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Review Article

Advances in Sulfonamide Research: Synthesis, Mechanisms, and Biomedical Applications

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ABSTRACT

A number of drug groups are based on Chemistry of sulfonamide (or sulfanilamide) functional groups. Because of their various pharmacological properties, such as anti-t dihydropteroate synthetase and anti-carbonic anhydrase, in vivo sulfonamides can be used to treat a variety of illnesses, including inflammation, glaucoma, thyroiditis, diuresis, and hypoglycaemia. In veterinary medicine, sulfamethazine (SMZ) is a frequently used sulfonamide medication that treats cattle illnesses such respiratory and gastrointestinal tract infections by acting as an antibacterial substance. The treatment of bacterial infections was transformed by the innovative synthetic antimicrobial medication sulfanilamide. This review explores its synthetic processes, historical relevance, underlying mechanism of action and the connection between structure and activity. The discovery of sulfanilamide, which provided a focused strategy to fight bacterial infections, signalled a revolution in medicine. The development of a wide variety of sulfa medications was made possible by its manufacture, which included crucial processes including sulfonation and amination. By interfering with bacterial folic acid synthesis, the mechanism of action, which is based on competitive inhibition of dihydropteroate synthetase, eventually stops bacterial growth and replication. Sulfanilamide's lasting significance as a key substance in the field of antimicrobial chemotherapy is highlighted in this study.

INTRODUCTION

Sulfonamides (SN), sometimes referred as sulfanilamide, are a significant category of artificial antibacterial drugs that are utilized pharmacologically as all-encompassing remedies for bacterial infections in both People and animals. [Ovung Aben et.al., 2021]. Sulphonamides, another name for sulphanilamides, are an important class of synthetic antimicrobial

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medications that have a wide range of efficacy against bacterial infections. These substances are known as organo-sulphur compounds because they have characteristic heterocyclic rings with six or five members and the SO_2NH_2 group. They are highly effective against pyogenic bacterial illnesses brought on by Salmonella, Shigella, E. Coli, Enterobacter, Salmonella, Klebsiella, and Nocardia, among other microorganisms that are both gram-positive and gram-negative. They're particularly efficient against microorganisms that are gram-positive, such as S. pyogenes and S. pneumoniae. Their usefulness against gram-negative bacteria, like E.coli and K.pneumoniae, is comparatively lower. Despite their active antibacterial properties, sulphanilamides face significant challenges posed by antibiotic resistance. [Gagandeep Kaur Et.al.2023]. The first medications to be widely and consistently used as chemotherapeutic and preventative agents against a variety of diseases were sulfonamides, sometimes known as sulfa medicines. Over 30 medicines Clinically used medications with this property include nonpeptidic vasopressin receptor antagonists, translation initiation inhibitors, antibacterial, antiprotozoal, antifungal, anti-inflammatory, and antihypertensive drug bosentan. Several significant derivatives of sulfonamides are employed as commercially significant Inhibitors of carbonic anhydrase. Rheumatoid arthritis, ulcerative colitis, scalds, and male erectile dysfunction (as caused by The more well-known phosphodiesterase-5 inhibitor sildenafil by its brand name, Viagra), being overweight, and infections of the urinary tract, intestines, and eyes can all be effectively treated with them. Sulfonamides have been utilized more recently in Alzheimer's illness, as an amprenavir, an antiviral HIV protease inhibitor, and as an anti-cancer drug.[Aneta Kołaczek Et.al 2014]

Sulfanilamide is commonly used as a medication to address internal infections and as a topical medication or powder to address surface infectionsIt is a member of the antibacterial drug class called sulfanilamideDepending on the kind of infection, a medication or cream may be recommended to treat it. Common diseases treated by sulfanilamide include strep throat, vaginal infections, urinary tract infections, and some staph infections. [Khalaf Husam S. et al. (2015). One sulfonamide antibiotic is sulfanilamide. Sulfonamides are synthetic bacteriostatic antibiotics that have broad-spectrum activity against a range of gram-positive and gram-negative bacteria. However, many resistant strains may exist within a single species. Sulfonamides stop bacteria from growing by acting as competitive inhibitors of p-aminobenzoic acid in the folic acid metabolism cycle. However, as the sulfonamide salts that are soluble are extremely alkaline and causing tissue irritation, parenteral administration is challenging. All tissues have a large distribution of sulfonamides. Ocular, synovial, peritoneal, and pleural fluids all reach elevated levels. CSF levels are elevated in meningeal infections even though these medications are no longer used to treat meningitis. Pus inhibits their antimicrobial properties. [Schnitker, Maurice A. et al., 1938].

