IMPORTANCE OF SULFONAMIDE MOIETY IN CURRENT AND FUTURE THERAPY

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(Abstract): Sulfonamides and their different derivatives are extensively used in therapy due to their pharmacological properties. Sulfonamides became amongst the oldest synthesized antimicrobial agents and are still widely used today to treat different microbial infections. Clinical treatment with sulfonamides has regained confidence with the use of a combination of sulfamethoxazole and trimethoprim to treat urinary tract bacterial infections. Today, they are widely used as antimicrobial agents, chiefly because of their low cost, low toxicity and excellent activity against bacterial diseases. Over the course of time, the application of sulfonamides has been extended from their use as antimicrobial agents to anticancer agents, antiglaucoma agents, inhibitors of γ-secretase, cyclooxygenase-2 and lipoxygenase, anticonvulsant agents, hypoglycemic agents. Keywords: SULFONAMIDES, ANTIMICROBIAL, LOW TOXICITY.

The introduction of sulfonamides in 1935 marked a turning point, a true “therapeutic revolution”, and opened the era of “miracle drugs”. After the discovery of penicillin followed by other antibiotics sulfonamides became less used, but later they started to attract attention for their synergic activity in the combination with trimethoprim.

Sulfonamides proved to be the starting point for a series of structural changes and this has led to the discovery of new drugs or classes of drugs used today not just in combating bacterial infections, but also in other diseases. They have widespread use in a variety of applications including antibacterial agents, antitumor agents, diuretics, carbonic anhydrase inhibitors, hypoglycaemic agents, thyroid inhibitors, and protease inhibitors (1). In recent years, molecules containing sulfamide group have also been investigated as inhibitors of ATP-sensitive potassium channels, carboxy-peptidase A, γ-secretase, glycosidase, HCV polymerase (NS5B), HIV-1 integrase, HIV-1 protease, histone deacetylase, human chymase, human leukocyte elastase, kinesin spindle protein, monoamine reuptake, plasma cell membrane protein-1, and thrombin; as agonists of androgen receptor, β3-adrenergic receptor, and as antagonists of CXCR2 (2).

The chemical class of sulphonamides shares a common sulfanilamide moiety with
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an aromatic amino group at the C₄-position, differing in the substitution of sulfamoi

Fig. 1. The backbone of the sulphonamides

The characterization of sulfonamides as chemotherapics is more than half a century old. Since then, the sulfonamide group - SO₂NH- has been found as a key structural motif shared by a large number of bioactive compounds, spanning a wide variety of biological effects, such as antimicrobial activity, specific enzyme inhibition, hormone regulation, among others. They are usually classified as short-acting sulfonamides, with half lives (in serum) of 5–10 hours (i.e. sulfisoxazole, sulfadiazine and sulfamethizole); intermediate-acting sulfonamides, with half lives of 10–12 h (i.e. sulfamethoxazole, sulfadimethoxine and sulfamethazine); and finally long-acting sulfonamides, with half lives from 40 h onwards (i.e. sulfadoxine and sulfamethoxypyridazine) (3). Sulfadiazine and more recent compounds, including sulfa- furazol (sulfisoxazole), sulfa-methoxazo- zole, sulfametrole, sulfacitine and sulfame- thizole, are quickly absorbed and eliminated. Compared with the older generation they are more soluble, less toxic, and probably less allergenic. Long-acting sulfona- mides include sulfamethoxydiazine, sulfa- methoxine, and other compounds, of which many are no longer available, due to the fact that they were associated with severe hypersensitivity reactions.

SULFONAMIDES AS ANTIVIRAL AGENTS

The effectiveness of sulfonamides has also been proven over time in the context of viral infections. A large number of structurally novel sulfonamide derivatives have ultimately been reported to show substantial antiviral activity in vitro and in vivo. Hepatitis C virus (HCV) is a common pathogen that can lead to cirrhosis, hepatocellular carcinoma (HCC), and liver failure. It is estimated that 170 million people were infected worldwide by the year 2000, and that the virus is responsible for at least 10,000 deaths annually in the United States alone. Moreover, existing therapies are hampered by drug-related toxicities. Therefore, there is a particular need for new therapies directed to genotype 1 HCV infection. An attractive strategy for the treatment of liver infection with hepatitis C virus was the synthesis of some compounds with sulfonamidic structure (4). On the other hand, Delavirdine (Figure 2), a second-generation bis(heteroaryl) piperazine, is licensed for the treatment of HIV infection and it is used in combination with other anti-HIV agents (5).

