

## SYNTHETIC ANTIBACTERIAL DRUGS:SULFONAMIDES, TRIMETHOPRIM AND QUINOLONES

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### Knowledge Objectives:

#### Sulfonamides:

Know the basic sulfonamide structure and how it relates to PABA

Know in a general way the folate synthesis pathway, and where it is affected by sulfonamides and trimethoprim

Know why they are selectively toxic to microorganisms

Know important factors of disposition, i.e. : rapid absorption, high degree of plasma protein binding, metabolism by acetylation, renal elimination.

Know major toxicities and side effects (especially hematological and dermatological)

How do bacteria become resistant?

Compare mechanism of action of trimethoprim to that of SA's

What combinations are used?

Why is this an effective combination?

Know the major differences between short acting vs. long acting SA's (disposition, toxicity)

Know names of 4 major short acting and 1 long acting sulfonamide

When would non-absorbable SA's be used?

Know major uses for bacterial and non-bacterial infections

#### Quinolones (oxacin drugs)

What is their common structural feature?

How do they work?

Why are they selectively toxic?

What side effects are known?

What is their general clinical usefulness?

### **Important Drugs:**

#### Sulfonamides

sulfamethoxazole

sulfisoxazole

sulfadiazine

sulfadoxine

sulfacetamide

sulfasalazine

#### Trimethoprim

#### Combinations

Cotrimoxazole (Sulfisoxazole + Trimethoprim)

Cotrimazine (Sulfadiazine + Trimethoprim) (Canada only)

Sulfadoxine + Trimethoprim

Fansidar (Sulfadoxine + Pyrimethamine)

#### Quinolones

nalidixic acid (prototype)

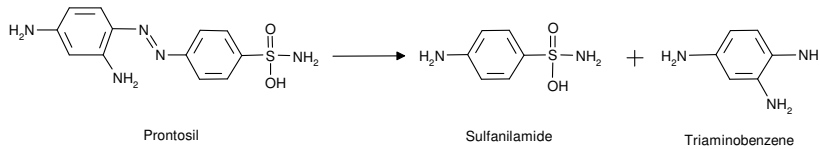
norfloxacin

ciprofloxacin

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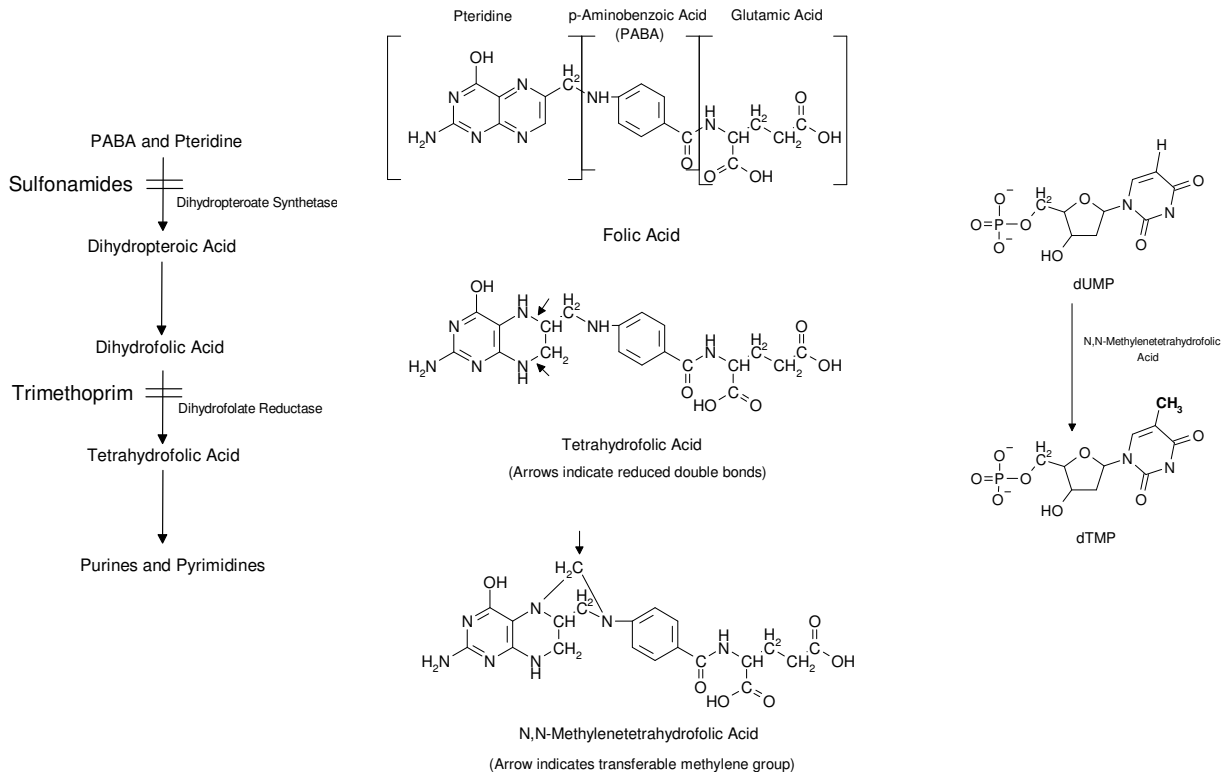
Antibiotics are, by definition, natural products biosynthesized by microorganisms that are toxic to other species of microorganisms. Sulfonamides, trimethoprim and quinolones are man-made drugs and are therefore, strictly speaking, not antibiotics, but synthetic antibacterial agents.

