Sulphanilamide: A Privileged Scaffold with Diverse Pharmacological Actions

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Abstract: Sulphanilamide is also known as sulpha drug. This drug is the first chemotherapeutic agent for gram-positive and gram-negative bacteria because it has a wide range of pharmacological activities like oral diuretics (furosemide, indapamide, chlorthalidone, thiazides), anti-inflammatory (celecoxib), anticancer (E7070), antiviral (Darunavir) ,carbonic anhydrase (CA) inhibitors (CAIs) (acetazolamide, dichlorophenamide, dorzolamide and brinzolamide), antiepileptics (zonisamide and sulthiame), for rheumatoid arthritis (Sulfasalazine), antibacterial (Sulfadiazine), as ophthalmological (Dorzolamide) anticonvulsant (Zonisamide),cyclooxygenase 2 (COX2) inhibitors (valdecoxib).Sulpha drug shown good activity against breast cancer cell. Sulpha derivatives are used for conjunctivitis,treatment of acne,toxoplasmosis and urinary tract infections.Hypoglycaemia and carbonic anhydrase inhibition are the two main inverse effects of sulphonamide derivatives**.**Due to the multiple resistance attained by existing antibiotic drugs, there are ample need to synthesize new derivatives of sulphanilamide for infection because of bacteria and fungus. Sulphanilamide- derived drugs are competitive inhibitors for the folic acid synthesise enzymes present in microorganisms. Sulpha drugs have a growth static effect on micro-organisms. Sulphanilamide has been used to treat a wide range of bacterial infections, including pneumonia, meningitis and streptococcal infections.Bacterial resistance of sulphanilamide has become a significant problem in recent years, and the drug is now rarely used as a first-line treatment for bacterial infections.In this review article, we emphasize only the variously synthesized new derivatives of sulphanilamide with above mentioned pharmacological effects.

Keywords: Sulphanilamide, gram-positive bacteria, gram-negative bacteria, anticancer and diuretic

Introduction

Sulphanilamides are a crucial class of synthetic antimicrobial drugs with broad-spectrum activity against bacterial infections in humans and animals. Sulphanilamideshave a distinct 6- or 5-membered heterocyclic ring and are organo-sulphur compounds containing the SO_2NH_2 and/or -SO_2NH- group[1-2]. They are effective against pyogenic bacterial infections caused by Gram-positive and Gram-negative bacteria, such as *E. coli, Salmonella, Nocardia, Klebsiella, Shigella, and Enterobacter*. It is particularly effective against gram-positive bacteria, including *Streptococcus pneumoniae* and *Streptococcus pyogenes*. However, it is less effective against gram-negative bacteria, such as *Escherichia coli* and *Klebsiellapneumoniae.* Sulphanilamideshave been widely used as antimicrobial agents. While they have active antibacterial properties, their antibiotic resistance remains a significant challenge [3].

Sulphanilamidederivatives have shown numerous biological activities, such as antimicrobial[4-5], antihypertensive[6], anti-HIV[7-8], translation initiation inhibitors[9], anticancer[10-12], cyclooxygenase-2 inhibitors[13],anticonvulsant[14], ant migraine agents[15], carbonic anhydrase inhibitors[16],hypoglycaemic protease inhibitors[17], antidiabetic agents[18] and herbicides[19].Sulpha drug shown good activity against breast cancer cell[20].