SULFONAMIDES AS ANTIBACTERIAL AGENTS

They are used in urinary tract infections, meningitis, streptococcal pharyngitis, bacillary dysentery, trachoma, chancroid, malaria, toxoplasmosis, nocardiosis, and conjunctivitis. The most popular sulfonamides are p-aminobenzensulfonamides, or sulfanilamides, which are bacteriostatic due to their resemblance to p-aminobenzoic acid (PABA), used by bacteria in the biosynthesis of folic acid required for their growth (6). They interfere with the use of p-aminobenzoic acid (PABA) in the bio-
synthesis of tetrahydrofolic acid, which is a growth factor that is vital for bacterial metabolism. Sulfonamides have a wide range of antimicrobial activity against both Gram-positive and Gram-negative bacterial strains. These drugs act on the bacteria themselves and either prevent their growth (bacteriostatic) or act as germicides (bactericidal).

The topical use of sulfonamides has been limited, because of the high risk of hypersensitivity.

Nevertheless, sulfacetamide and sulfadicramide are still used topically for eye infections.

Because systemic antibiotics are ineffective in reducing bacterial counts in granulation wounds, the use of a suitable topical antibacterial agent may substantially decrease wound sepsis and benefit overall management. The actions of topical 1% silver sulfadiazine and of topical 5% mafenide acetate in Acinetobacter strains wound infection have been investigated (7). Metal-based drugs for the treatment of many ailments have gained much attention over the last decade. The ability of metal ions to bind \textit{in vivo} with proteins and peptides is an important feature of metal-based drugs. Simple and $N$-substituted sulphonamides have attracted much attention in this context. Modified toxicological and pharmacological properties have been observed when some of these sulphonamides are administered in the form of their metal complexes. For example, Ag(I)-sulfadiazine, Ce(III)-sulfadiazine, Ni(II)-sulfadimethoxine and Cu(II)-sulfacetamide have shown higher antimicrobial activity than free ligands. Several authors have conducting studies on the coordination forms of sulphonamides with Cu (II), reported the versatility of these ligands and the importance of their complexes in coordination chemistry (8). Some sulphonamide complexes have proved to be relevant catalysts in chemical reactions, such as Zn-sulfonamide complexes that catalyze enantio selective cyclopropanations, and also reagents for the cleavage of nucleic acids. On the other hand, numerous sulphonamide complexes have been studied as simple models of metal-protein interactions. In addition, some metal sulfonamides have drawn much attention due to the fact that they are mainly used in medicine as antibacterial drugs (9).

Sulfonamides and their different derivatives are among the most widely used antimicrobial agents, chiefly because of their low cost, low toxicity and excellent activity against bacterial diseases.

**SULFONAMIDES AS ANTICANCER AGENTS**

Among the wide range of compounds tested as antitumor agents, sulphonamides have attracted great attention, as many sulphonamide derivatives were reported to have interesting antitumor activity.

Recently, it has been showed that β-carbonic anhydrase from Mycobacterium tuberculosis inhibited by several sulfonamides at low concentration. Sulfa methoxazole was shown to inhibit dihydropteroate synthase of Mycobacterium avium and affected the growth of three strains of Mycobacterium avium complex with MIC50/80 about 30 mg/mL. Also other sulfonamides were active against Mycobacterium avium complex (10).

There are a variety of mechanisms for their anticancer action, such as disruption of microtubule assembly, cell cycle arrest in the G1 phase, functional suppression of the transcriptional activator NF-Y, angiogenesis and carbonic anhydrase inhibition (11). The most prominent of these mechanisms was the inhibition of carbonic anhydrase isozymes (12). It has been shown that
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two carbonic anhydrase isozymes (CA IX and CA XII) are prominently associated in many tumors. They are involved in crucial processes associated with cancer progression and response to therapy. Aromatic or heteroaromatic sulfonamides have been shown to reverse the effect of tumor acidification; consequently they inhibit the growth of cancer cells and suppress carbonic anhydrase-mediated tumor invasion (13).

Methanesulfonamides (CH$_3$SO$_2$NH$_2$) are also used in drug industry because of their biological activity on a large scale. Methanesulfonamide derivatives have DNA binding ability, show cytostatic effects, and some of them, such as Amsacrine (Fig. 2), are used in cancer chemotherapy. In addition, some sulfonyl hydrazines are known to have antineoplastic effects which prevent malignant cells growth and spread (14).

