INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Study

Synthesis, Mechanism of action And Characterization of Sulphonamide

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ARTICLE INFO

Published: 18 May 2025
Keywords:
Sulfanilamide, History, Antimicrobial activity, antibiotic, Synthesis, Structure activity Relationship, mechanism of action
DOI:
10.5281/zenodo.15458257

ABSTRACT

One of the first synthetic antimicrobials, sulfonamides, were essential to the creation of contemporary chemotherapy. These substances, which were first used in the 1930s, transformed the way bacterial infections were treated and set the stage for the later discovery of antibiotics. Beyond their historical relevance, sulfonamides' structural diversity and wide range of pharmacological potential continue to pique research attention. The chemical structure, modes of action, production methods, and a variety of biological functions of sulfonamides are all covered in detail in this article. The study also looks at new therapeutic uses that go beyond antibacterial ones, such as anti-inflammatory, anticancer, and antidiabetic effects. There is also discussion of recent developments in overcoming resistance and improving efficacy through structural alterations and innovative drug delivery methods. This study emphasizes the continued significance and potential of sulfonamide molecules in pharmaceutical sciences by reexamining both traditional and modern.

INTRODUCTION

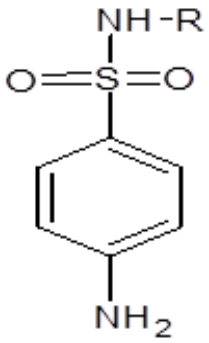

Fig: General structure of sulphonamide

One important class of synthetic antibacterial drugs created in the early 20th century is sulfonamides, commonly referred to as sulfanilamides. By functioning as competitive antagonists of p-amino benzoic acid (PABA), which is essential for bacterial DNA synthesis, they primarily limit the synthesis of folic acid in bacteria. Because of their structural resemblance to PABA, sulfonamides are able to inhibit the enzyme dihydropteroate synthetase, which eventually results in bacteriostatic rather than

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

bactericidal effects.[Iliyan Ivanov *et.al*.2024][1]. One important class of synthetic antimicrobial drugs that are used pharmacologically as broad-spectrum therapies for bacterial infections in both humans and animals are sulfonamides (SN) or sulfanilamides.In 2019, Dr. S. Mundal and associates.SN structures are organo-sulfur compounds with the -SO2NH2 and/or -SO2NH- group that are characterized by the presence of a sulfanilamide group and distinct 6- or 5-membered heterocyclic rings. SNs can cause a variety of unwanted side effects, including digestive and respiratory issues, and they are not readily biodegradable. Headaches, nausea, vomiting, lightheadedness, candidiasis, and folate deficiency are a few of the non-allergic side effects of SN medications. High dosages of SN medicines can cause some of the most serious side effects, including toxic epidermal necrolysis and Stevens-Johnson syndrome. [Ovung Aben *et.al.*, 2021][2].

