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A REVIEW ON SULFONAMIDES

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Abstract:

*Sulfonamide drugs were the first antimicrobial drugs. The first sulfonamide was trade named Prontosil, which is a prodrug **Prontosil**, the first commercially available antibacterial with a relatively broad effect*

The sulphonamides or sulfa drugs competitively inhibit folic acid synthesis in micro-organisms and subsequently inhibit multiplication of bacteria but do not actively kill them. They have been used against most gram-positive and many gram-negative bacteria, some fungi, and certain protozoa.

Keywords-*SAR of sulfonamides*

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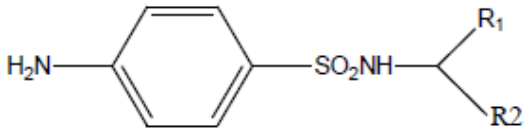
INTRODUCTION:

Sulfonamide derivatives medical groups discovery can be more similar to a string of distinguished pearls. They have in common the same main core but they differ in their bioactivities. Sulfonamides having functional group (R - SO2 - NH2) called sulfonamide group are compounds having potential of antimicrobial activity. They have their familiarity as amide derivatives of sulfonic acid because they are synthesized by introduction of amino group in sulfonic acid after repla cing its hydroxyl group. The structure - activity study on the sulfonamide azo dyes was performed and the reductive cleavage of azo linkage to release the active antibacterial product, sulfonamide, was concluded. Today, sulfonamide trimethoprim combinations are used extensively for opportunistic infections in patients with AIDS in addition to urinary tract infection and burn therapy. Resistance is most likely a result of a compensatory increase in the biosynthesis of p - aminobenzoic acid (PABA) by bac teria although other mechanisms may play a role.Resistance of E Coli strains to sulfonamide has been shown due to their containing sulfonamide - resistant dihydropteroate Syntheses.The lipophilicity of the N1 group has the largest effect on protein binding, and generally, the more lipids soluble a sulfonamide is the more of it will be protein bound. The aniline (N4) amino group is very important for activity because any modification of it other than to make prodrugs results in a loss of activity.[1,2]



The general structure of sulfonamides, If R=R1=H is sulfanilamide

Classification of sulfonamides

Most of the sulfonamides used currently are N1-derivatives. Based on the structural variations, Johnson divided sulfonamides into three groups as follows

a. Aryl derivatives (sulfamethoxazole, hydrochlorothiazide, sulphanilamide)

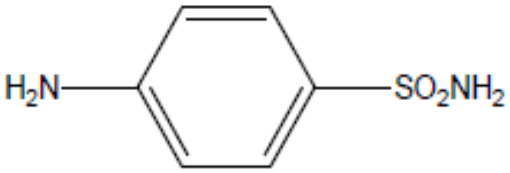
b. Heterocyclic derivatives containing six-membered rings (e.g. pyridine, pyrimidines, pyridazines and pyrazines).

c. Heterocyclic derivatives containing five-membered rings (e.g. thiazole, oxazole, isoxazole, 1,3,4- thiadiazole and yrazole).

Classification of sulfonamides is based on chemical structure, duration of action, spectrum of activity and therapeutic applications. The classification rate of absorption and half-life appears to be clinically relevant. Based on this the sulfonamides are classified into three groups.

Short Acting:

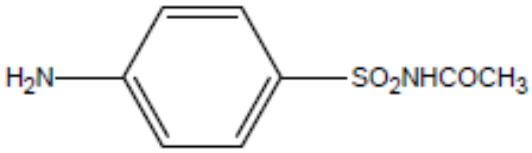
Sulfonamides with a half-life less than 10 hours. (e.g. sulfamethazole, sulfisoxazole and sulfanilamide have been used for the treatment of urinary tract infections).



Sulfanilamide

Intermediate Acting:

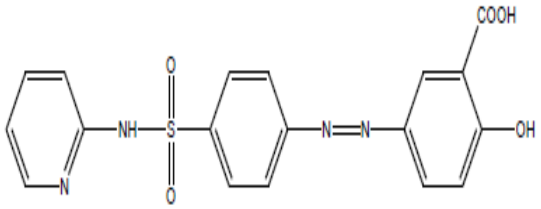
Sulfonamides with a half-life between 10-24 hours. (e.g. sulfamethoxazole, sulfacetamide and sulfadiazine have been used for various infections especially active against invasive aspergillosis in AIDS patients).



