



**AN INSIGHT INTO SYNTHETIC AND PHARMACOLOGICAL
PROFILE OF SULPHANILAMIDE****GAGANDEEP¹, KAUR H², LATA S^{3*}, BHANDARI DD⁴ AND SINGH G⁵**^{1,2,3}ASBASJSM College of Pharmacy, Bela (Ropar) 140111, Punjab, India⁴University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, 160014
India⁵IET Bhaddal Technical Campus, Mianpur (Ropar), 140108, Punjab, India***Corresponding Author: Dr. Suman Lata; E Mail: sumanlata.2722005@gmail.com**Received 15th April 2023; Revised 8th June 2023; Accepted 23rd Sept. 2023; Available online 1st June 2024<https://doi.org/10.31032/IJBPAS/2024/13.6.8124>**ABSTRACT**

Sulphanilamide, known as a sulpha drug, possesses diverse pharmacological activities, making it a valuable chemotherapeutic agent for combating both bacteria gram-positive and gram-negative. This compound exhibits a broad spectrum of effects, including anti-hypoglycemic, diuretic, anti-hypertensive, antifungal, antibacterial, anti-inflammatory, and antiretroviral properties. Given the increasing prevalence of antibiotic resistance among existing drugs, there is a pressing need to develop novel derivatives of sulphanilamide to effectively combat bacterial and fungal infections. One key mechanism by which sulphanilamide derivatives combat microorganisms is through their competitive inhibition of folic acid synthesis enzymes. This action serves to hinder the growth of microorganisms. Consequently, in this comprehensive review, we highlight the synthesis of novel derivatives of sulphanilamide that exhibit the aforementioned pharmacological effects. By focusing on these newly synthesized derivatives, we aim to address the urgent need for effective therapeutic agents against bacteria and fungi in light of the growing resistance to conventional antibiotics.

Keywords: Sulphonamide, Synthesis, Pharmacology, Antibacterial, heterocyclics**INTRODUCTION:**

Sulphanilamides, also known as synthetic antimicrobial drugs with an sulphonamides, represent a crucial class of extensive variety of effectiveness against

bacterial infections. These compounds feature distinctive six or five membered heterocyclic rings and contain the SO_2NH_2 group, making them organo-sulphur compounds [1-2]. They exhibit potent activity against pyogenic bacterial infections caused by both Gram-positive and Gram-negative bacteria, including *E-coli*, *Enterobacter*, *Salmonella*, *Klebsiella*, *Shigella*, and *Nocardia*. Notably, they display remarkable efficacy against gram-positive bacteria for instance *S.Pneumoniae* and *S.pyogenes*, although 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 [3].

In addition to their antimicrobial activity, sulphanilamide derivatives exhibit a plethora of biological actions spanning antihypertensive [4], translation initiation inhibition [5], antimicrobial [6-7], anticancer [8-10], cyclooxygenase-2 inhibition [11], anticonvulsant [12], anti-HIV [13, 14], antimigraine [15], carbonic anhydrase inhibition [16], hypoglycemic protease inhibition [17], antidiabetic [18], and herbicidal [19] effects. Sulpha drugs have demonstrated promising activity against breast cancer cells [20]. Azetolamide and methazolamide, two sulpha drugs, are widely used as

antiglaucoma agents [21]. Numerous other sulpha derivatives find application in the treatment of conjunctivitis [22], acne [23], toxoplasmosis [24], and urinary tract infections [22-26].

By highlighting the multifaceted pharmacological effects and diverse therapeutic applications of sulphanilamide and its derivatives, this unique review aims to underscore the immense potential of these compounds in addressing various medical challenges and fostering novel treatment approaches.

The mechanism of action of sulphanilamide is by inhibition of the enzyme dihydropteroate synthase. This particular enzyme acting a decisive role in the folic acid bacterial synthesis [27]. Folic acid serves as a vital precursor for the synthesis of DNA, RNA, and other essential molecules within bacterial cells.