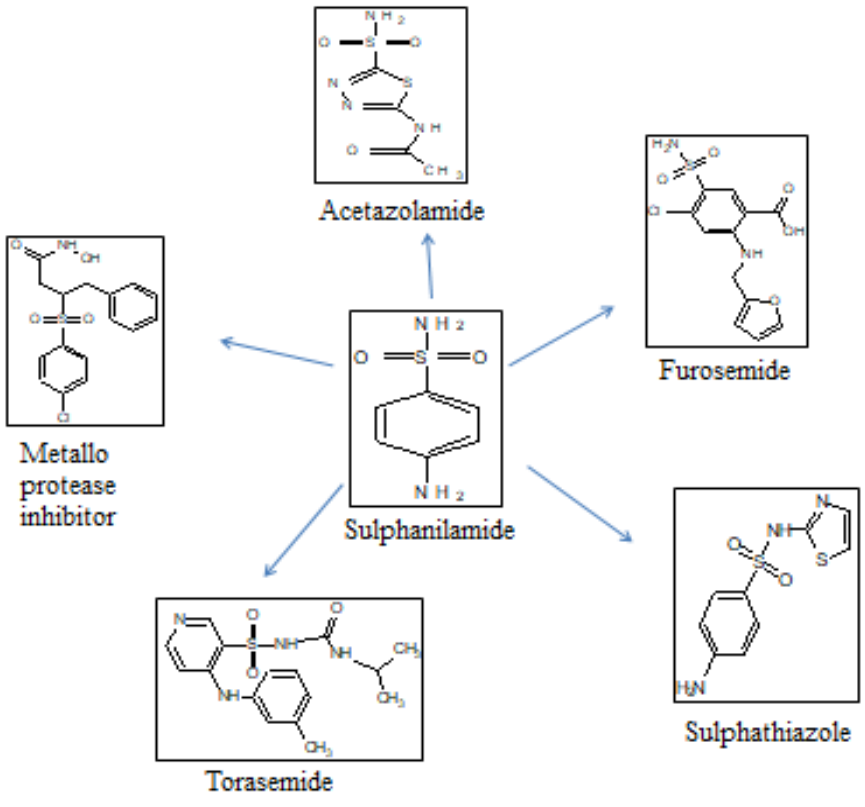


Figure:1. Marketed Preparations of Sulphonamide

Azetolamide and methazolamide sulpha drugs are widely used as antiglaucomaagents[21]. Many other sulpha derivatives are used for conjunctivitis[22],treatment of acne[23],toxoplasmosis[24] and urinary tract infections[25-26].Sulphanilamide derivatives acetazolamide used as a carbonic anhydrase inhibitor[27-28] ,furosemide act as a diuretic[29],sulphathiazole act as a antibacterial agent[30],torasemide act as a hypoglycemic agent[31] and metalloprotease inhibitor[32-33].

The mechanism of action of sulphanilamide involves the inhibition of the enzyme dihydropteroate synthase, which is essential for the bacterial synthesis of folic acid [34]. Folic acid is an important precursor for the synthesis of DNA, RNA, and other essential molecules in bacterial cells. By inhibiting dihydropteroate synthase, sulphanilamide blocksthe synthesis of folic acid and hence inhibits the growth and replication of bacteria.

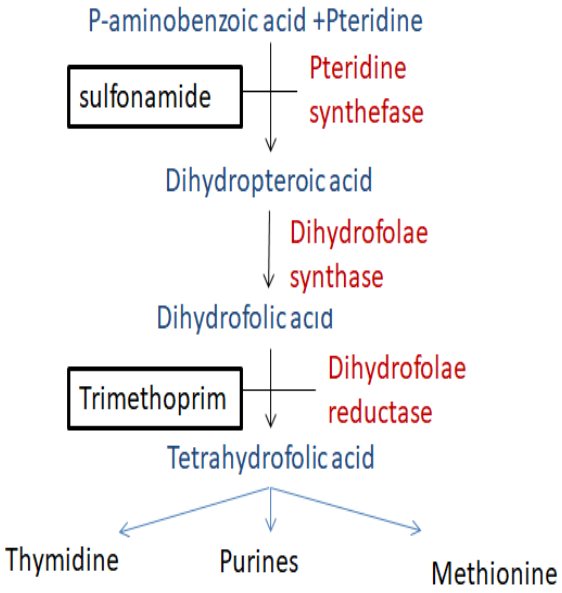
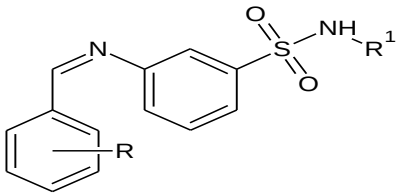


Figure: 2. Mechanism of Action of Sulphonamide

Despite its declining use as an antibiotic, sulphanilamide remains an important molecule in the history of medicine. Its discovery paved the way for the development of other antibiotics, and it is still studied for its potential therapeutic applications, such as in the treatment of cancer and parasitic infections [35]. However, bacterial resistance to sulphanilamide has become a significant problem in recent years, and the drug is now rarely used as a first-line treatment for bacterial infections.