Sulfacetamide

Long Acting:

Sulfonamides with a half-life longer than 24 hours. (e.g. Sulfadimethoxine and Sulfadioxine have been used for the treatment of ulceration colitis).



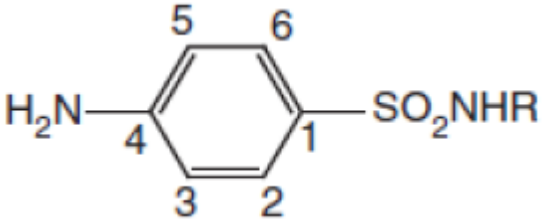
Sulfasalazine

Chemistry

In chemistry, the sulfonamide functional group is -S (=O)2-NH2, a sulfonyl group connected to an amine group. The general formula is RSO2NH2, where R is some organic group. Individual members differ in the nature of N1 (sulfonamide N) substitution, which governs solubility, potency and

pharmacokinetic property. A free amino group in the *p*- position (N4) is required for antibacterial activity. The sulphonamide family includes sulfadiazine, sulfamethizole (brand name: Thiosulfil Forte), sulfamethoxazole (Gantanol), sulfasilazine (Azulfidine), sulfisoxazole (Gantrisin), and various high-strength combinations of three sulfonamides. Sulfa drugs kill bacteria and fungi by interfering with cell metabolism. They were the wonder drugs before penicillin and are still used today.Because sulfa drugs concentrate in the urine before being excreted; treating urinary tract infections is one of their most common uses. Sulfa drugs can have a number of potentially dangerous interactions with prescription and over-the-counter drugs (including PABA sunscreens), and are not appropriate for patients with some health conditions. Be sure your doctor knows about any other medications you take and your full health history before taking sulfonamides[3,4]

SAR of Sulphonamides

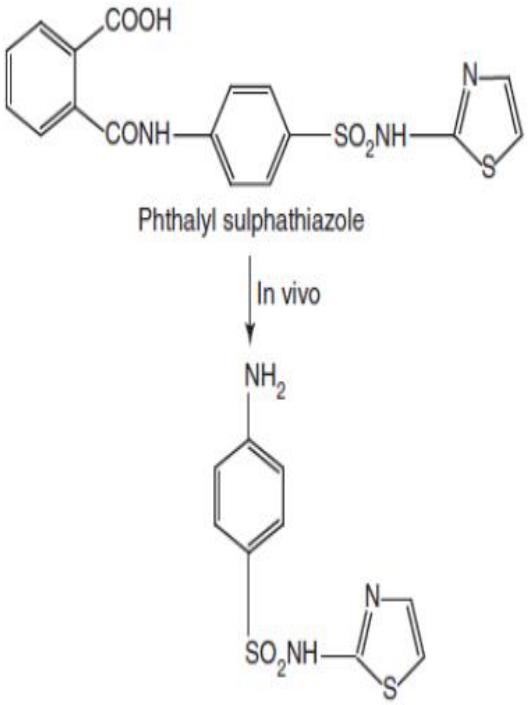


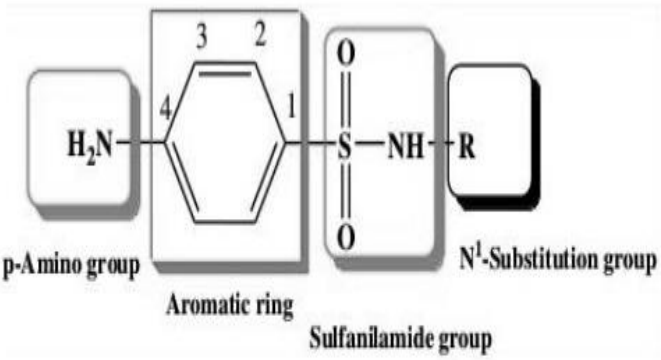
The major features of SAR of sulphonamides include the following:

- Sulphanilamide skeleton is the minimum structural requirement for antibacterial activity.

- The amino- and sulphonyl-groups on the benzene ring are essential and should be in 1 and 4 position.

- The **N-4** amino group could be modified to be prodrugs, which are converted to free amino function in vivo.

