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Antimicrobial Sulfonamides: An Objective Review

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Summary
Sulfonamides were the first antibiotics widely employed in the treatment of human and animal bacterial infections. They are competitive antagonists and structural analogues of p-aminobenzoic acid, disrupt the folate pathway, essential in bacteria and primitive eukaryotes, and target the enzyme dihydropteroate synthase. The abusive use of antimicrobials in humans, animals and the incorrect disposal of medicines, contaminating the environment, have contributed to the increase of bacterial resistance worldwide, and the notability of sulfonamides has been reduced due to the increasing increase of this resistance, being essential the search for new molecules with antibacterial activity against these multi-resistant bacteria as well as the responsible use and correct management of waste. with sulfonamides showing promise for further research as an important class of antimicrobials.
Key words: *Antimicrobial sulfonamides, antibiotics, bacteriostatics, antimicrobial resistance.*

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I. INTRODUCTION

In 1935 the German pathologist Gerhard Domagk (1895-1964) published the results of experiments carried out in 1932, showing that the azo dye Prontosil® (Figure 1.A), even inactive *in vitro*, had the most pronounced chemotherapeutic effect ever observed *in vivo*, where all infected animals survived without symptoms[1]. It was the first antibacterial drug and the first commercially available sulfonamide antibiotic, it is, in the body, metabolized into its active drug form, sulfanilamide (Figure 1C)[2].

II. METHODOLOGY

The present study is an integrative, objective review, with a search for scientific publications on the researched theme, from databases of scientific journals, academic and specialized websites on the internet, using search tools such as Google, Google Scholar and Periodicos CAPES, using descriptors related to the subject, such as "antibiotics", "antibacterial activity", "sulfonamides", "trimethoprim", "sulfonamide resistance", "environment", "research for the discovery of new sulfonamide compounds", etc. and performing a critical evaluation and synthesis of the data obtained on antimicrobial sulfonamides, from the first studies that led to the discovery of antibacterial activity to recent research, which seeks the discovery of new sulfonamides with antimicrobial activity. Studies addressing the discovery, development, use and impact of sulfonamides were used as inclusion criteria, including information on the authors, year of publication, methodology, results, and conclusions. Exclusion criteria included studies that were not related to the subject or that did not meet the criteria defined by the author, such as websites that did not present information about references of the information provided.

III. SULFONAMIDES

Sulfonamides have a -SO2-NH2 functional group, a sulfonyl group linked to an amine group. Antimicrobial sulfonamides (SN), also known as sulfa drugs, are synthetic chemotherapeutic agents, used to treat human and animal bacterial infections, acting against a broad spectrum of gram-positive bacteria, many of which are Gram-negative, including *Klebsiella, Salmonella, Escherichia coli* and *Enterobacter species*, as well as showing inhibitory activity against some fungi (*Pneumocystis jiroveci*) and protozoa (Toxoplasma, Plasmodium, Coccidia)[3,4].

