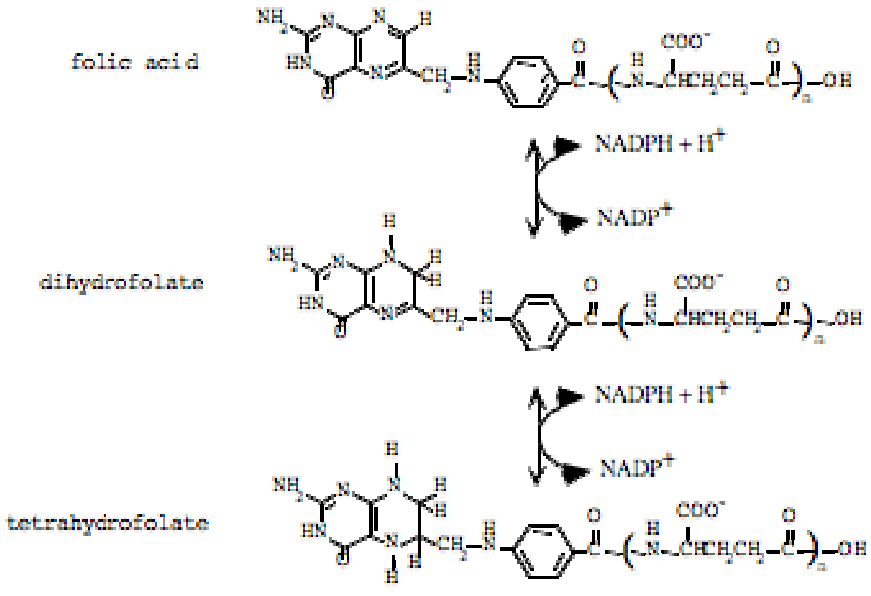
- Competitive enzyme inhibitors
- Bacteriostatic agents
- Not ideal for patients with weakened immune systems
- Mimic the enzyme substrate - *para*-aminobenzoic acid (PABA)
- Bind to the active site and block access to PABA
- Reversible inhibition
- Resistant strains produce more PABA

Mechanism of action

Metabolic differences between bacterial and mammalian cells

Dihydropteroate synthetase is present only in bacterial cells

Transport protein for folic acid is only present in mammalian cells

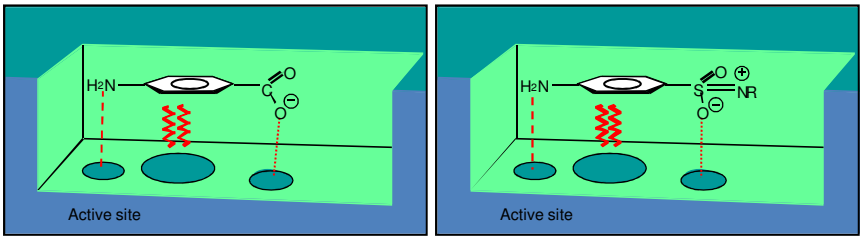


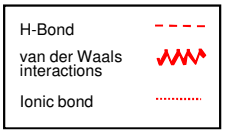
Processing of folic acid in humans

Mechanism of action

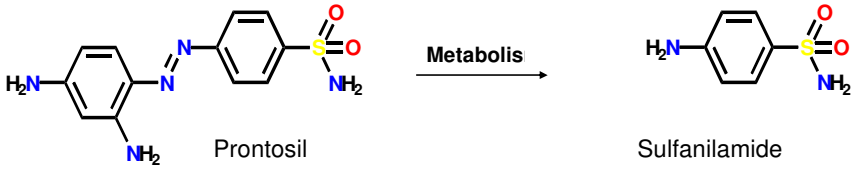
Binding interactions

The sulfonamide chemical nucleus resembles p-aminobenzoic acid (PABA).





Lead Compound



Prontosil

Sulfanilamide

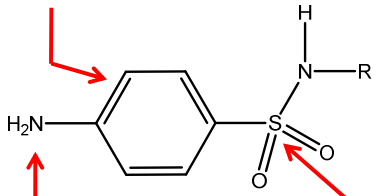
Notes

- Prontosil - red dye
- Antibacterial activity *in vivo* (1935)
- Inactive *in vitro*
- Metabolised to active sulfonamide
- Acts as a prodrug
- Sulfanilamide - first synthetic antibacterial agent acting on a wide range of infections

Structure-activity relationship (SAR)

Other aromatic rings or introducing other groups onto the benzene ring will decrease or lose the antibacterial activities.