Side effects

- Sulfonamides can result in a number of undesirable side effects, such as hypersensitivity reactions, hemopoietic diseases, and urinary tract problems.
- It may cause a severe allergic reaction if taken in excess. Stevens Johnson syndrome, also known as toxic epidermal necrolysis, is among the most severe.
- The intriguing side effect of A some of the initial sulfonamide medications, which were

made from dyes that are azo, was that they made the patient momentarily N.B. Stevens-Johnson syndrome (SJS) is a condition that potentially fatal skin disorder in which the epidermis separates from the dermis as a result of cell death.

- It is believed that the syndrome is a hypersensitivity complex that affects the mucous membranes and skin. [Israa Talib Humedy. Et.al.2015]

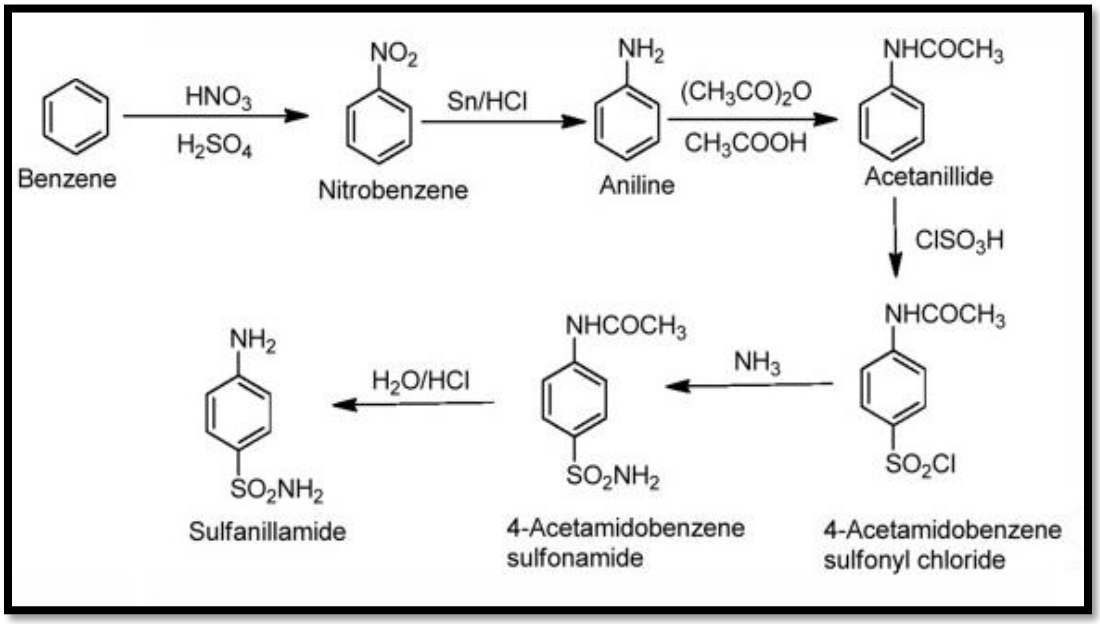
Adverse reactions

- Rash and hives are the most typical signs of a hypersensitivity reaction to sulfa medications. However, hypersensitivity to sulfa medications can cause a number of potentially fatal symptoms, such as fulminant hemolysis, thrombocytopenia, agranulocytosis, toxic epidermal necrolysis, Stevens-Johnson syndrome, and hemolytic anaemia hepatic necrosis, among others.
- The chemical structures of sulfonamide antibiotics are linked to the class's hypersensitivity reactions.[Dr. s. mondal Et.al.2019].