By inhibiting dihydropteroate synthase, sulphanilamide effectively disrupts the synthesis of folic acid. This inhibition, in turn, hampers the growth and replication of bacteria. As a result, the bacterial cells are unable to produce sufficient folic acid, which is necessary for various cellular processes and essential components. Consequently, the inhibition of folic acid synthesis by sulphanilamide ultimately impedes bacterial growth and impairs their ability to proliferate effectively.

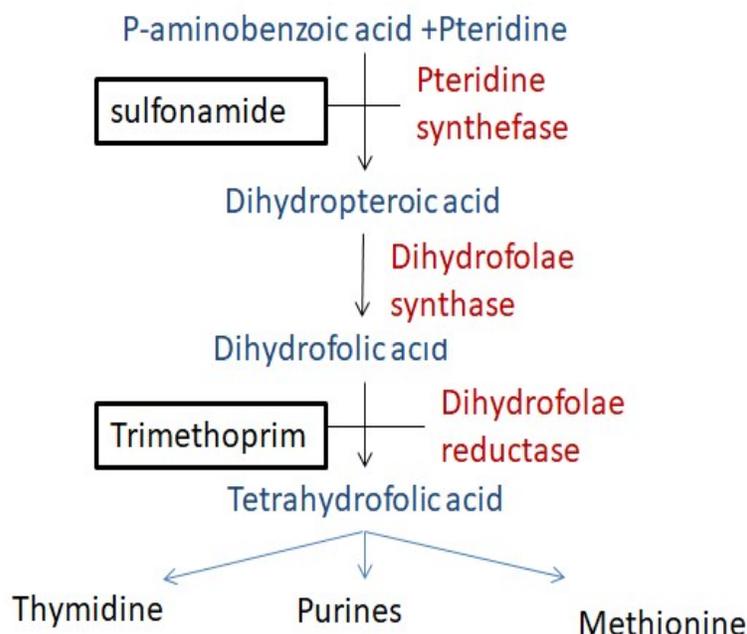


Figure 1: Mechanism of Action of Sulphanilamide

Sulphanilamide holds a significant place in the annals of medical history, as its discovery marked a pivotal milestone in the development of antibiotics. It served as a trailblazer, laying the foundation for the subsequent exploration and creation of other antibiotics that revolutionized the field of medicine. Despite its diminishing usage as an antibiotic in contemporary practice, sulphanilamide continues to be a subject of scientific investigation due to its potential therapeutic applications.

Researchers continue to explore the diverse potential uses of sulphanilamide in various areas, including the treatment of cancer and parasitic infections [28]. The molecule's pharmacological properties and mechanisms of action make it a candidate worth

investigating for these challenging medical conditions.

However, it is essential to acknowledge that bacterial resistance to sulphanilamide has emerged as a significant issue in current years. Antibiotic abuse and overuse have hampered the efficiency of sulphanilamide and other antibiotics by fostering the emergence of resistant bacterial strains. Consequently, sulphanilamide is now seldom utilized as a first-line treatment for bacterial infections, with alternative antibiotics being preferred to combat resistant strains.

While the prominence of sulphanilamide as an antibiotic has waned, its historical significance and ongoing research into its therapeutic potential underscore its lasting

impact on the field of medicine and the development of antimicrobial agents.

Chemistry of Sulphanilamide:

Sulphanilamide consists of a sulphonyl group ($S(=O)_2$) connected to an amine group (NH_2). A sulphanilamide compound's typical formula is RSO_2NH_2 , where R stands for different organic alkyl groups.

Sulpha drugs are a class of medications that belong to the sulphonamide family.

Different sulpha drugs diverge in the nature of N1 (sulphonamide nitrogen) substitution, which influences properties such as solubility, potency, and pharmacokinetics.

Sulpha drugs exert their antimicrobial effects by interfering with the metabolism of bacteria and fungi. They were considered ground breaking medications before the discovery of penicillin and continue to be used in certain applications today.