IV. MECHANISM OF ACTION OF ANTIMICROBIAL SULFONAMIDES

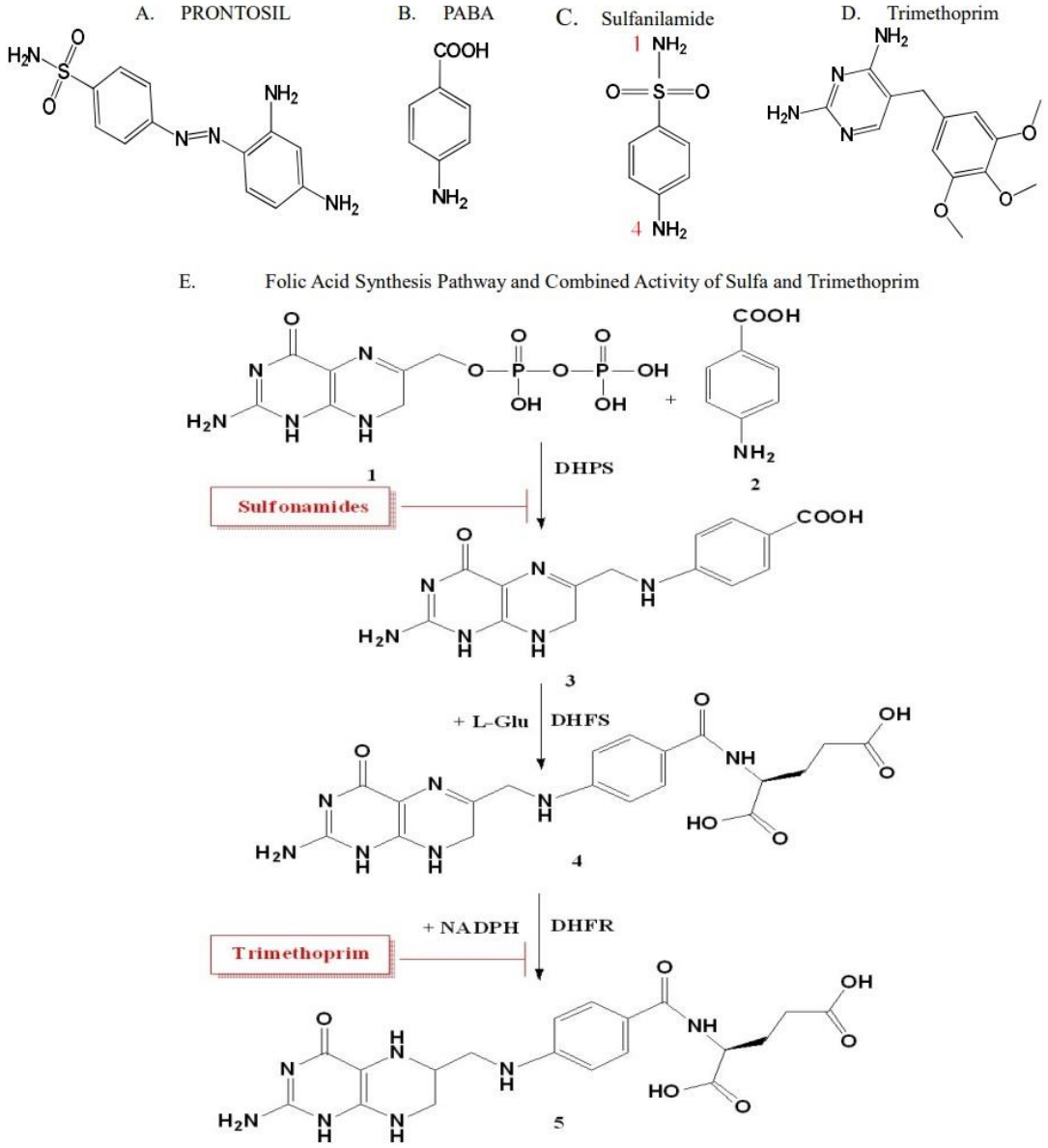


Figure 1: PRONTOSIL, PABA, Sulfanilamide, Trimethoprim and Folic Acid Synthesis Pathway and Combined Activity of Sulfa and Trimethoprim Inhibiting Folate Synthesis. A. First antibacterial drug and first of the commercially available sulfonamide antibiotics[2]. **B.** Substrate for the DHPS (dihydropteroate synthase) enzyme in the folic acid synthesis pathway. Suffers competitive inhibition with sulfonamides on the DHPS enzyme[3]. **C.** Sulfonamide with antibacterial activity, presents the minimum structural prerequisites for an antibacterial action: sulfur directly linked to the benzene ring, the para-NH2 group (N4 position) free. Shows structural similarity to PABA (p-amino benzoic acid)[11]. **D.** Competitive inhibitor of DHFR (dihydrofolate reductase), preventing the reduction of dihydrofolic acid (DHFA) to tetrahydrofolic acid (THFA) catalyzed by DHFR[4]. **E.** Steps in the folic acid synthesis pathway include: (i) condensation of dihydropteridine pyrophosphate (DHPP) (1) with p-amino benzoic acid (PABA) (2) by dihydropteroate synthase (DHPS, EC 2.5.1.15) to form dihydropteroate (DHP) (3); (ii) addition of glutamate to DHP by dihydrofolate synthase (DHFS, EC 6.3.2.12) to form dihydrofolate (DHF) (4) and (iii) reduction of DHF to form tetrahydrofolate (THF) (5), catalyzed by dihydrofolate reductase (DHFR, EC 1.5 .1.3). THF produced by this pathway is required for one of the carbon transfer reactions in the biosynthesis of a range of biomolecules such as nucleotides and amino acids.[5].
Source: Adapted from Capasso et al. (2014)[5], modified by the author.

The synthesis and maintenance of folic acid in its physiological states is necessary to participate in the metabolism of folate/homocysteine and, therefore, in the biosynthesis of purines and pyrimidines, which is

essential for cell growth[5]. At least two steps of the folic acid synthesis pathway, essential in primitive bacteria and eukaryotes, are targeted by antibacterial drugs: DHPS (dihydropteroate synthase) is targeted by sulfonamides, while DHFR (dihydrofolate reductase) is targeted by trimethoprim (TMP) (Figure 1.D) and its congeners[5].