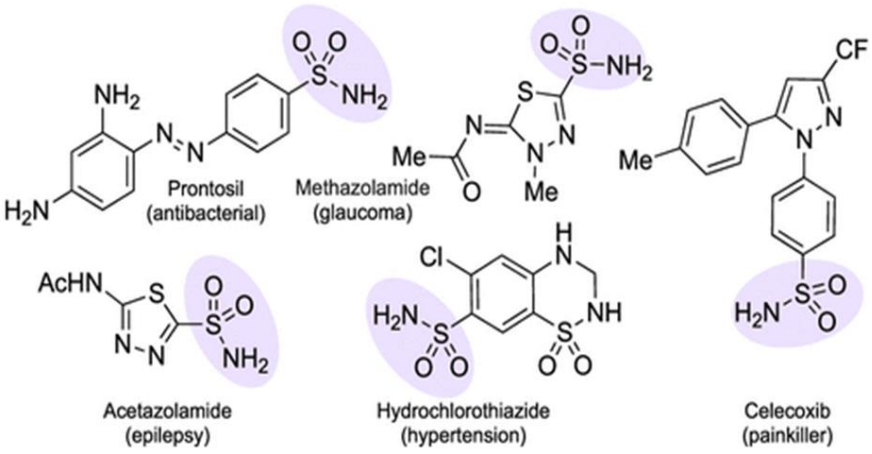


Fig. Primary sulfonamide-containing drugs

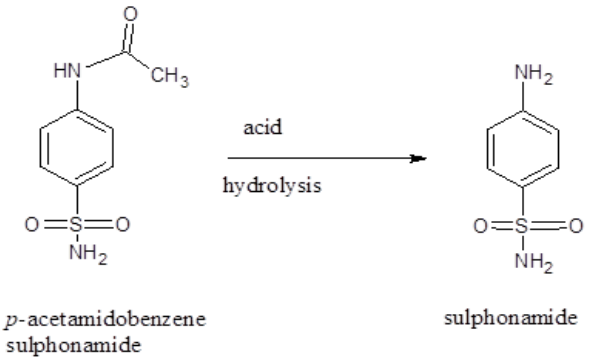
A medicines, were initially employed systemically as chemotherapeutic and preventative treatments for a variety of diseases. Numerous medications with this functional group are used in clinical settings to treat a variety of illnesses, such as high blood pressure, bacterial and parasite infections, inflammatory responses, some tumor types, Alzheimer's disease, and a number of viral infections, including the corona virus. Sulfonamides are substances with a broad structural makeup. Many chemical modifications were investigated following the discovery of sulfonamides, and molecules with a heterocyclic ring replacing one of the SO2NH2 group's hydrogen atoms produced the best biological outcomes. There are dozens of sulfonamide derivatives with different pharmacological effects that have been found recently. R1 could be hydrogen, alkyl, aryl, heteroaryl, etc. in this primary structure. [Baraa G. Alani *Et.al.* 2024][3]. Sulfonamides belong to a significant chemical class with a wide range of biological applications. Over the past few decades, a wide range of sulfonamide conjugate pharmacological activities have been reported. In addition, other lead compounds with sulfonamide action are currently being tested in clinical settings to treat a range of diseases. Because of these factors, organic synthesis research has consistently focused on developing an efficient method for sulfonamide synthesis.[Kaur Gagandeep et al., 2023][4]. Numerous studies have been published over time by researchers demonstrating the effectiveness of sulfonylation and alkylation processes in the production of sulfonamide. The most popular synthesis method involves sulfonyl chloride

reacting with primary or secondary amines in the presence of either organic or inorganic bases. [Mohamed S.A.El-Gabya *et.al* 2020][5]. For many years, sulfonamides have been used to treat Gram+ and Gram-bacterial strains that are connected to a number of infectious diseases. By competing with and preventing p-amino benzoic acid (PABA) from attaching to the dihydropteroate synthase (DHPS) enzyme's binding site, these broad-spectrum synthetic pharmaceutical drugs interfere with the vital bacterial dihydrofolic acid synthesis pathway. One essential component that bacteria require for the synthesis of DNA and RNA is folic acid. Sulfonamides disrupt the process that produces folic acid, which hinders the ability of the bacterial cells to divide and multiply. In addition to their antibacterial qualities, sulfonamides and their derivatives are frequently prescribed as insulin release inducers, antiviral, antifungal, anti-inflammatory, and anti-cancer drugs. [Hira Saleem. *Et.al.* 2018][6]. Despite its advantages, there are a number of things that make it difficult to prescribe. For the treatment of angina pectoris, the European Medicines Agency has advised physicians to limit the use of drugs that include trimetazidine. Patients who experience dizziness, tinnitus, or visual abnormalities shouldn't be prescribed the medication. For individuals with stable angina pectoris who are unable to tolerate first-line antinational therapies, it is recommended as an adjuvant therapy. The government also pointed out that trimetazidine is linked to a risk of movement disorders, including tremors, Parkinsonian symptoms, restless legs syndrome, and unstable gait. The committee recommended adding new warnings and contraindications to reflect the possible dangers of these movement disorders.[Iliyan Ivanov *et.al*.2024][7].

SYNTHESIS OF SULFONAMIDE:

Step1: Synthesis of p-acetamido benzene sulphonyl chloride:

Fill a two-mouth round-bottom flask with 25g of powdered acetanilide, a reflux condenser, and a dropping funnel.
2. Using a dropping funnel, gradually pour 63 milliliters of chlorosulfonic acid into it while shaking it often. Attach a guard tube made of calcium chloride to it.
3. For approximately two hours, heat the material to 60–70°C. P-acetamido benzene sulphonyl chloride separated out of the mixture after it was cooled and then poured over crushed ice.
4. After filtering, rinse with cold water and pat dry.