Sulfonamides were the first successful selectively toxic antibacterial drugs. Prontosil (see below) was discovered by Gerhard Domagk in 1936, and used to successfully treat puerperal sepsis (childbirth fever) in London. Prontosil is converted by cellular enzymes to sulfanilamide, the prototype of all sulfonamides.

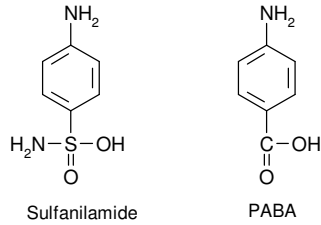


### MECHANISM OF SULFONAMIDE TOXICITY:

Sulfonamides interfere with bacterial folic acid synthesis. Folic acid is a 1-carbon donor, required for the *de novo* biosynthesis of purines and pyrimidines.



Sulfonamides prevent synthesis of dihydropteroic acid, a folic acid precursor. They mimic para-aminobenzoic acid and block dihydropteroate synthetase.



Sulfonamides are bacteriostatic drugs; they stop DNA synthesis and prevent cell division.

#### SELECTIVE TOXICITY:

Sulfonamides are selectively toxic to bacteria because folate synthesis is obligatory in bacteria; eukaryotes obtain folate preformed in the diet.

#### DISPOSITION OF SULFONAMIDES

##### ABSORPTION

Normally given orally or applied topically; some soluble salts given parenterally

Readily absorbed from GI tract, achieving peak blood levels in 30 min, except for those designed to remain in intestine (see below)

##### DISTRIBUTION

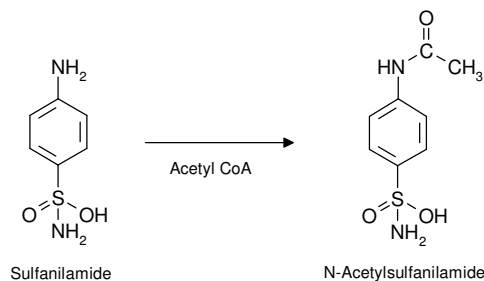
Highly plasma protein bound; will displace other bound drugs and bilirubin. Sulfonamides given in late term can induce neonatal jaundice

Distributed in total body water, readily enter CNS, synovial and ocular fluid, fetal circulation and milk

##### METABOLISM

Primarily by acetylation at free amino group; some oxygenation of aromatic ring and/or side chain.

Acetylated metabolites inactive



## ELIMINATION

Majority eliminated unchanged

Concentrated in urine; useful in urinary tract infections; older sulfonamides actually formed crystals in tubules and ureter

## TOXICITY

Relatively low CTI (relative to most antibiotics); toxicity occurs in about 5% of patients

1) Renal toxicity -- Older sulfonamides crystallized in urine (doses of 8-10 grams of drug given daily)

Risk minimized with advent of newer, more soluble forms; still prudent to give extra fluids

2) Blood dyscrasias -- Hemolytic anemia, agranulocytosis, aplastic anemia, thrombocytopenia  
Immune response to sulfonamide hapten?