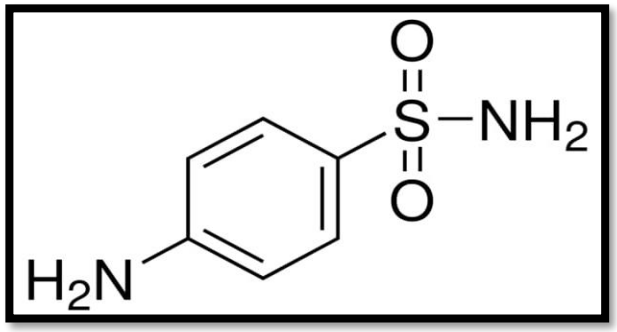
History:

Year	Biological activity reported
1917	To improve quinine derivatives' bactericidal qualities, a chemical was added at the Rockefeller Institute.
1927	A Bayer subsidiary started testing colors to see how well they prevented streptococcal infections.
1932	Gerhard Domagk started researching a bright red dye that was eventually called Prontosil. Prontosil (azo dye) was found to have protecting properties.
1033	The first clinical case study of prontosil was described by Foerster. The 10-month-old girl who survived was administered Prontosil.
1935	Prontosil was found to be a pro-drug of sulfanilamide. Sulfa was originally utilized in the United States with no results. After conducting a structure-activity analysis of the sulfonamide azo dyes, Refouel and his colleagues came to the conclusion that the azo linkage was reductively broken, releasing sulfanilamide, the active antibacterial agent..
1937	"Sulfanilamide" was released when protosil was broken down, and several sulfonamides were created.
1938	Working non-azo dyes showed that prontosil, a dye having a sulfonamide chain, was effective in preventing streptococci from growing. The first sulfonamide to be sold was sulfapyridine.
1939	Domagk was given the Nobel Prize in Physiology or Medicine for finding the chemotherapeutic efficacy of prontosil.
1968	Sulfa combined with Trimethoprim to show antibiotic activity.

Synthesis:



Physical And Chemical Properties:

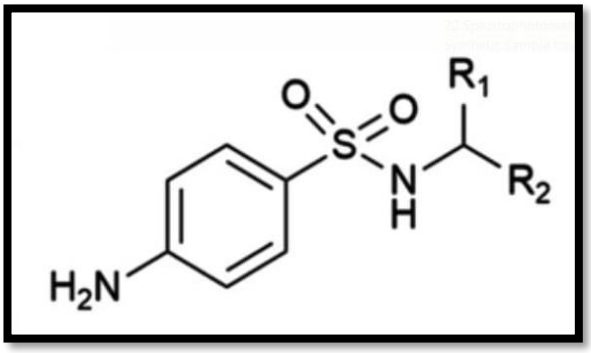


Structure Sulfanilamide

IUPAC Name	4-aminobenzenesulfonamide
Molecular formula	$C_6H_8N_2O_2S$
Molecular mass	172.205 g.mol
Melting point:	329 – 331°c
Form:	White crystalline form
Pka	10.6 (at 20°c)
Color	Yellowish White
Water solubility	Sparingly soluble
Vapor pressure	0.0000073[mmHg]
Stability	Sensitive to light
PH	2.7

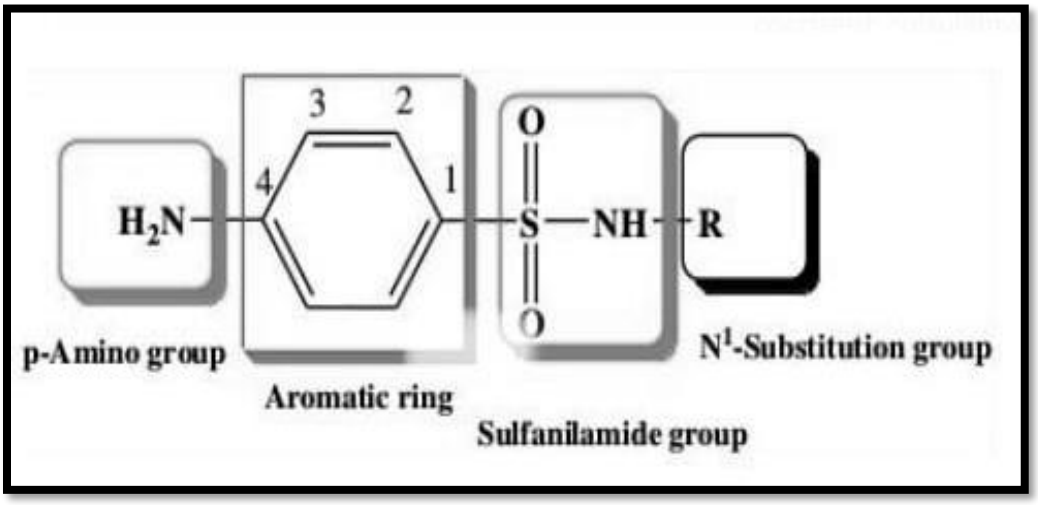
category	Antibiotic, Antimicrobial

Chemistry:



