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A SHORT REVIEW ON: SULPHONAMIDES

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ABSTRACT

Sulfonamides/sul.fon.amides/ (sul-fon´ah-mīd) are one of the organosulphur compounds containing the $-SO_2NH_2$ and/or $-SO_2NH-$ group(s). The sulfonamides 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. Medically important sulphonamides.

KEYWORDS: **Organosuphur compounds, Gram-negative bacteria, Gram-positive bacteria.**

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INTRODUCTION

Sulfonamide or sulphonamide is the basis of several groups of drugs. The original antibacterial sulfonamides (sometimes called sulfa drugs or sulpha drugs) are synthetic antimicrobial agents that contain the sulfonamide group. Some sulfonamides are also devoid of antibacterial activity, e.g., the anticonvulsant sultiame.

The sulfonylureas and thiazide diuretics are newer drug groups based on the antibacterial sulfonamides. Sulfa allergies are common, hence medications containing sulfonamides are prescribed carefully. It is important to make a distinction between sulfa drugs and other sulfur-containing drugs and additives, such as sulfates and sulfites, which are chemically unrelated to the sulfonamide group, and do not cause the same hypersensitivity reactions seen in the sulfonamides.Because sulfonamides displace bilirubin from albumin, kernicterus (brain damage due to excess bilirubin) is an important potential side effect of sulfonamide use.

STRUCTURE AND NOMENCLATURE

Sulfonamides are represented by general structure (1.004) in which R may be alkyl, aryl or hetero aryl groups and R_1/R_2 may also be hydrogen, alkyl, and aryl or hetero aryl groups. Sulfonamides are written as alkanesulfonamides or are nesulfonamides (1.005) (Fig-1.2).

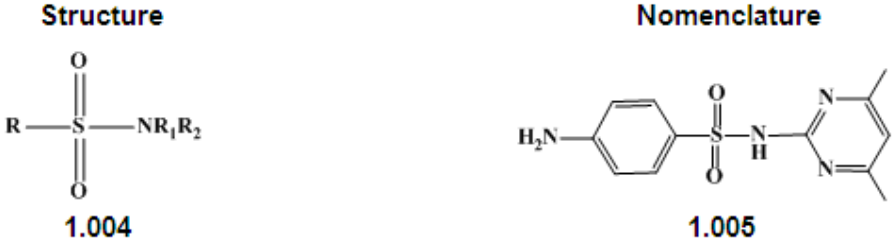


Figure 1.2
4-Amino-N-(4,6-dimethylpyrimidin-2-yl)benzene sulphonamide

CLASSIFICATION OF SULFONAMIDES

Classifications of sulfonamides are based on chemical structure, duration of action, spectrum of activity and therapeutic applications. Common classification of sulfonamides is based on their therapeutic applications. There are three groups of sulfonamides according to their duration of action

(a) SHORT ACTING SULFONAMIDES

These are preferred for systemic infections as they are rapidly absorbed and rapidly excreted. For example, sulfadiazine (1.006), sulfadimidine or sulfamethazine (1.007), and sulfamethoxazole (1.008) in Fig.-1.3 have been used for the treatment of urinary tract infections[1].

(b) *INTERMEDIATE OR MODERATE ACTING SULFONAMIDES*

These are used for infections requiring prolonged treatment. For example, sulfacetamide (1.009), sulfadoxine (1.010), *etc* (Fig.-1.3). The sulfadoxine is an ultra-longlasting sulfonamide often used in combination with pyrimethamine to treat or prevent malaria. It is also used, usually in combination with other drugs, to treat or prevent various infections in livestock[2].