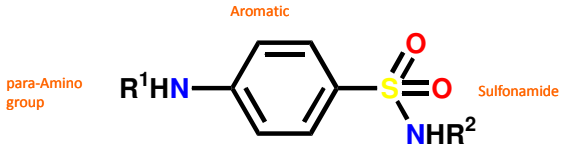
Monosubstitution will enhance the potency; heterocyclic rings have better activites. Bis substitution will lose their activities.



Sulfone group must be in the para position of the aniline. Other amide group decreases the activity.

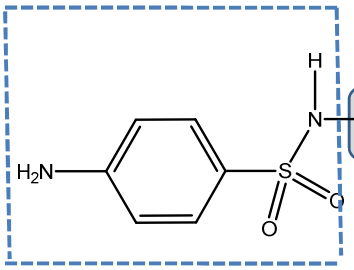
Unsubstituted or potential amino group are essential for antimicrobial activities.

Structure-Activity Relationships



- *para*-Amino group is essential (R^1=H)
- *para*-Amido groups (R^1=acyl) are allowed
  - inactive *in vitro,* but active *in vivo*
  - act as prodrugs
- Aromatic ring is essential
- *para*-Substitution is essential
- Sulfonamide group is essential
- Sulfonamide nitrogen must be primary or secondary
- R^2 can be varied

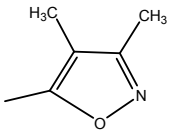
Basic Structure



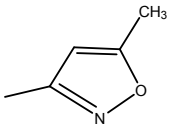
The chemical modification of this part of the molecule Increases activity and modifies some pharmacological properties.

This part of the molecule can not be modified chemically without loss of antibacterial activity

Sulfonaoxazole R =

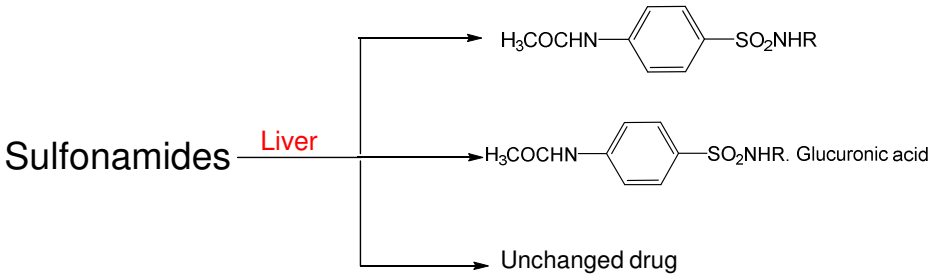


Sulfonaisooxazole R =



Highly Soluble Sulfonamides Used for Urinary Tract Infections:
A few very water-soluble sulfonamides, eg, sulfisoxazole (sulfafurazole) and sulfasomidine, are rapidly excreted via the urinary tract (>90% in 24 hr) mostly in an unchanged form; because of this, they are primarily used to treat urinary tract infections.

Sulfonamides - Drug Metabolism



Poorly Soluble Sulfonamides Used for Intestinal Infections:

Some sulfonamide derivatives, such as sulfaguanidine, are so insoluble that they are not absorbed from the GI tract (<5%). Phthalylsulfathiazole and succinylsulfathiazole undergo bacterial hydrolysis in the lower GI tract with the consequent release of active sulfathiazole. Salicylazosulfapyridine (sulfasalazine) is also hydrolyzed in the large intestine to sulfapyridine and 5-aminosalicylic acid, an anti-inflammatory agent that might be used for management of ulcerative colitis in dogs.

Sulfonamides can be represented by the following groups

Drugs used to resorbtive action (well absorbed from the gastrointestinal tract)

A. *Short action:*	sulfadimezin Etazol, Sulfazin Urosulfan
B. Long-acting:	sulfapiridazin, sulfadimetoksin
C. Super-long action:	sulfalen

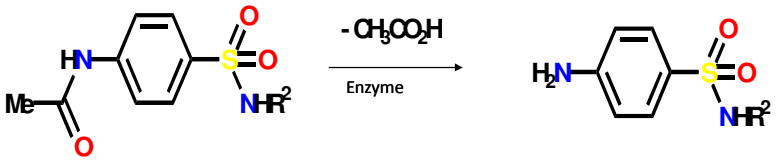
Drugs that act in the intestinal lumen (poorly absorbed from the gastrointestinal tract)

ftalazol

Preparations for topical use

- Sulfatsil sodium
- Sulfazin silver salt

Prodrugs of sulfonamides

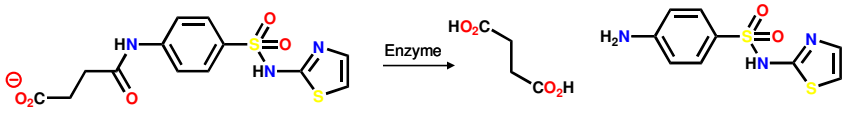


Notes

- Amide group lowers the polarity of the sulfonamide
- Amide cannot ionise
- Alkyl group increases the hydrophobic character
- Crosses the gut wall more easily
- Metabolised by enzymes (e.g. peptidases) *in vivo*
- Metabolism generates the primary amine
- Primary amine ionizes and can form ionic interactions
- Ionised primary amine also acts as a strong HBD