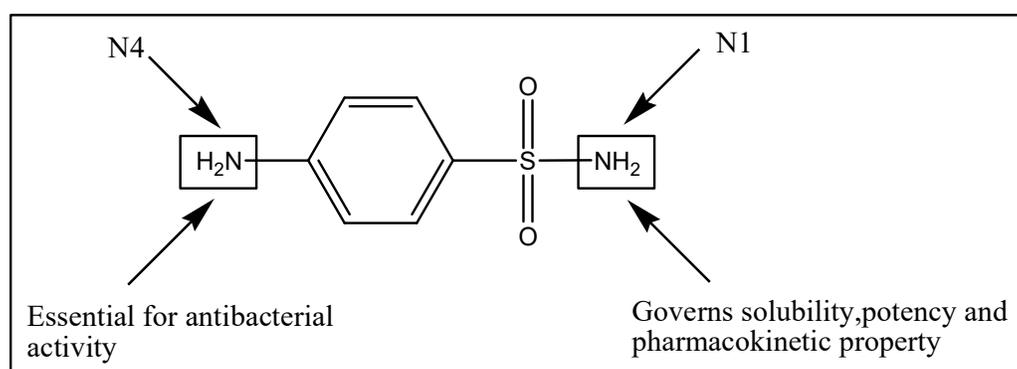


Figure 2: Chemistry of Sulphanilamide

Sulphanilamides are a versatile class of compounds with various applications, making the development of general and effective methods for their synthesis desirable. Over the years, several synthetic methods have been reported, and I can provide you with a brief overview of some common and recent approaches. These methods typically involve the use of sulfonyl chloride, transition metals as catalysts, or Grignard reagents.

Synthesis of Sulphanilamide from thiols:

A common technique for making sulphanilamide is the sulfonylation of

amines with chlorides in the incidence of a base [29]. In this synthesis method, sulphonyl chlorides are attacked by ammonia, 1° , or 2° amines nucleophilically when a base is present. Although effective, this approach depends on the availability of sulphonyl chlorides, which can occasionally be difficult to handle or store.

There are several ways to create sulphonyl chlorides from the equivalent thiols. Blowing chlorine gas (Cl_2) into an aqueous acid solution or a biphasic mixture containing the thiol is one such method [30]. In order to produce sulphonyl chlorides,

sulphonic acids can also be treated with chlorinating chemicals like thionyl chloride (SOCl₂), phosphorus oxychloride (POCl₃), or phosphorus pentachloride (PCl₅) [31].

H₂O₂-SOCl₂ has recently been found to directly oxidise thiols into sulphanilamides [32]. The matching sulphanilamides were produced using this approach in good yields and with incredibly fast reaction times.

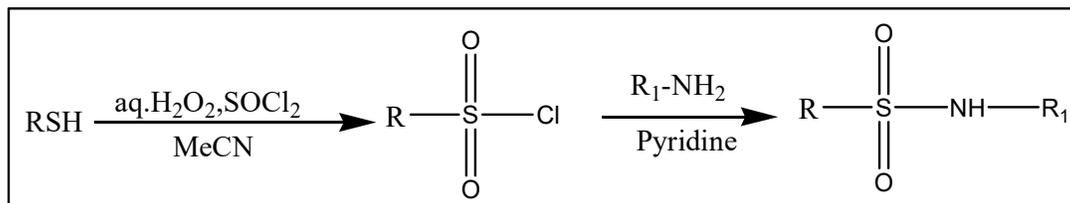


Figure 3: Conversion of thiols into sulphanilamide

Wright *et al.* established a unique approach for the synthesis of a sulphonyl chloride in situ utilising sodium hypochlorite, often known as commercial bleach, to produce sulphanilamide from thiols [33]. This methodology offers several advantages, including the ready availability of the reagents and the ability to control the amount of oxidant used.

In their study, the researchers first oxidize the thiol using sodium hypochlorite, generating the corresponding sulphonyl chloride. The use of sodium hypochlorite as

an oxidant allows for a controlled oxidation process. After that the sulphonyl chloride reacted with benzylamine to produce sulphanilamide with upto high efficiency 98% yield.