(c) LONG ACTING SULFONAMIDES

These are rapidly absorbed and slowly excreted. For example, sulfametopyrazine, sulfasalazine (1.011), which is marketed as azulfidine in the U.S. and salazopyrin & sulazine in Europe and Hong Kong, was developed over 70 years ago specifically to treat rheumatoid arthritis. Sulfasalazine is a

derivative of mesalazine and is formed by combining sulfapyridine and salicylate with an azo bond. It may be abbreviated SSZ. Sulfasalazine is also used in the treatment of inflammatory bowel disease including ulcerative colitis and Crohn's disease. In addition to these, there are different types of sulfonamides which have been used in various types of infections. For example, sulfabenzamide (1.012) used in mucous membrane, sulfacetamide sodium (1.013) used for superficial ocular, sulfadiazine (1.006) used in urinary tract infection and sulfamethizole (1.014) used in bacterial infections[3] (Fig.-1.3).

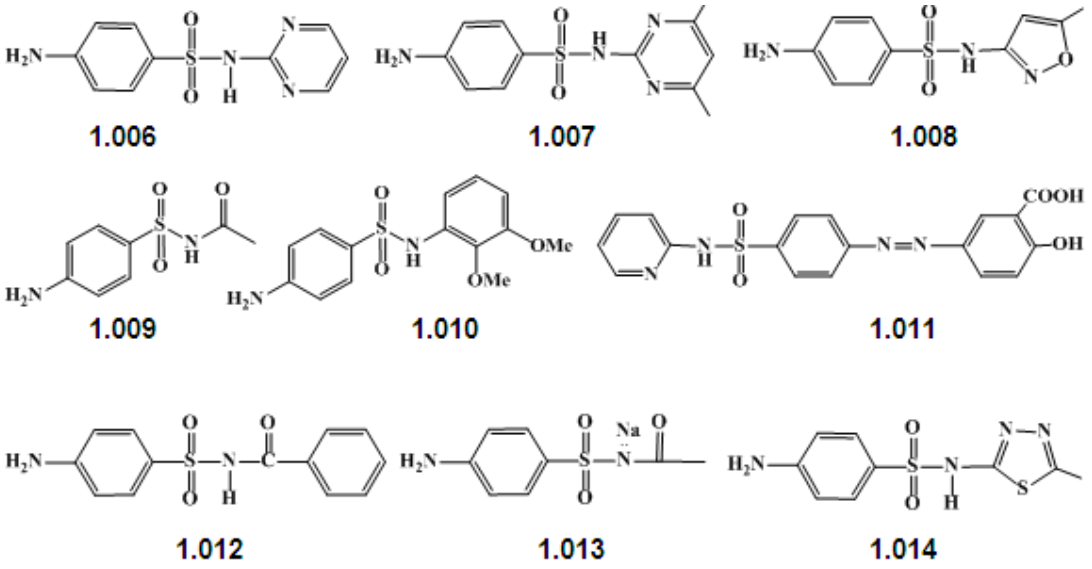


Figure 1.3

BIOLOGICAL ASPECTS OF SULFONAMIDES

Sulfonamides represent an important class of medicinally effective molecules and are known to possess wide variety of biological activities. In reference to anti-baterial activity, sulfonamines (1.015) are structural analogues of *p*-aminobenzoic acid or PABA (1.016) which is essential for the synthesis of DNA in the bacteria. The sulfonamides compete with PABA for the enzyme dihydropteroate synthetase and as result the growth of bacteria inhibited because of inhibition of formation of dihydrofolate (1.017), tetrahydrofolate and subsequently bacterial DNA (Fig.-1.4).

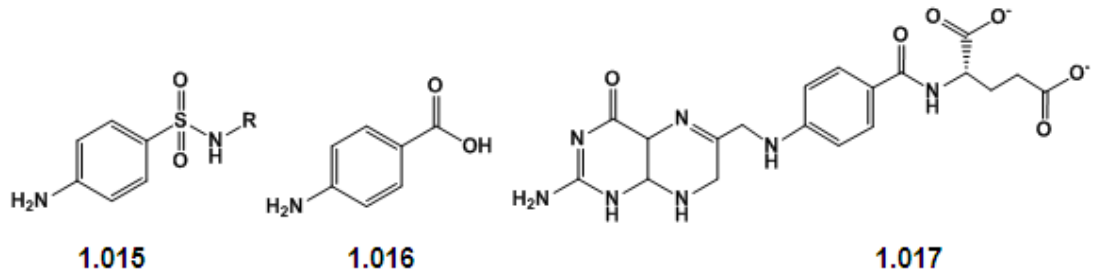


Figure 1.4

Structural similarity between PABA and sulfonamides is the basis for the inhibitory activity of sulfa drugs on dihydrofolate biosynthesis