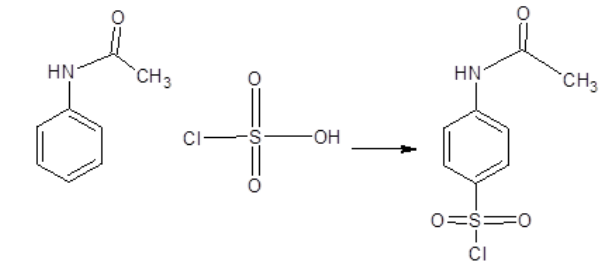


p-acetamidobenzene sulphonamide

sulphonamide

Step2: Synthesis of p-acetamido benzene sulphonamide:

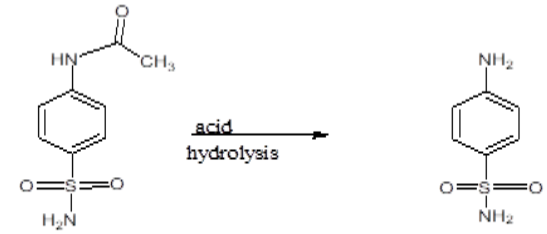
1.Put all of the p-acetamido benzene sulphonyl chloride in a 500 ml flask with a round bottom.
2. Shake in 120 milliliters of water and 120 milliliters of concentrated ammonia.
3. For 30 minutes, heat the mixture to 70°C. Cool the mixture in ice bath and acidify the reaction mixture with dilute sulphuric acid.
4. Filter the p-acetamido benzene sulphonamide that precipitated, rinse with cold water, and bake at 100°C to dry.



Acetanilide | Chlorosulphonic acid | *p*-acetamidobenzene sulphonylchloride

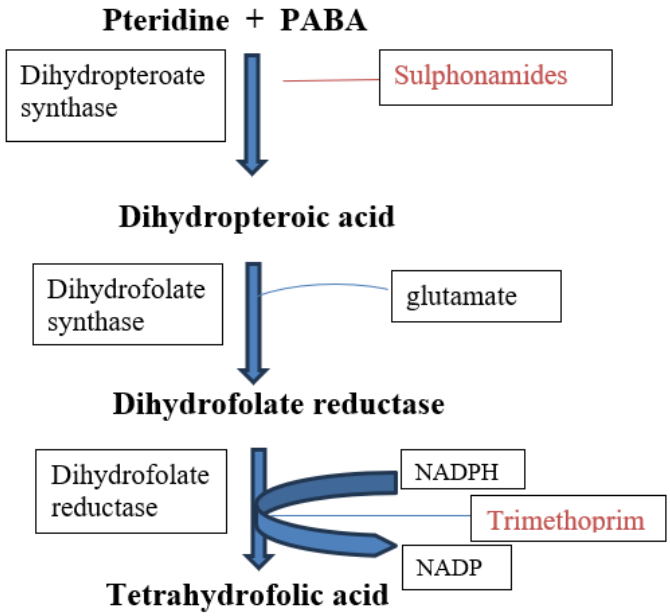
Step 3: Synthesis of p-aminobenzene sulphonamide:

1. Fill a 500 ml flask with the crude p-acetamidobenzene sulphonamide and add 30 ml of water and 10 ml of strong hydrochloric acid. 2. Boil the mixture for 30 to 45 minutes while it is refluxing. After allowing the solution to cool to ambient temperature, heat it for a little while longer until the solid separates. 3. Add 2 grams of charcoal to the cooled solution, bring it to a boil, and then use a suction filter. In a one-liter beaker, carefully add 16 g of solid sodium bicarbonate in little amounts while stirring constantly. This is the filtrate of the mixture, which is a solution of sulphonamide hydrochloride. 4. Following the gas evolution, the suspension is tested on litmus paper; if it remains acidic, more sodium bicarbonate is added until it becomes neutral. After cooling in ice, use suction to remove the sulphonamide. 5. The yield from recrystallization of alcohol is 15 g, m.p. 162^0c.



p-acetamidobenzene sulphonamide | Sulphonamide

MECHANISM OF ACTION:



1.Folic Acid Synthesis Inhibition
The enzyme dihydropteroate synthase (DHPS), which transforms para-aminobenzoic acid (PABA) into dihydropteroic acid, a precursor to folic acid, is inhibited by sulphonamides.

2.PABA competition
By competing with PABA for binding to the DHPS active site, sulphonamides limit the production of dihydropteroic acid and, eventually, folic acid.