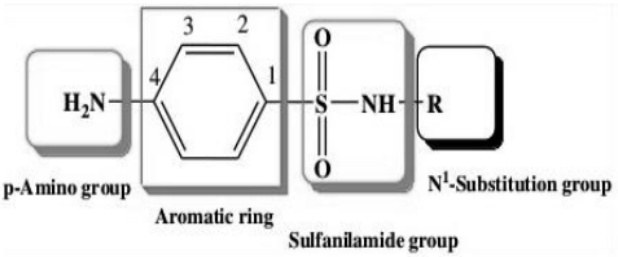




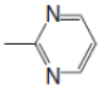
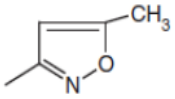
- Sulphur atom should be directly linked to the benzene ring.
- Replacement of benzene ring by other ring systems or the introduction of additional substituents on it decreases or abolishes its activity.
- Exchange of the **–SO2NH** group by **–CONH** reduces the activity.
- On **N-1**-substituted sulphonamides, activity varies with the nature of the substituent at the amino group. With substituents imparting electron-rich characters to **SO2 group**, bacteriostatic activity increases.
- Heterocyclic substituents lead to highly potent derivatives, while sulphonamides, which contain a single benzene ring at **N-1 position**, are considerably more toxic than heterocyclic ring analogues.
- The free aromatic amino groups should reside para to the sulphonamide group. Its replacement at ortho or meta position results in compounds devoid of antibacterial activity.
- The active form of sulphonamide is the ionized, maximum activity that is observed between the pKa values **6.6– 7.4.**
- Substitutions in the benzene ring of sulphonamides produced inactive compounds.

- Substitution of free sulphonic acid **(–SO3H**) group for sulphonamido function destroys the activity, but replacement by a sulphinic acid group **(–SO2H**) and acetylation of **N-4** position retains back the activity.
- *Meta-Sulphonamides* bind to the basic centres of arginine, histidine, and lysine sites of proteins. The binding groups are alkyl, alkoxy, and halides. The binding affects the activity of sulphonamides; protein binding appears to modulate the availability of the drug and its half-life.
- The lipid solubility influences the pharmacokinetic and antibacterial activity, and so increases the half-life and antibacterial activity in vitro. [5,6,7]

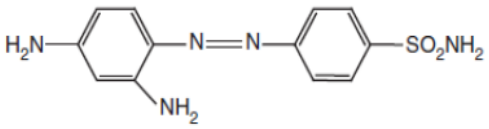
Structures of Sulfonamide derivatives



N-1 Substituted sulphonamides

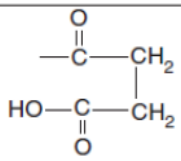
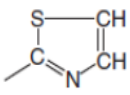
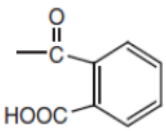
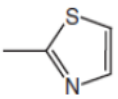
Name	R	R^1
Sulphanilamide	–H	–H
Sulphacetamide	–H	$-COCH_3$
Sulphadiazine	–H	
Sulphamethoxazole	–H	

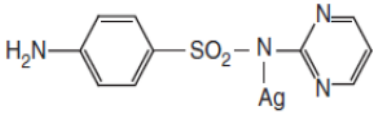
N-4 substituted suphonamides



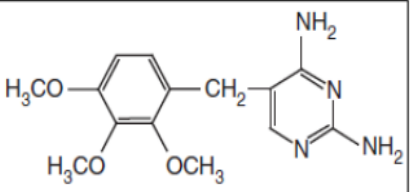
Prontosil

N-1 and N-4 substituted suphonamides

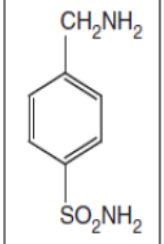
Name	R	R_1
Succinyl sulphathiazole		
Phthalylsulphathiazole		