Folic acid (also known as folate, vitamin M, vitamin B_9, vitamin B_c or folacin, pteroyl-L-glutamic acid, pteroyl-L-glutamate, and pteroylmonoglutamic acid) is itself not biologically active but its biological importance is due to tetrahydrofolate and other derivatives after its conversion to dihydrofolic acid in the liver.[4] The human body needs folate to

synthesize DNA, repair DNA, and methylate DNA as well as to act as a cofactor in certain biological reactions. It is especially important in aiding rapid cell division and growth, such as in infancy and pregnancy. Children and adults both require folic acid to produce healthy red blood cells and prevent anemia. Common symptoms of folate deficiency include diarrhea, macrocytic anemia with weakness or shortness of breath, nerve damage with weakness and limb numbness, pregnancy complications, mental confusion, forgetfulness or other cognitive declines, mental depression, sore or swollen tongue, peptic or mouth ulcers, headaches, heart palpitations, irritability, and behavioral disorders. Low levels of folate can also lead to homocysteine accumulation. DNA synthesis and repair are impaired and this could lead to cancer development[5].

Dihydrofolate reductase (DHFR)

is an enzyme that reduces dihydrofolic acid to tetrahydrofolic acid, using NADPH as electron donor, which can be converted to the kinds of tetrahydrofolate cofactors used in 1-carbon transfer chemistry. In humans, the DHFR enzyme is encoded by the *DHFR* gene. It is found in the q11→q22 region of chromosome-5. Bacterial species possesses distinct DHFR enzymes (based on their pattern of binding diaminoheterocyclic molecules) but mammalian DHFRs are highly similar (Fig.-1.5).

