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Review Article

A short review on Sulphonamides with antimicrobial activity

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Abstract

Sulfonamides are one of the organosulphur compounds containing the $-SO_2NH_2$ and/or $-SO_2NH-$ group(s). 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: Antimicrobial activity Gram-negative bacteria, Gram-positive bacteria, Substituted Sulfonamides.

1. Introduction

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 replacing its hydroxyl group.[1] 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.[2] Today, sulfonamide trimethoprim combinations are used extensively for opportunistic infections in patients with AIDS in addition to urinary tract infection and burn therapy.[3] Resistance is most likely a result of a compensatory increase in the biosynthesis of p-aminobenzoic acid (PABA) by bacteria although other mechanisms may play a role.[4] Resistance of *E Coli* strains to sulfonamide has been shown due to their containing sulfonamide- resistant dihydropteroate Syntheses.[5] 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 [6]. 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 [7].

2. Structure and nomenclature

Sulfonamides are represented by general structure (Figure 1) in which R may be alkyl, aryl or hetero aryl groups and R1/R2 may also be hydrogen, alkyl, and aryl or hetero aryl groups. Sulfonamides are written as alkane sulfonamides or are nesulfonamides [8].

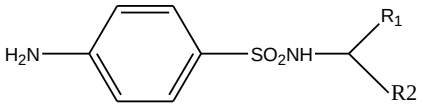


Figure 1: The general structure of sulfonamides, If R=R1=H is sulfanilamide

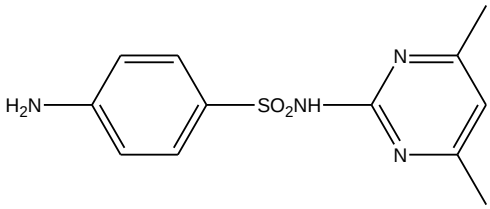


Figure 2: 2-Amino-N-(4, 6-dimethylpyrimidin-2-yl) benzene sulphonamide

3. Classification of sulfonamides

- ❖ Most of the sulfonamides used currently are N1-derivatives. Based on the structural variations, Johnson [9] 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 [10].

3.1 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).

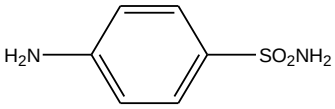


Figure 3: Sulfanilamide

3.2 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).

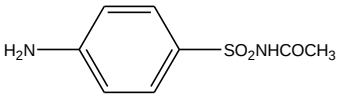


Figure 4: Sulfacetamide

3.3 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).

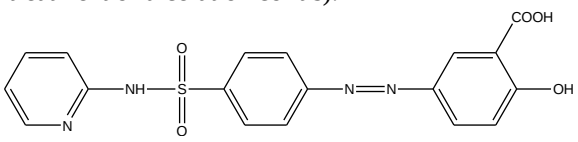
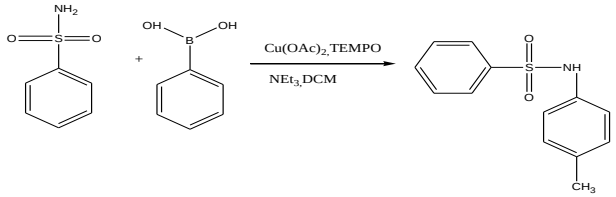


Figure 5: Sulfasalazine

4. Synthetic aspects of sulfonamides

4.1 Synthesis of sulfonamide with boronic acid derivatives

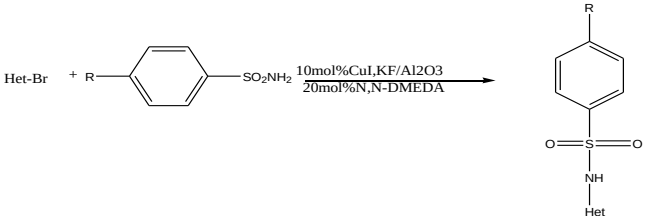
The second metal, used more often, is Cu. It is more likely to be used for large scale synthesis. An effective method for *N*-arylation on sulfonamide using 0.1 equivalent of copper(II) acetate in air and arylboronic acid to get *N*-arylsulfonamide near-quantitative yield [11] .



Scheme 1.1

4.2 Synthesis of *N*-(hetero aryl) benzene sulfonamides from hetero aryl bromides

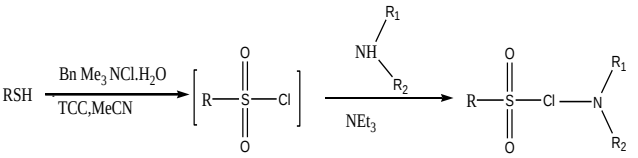
The reaction of hetero aryl bromides such as 2-bromopyridine, 3-bromopyridine, or 3-bromothiophene with benzene or *p*-toluene sulfonamides gave the corresponding *N*-(hetero aryl) benzenesulfonamides [12].