3) Dermal toxicity -- rashes, pruritus, erythema, exfoliative dermatitis (Stevens-Johnson syndrome can be fatal)

Again probably an immune response

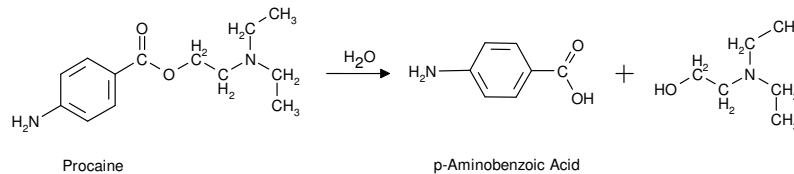
4) Other rare but serious side effects -- hepatitis, drug-induced fever

5) Less serious side effects -- headache, gi discomfort (nausea, loss of appetite)

**BACTERIAL RESISTANCE:** Bacteria become resistant to sulfonamides by:

1) Synthesizing large amounts of PABA. It takes 5,000 to 25,000 molecules of sulfonamide to compete with 1 molecule of PABA. Resistant cells synthesize PABA at 70x the rate of normal cells.

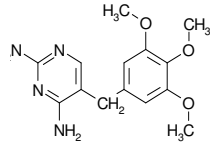
- PABA from pus can compete with sulfonamides (also preformed nucleotides)
- PABA can be produced by hydrolysis of procaine



2) Bacterial dihydropteroate synthetase is altered so that it no longer is inhibitable by sulfonamides

3) Bacteria utilize "salvage pathway" which bypasses 1-carbon synthesis of bases

Genes for sulfonamide resistance are transferred by R-plasmids. Generally, one resistance phenotype will confer resistance to all sulfonamides. Cross-resistance to sulfonamides and other drugs also occurs (multiple genes on same plasmid)



Trimethoprim

**TRIMETHOPRIM** -- Introduced in 1969 as a combination with sulfonamides; synergizes sulfonamide activity and minimizes bacterial resistance

**Cotrimoxazole** (Bactrim, Septra): 1 part trimethoprim/5 parts sulfamethoxazole

**Cotrimazine:** 1 trimethoprim/ 5 sulfadiazine

Blocks bacterial dihydrofolate reductase (similar to methotrexate); acts at a different step of the same folate synthetase pathway inhibited by sulfonamides

100,000x higher affinity for bacterial than mammalian enzyme

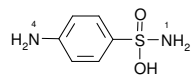
Not only provides synergy with sulfonamides, but because 2 compounds act at different points on same pathway, chances of resistance developing are a geometric product (much smaller)

Synergy apparent in treatment of non-bacterial respiratory infections, but not absolute; for uncomplicated UTI, trimethoprim alone is just as effective as combination.

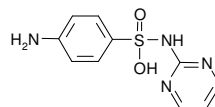
#### INDIVIDUAL SULFONAMIDES:

Historically classified as short-acting, long-acting and non-absorbed, according to their rates of absorption and distribution.

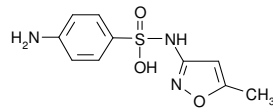
All structurally similar, except for substituents on N1 nitrogen; substitution of N4 nitrogen terminates activity (acetylation site)



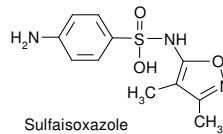
Sulfanilamide



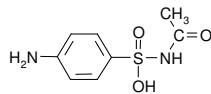
Sulfadiazine



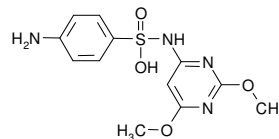
Sulfamethoxazole



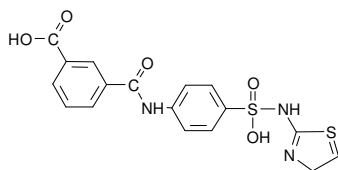
Sulfisoxazole



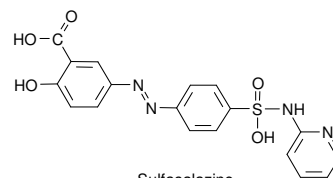
Sulfacetamide



Sulfadimethoxine



Phthalylsulfathiazole



Sulfasalazine

**Sulfisoxazole, Sulfamethoxazole, Sulfadiazine:** short acting sulfonamides; rapidly absorbed and excreted

3 most commonly prescribed sulfonamides, last 2 in combination with trimethoprim.