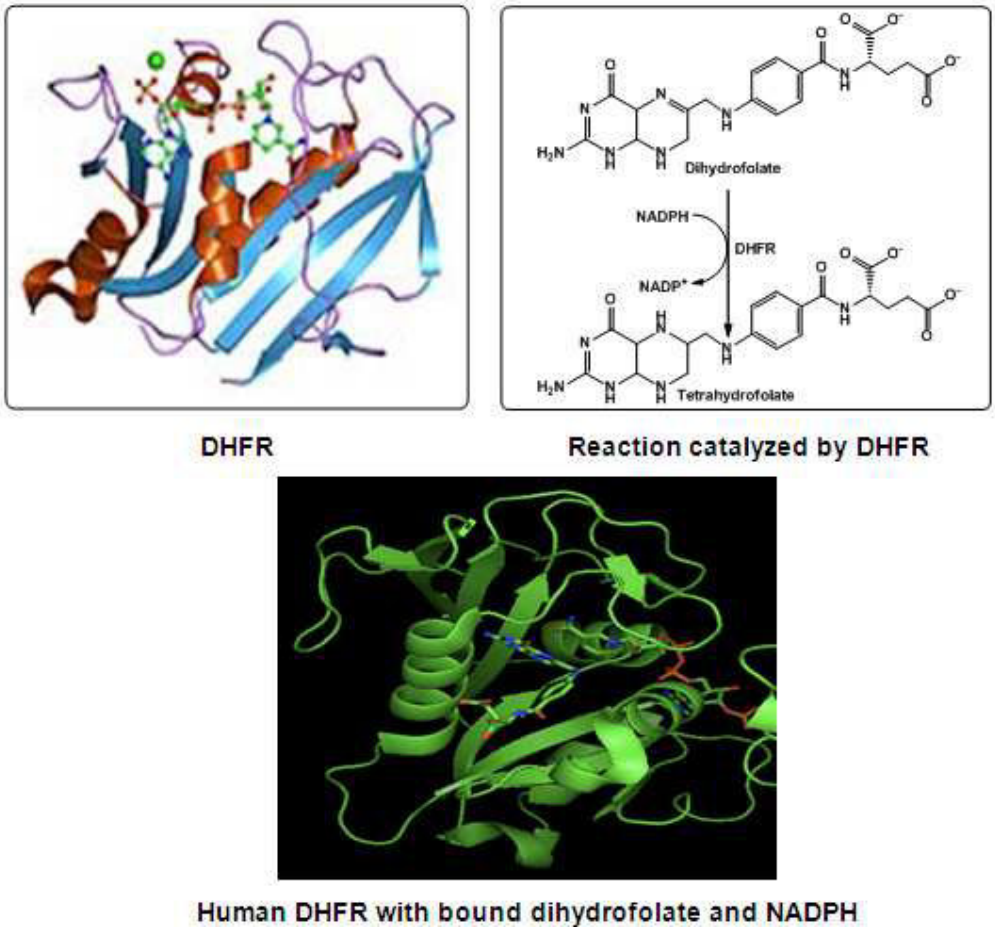


Figure 1.5
Structure and reaction of DHFR

A dihydrofolate reductase (DHFR) inhibitor is a molecule that inhibits the function of dihydrofolate reductase, and is a type of antifolate. The sulfonamides in combination with trimethoprim have been used to prevent the synthesis of tetrahydrofolate (Fig.-1.6).