Scheme 1.2

4.3 Synthesis of sulfonamides via reaction with trichlorocyanuric acid (TCCA):

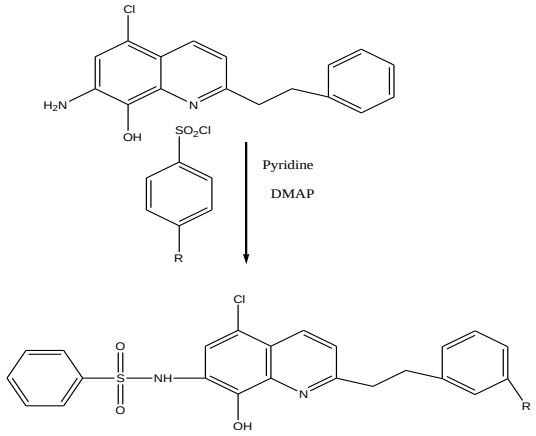
Trichlorocyanuric acid (TCCA) and benzyltrimethyl ammonium chloride in water were used to generate a controlled amount of chlorine into aprotic solvent (MeCN).[13]



Scheme 1.3

4.4 Synthesis of *N*-(2- substituted-styryl)-5-chloro-8-hydroxyquinolin-7-yl)-benzene sulphonamides

2-styryl-7-amino-5-chloroquinoline-8-ols treated with benzenesulfonyl chlorides to give *N*-(2- substituted-styryl)-5-chloro-8-hydroxyquinolin-7-yl)-benzenesulfonamides [14] .



Scheme 1.4

5. Chemistry of Sulfonamides

In chemistry, the sulfonamide functional group (also spelt sulphonamid) is -S (=O)$_2$-NH$_2$, a sulfonyl group connected to an amine group. The general formula is RSO_2NH_2, 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 [15]

6. Biological aspects of sulfonamides

Sulfonamides represent an important class of medicinally effective molecules and are known to possess wide variety of biological activities.

6.1 Antimicrobial activity

4-Amino-N-(6-metyl-benzothiozol-2-yl)-benzene sulfonamide derivatives (Figure 6) were reported to show Antibacterial Activity.[16]

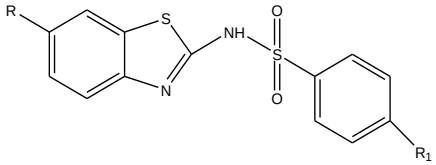


Figure 6

N-(4-Amino-phenyl)-4-(4-bromo-phenyl)-4oxo-butyramide derivatives (Figure 7) were reported to show Antibacterial Activity. [17]

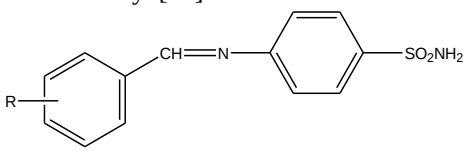


Figure 7

N-(4-Amino-phenyl)-4-(4-bromo-phenyl)-4oxo-butyramide derivatives (Figure 8) were reported to show Antibacterial Activity. [18]

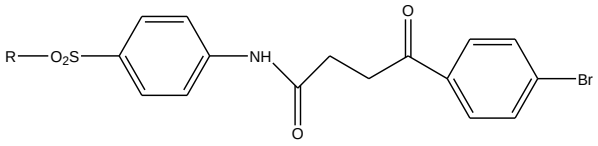


Figure 8

4-Dipropylsulfamoylphenyleamino) methyle1) benzamide). derivatives (7) were reported to show Antibacterial Activity.[19]

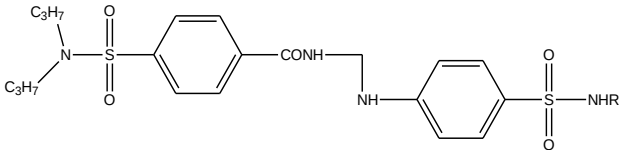


Figure 9

4-(Benzyidene-amino)-N-(5-methyl-isoxazol-3yl)-benzene sulfonamide derivatives (Figure 10**)** were reported to show Antibacterial Activity.[20]

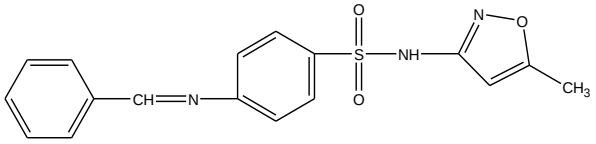


Figure 10

4-(3,5-Dimethyl-1*H*-pyrazol-4-ylamino)-benzene sulfonamide derivatives (Figure 11)were reported to show Antibacterial Activity.[21]

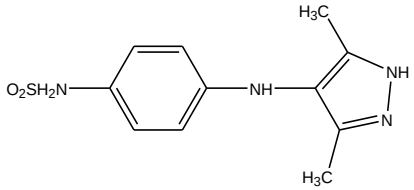
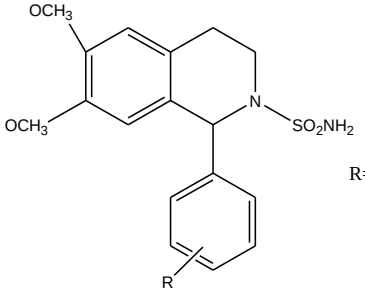


Figure 11

6.2 Anticonvulsant activity

A series of 1-aryl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-sulfonamides. The new compounds incorporate the main features of the above-mentioned anticonvulsants and a sulfonamide function capable to inhibit the enzyme carbonic anhydrase, which represents an attractive target in epilepsy. Pharmacological effects were evaluated in vivo against audiogenic seizures in DBA/2 mice and in vitro against several CA isoforms. Some of the new molecules showed anticonvulsant properties better than topiramate, but weak inhibitory activity and low selectivity in enzymatic assay [22].



R=H, 4-Br, 4-Cl, 4-CN, 4-F, 4-CH3, 3-NO2, 4-NO2, 3-NH2, 4-NH2

Figure 12

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