This method provides a convenient and practical approach to sulphanilamide synthesis, utilizing easily accessible reagents and enabling control over the oxidation process. Sodium hypochlorite is used as an oxidizing agent offers advantages in terms of simplicity and cost-effectiveness.

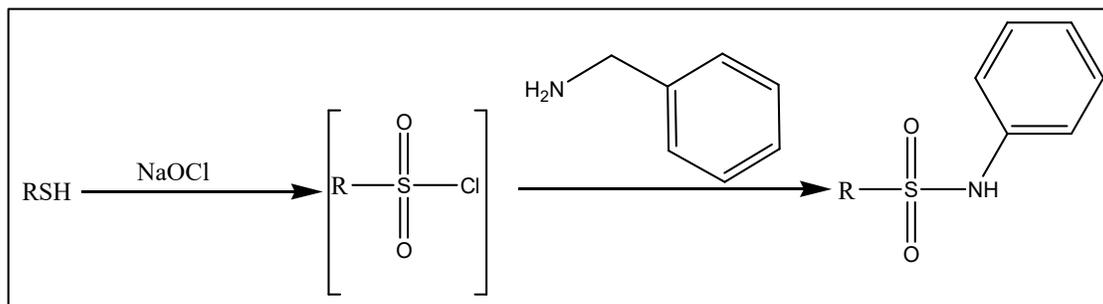


Figure 4: Sodium hypochlorite as mediated oxidation of thiols

Bonk *et al.* trichlorocyanuric acid (TCCA) and benzyltrimethyl ammonium chloride were added to water to produce a regulated quantity of chlorine in an aprotic solvent, especially acetonitrile (MeCN), to create a modified approach for the manufacture of sulphanilamides [34]. Compared to using hypochlorite, this modification has the benefit of manufacturing high-purity chlorine.

The research team induced the reaction in their study by mixing water with trichlorocyanuric acid and benzyltrimethyl ammonium chloride, which resulted in the regulated production of chlorine. The aprotic solvent MeCN was used to carry out

the reaction. As an oxidising agent, the procedure generates high-purity chlorine.

The inclusion of the ensuing amine into a one-pot reaction is a noteworthy innovation made by Bonk *et al.* By adding the amine directly into the reaction mixture, the sulphonyl chloride is generated in situ. This streamlined approach allows for the efficient synthesis of sulphanilamide within a short timeframe, typically under one hour.

This modified method offers the advantages of high-purity chlorine production and the convenience of conducting the entire sulphanilamide synthesis in a one-pot reaction.

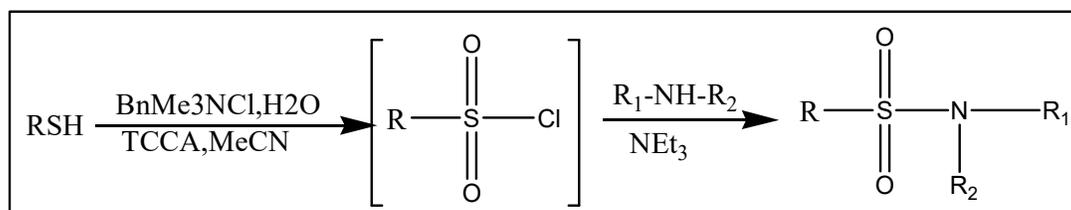


Figure 5: Synthesis of sulphanilamide with trichlorocyanuric acid

Synthesis of sulphanilamide from transition metal catalysts:

Extensive research has been done on the synthesis of sulphanilamide utilising transition metal catalysts, notably through cross-coupling processes for C-N bond formation. The palladium-catalyzed Buchwald-Hartwig reaction, often known as N-arylation, is a well-known example [35]. The N-arylation of sulphanilamides has

been investigated using several transition metal catalysts.