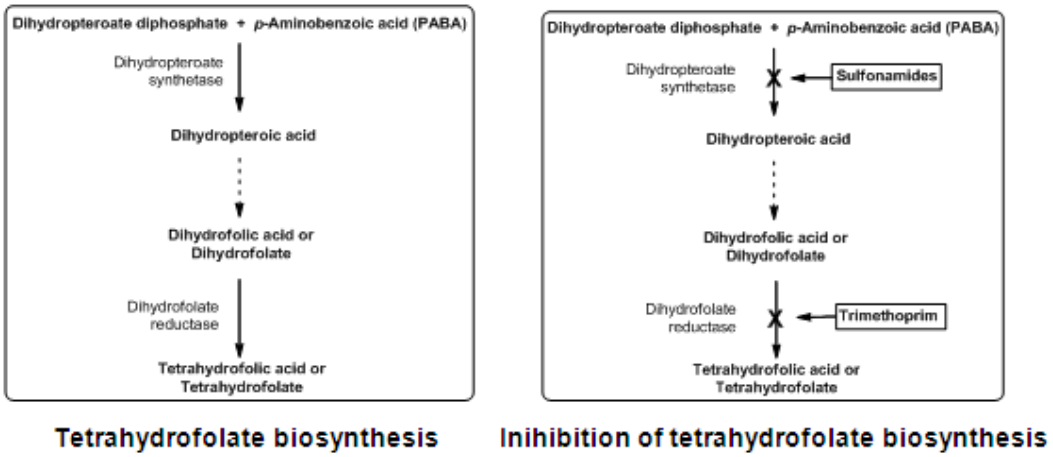


Figure 1.6
THF biosynthesis and its inhibition

Literature survey revealed that sulphonamides have many other activities like insulin releasing,[6] carbonic anhydrase inhibitory,[7] anti-inflammatory,[8] and anti-tumor activity.[9] Benzenesulfonamides have also been reported to use as aldose reductase inhibitors (ARIs), potent human pregnane X-receptor (Hpxr) agonists and anti-prostate cancer agents[10]. More than five thousand analogues of sulfonamides have been synthesized and some of them are in use as drugs. Some important examples include: Sulfamethoxazole-trimethoprim (Septran) (1.018) as anti-bacterial, acetazolamide (Diamox) (1.019) as anti-glaucoma and anti-epileptic, zonisamide (1.020) as anti-seizure, sulfadoxine (1.021) and its combination with pyrimethamine as anti-malarial, celecoxib (1.022) as COX-inhibitor which has been approved for arthritis and diuretics. Piretanide (1.023) and furosemide (Lasix) (1.024) have been extensively used since 1964 in the treatment of oedema and hypertension. Nimesulide (1.025) and valdecoxib (1.026) have been used as non-steroidal anti-inflammatory drugs (NSAIDs). (Fig. 1.7)

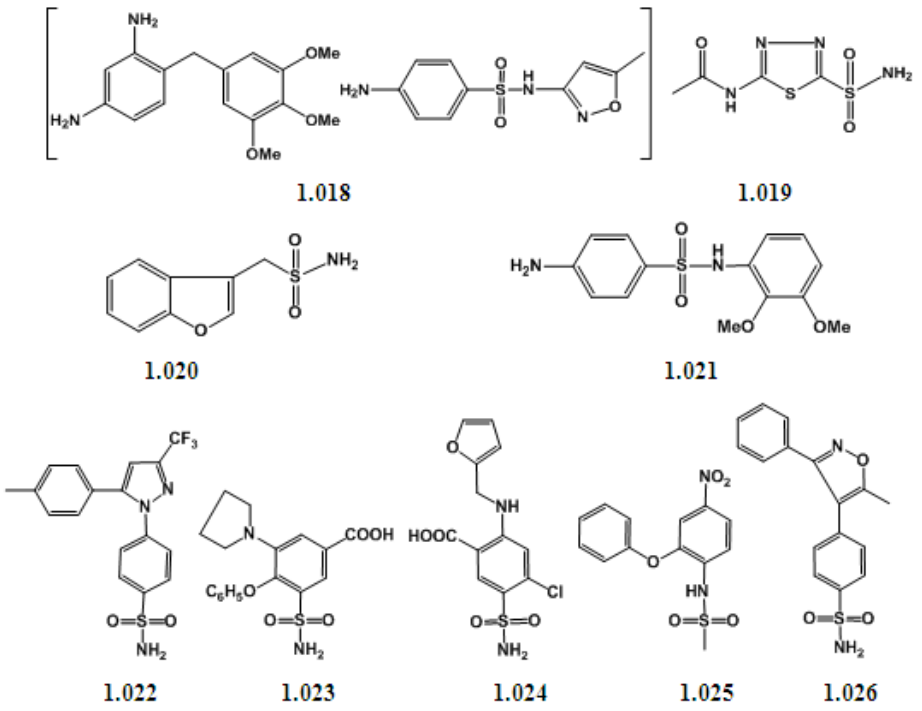
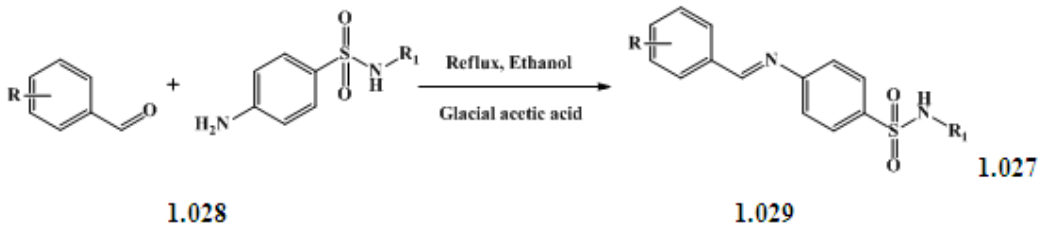