Examples of Prodrugs of Sulfonamides

Succinyl sulfathiazole



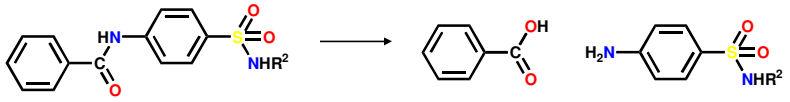
Succinyl sulfathiazole | Succinic acid | Sulfathiazole

Notes

- Acts as a prodrug of sulfathiazole
- Ionized in the alkaline conditions of the intestine
- Too polar to cross the gut wall
- Concentrated in the gut
- Slowly hydrolysed by enzymes in the gut
- Used for gut infections

Examples of Pro drugs of Sulfonamides

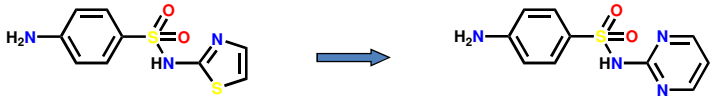
Benzoyl prodrugs



Benzoyl prodrug | Benzoic acid | Sulfonamide

- Too hydrophobic to cross gut wall
- Slowly hydrolyzed by enzymes in gut
- Used for gut infections

Sulfonamides with reduced toxicity



Sulfathiazole Sulfadiazine

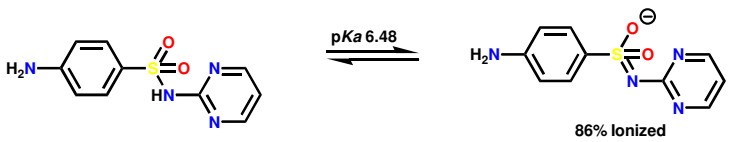
Notes

- Thiazole ring is replaced with a pyrimidine ring
- Pyrimidine ring is more electron-withdrawing
- Sulfonamide NH proton is more acidic and ionizable
- Sulfadiazine and its metabolite are more water soluble
- Reduced toxicity
- Silver sulfadiazine is used topically to prevent infection of burns

PK & Pka

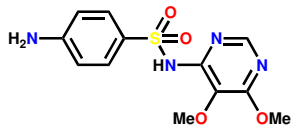
Absorbed from the stomach and small intestine → distributed widely to tissues and body fluids CNS, CSF, placenta, fetus

Hepatic metabolism → acetylated or glucuronidated and excreted in the urine



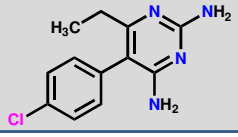
Examples of Sulfonamides

Sulfadoxine



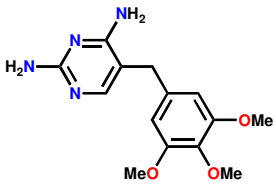
- Long lasting antibacterial agent
- Once weekly dosing regime

- Sulfadoxine + pyrimethamine = Fanisdar
- Used for the treatment of malaria

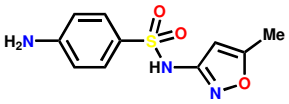


Pyrimethamine

Examples of Sulfonamides



Trimethoprim



Sulfamethoxazole

- Sulfamethoxazole + trimethoprim = co-trimoxazole
- Agents inhibit different enzymes in same biosynthetic pathway
- Strategy of sequential blocking
- Allows lower, safer dose levels of each agent

Sulfonamides for local use

Sulfonamides used topically for the treatment and prevention of eye infections. For this purpose, the most commonly used water-soluble sodium sulfatsil-. It is quite effective and does not irritate. It is used for the treatment and prevention of gonorrheal eye disease in neonates and adults, conjunctivitis, blepharitis, corneal ulcers and others.

Sulfonamide can be used in wound infection (wound typically by dusting). It should be borne in mind that in the presence of pus, wound discharge, necrotic masses containing large amounts of para-amino benzoic acid, sulfonamides little or ineffective. They should only be used after primary treatment of wounds or in a "clean" wounds.

Sulfazin synthesized silver salt (Sulfargin), which has in its molecule an atom of silver. The drug is used only locally for burn wounds. Is released from the drug enhances the antimicrobial action of silver Sulfazin and promotes healing of wounds. Included in the ointment "Sulfargin."