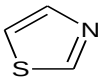
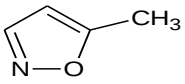
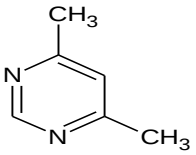
Anti-bacteria activity

Halve et al.[36]synthesized a series of novel Azomethines derived from sulphonamides and evaluated their antibacterial activity against Gram-positive bacteria, including *Staphylococcus aureus* and *Bacillus subtilis*, and Gram-negative bacteria such as *Pseudomonas aeruginosa*and *Escherichia coli*. The researchers used the disc diffusion assay, with streptomycin and penicillin-G as reference standard drugs. The Azomethine compounds contained different side chains but had the same central moiety. Interestingly, the azomethines containing a 5-methyl isoxazole moiety exhibited excellent antibacterial activity against all bacterial strains tested.



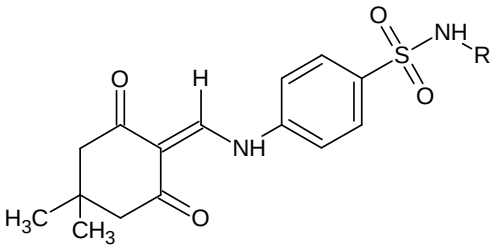
R= p-OH; p-CH2CHOCH2; o-NO2; m-CH2=CH-CH2

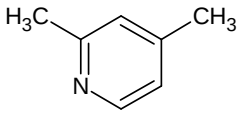
R1=

a) H(sulphanilamide) b)  c)  d) 

Sulphathiazole Sulphomethoxazole Sulphadimidine

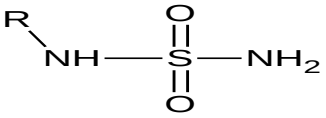
Ghorab .et al;[37] study involved the design and synthesis of a series of 4-(4,4-dimethyl-2,6-dioxocyclohexylidene) benzene sulphonamide derivatives, which were screened for their antimicrobial activity against various gram-positive and gram-negative bacteria, as well as fungi. The synthesized compounds exhibited comparable antimicrobial activity, with some of the compounds showing greater potency than the reference drug, Ciprofloxacin. Furthermore, molecular docking simulations were conducted to analyze the binding modes of the target compounds in the active site of dihydropteroate synthase (DHPS).

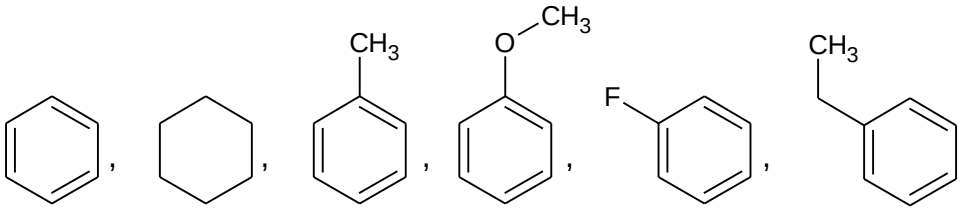


R= COCH3, 

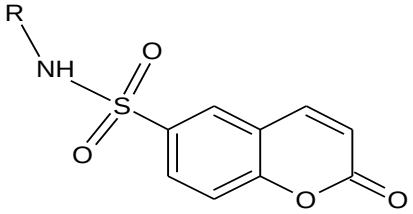
Intriguingly, the most potent compounds showed similar binding interactions to sulphanilamide in the DHPS active site, but with lower binding energy. These findings suggest that the synthesized sulphonamide derivatives could serve as promising antimicrobial agents and could be further developed for clinical use.

Dupont et al.[38] developed a series of novel sulphonamide derivatives from chlorosulfonyl isocyanate (CSI) through a three-step (carbomoylation,sulphamoylation,deprotection) synthesis process. The synthesized compounds were then evaluated for their antibacterial activity against pathogenic strains of gram-positive and gram-negative bacteria, specifically *Escherichia coli* and *Staphylococcus aureus*. The results of the in-vitro tests showed promising bacteriostatic activity of these newly prepared compounds against all bacterial strains used, as determined through dilution and minimal inhibition concentration (MIC) methods.