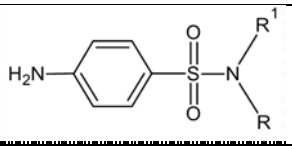
3. Folic Acid Depletion

The production of nucleic acids, like DNA and RNA, which are necessary for bacterial growth and replication, decreases as folic acid levels in bacteria fall.

4. The Effect of Bacteriostatics

Sulphonamides have a bacteriostatic action, which means that instead of completely eliminating germs, they prevent them from growing and replicating.

Drug profile:

Parameter	Information
Drug Name	Sulphonamide
IUPAC Name	4-aminobenzenesulfonamide
Structure	
synonyms	Sulfa drug, sulfanilamide
Chemical formula	$C_6H_8N_2O_2S$
Molecular weight	140.2g/mol.
Appearance	White or yellowish-white crystals or fine
Odour	Odourless
Melting point	164.5^0c – 166.5^0c
Solubility	Soluble in aq. alkali, ethanol, glycerol, hydrochloric acid, propylene glycol Insoluble in benzene, chloroform, diethyl ether, petroleum ether
Theoretical yield	25.48g
Practical yield	22.32g
Percentage practical yield	87.59%
category	synthetic antimicrobial drugs
Uses	• Urinary tract infections • Antibacterial • antimicrobial • anti-inflammatory • Respiratory tract infections • Anti-diuretics • antimalerial • burn therapy

CHARACTERIZATION OF SULPHONAMIDE

One way to describe the class of antimicrobials known as sulphonamides is by their:

The Structure of Chemicals

1. Sulphonamide group: The antibacterial activity of sulphonamides is attributed to their sulphonamide group (-SO2NH2).
2. Aromatic ring: A lot of sulphonamides have an aromatic ring structure, which helps them interact with biological targets and be lipophilic.

Action Mechanism

1. Inhibition of folic acid synthesis: By competing with para-aminobenzoic acid (PABA) for the enzyme dihydropteroate synthase, sulphonamides prevent bacteria from synthesizing folic acid.
2. Bacteriostatic activity: Sulphonamides usually have bacteriostatic properties, which means they prevent germs from growing instead of destroying them.

Chemical and Physical Characteristics

1. Solubility: The solubility of sulphonamides in organic solvents and water varies.
2. Sulphonamides' ionization state and capacity to interact with biological targets can be influenced by their pKa.
3. Stability: Sulphonamides may degrade over time or under specific environmental circumstances, but they can remain stable in a variety of situations.

Drug interactions and pharmacokinetics

1. Absorption: Depending on the particular component, sulphonamides may be absorbed topically or orally.
2. Distribution: Sulphonamides have the ability to reach different bodily fluids and tissues.
3. Metabolism: A number of liver enzymes are capable of breaking down sulphonamides.
4. Excretion: Urine is usually where sulphonamides are eliminated.

Clinical Application

1. Antibacterial activity: Skin and urinary tract infections are among the bacterial infections that sulphonamides are used to treat.
2. Combination therapy: To increase their effectiveness, sulphonamides are frequently used in conjunction with other antimicrobials, such as trimethoprim.

Consequences and Harmfulness

1. Allergic reactions: Skin rashes and Stevens-Johnson syndrome are among the allergic reactions that sulphonamides can induce.
2. Hematologic toxicity: Aplastic anemia and agranulocytosis are two examples of hematologic toxicity that sulphonamides can induce.
3. Additional adverse effects: Sulphonamides may also result in photosensitivity and gastrointestinal issues.

AKNOWLEDGMENT:

We appreciate and extend our sincere gratitude to Prof. Dr. Lokhande, R.P., who made the work possible. His direction and counsel saw me through the entire paper-writing process. We also like to express our gratitude to our institute for providing us with this review article opportunity.

CONCLUSION:

One innovative antibacterial agent that has had a big impact on medicine is sulfanilamide. Its extensive history, various synthetic techniques, structure-activity connections, wide range of uses, and mechanism of action are all covered in this review. 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 sulfanilamide and its derivatives. The sulfonamide group and its substituents play a critical role in determining antibacterial action, according to the structure-activity relationship analysis. Sulfanilamide's ability to treat a variety of bacterial diseases, such as 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 a competitive

inhibitor of dihydropteroate synthetase, 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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HOW TO CITE: Dhobale Sushmita*, Gholap Rutuja, Khutal Tejaswinee, Dr. Lokhande R. P., Synthesis, Mechanism of action And Characterization of Sulphonamide, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 5, 3005-3011. https://doi.org/10.5281/zenodo.15458257