Sulfonamides are competitive antagonists and structural analogues of p-aminobenzoic acid (PABA) (Figure 1.B)[6,3], disrupting the folate pathway by inhibiting and replacing PABA in the DHPS enzyme, which catalyzes the condensation of 6-hydroxymethyl-7,8-dihydropterin-pyrophosphate (DHPP) with PABA, through the formation of a bond between the amino nitrogen of PABA and the C9 carbon of DHPP with the elimination of pyrophosphate, in the production of the intermediate folate 7,8-dihydropterate[5,7,8]. Sulfa drugs do not cause disturbances in animal cells because they do not synthesize folate, but acquire it through food[6].

The combined activity of sulfonamide and trimethoprim (Figure 1.E) results in further sequential blockade of folic acid synthesis, acting synergistically, where trimethoprim reversibly binds to DHFR inhibiting its activity and preventing the reduction of dihydrofolic acid (DHFA) to tetrahydrofolic acid (THFA), catalyzed by DHFR[4,9] required for one-carbon transfer reactions in the biosynthesis of a variety of biomolecules, such as nucleotides and amino acids[5]. Trimethoprim exhibits structural similarity to DHF, making it a competitive inhibitor of chromosomal DHFR ubiquitous in bacteria, fungi, and protozoa, but not in mammalian DHFRs, which are resistant to TMP[4,5,9].

V. PHARMACOLOGY, CLINICAL USE, AND ADVERSE EFFECTS OF ANTIMICROBIAL SULFONAMIDES

Sulfonamides are drugs with bacteriostatic activity, they are structural analogues and competitive inhibitors of PABA in the DHPS enzyme in the folic acid metabolism cycle[6,9]. Sulfonamides with antimicrobial activity (with an aromatic amine) have the same basic structure derived from sulfanilamide[10] (Figure 1.C), which presents the minimum structural prerequisites for an antibacterial action, where the obtaining of sulfonamides with different physical, chemical, pharmacological and antibacterial properties can be obteined with the introduction of several radicals in this substance. However, sulfur needs to be linked directly to the benzene ring, the para-NH_2 group (N4 position) is essential and can only be replaced by molecules that can be converted, *in vivo*, into a free amino group. Substitutions in the NH_2 group (N1 position) have diverse effects on the antibacterial activity of the molecule, where the substitution of heterophilic aromatic nuclei in N1 results in highly potent compounds[11].