R= 

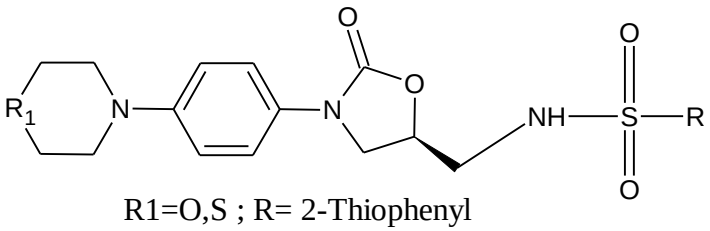
Neda Mostajeran et al.[39] reported the synthesis of a series of novel coumarin-6-sulphonamides as potential antibacterial agents. The researchers evaluated the in-vitro efficacy of these compounds against both Gram-positive and Gram-negative bacteria. The results showed that the antibacterial activity of the new coumarin sulphonamides against Gram-negative bacteria was lower than that against Gram-positive bacteria. However, the coumarin sulphonamides that contained heterocycle rings demonstrated higher antibacterial activity against Gram-negative bacteria compared to Gram-positive bacteria.



R=4-Methyl-2aminopyridine
6-Methyl-2aminopyridine

The in-vitro antibacterial activities of all the synthesized compounds were screened against Escherichia coli and Staphylococcus aureus bacteria. These findings suggest that coumarin-6-sulfonamides with heterocycle rings may have potential as antibacterial agents, particularly against Gram-negative bacteria.

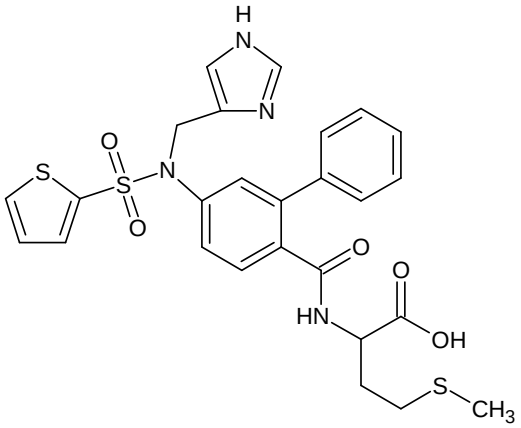
Kamal et al.[40] undertook the design and synthesis of a series of linezolid-like oxazolidino-sulphonamides as part of their efforts to develop new antimicrobial agents with improved properties. The researchers also investigated the correlation between the calculated lipophilicity values (C log P) and the antimicrobial activity of the synthesized compounds. The study found that the majority of the synthesized compounds exhibited good to moderate activity against a range of Gram-positive and Gram-negative bacteria, as well as fungal strains. Notably, two of the compounds showed significant activity against a panel of Gram-positive and Gram-negative bacteria, with a MIC value of 2.0-6.0 μg/ml. These compounds also displayed activity against Candida albicans, with a MIC value of 4.0μg/ml. These findings suggest that the synthesized linezolid-like oxazolidino-sulphonamides may have potential as effective antimicrobial agents



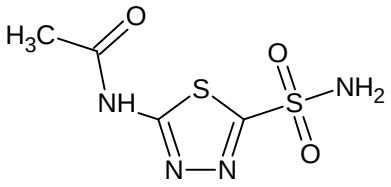
R1=O,S ; R= 2-Thiophenyl

Anti-cancer activity

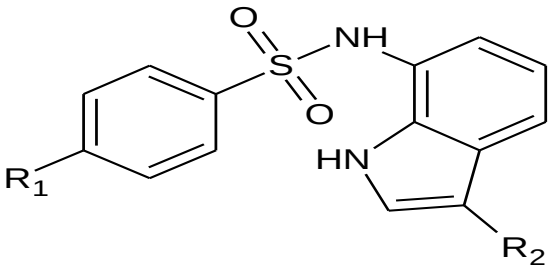
Gottleib et al;[41] reported the synthesis of sulphonamide compounds containing methionine and aniline, which were investigated for their ability to inhibit protein farnesyl transferase and geranylgeranyl transferase. Their study revealed that one of the synthesized compounds exhibited potent inhibition of protein farnesyl transferase, with an IC50 value of 20 nanomolar. These findings suggest that this compound could have potential as a therapeutic agent for diseases that involve the dysregulation of protein prenylation, such as cancer and cardiovascular disease.