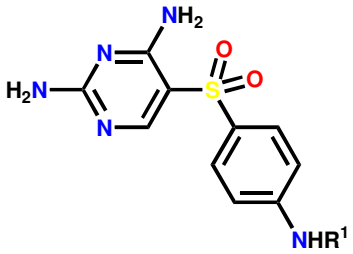
ANTIMETOBOLITE ANTIBIOTICS

TOXICITY

1. Sulfonamides

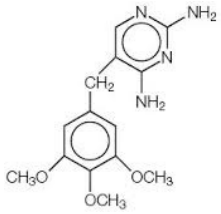
- Hypersensitivity: allergic reactions including skin rashes and fever. Cross allergy may occur wit chemically related drugs (thiazides, hypoglycemics)
- GI: nausea, vomiting and diarrhea
- Hematotoxicity: they are rare. Granulocytopenia, thrombocytopenia and aplastic anemia
- Nephrotoxicity: they may precipitate in the urine at acidic pH, causing crystalluria and hematuri

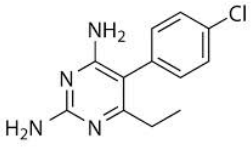
Sulfones



- Thought to inhibit dihydropteroate synthetase
- Used in the treatment of leprosy

TRIMETHOPRIM & PYRIMETHAMINE





ANTIFOLATE DRUGS

CLASSIFICATION AND PHARMACOKINETICS-2

Trimethoprim

- This drug is structurally similar to folic acid.
- It is a weak base and is trapped in acidic environments, reaching high concentrations in prostatic and vaginal fluids.
- A large fraction of trimethoprim is excreted unchanged in the urine.
- The half-life of this drug is similar to that of sulfamethoxazole (10—12 h).

ANTIFOLATE DRUGS

MECHANISMS OF ACTION-2

2. Trimethoprim

- Trimethoprim is a selective inhibitor of bacterial dihydrofolate reducate that prevents formation of the active tetrahydro form of folic acid.

3. Trimethoprim plus sulfamethoxazole

- When the 2 drugs are used in combination, antimicrobial synergy results from the sequential blockade of folate synthesis.
- The drug combination is bactericidal against susceptible organisms

ANTIMETOBOLITE ANTIBIOTICS
CLINICAL USE-2

2. Trimethoprim-sulfamethoxazole (TMP-SMX)

is effective against *P jiroveci* pneumonia, shigellosis, systemic salmonella infections, uti, prostatitis, respiratory pathogens pneumococcus, *H.influenzae* and *Moraxella catarrhalis*

- TMP-SMX is also the drug of choice in nocardiosis, a possible backup drug for cholera, typhoid fever, and shigellosis, and has been used in the treatment of infections caused by methicillin-resistant staphylococci and Listeria monocytogenes.

ANTIMETOBOLITE ANTIBIOTICS
TOXICITY-2

- **Trimethoprim**
- Trimethoprim may cause the predictable adverse effects of an antifolate drug, including megaloblastic anemia, leukopenia, and granulocytopenia.
- These effects are usually ameliorated by supplementary folinic acid.
- The combination of TMP-SMX may cause any of the adverse effects associated with the sulfonamides.
- AIDS patients given-SMX have a high incidence of adverse effects, including fever, rashes, leukopenia

ANTIMETOBOLITE ANTIBIOTICS DRUG INTERACTION

- Competition with warfarin, hypoglycemic drugs sulfonylureas, phenytoin and methoteraxate for plasma protein binding transiently increases the plasma levels of these drugs
- Sulfonamides can displace bilurubin from plasma proteins, with the risk of kernicterus in the neonate if use in the third trimester of pregnancy

BACTERIAL RESISTANCE

A rapidly increasing problem. However, it is lower with the combination compared to agents used alone.

In a survey of children in Memphis Tennessee 29% isolates were penicillin resistant, and 25% of these were resistant to TMP-SMZ.

Emergence of TMP-SMZ resistant S.aureus and Enterobacteriaceae is a serious problem in AIDS patients!

Resistance is often due to the acquisition of a plasmid that codes for an altered dihydrofolate reductase.

RESISTANCE

- Production of a mutated dihydropteroate synthetase that has reduced affinity for binding of sulfonamides. Resistance is transmitted among Gram-negative bacteria by plasmids. Resistance in *Staphylococcus aureus* occurs as a result of xessive synthesis of PABA. Some resistant bacteria have reduced uptake of sulfonamides.
- Bacteria which utilize exogenous folic acid are resistant to sulfonamides.