Chart 1 summarizes the route of administration, chemical structure, pharmacological activity, and therapeutic use of some antimicrobial sulfonamides and associations of therapeutic importance.

With the exception of sulfosasalazine, a prodrug that has low intestinal absorption, where it is degraded by bacteria into sulfapyridine and 5-aminosalicylic acid (5-ASA), active drug, exerting an anti-inflammatory effect locally in the intestine, being used in the treatment of ulcerative colitis, oral sulfonamides, such as sulfisoxazole, sulfamethoxazole, and sulfadiazine, are absorbed by the gastrointestinal tract, mainly in the small intestine[11]. They bind to plasma proteins, mainly albumin, diffusing throughout body tissues and organic fluids, however their concentration in the cerebrospinal fluid and in the aqueous and vitreous humors varies with the type of sulfa, with sulfadiazine and sulfissoxazole reaching cerebrospinal fluid concentrations that may be effective against infections in the meninges. They cross the placenta reaching the fetal circulation and amniotic fluid at levels sufficient to exert antibacterial as well as toxic effects and should not be administered to pregnant women in early pregnancy and close to delivery, as well as to newborns, especially premature infants, as they compete with bilirubin for binding sites in serum albumin. displacing the bilirubin bound to plasma albumin, and this free bilirubin can be deposited in the basal ganglia and subthalamic nuclei of the brain, causing *Kernicterus*[10,11].

They present hepatic metabolization and mainly renal excretion, but are also eliminated in small amounts in feces, bile, breast milk and other secretions[10,11].

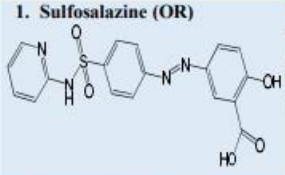
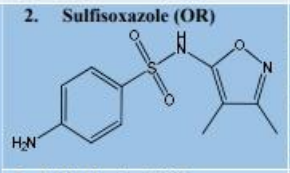
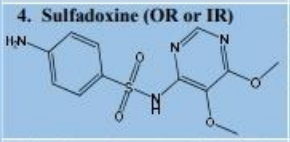
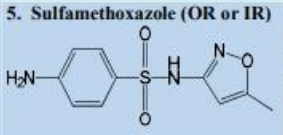
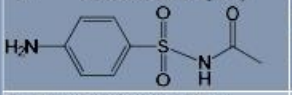
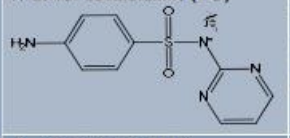
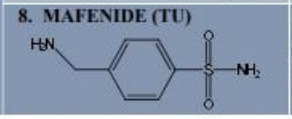
Sulfadoxine, considered long-acting sulfonamide, is rapidly absorbed, but has slow excretion, which increases its serum half-life, and is used in association with pyrimethamine for prophylaxis and treatment of malaria caused by strains of *Plasmodium falciparum* resistant to mefloquine, chloroquine, as well as in the treatment of toxoplasmosis[10,11].

Among sulfonamides for topical use, sulfacetamide is used as a sodium salt solution used in the treatment of ophthalmic infections. Silver sulfadiazine and mafenide are used topically to prevent infections by gram-positive and gram-negative bacteria in wounds resulting from burns[10,11].

With the advancement of bacterial resistance to sulfonamides, treatment with isolated sulfonamides for the treatment of infections is limited to a few indications, however, the combination of sulfonamide with trimethoprim is applied in several infectious processes, comparing its activity to broad-spectrum antibiotics[9,10,11].

Chart I. Route of administration (ADM), chemical structure, pharmacological activity and therapeutic use of some sulfonamides.

Sulfonamides: They are structural analogues and competitive inhibitors of PABA in the DHPS enzyme, preventing the synthesis of folate. All sulfonamides have a similar spectrum and mechanism of action, acting on bacterial microorganisms, fungi and protozoa, presenting bacteriostatic action, and are generally used in association with trimethoprim or pyrimethamine, with synergistic action on the folate synthesis pathway, inhibiting DHFR. Adverse effects that may arise after the use of sulfonamides are numerous and varied, with emphasis on nephrotoxicity caused by crystalluria, effects on the hematopoietic system and hypersensitivity reactions, including erythema multiforme Stevens-Johnson type[11].