Palladium (Pd), one of these catalysts, has received much research. For instance, the ideal base-solvent combination for Pd-catalyzed sulphonamidation of aryl nonafluorobutanesulphonates has been discovered to consist of the biaryl phosphine ligand t-BuXPhos, K₃PO₄ as the base, and tert-amyl alcohol as the solvent. These reactional circumstances have demonstrated

high tolerance for a range of functional groupings. The drawback of this approach is that 2,6-disubstituted aryl nonaflates do not engage in the reaction effectively [36] (Figure 6).

This Pd-catalyzed sulphonamidation technique offers a flexible and effective way

to synthesise sulphanilamides by using the right ligands and reaction conditions. However, while employing this approach, it is important to take into account the unique restrictions on 2,6-disubstituted aryl nonaflates.

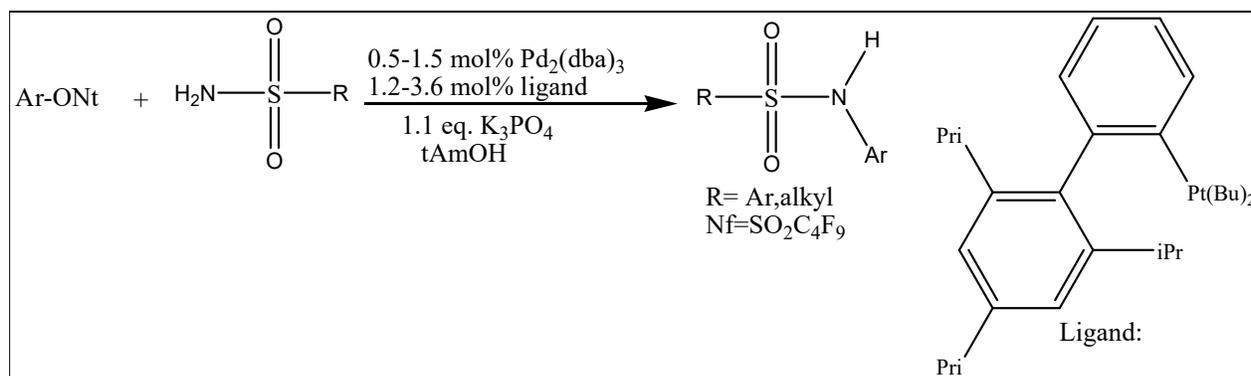


Figure 6: Pd-catalyzed sulphonamidation

Guo *et al.*, conducted research on the coupling reactions between aryl bromides/iodides and copper(I) to create sulphanilamides [37]. They found that employing an amino acid as a ligand offers a number of benefits, including simple removal following the reaction, throughout the optimisation process. N-methylglycine and N,N-dimethylglycine were determined to have the maximum efficacy when combined with Cu(I) after a number of amino acids were examined.

The researchers used N,N-dimethylformamide (DMF) as the solvent and K₃PO₄ as the base in their optimised

reaction conditions. These conditions enabled the generation of the desired N-arylsulphalinamides with high yields, up to 99%.

With the aid of aryl bromides/iodides and copper(I) catalysts, this process provides a useful and effective way for the synthesis of sulphanilamides. Amino acids can be used as ligands, which has advantages such simple ligand removal after reactions. In the synthesis of N-arylsulphanilamides, the mixture of N-methylglycine or N,N-dimethylglycine with Cu(I) catalyst, K₃PO₄ base, and DMF solvent has outstanding performance.