**SULFONAMIDES AS ANTIGLAUCOMA AGENTS**

Several sulfonamides, such as acetazolamide, methazolamide, ethoxzolamide or dichlorophenamide, are clinically used as systemic antiglaucoma agents for more than 50 years. In the mid 90s, the first clinically used, topically effective antiglaucoma sulfonamide, dorzolamide, was discovered (15). More recently, another topically acting antiglaucoma sulfonamide is also available: brinzolamide (Figure 2), However the main drawback of these compounds, and of many sulfonamides reported so far in the literature, is their lack of selectivity, as they usually inhibit most of the catalytically active isoforms of carbonic anhydrase in the low nano/micromolar range (16).

**SULFONAMIDES IN ALZHEIMER’S DISEASE**

Furthermore, recent studies suggest that carbonic anhydrase activation may provide a novel therapy for Alzheimer’s disease (17), the most prevalent form of dementia that affects approximately 24 million people worldwide. A number of structurally diverse γ-secretase inhibitors have been reported and several advanced into clinical trials. Recently, the structure–activity relationships of a series of N-bridged bicyclic sulfonamides as inhibitors of γ-secretase have been reported (18). Begacestat (Fig. 2) is a novel thiophene sulfonamide gamma-secretase inhibitor that selectively inhibits cleavage of amyloid precursor protein (APP) (19).

**SULFONAMIDES AS ANTICONVULSANT AGENTS**

A new class of anticonvulsant structures that belong to the family of sulfamides has been designed. In recent years, several compounds, such as topiramate and zonisamide (Fig. 2) have been approved as anticonvulsant drugs. Their anticonvulsant action is probably due to CO$_2$ retention secondary to inhibition of red cell and brain carbonic anhydrase enzyme, but other mechanisms of action, such as sodium channels blockade were proved for some of them (20).

**SULFONAMIDES AS COX-2 AND LIPÖXYGENASE INHIBITORS**

Sulfasalazine (salicylazosulfapyridine), a compound in which sulfapyridine is linked to 5-aminosalicylate by a diazo bond has been and still is widely used to treat ulcerative colitis and regional ileitis (Crohn’s disease). Sulfasalazine is not used for the antibacterial properties of the sulfapyridine, but for the local anti-inflammatory effect of 5-aminosalicylate. Selective cyclooxygenase-2 inhibitors (COX-2) (Celecoxib, Parecoxib, Valdecoxib) are compounds with sulfonamide struc-
ture that are indicated for the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis but also for the treatment of primary dysmenorrhea.

Recently, sulfonamide group has been found to be the key constituent of a new class of compounds as potential inhibitors of lipoxygenase (21), enzyme that catalyzes the oxidation of polyunsaturated fatty acids.

Fig. 2. Drugs with sulfonamide structure
SULFONAMIDES AS HYPOGLYCEMIC AGENTS

Sulfonylureas are known to act by closing the adenosine triphosphate-sensitive potassium (KATP) channels in the pancreas through binding to the sulphonylurea receptor (SUR) 1 (an integral component of pancreatic KATP channels), leading to beta cell insulin release. The beta cells of patients taking these drugs are chronically stimulated. Sulfonylureas have been regarded as being unsuitable for overweight diabetics, who primarily need to lose weight. However, KATP channels are also found in coronary vascular smooth muscle cells and cardiomyocytes, but here the SUR components are of the SUR 2A and SUR 2B subtypes, respectively (22).

OTHER APPLICATIONS OF SULFONAMIDES

Today, one of the most widely used sulfonamide drugs is sildenafil, marketed as Viagra®. It is a drug used to treat erectile dysfunction and pulmonary arterial hypertension by inhibiting cGMP specific phosphodiesterase type 5, an enzyme that regulates blood flow in the penis. Sildenafil, as a selective PDE5 inhibitor, inhibits cGMP degradation and improves the relaxation of the smooth muscles in the corpus cavernosum (23).

CONCLUSIONS

Compounds with sulfonamide structure enjoy a vast applicability. In this context, they have been widely studied for many years, for their chemotherapeutic activity. The application of sulfonamides has greatly been extended over the years from their function as antimicrobial agents to COX-2 inhibitors, diuretics, carbonic anhydrase inhibitors and even as an anti-impotence drug. In conclusion, sulfonamides represent a diverse and relevant class of therapeutic drugs. The sulfonamide group remains a important strating point for the discovery of new compounds to treat an increasing portfolio of diseases.

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