ADM	DRUG	PHARMACOLOGY	THERAPEUTIC USE
NON-ABSORBIBLE ORAL	**1. Sulfosalazine (OR)** 	- Poorly absorbed from the gastrointestinal tract (GIT)[9,10]. - Pro-drug that has low intestinal absorption, where it is degraded by bacteria into sulfapyridine and 5-aminosalicylic acid (5-ASA - active drug), exerting an anti-inflammatory effect locally in the intestine[10].	Treatment of inflammatory bowel disease, particularly in the treatment of ulcerative colitis and Crohn's disease[9,10].
ABSORBABLE ORAL	**2. Sulfisoxazole (OR)** 	- It is rapidly absorbed by the GIT and excreted by the kidneys, reaching concentrations in the urine greater than in the blood. In the cerebrospinal fluid (CSF) the concentration reaches about 1/3 of the blood[11]. - Activity against *Streptpcoccus pyogenes*, *S. Pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Escherichia coli* and *Nocardia*[11].	Sulfisoxazole + Erythromycin Ethylsuccinate is used to treat lower urinary tract infection (UTI) and in children with otitis media[11].
	3. Sulfadiazine (OR) 	- Rapidly absorbed from the GIT and excreted by the kidneys. It is distributed throughout all body fluids and tissues, including the aqueous humor, tears and cerebrospinal fluid, where it reaches 70% of blood concentration[11]. - Activity similar to sulfisoxazole, with adequate activity against *Toxoplasma gondii*[11].	sulfadiazine + pyrimethamine is used for treatment of toxoplasmosis[11].
	4. Sulfadoxine (OR or IR) 	- Rapid absorption from the GIT and slow renal excretion, increasing its serum half-life, long-acting sulfonamide[10,11]. - Activity similar to sulfisoxazole, with some activity against *Plasmodium falciparum*[10,11].	Sulfadoxine + Pyrimethamine is used for treatment of toxoplasmosis and malária (*P. falciparum*)[10,11].
	5. Sulfamethoxazole (OR or IR) 	- Rapid absorption from the GIT and prolonged renal excretion, spreading throughout the body, reaching therapeutic levels in bile and CSF[10,11]. - Associated with trimethoprim, formulated in a ratio of 5:1 (sulfa:trimethoprim), it reaches serum levels of 20:1, presenting broad-spectrum activity[10,11].	It is used for treatment of UTI and systemic infections by sensitive germs, drug of choice for treatment and prophylaxis of *Pneumocystis jiroveci* infections in AIDS patients[10,11].
TOPICAL USE	**6. Sulfacetamide (OU)** 	- It has water solubility 90 times greater than sulfadiazine, penetrates into liquids and ocular tissues in high concentration[11]. - Sulfisoxazole-like activity[11].	Treatment of ophthalmic infections by susceptible microorganisms[11].
	7. Silver Sulfadiazine (TU) 	- It is the least toxic sulfonamide, presented as a cream for topical use[10,11]. - Activity on Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa* and *Candida albicans*[10,11].	Treatment and prevention of infections in burn patients, as well as in gynecological vaginal infections[10,11].
	8. MAFENIDE (TU) 	- Available for topical use, but can be absorbed into burn sites[11]. - Activity on a variety of Gram positive and Gram negative bacteria[11].	Prevention of colonization of burns by bacteria[11].

Source: Adapted from Bruton et al (2019)[11], modified by the author. ADM: route of administration; PABA: p-amino benzoic acid; DHPS: dihydropteroate synthase; GIT: gastrointestinal tract; UTI: urinary tract infection; CSF: cerebrospinal fluid; OR: oral route; IR: intravenous route; TU: topical use; OU: ophthalmic use.