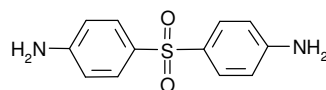
**Sulfadimethoxine:** Long-acting sulfonamide (poorly excreted); quite toxic but useful in protozoal infections, especially in AIDS patients

Silver salt of **Sulfadiazine**, topical use in burns.

**Sulfacetamide**, topical use in eye, due to low irritation.

Poorly absorbed sulfonamides: e.g. **Phthalylsulfathiazole**; used to sterilize the gut prior to bowel surgery (aminoglycosides preferred). Non-absorbed, gut flora cleave N4 group.

**Dapsone:** Antileprosy drug. Not a sulfonamide in strict sense, but a related compound (sulfone) with same mechanism of action



Dapsone

## CLINICAL USES OF SULFONAMIDES

Limited due to resistance problems, but addition of trimethoprim has greatly extended their usefulness.

Useful against most (non-resistant) Gram+ and many Gram- bacteria

Commonly used (normally as cotrimoxazole) in lower urinary tract infections, particularly due to E. Coli, and prostatitis; trimethoprim alone also used; quinolones are replacing them as drug of choice.

Once commonly used in bacterial dysentery due to shigella and salmonella; resistance limited use, but became useful again as combination with trimethoprim

Sometimes used in meningococcal infections; other antibiotics preferred.

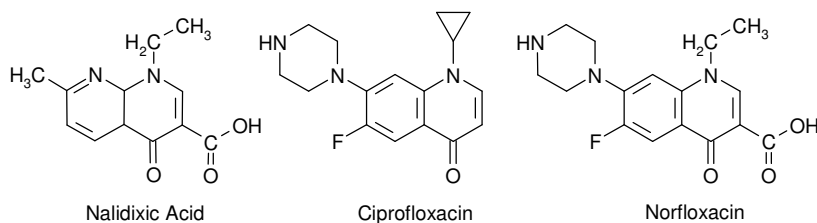
Topical sulfonamides used in eye (conjunctivitis) and prophylactically for burns

Protozoal infections; very important role for sulfonamides and trimethoprim, since these infections respond poorly to antibiotics

- Chlamydia, nocardia, toxoplasma
- chloroquine resistant plasmodium falciparum
- Pneumocystis carinii in immune compromised (AIDS) patients; high incidence of drug toxicity in these patients; sometimes trimethoprim alone used. Combination used as low-dose prophylaxis.

## QUINOLONES

The earliest prototype drug, **Nalidixic acid**, was previously used in a limited capacity for Gram-urinary tract infections. More recently developed fluoroquinolones (**Ciprofloxacin**, **Norfloxacin**, e.g.) have a much broader spectrum of action. Their full therapeutic potential is still being realized.



## MECHANISM OF ACTION

Inhibit DNA gyrase, a bacterial Topoisomerase, which controls the topology of supercoiled DNA. These agents thereby interfere with a number of nucleic acid synthesis processes including replication, transcription and repair.

## SELECTIVE TOXICITY

The mammalian Topoisomerase is much less sensitive to inhibition by these drugs.

## BACTERIAL RESISTANCE

Resistance is not wide-spread, and not completely understood. R-plasmids have not been identified. Resistant bacteria appear to have an altered DNA gyrase, and/or altered drug transport properties.

## TOXICITY

Toxic side effects are rare, and include gi disturbances (nausea, vomiting, diarrhea is rare), CNS effects (headache, dizziness, restlessness, insomnia), and allergic skin reactions (rash, urticaria, pruritus).

## CLINICAL USES

Urinary tract infections: Nalidixic acid has limited use. Newer quinolones are very useful, and, along with cotrimoxazole, are becoming drugs of choice for both complicated and uncomplicated UTI, especially those caused by enterobacteria.

Gonorrhea: Useful, especially vs.  $\beta$ -lactam-resistant strains

Diarrhea: Used vs. Shigella, toxigenic E. Coli, salmonella, and typhoid

Respiratory infections: Bacterial and non-bacterial (Hemophilus, Streptococcus, Pseudomonas, Chlamydia, Mycoplasma, Legionella)

Osteomyelitis

These are potentially very useful agents, whose potential has probably not yet been fully tapped.