Silver sulphadiazine



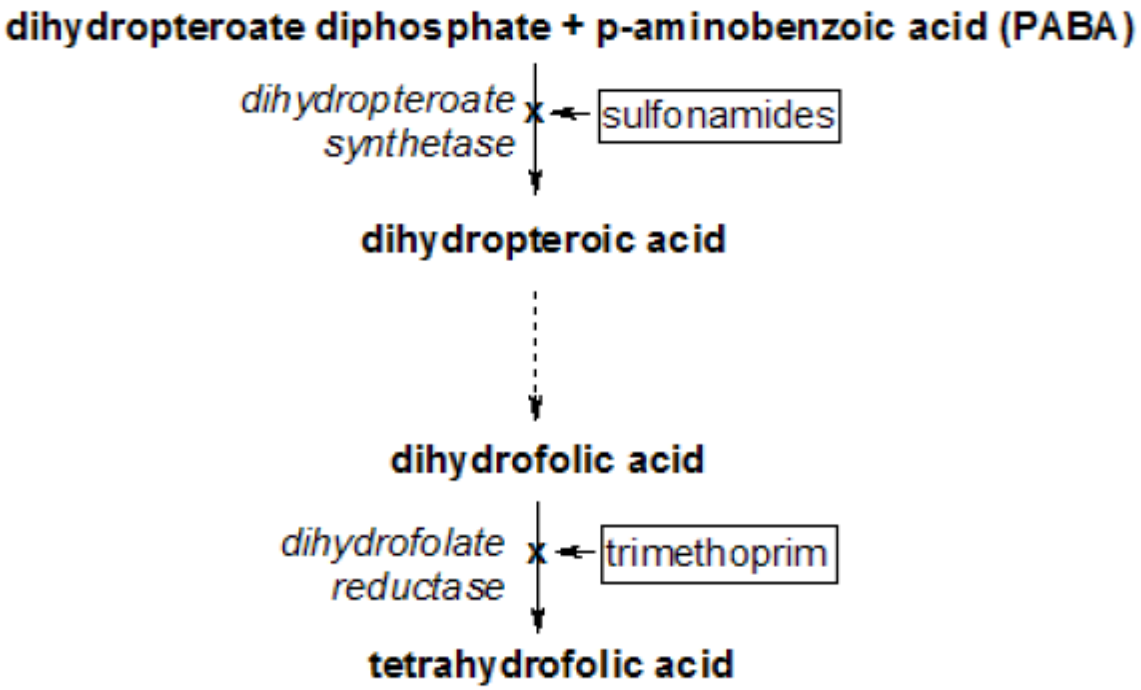
Trimethoprim



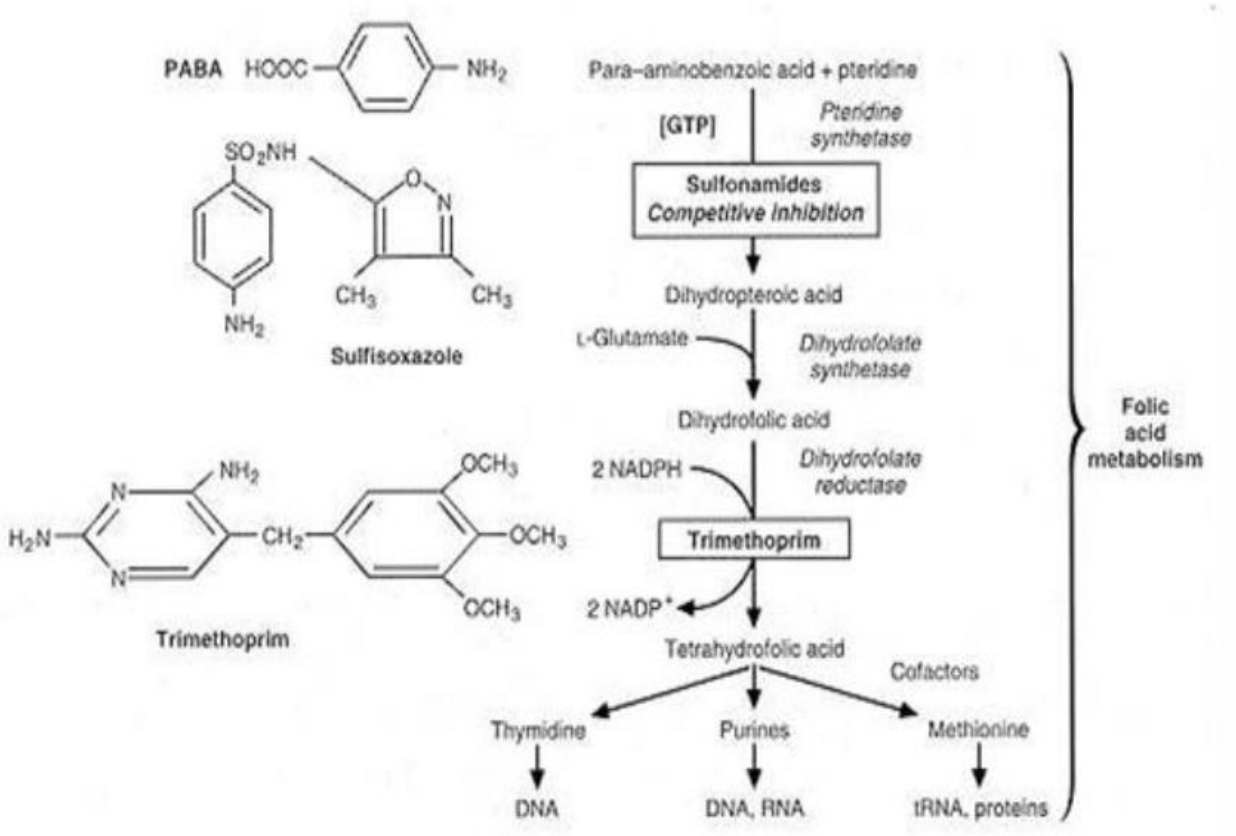
Mafenide

Mechanism of action of Sulfonamide:

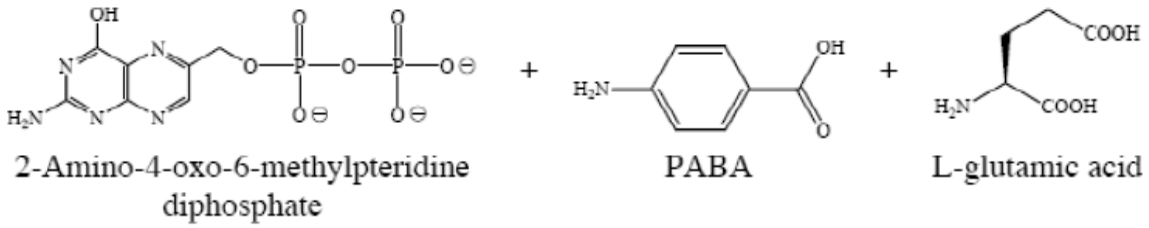
- PABA is an essential nutrient for some bacteria and is sometimes called Vitamin Bx However, PABA is not essential to human health, and is therefore not officially classified as a vitamin. Although humans lack the ability to synthesize folate from PABA, it is sometimes marketed as an essential nutrient under the promise that it can stimulate intestinal bacteria.
- PABA is an intermediate in bacterial synthesis of folate. Sulfonamides are chemically similar to PABA, and their antibacterial activity is due to their ability to interfere with conversion of PABA to folate by dihydropteroate synthetase, and subsequent utilization, by bacteria.
- ***Dihydropteroate synthetase*** is an enzyme.It produces dihydropteroate in bacteria, but does not function in humans. This makes it a useful target for sulfonamide antibiotics, which compete with the PABA precursor.
- It acts upon 4-Aminobenzoic acid (PABA} and dihydropteridine-hydroxymethyl-pyrophosphate.