Sulfamethoxazole is the most widely used sulfonamide antibiotic in therapy today, mainly in combination with trimethoprim, which also interferes with folic acid synthesis, being used for the treatment of a wide variety of infections by sensitive germs, such as urinary tract infections, respiratory tract infections, gastrointestinal tract infections, as well as for patients with *Pneumocystis jiroveci* infections[9,11,12]. The combination of sulfadiazine and pyrimethamine is the treatment of choice for toxoplasmosis[10,11]. Sulfamethoxazole or sulfadiazine are effective in the treatment of infections caused by *Nocardia* species. Sulfonamides can also be used in the prophylaxis of streptococcal infections and recurrences of rheumatic fever[11].

The adverse effects that may arise after the use of sulfonamides are numerous and varied. Complaints of nausea, vomiting, abdominal pain, anorexia, bitter mouth sensation and other digestive disorders have been evidenced in individuals who use oral sulfonamides, which may be of central origin, due to intoxication of the nervous system[10,11].

Nephrotoxicity is a consequence of crystalluria that occurs with older and less soluble sulfa drugs at acidic pH, such as in urine, with the crystals depositing in the renal tubules causing obstructive processes and kidney damage. The incidence of nephrotoxicity is lower with the use of more soluble sulfa drugs, such as sulfisoxazole, but may still exist with the use of sulfadiazine and sulfamethoxazole, due to low solubility. The increase in pH and diuresis (through increased fluid intake) favors the solubilization of sulfonamides, and is recommended[10,11].

The hematopoietic system can be affected with the use of sulfonamides, causing acute hemolytic anemia in patients with G6PD (glucose-6-phosphate-dehydrogenase) deficiency, agranulocytosis and aplastic anemia[10,11].

Hypersensitivity reactions to sulfonamides, with cutaneous-mucosal manifestations resulting from a vasculitis process, may arise, especially morbilliform, scarlatiniform, urticarial eruptions, erysipeloids, pemphigoids, purpuric and petechial eruptions, as well as erythema nodosum, erythema multiforme type Stevens-Johnson, Behçet's syndrome, exfoliative dermatitis and photosensitivity. In rare cases, focal or diffuse hepatic necrosis and pancreatitis related to direct toxic action or hypersensitivity may occur in some patients, with patients usually presenting with headache, nausea, vomiting, fever, hepatomegaly, jaundice, and laboratory evidence of hepatocellular dysfunction 3 to 5 days after initiation of sulfonamide treatment, which may progress to acute yellow atrophy and death. Currently, the manifestations of neurotoxicity mentioned above and the cases of interstitial nephritis, pneumonitis and bronchitis related to hypersensitivity are also rare[10,11].

VI. RESISTANCE TO SULFONAMIDES AND TRIMETHOPRIM

Sulfonamide resistance can occur due to mutations that (I) lead to excess PABA production, (II) DHPS production with low sulfonamide affinity, or (III) decreased permeability to sulfonamide[9]. Sulfonamides act as competitive inhibitors of the DHPS enzyme, encoded by the folP gene[14]. Sulfonamide resistance occurs mainly due to mutations in the folP gene or through the acquisition of alternative DHPS genes (*sul1-sul4* genes) transmitted by plasmids, integrons, and transposons, which encode mutant DHPS enzymes with low affinity for sulfonamides, but with normal affinity for pABA[15,16]. *Sul* genes are the most common mechanism of sulfonamide resistance and have been detected in a wide range of bacterial species from many different environments, including agricultural soils and wastewater[13].

Studies have demonstrated the spread of resistance to multiple drugs, including sulfonamides, in bacteria isolated from animals, as well as the identification of antimicrobial resistance genes (including *Sul* genes) in soil and feces in animal production environments[17,18].