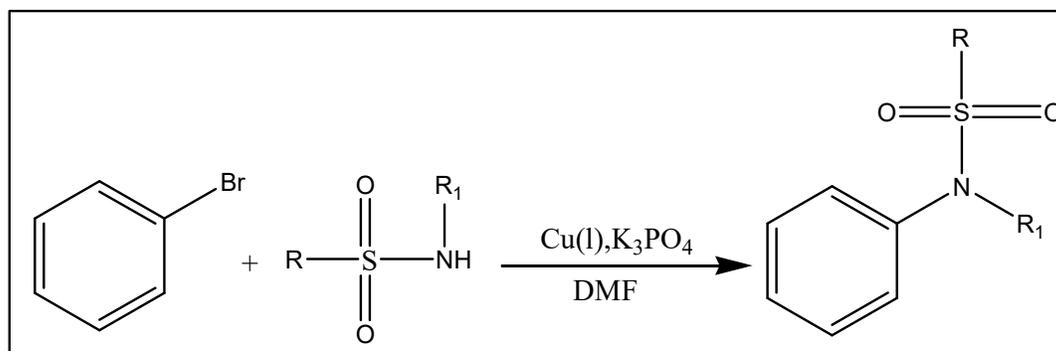


Figure 7: Formation of arylsulphanilamide

The indium-catalyzed sulfonylation of amines is a simple and effective technique for the production of sulphanilamide [38]. This process enables the synthesis of a wide variety of sulphanilamides with high yields. In terms of substrate range, it exhibits generality by working with anilines that are less nucleophilic and sterically hindered. Additionally, this technique may be used to create sulphonic esters from sulphonyl chlorides and alcohols, thus it is not just restricted to the manufacture of sulphanilamide.

The indium-catalyzed sulfonylation reaction offers a versatile and effective approach to access a wide variety of sulphanilamide compounds. It demonstrates good reactivity even with challenging substrates, enabling the synthesis of sulphanilamide that are otherwise difficult to access using other methods. Additionally, the application of this methodology extends beyond sulphanilamide synthesis to the preparation of sulphonic esters, providing further synthetic versatility.

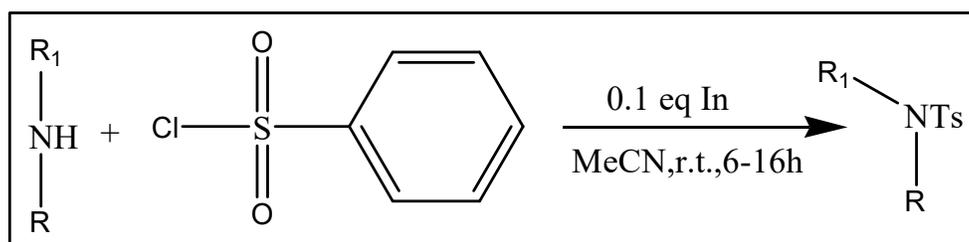


Figure 8: Indium-catalyzed sulfonylation

Sulphonyl chlorides, which serve as important intermediates in sulphanilamide synthesis, can be obtained from sulphonic acids. Microwave irradiation is a facile and

useful technique for this synthesis that has demonstrated excellent functional group tolerance and high yields [39] (Figure 9).

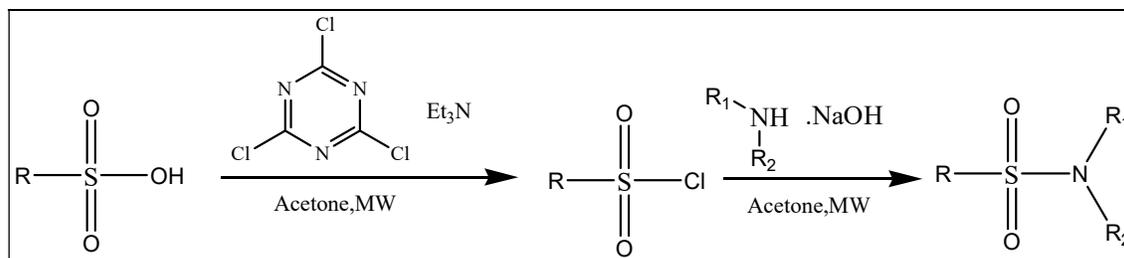


Figure 9: Synthesis of sulphanilamides with using microwaves irradiation

Furthermore, the synthesis of sulphanilamides can also be accomplished using classical heating methods, resulting in good to excellent yields [40].

