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Sulphonamides: A Pharmaceutical Review

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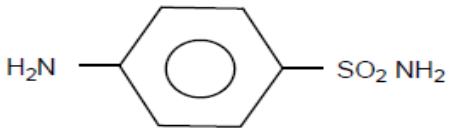
Abstract : *Sulphonamides are the first effective chemotherapeutic agents used for bacterial infection in humans. Sulfonamides have a wide range of pharmacological activities such as Oral hypoglycemic, antileprotic, anti epileptic, anti-hypertensive, anti-bacterial, anti-protozoal, anti-fungal, anti retroviral, anti cancer, antiinflammatory, and used as diuretic. This review consists of a discussion on the various pharmacological effects of sulfonamides.*
Keywords: *Sulphonamides , Anti microbial activity, sulphonyl ureas, pharmacological activity.*

I. Introduction

In chemistry, sulphonamide is SO_2NH_2 functional group. The compounds which contain this functional group are called as sulphonamides. The general formula of sulphonamides RSO_2NH_2. The term sulfonamide(sulphonamide) is also usually employed as a generic name for the derivatives of para amino benzene sulphonamides. Sulphonamides are derivatives of para amino benzene sulphonamide. The nitrogen atom of $– SO_2NH_2$ is numbered as 1 and the $– NH_2$ group as 4.

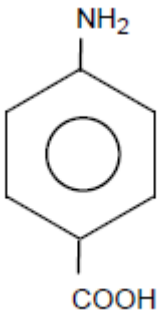


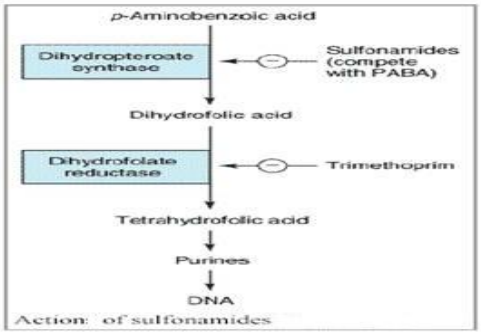
Sulphanilamide

II. Pharmacological activities of suphonamides

Antimicrobial activity:

Antimicrobial activities of the sulfonamides depend on substituent and their position in the benzene ring. Sulphonamides are bacteriostatic in nature. The sulphonamide sensitive micro-organisms require p-Amino benzoic acid (PABA) for the synthesis of folic acid which is essential for the synthesis of DNA and RNA. Due to structural resemblance of suphonamides with PABA, sulphonamides competitively inhibit PABA. This causes folic acid deficiency, resulting in arrest of bacterial growth and cell division.





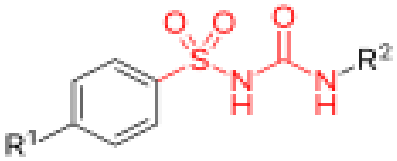
P- Amino benzoic acid

As antimicrobial agents Sulphonamides inhibit Gram-positive and Gram-negative bacteria, Nocardia, Chlamydia trachomatis and some Protozoa. Some enteric bacteria such as E.coli, Kelbsiella, Salmonella, Shigella and Enterobacter are inhibited. Sulphonamides are used in the treatment of tonsillitis, septicemia, meningococcal meningitis, bacillary dysentery and number of infections of urinary tract. Pneumocystis carinii pneumonia: eg. Trimethoprim and Sulphamethoxazole

• Cerebral toxoplasmosis: eg. Pyrimethamine – Sulphadiazine
• Urinary tract infection: eg. Sulphamethizole
• Nocardiosis: eg. Sulphadiazine, Sulphisoxazole
• Respiratory tract infection: eg. Sulphalene
• Dermatitis herpetiformis: eg. Sulphapyrimidine
• Menincoccal infection: eg. Sulphadiazine
• Burn therapy: eg. Silver sulphadiazine
• Conjunctivitis and Superficial ocular infections: eg. Sulphacetamide
• Traveler's diarrhea (or) GIT infection: eg. Sulphaguanidine
• Chloroquine resistant malaria: eg. Sulphadoxime with Pyrimethamine
Antileprotic agent: eg. Dapsone
M.S.A. El-Gaby et al., reported that Several sulfonamides containing pyrroles and pyrimidines were exhibited a remarkable antifungal activity compared with the standard fungicide mycostatine.

Hypoglycemic activity:

Sulphonyl ureas used as oral hypoglycemic agents. Sulphonyl ureas contain sulphonamide functional group in their structure.