DHPS has a α/β TIM barrel structure, and it has been observed that many of the drug resistance point mutations are located within two flexible and conserved loops (loop1/loop2), where Phe33, Thr67, and Pro69 are sites of resistance mutations and form key elements of the PABA binding site (FIGURE 2)[5,7].

Yun et al. (2012) report computational studies on catalysis and resistance to sulfonamides in DHPS, through the performance of enzyme-catalyzed reaction in crystalline DHPS, showing that the results support an SN1 reaction mechanism (Figure 2A) through the formation of a new pterin cationic intermediate, and that two conserved loops generate a substructure during catalysis that creates a specific binding pocket for PABA, where this substructure, together with the pterin binding pocket, explains the role of the residues of the conserved active site and reveals how sulfonamide resistance arises (Figure 2B-E)[7].

Trimethoprim is a synthetic drug, often used in combination with sulfonamides, introduced for clinical use in Europe in the early 1960s. Its widespread use in the treatment of human infections has led to bacteria also developing resistance mechanisms. Only a single amino acid substitution in DHFR, Phe98 to Tyr98, found in all clinical isolates of Staphylococcus aureus tested so far, was found to be the molecular origin of TMP resistance[5,19].

VII. RESEARCH FOR THE DISCOVERY AND DEVELOPMENT OF NEW SULFONAMIDE ANTIBIOTICS

Although sulfonamides are primarily known as synthetic compounds, several examples have also been discovered from natural sources[20]. However, the synthesis of sulfonamides has aroused great interest from several scientific study groups, with several scientific researches and publications being carried out. Sulfonamide derivatives have been obtained through computational studies (*in silico*), microbial genomics, synthetic organic chemistry, X-ray crystallography, molecular modeling, with sulfonamides being used as building blocks, combinations of sulfonamides and other drug molecules, coordination of metals (Cu, Au, Co, Ni, Zn and Cd), antibacterial and cytotoxic evaluation being used for the development of new formulations, which can lead to the discovery of new antibiotics[5,21,22,23,24,25].