Chavasir *et al* For the production of sulphanilamides, the trichloroacetonitrile-triphenylphosphine combination ($\text{Cl}_3\text{CCN}/\text{PPh}_3$) was used [41]. It was found that using a 3:3:1 ratio of Cl_3CCN , PPh_3 , and sulphonylic acid with dichloromethane as the solvent resulted in the highest yield. However, the reproducibility of yields in

different solvents and ratios was not consistent. Notably, this methodology offers the advantage of being applicable not only to aromatic sulphonyl chlorides but also to heterocyclic and aliphatic sulphonyl chlorides (Figure 10).

These diverse synthetic approaches provide flexibility in the synthesis of sulphanilamides, allowing for the utilization of different reaction conditions and substrates, expanding the scope of accessible sulphanilamide derivatives.

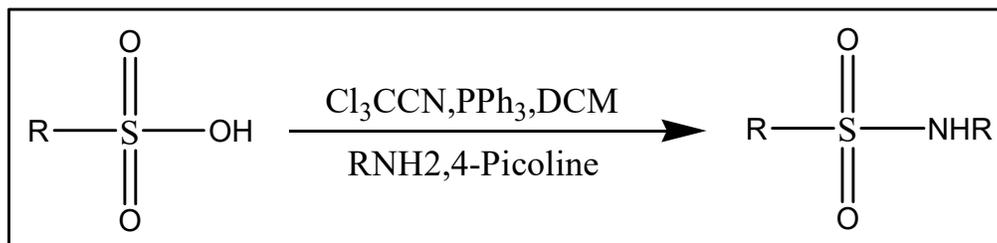


Figure 10: Prepared sulphanilamide from trichloroacetonitrile-triphenylphosphine complex

Revankar *et al.* used moderate and targeted oxidants to establish a novel method for the synthesis of 2-amino-9H-purin-6-sulfonamide [42]. The oxidation of 2-amino-9H-purin-6-sulfenamide utilising meta-chloroperoxybenzoic acid (m-CPBA) as the oxidant was the main focus of their work.

The researchers found that using one equivalent of meta-chloroperoxybenzoic acid resulted in a 48% yield of the target compound (Figure 11). When higher amounts of m-CPBA (4 equivalents) were employed, a slightly improved yield of 53% was obtained.

This methodology offers a mild and selective approach for the synthesis of 2-amino-9H-purin-6-sulphanilamide. By utilizing m-CPBA as the oxidant, the

researchers were able to achieve the desired sulphanilamide product with reasonable yields.

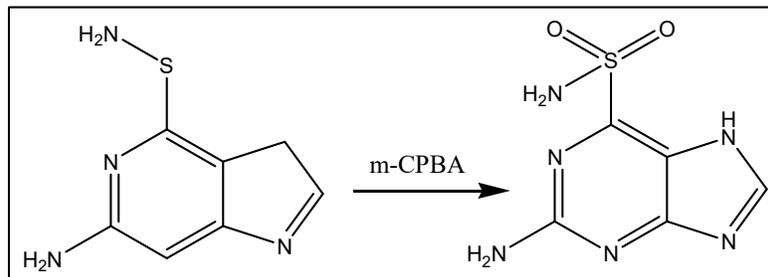


Figure 11: Indium-catalyzed sulphonylation

CONCLUSION:

In conclusion, several techniques have been published and thoroughly researched for the synthesis of sulphanilamide derivatives. Due to their wide spectrum of biological actions, these compounds are regarded as crucial "scaffolds" in medicinal chemistry for the synthesis of drugs. Additionally, sulphanilamide derivatives find practical applications in the organic chemistry industry, including the production of health products, food colorants, and more.

Given their significance in both medicinal and industrial fields, it is crucial to continue research efforts aimed at synthesizing novel compounds containing the sulphonamide group. By exploring new synthetic methodologies and designing innovative derivatives, scientists can contribute to expanding the knowledge and potential applications of sulphanilamide compounds. Such research projects can lead to the development of improved drugs, as well as

novel functional materials with beneficial properties for various industries.

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