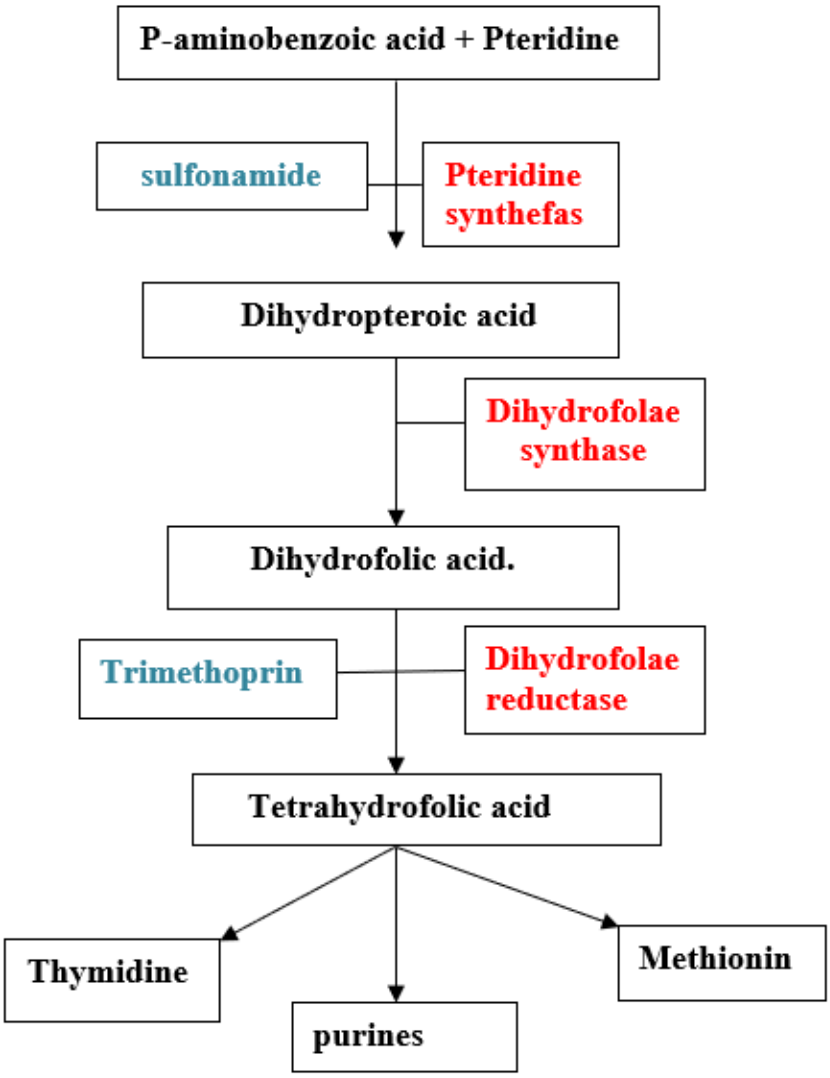
The suffarmoyl functional group is joined to aniline at the 4-position to form sulfanilamide, a sulfonamide. It functions as an antibacterial agent, a drug allergen, and an inhibitor of EC 4.2.1.1 (carbonic anhydrase). It is a sulfonamide, a sulfonamide antibiotic, and a substituted aniline. [Tanmay Sarkar Et.al 2019]