General structure of sulphonyl ureas

Sulphonyl ureas widely used in the management of diabetes mellitus type2. They act by increasing insulin release from the beta cells in the pancreas. Sulfonylureas bind to and close ATP-sensitive K^+(K_{ATP}) channels on the cell membrane of pancreatic beta cells, which depolarizes the cell by preventing potassium from exiting. This depolarization opens voltage-gated Ca^{2+} channels. The rise in intracellular calcium leads to increased fusion of insulin granulae with the cell membrane, and therefore increased secretion of insulin.

Diuretic activity:

Sulphonamides are also used as diuretics. They are primarily used to treat hypertension and edema. Eg: Acetazolamide, Furosemide, Bumetanide, Azosemide etc. Acetazolamide is a carbonic anhydrase inhibitor, hence causing the accumulation of carbonic acid. The enzyme carbonic anhydrase is found here, allowing the reabsorption of bicarbonate, sodium, and chloride. By inhibiting this enzyme, these ions are excreted, along with excess water, lowering blood pressure.

Loop diuretics act on the Na^+-K^+-$2Cl^-$ symporter (cotransporter) in the thick ascending limb of the loop of Henle to inhibit sodium, chloride and potassium reabsorption. This is achieved by competing for the Cl^- binding site. Because magnesium and calcium reabsorption in the thick ascending limb is dependent on the positive lumen voltage gradient set up by potassium recycling through renal outer medullary potassium channel, loop diuretics also inhibit their reabsorption. By disrupting the reabsorption of these ions, loop diuretics prevent the generation of a hypertonic renal medulla. Without such a concentrated medulla, water has less of an osmotic driving force to leave the collecting duct system, ultimately resulting in increased urine production. Loop diuretics cause a decrease in the renal blood flow by this mechanism.

Anti epileptic activity:

The sulphonamides with antiepileptic activity are Sultiame, Acetazolamide, Methazolamide, Zonisamide, Topiramate etc. Masereel B et al., reported that Acetazolamide and topiramate, two carbonic anhydrase inhibitors with antiepileptic properties. Some of these derivatives showed very high inhibitory potency against three carbonic anhydrase (CA) isozymes, such as CA I, CA II, and CA IV, involved in important physiological processes. Topiramate, a recently developed antiepileptic drug possessing a sulfamate moiety, also shares this property, although earlier literature data reported this compound to be a weakmoderate CA I, II, and IV inhibitor. The valproyl derivative of acetazolamide (5-valproylamido-1,3,4-thiadiazole-2-sulfonamide) was one of the best hCA I and hCA II inhibitor in the series and exhibited very strong anticonvulsant properties in an MES test in mice. It was observed that some lipophilic derivatives, such as 5-benzoylamido-, 5- toluenesulfonylamido-, 5-adamantylcarboxamido-, and 5- pivaloylamido-1,3,4-thiadiazole-2-

sulfonamide, show promising in vivo anticonvulsant properties and that these compounds may be considered as interesting leads for developing anticonvulsant or selective cerebrovasodilator drugs.

Anti cancer activity:

In the context of studying the treatment of cancer Sapna Rani et. al. has found the significant effects of the derivatives of the sulfonamides, this promotes them to design novel derivatives by the means of in-silico resources with anticancer effects. They performed this study with the help of Chemdraw Ultra 7.0, AutoDock Vina (Python Prescription 0.8), and PaDEL software. Their results revealed that ligand-protein interaction affinity of all designed molecules ranges from -6.8 Kcal/mol to -8.6 Kcal/mol which is approximately comparable to pre-existing human topoisomerase II inhibitor i.e. etoposide (CID: 36462, ligand-protein interaction affinity is -9.7 Kcal/mol)

Antiprotozoal activity:

In 2007, Da silva et al demonstrated that synthetic *N*-quinolin-8-yl-arylsulfonamides and their complexes present significant *in vitro* antiparasitic activity against *Trypanosoma cruzi* and *Leishmania chagasi* and *L. amazonensis.* Antiprotozoal activity of N-quinoline-8-yl-arylsulfonamides and their copper and zinc complexes was reported.

Anti inflammatory activity:

In 2008, 2-pyrazoline bearing benzenesulfonamide derivatives were synthesized by condensing chalcones with 4-hydrazinonbenzenesulfonamide hydrochloride. These compounds were tested for their anti-inflammatory activity in carrageenan-induced rat paw edema model and the compounds were found effective.

Antiretroviral activity:

Scozzafova A et al in 2002 reported several non nucleoside HIV reverse transcriptase or HIV integrase inhibitors containing sulfonamido groups. Most compounds with antiviral activity possessing this mechanism of action incorporate in their molecules primary sulfonamide groups. Some small molecule chemokine antagonists acting as HIV entry inhibitors also possess sulfonamide functionalities in their scaffold.

III. Conclusion

The wide pharmacological activity range of sulphonamides necessitates for further synthesis of novel sulphonamide derivatives and screening their activity against various diseases.

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