- In bacteria, antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthetase, DHPS. DHPS catalyses the conversion of PABA (*para*-aminobenzoate) to dihydropteroate, a key step in folate synthesis. Folate is necessary for the cell to synthesize nucleic acids (nucleic acids are essential building blocks of DNA and RNA), and in its absence cells will be unable to divide. Hence the sulfonamide antibacterials exhibit a bacteriostatic rather than bactericidal effect.
- **Folate** is not synthesized in mammalian cells, but is instead a dietary requirement. This explains the selective toxicity to bacterial cells of these drugs. These antibiotics are used to treat pneumocystis jiroveci pneumonia, urinary tract infections, shigellosis, and certain protozoan infections. The sulfonamide chemical moiety is also present in other medications that are not antimicrobials, including thiazide diuretics (including hydrochorothiazide, metolazone, and indapamide, among others), sulfonylureas (including glipizide, glyburide, among others), and acetazolamide.[8,9]



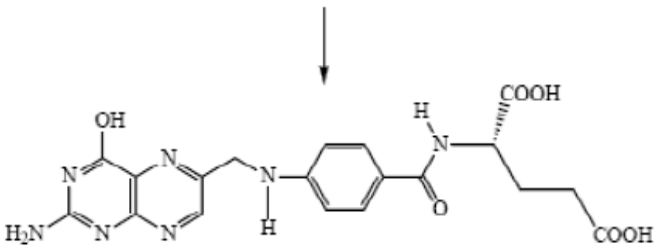
- Both trimethoprim and the sulfonamides interfere with folate metabolism in the bacterial cell by competitively blocking the biosynthesis of tetrahydrofolate, which acts as a carrier of one-carbon fragments and is necessary for the ultimate synthesis of DNA, RNA and bacterial cell wall proteins