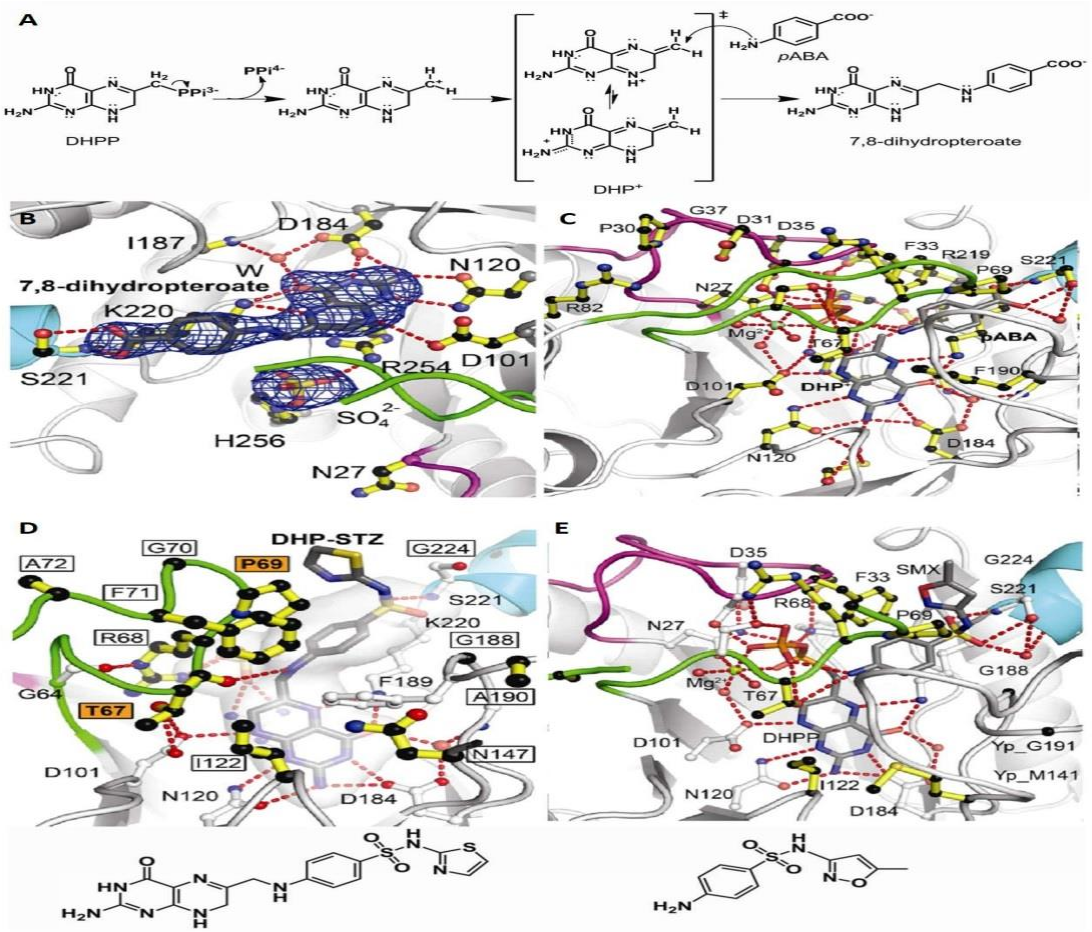


Figure 2: Catalytic, inhibition and resistance mechanisms to sulfa drugs. A. Proposed SN1 chemical reaction, catalyzed by DHPS (dihydropteroate synthase) with formation of 7,8-dihydropteroate. **B.** 7,8-dihydropteroate product generated by B. anthracis crystals (BaDHPS), after immersion of the crystals in DHPP (dihydropteridine pyrophosphate), PABA (p-amino benzoic acid) and Mg_2^+. **C.** Product 7,8-dihydropteroate generated by crystals of Y. pestis (YpDHPS), after immersion of the crystals in DHPP, PABA and Mg_2^+. In figures B and C, loop1 is shown in magenta, loop2 is shown in green. **D.** Crystalline BaDHPS embedded in DHPP and sulfathiazole (STZ) reveal a covalent DHP-STZ adduct linked to the active site and stabilized by an ordered loop2. Boxed residues are sites of sulfa drug resistance, and two key sites are marked in orange. The molecular envelope (light gray) encompasses the pterin-PABA and anion binding pockets. Note that the thiazole ring of STZ extends out of this pocket directly adjacent to Pro69. The structure of the DHP-STZ is shown below the figure. **E.** Stereo view of the crystalline YpDHPS active site occupied by DHPP, sulfamethoxazole (SMX) and an octahedrally coordinated Mg_2^+ ion. It has a structure very similar to that shown in figure 2.C, which contains PABA in place of SMX. A difference in the structure of PABA is that the DHPP is intact with the covalently bound pyrophosphate. Residue numbering corresponds to BaDHPS. The structure of SMX is shown below the figure. In both figures, loop1 is shown in magenta, loop2 is shown in green, and the N-terminus of the α helix Loop7 is shown in teal[7].

Source: Adapted from Yun et al. (2012)[7], modified by the author.

VIII. CONCLUSION

The execution of this study allowed us to highlight the importance of sulfonamides as an important class of synthetic antimicrobials. It was also observed that the extensive use of sulfonamides for human, veterinary and agricultural use, as well as the contamination of the environment by antibiotics, including sulfonamides, favors the acquisition and dissemination of bacterial resistance, constituting a public health problem worldwide. The search for new antibacterial agents is necessary and should be continuous, with research aiming at the development of new antibacterial agents that are effective in combating and treating infections caused by pathogenic microorganisms resistant to currently available treatment options, with sulfonamides as promising agents for these researches. In addition, strict control in the use of these new antimicrobials is essential to prolong the useful life in clinical use, not favoring the acquisition of antimicrobial resistance.

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