Teicher et al;[42] reported that acetazolamide 3, a sulphonamide derivative and a strong inhibitor of several carbonic anhydrase isozymes, may have potential as a modulator of anticancer therapies when combined with different cytotoxic agents such as alkylating agents, nucleoside analogs, and platinum derivatives. The potential mechanism of action is thought to be due to the acidification of the intratumoral environment resulting from carbonic anhydrase inhibition, although other mechanisms of action for this drug have not been ruled out. These findings suggest that acetazolamide 3 could have value as an adjunct therapy to enhance the efficacy of traditional cytotoxic treatments in cancer.



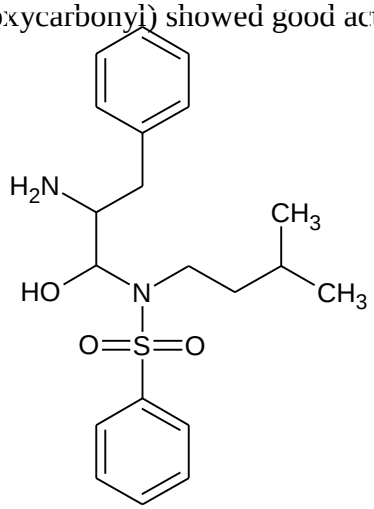
Owa et al;[43] has revealed a new class of sulphonamide compounds that demonstrate potent antitumor activity by blocking cell cycle progression in the G1 phase, rather than the mitotic (M) phase, as seen with other compounds such as E7010. The lead molecule for this class of compounds was used to synthesize a large series of N-7-indolyl-benzenesulphonamides, designated as type 24, which were subsequently evaluated for their potential as antitumor agents. These findings suggest that the newly discovered sulphonamide compounds have the potential to be developed into effective cancer treatments that target the G1 phase of the cell cycle.



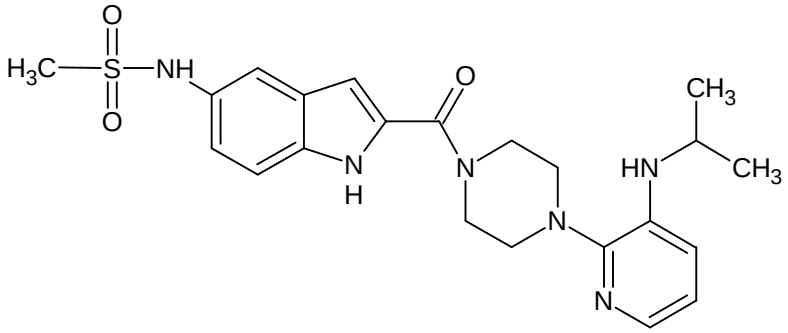
R1=MeO;Cl;NO2;NH2;CN
R2=H,Cl,OH

Anti-HIV activity

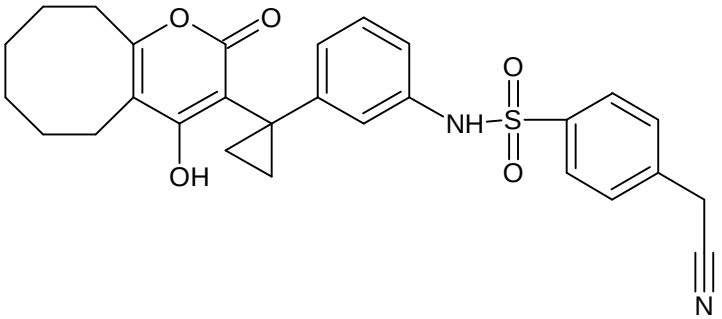
Vazquez et al.[44] Synthesized various hydroxyethylamino sulphonamides derivatives.The synthesized compound (benzyloxycarbonyl) showed good activity against retroviral.



Boyer et al.,[45]synthesized a series of various sulphonlamide derivatives. Synthesized a various sulphonyl moieties substituted at the 4-position of C3-phenyl ring substituents of thedihydropyran-2-one ring system. The compounds were shown to possess very good anti-hiv activity.



Harvey et al,[46]synthesized a cyclooctylpyranones sulphonamide substituted derivative. The compound had non-peptidic HIV protease inhibitor activity.



Conclusion

Sulphanilamide is an antimicrobial drug that inhibits bacterial folic acid synthesis and has a broad spectrum of activity against a range of bacteria. Although its use as an antibiotic has

declined due to bacterial resistance, it remains an important molecule in the history of medicine and is still studied for its potential therapeutic applications.

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