Structure Activity Relationship



1. The bare minimum structural prerequisite for antibacterial action is the sulfanilamide skeleton.
2. The benzene ring's amino and sulphonyl groups are crucial and belong in positions 1 and 4.
3. It is possible to modify the N-4 amino group to create prodrugs, which in vivo transform into free amino acids.
4. The sulfur atom and the benzene ring ought to be connected immediately. Its activity is reduced or eliminated when the benzene ring is swapped out for another ring system or when more substituents are added.
5. The activity is decreased when the -CONH group is substituted for the -SO_2NH group.
6. The type of substitution at the amino group affects the activity of N-1-substituted sulphonamides. Bacteriostatic activity rises when substituents give the SO2 group electron-rich characteristics.
7. Sulphonamides, which have a single benzene ring at the N-1 position, are significantly more poisonous than their heterocyclic ring counterparts, but heterocyclic substituents produce extremely potent derivatives.
8. The sulphonamide group should be next to the free aromatic amino groups. Compounds lacking antibacterial activity are produced when it is substituted in an ortho or meta position.
9. The ionized, maximal activity of sulphonamide, which is found between pKa values 6.6 and 7.4, is its active form.
10. Inactive compounds were created by substitutions in the benzene ring of sulphonamides; the activity was destroyed when a free sulphonic acid (–SO_3H) group was substituted for the sulphonamido function; however, the activity was restored when a sulphinic acid group (–SO_2H) was substituted, and the N-4 position was acetylated.
11. The basic centers of proteins' arginine, histidine, and lysine sites are where meta-sulphonamides attach. Halides, alkyl, and alkoxy are the binding groups. Sulphonamide action is impacted by the binding; protein binding seems to alter the drug's half-life and availability.
12. The halflife and antibacterial activity in vitro are increased by the lipid solubility, which also affects pharmacokinetics and antibacterial action[Dr. s. mondal Et.al.2019].

Mechanism Of Action:



[Gagandeep Kaur Et.al.2023].

Application:

Antibacterial effect:

Electron-withdrawing substitutions, such nitro groups, can boost the antibacterial activity of sulfonamide derivatives. Antibiotics are recognized to be chemotherapeutic agents that either kill or stop the growth of germs. Sulfonamides work against bacteria by serving as structural analogues and P-aminobenzoic acid (PABA) competitive inhibitors, which are necessary in order to produce folic acid, which in turn promotes the development of bacterial DNA. Because sulfonamides and PABA share structural similarities, sulfonamides can block dihydropteroate synthase and substitute PABA enzymes, which are crucial for producing folic acid. This inhibits the formation of tetrahydrofolate and dihydrofolate, which in turn prevents the growth, division, and replication of bacteria. Sulfonamides are bacteriostatic rather than bactericidal because they prevent cell division. [Baraa G. Alani Et.al. 2024].

Anti- inflammatory:

Pfizer has created NSAID sulfonamide derivatives such Celecoxib, Rofecoxib, and Valdecoxib as Cox-II specific inhibitors to treat osteoarthritis and

rheumatoid arthritis. Their method of reducing inflammation involves specifically blocking the Cyclo-oxygenase-2 (COX-2) enzyme, which is a major contributor to inflammation. Cox-2 is almost nonexistent in the majority of tissues under normal settings, but proliferative stimulation and inflammation cause it to be expressed, resulting in locally generated Cox-2 that regulates the process of inflammation. Acute and chronic inflammatory diseases, cancer, and some neurological conditions are linked to overexpression of Cox-2. [Baraa G. Alani Et.al. 2024**].**

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CONCLUSION:

One innovative antibacterial agent that has had a big impact on medicine is sulphanilamide. This review delves into its rich history, diverse synthetic methods, structure-activity relationships, broad applications, and elucidates its mechanism of action. The accidental discovery of its antibacterial qualities, which resulted in the creation of a class of life-saving medications, is highlighted in the historical trip. The synthesis section examines a range of methods, including both traditional and contemporary techniques, for making sulphanilamide and its derivatives. The sulfonamide group and its substituents play a critical role in determining antibacterial action, according to the structure-activity relationship analysis. Sulphanilamide’s ability to address a range of bacterial illnesses, including meningitis, pneumonia, and urinary tract infections, demonstrates its adaptability. Its promise in other therapeutic domains, like autoimmune illnesses and cancer, is also examined. Sulfanilamide functions mechanistically as an inhibitor of dihydropteroate synthase that is competitive, an essential enzyme in the manufacture of folic acid by bacteria. Bacterial growth and proliferation are eventually stopped by this disturbance of folate metabolism. In summary, sulfanilamide's legacy lives on as evidence of the value of chance in scientific research and the ongoing development of medicinal chemistry. Its position as a key component in the creation of antimicrobial agents is cemented by its historical relevance, wide range of applications, and well-understood mode of action.

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