- Cells use folic acid as a single-carbon atom building block for the construction of nucleic acids and other biological molecules. Inhibition of this process prevents growth and reproduction, but does not directly lead to cell death. Bacteria synthesize folic acid from 2-amino-4-oxo-6-methylpteridine diphosphate, *p*-aminobenzoic acid (PABA), and L-glutamic acid. Because sulfa drugs are structural mimics of PABA they may bind to dihydropteroate synthetase, one of the enzymes necessary for folic acid synthesis (reversible and competitive inhibition). With this enzyme inhibited, folic acid synthesis is prevented and cell growth and reproduction are halted.[10,11]

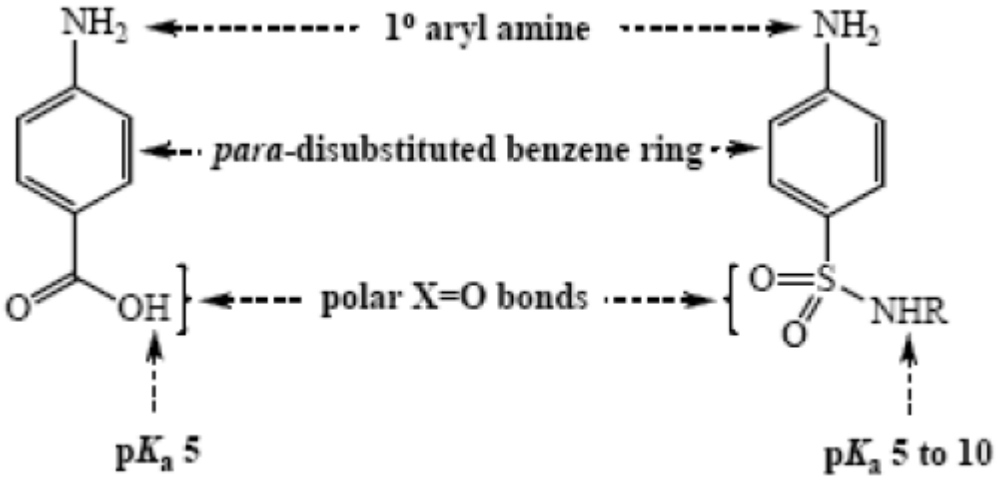


2-Amino-4-oxo-6-methylpteridine diphosphate + PABA + L-glutamic acid



Folic acid

- In addition, the two molecules are of nearly identical length (6.7 Å for PABA versus 6.9 Å for sulfanilide), both are roughly flat, and both have an equal distribution of charge (δ+ on the NH2 group and δ- on the COOH or SO2NHR groups). This effect can be seen more clearly by examining the electrostatic potential surfaces of these molecules.



Side effects:

- Sulfonamides have the potential to cause a variety of untoward reactions, including urinary tract disorders, haemopoietic disorders, and hypersensitivity reactions.
- When used in large dose, it may develop a strong allergic reaction. One of the most serious is *Stevens Johnson syndrome*(or toxic epidermal necrolysis).
- Some of the original sulfonamide drugs were derived from azo dyes and had the interesting effect of temporarily turning the patient red.

N.B- Stevens-Johnson syndrome (SJS) is a life-threatening condition affecting the skin, in which due to cell death the epidermis separates from the dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.[12,13,14]

Adverse reactions:

- The most common manifestation of a hypersensitivity reaction to sulfa drugs are rash and hives. However, there are several life-threatening manifestations of hypersensitivity to sulfa drugs, including Stevens-Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, hemolytic anemia, thrombocytopenia, and fulminant hepatic necrosis, among others
- The sulfonamide antibiotic chemical structures are implicated in the hypersensitivity reactions associated with the class.

  The first is the **N1 heterocyclic ring**, which causes a type I hypersensitivity reaction.

  The second is the **N4 amino nitrogen** that, in a stereospecific process, forms reactive metabolites that cause either direct cytotoxicity or immunologic response.[15,16]

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