Figure 1.7

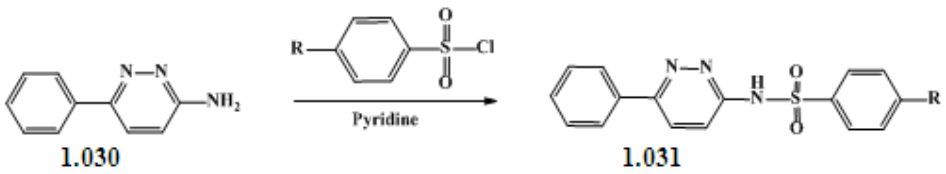
SYNTHETIC ASPECTS OF SULFONAMIDES

Aromatic aldehydes (1.027) and 4-aminobenzene sulfonamides (1.028) reacted in glacial acetic acid to form [(*E*)-phenylmethylidene]aminobenzenesulfonamides (1.029) (Scheme-1.1)[11].



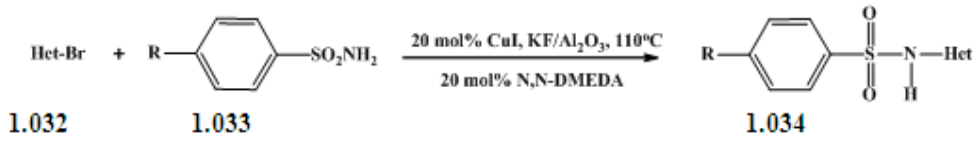
Scheme 1.1

The sulfonamide derivatives (1.031) were synthesized by the reaction of 3-amino-6-phenylpyridazine (1.030) with benzenesulfonyl chlorides in pyridine (Scheme-1.2)[12].



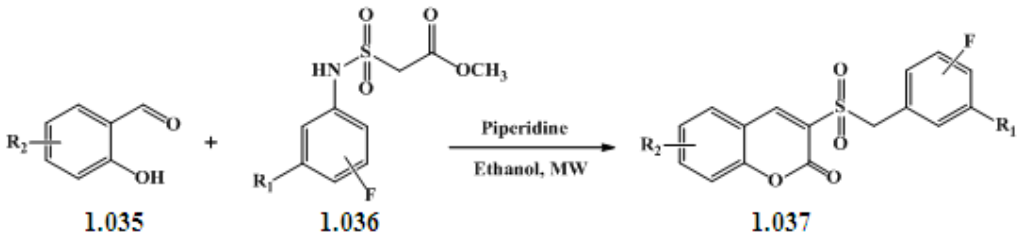
Scheme 1.2

The reaction of hetero aryl bromides such as 2-bromopyridine, 3-bromopyridine, or 3-bromothiophene (1.032) with benzene or *p*-toluenesulfonamides (1.033) gave the corresponding *N*-(hetero aryl)benzenesulfonamides (1.034) (Scheme-1.3)[13].



Scheme 1.3

The Knoevenagel condensation of 1.036 with substituted salicyladehydes (1.035) furnished *N*-fluoroaryl-coumarin-3-sulfonamides (1.037) (Scheme-1.4)[14].

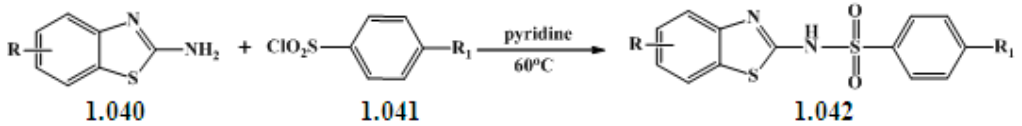


Scheme 1.4

2-styryl-7-amino-5-chloroquinoline-8-ols (1.038) treated with benzene sulfonamide to give *N*-(2-substituted-styryl)-5-chloro-8-hydroxyquinolin-7-yl)-benzenesulfonamides (1.039) (Scheme-1.5)[15].

Scheme 1.5

The sulfonamides (1.042) were prepared by heating of appropriate hetero arylamine (1.040) with selected benzenesulfonyl chlorides (1.041) in pyridine (Scheme-1.6).[16]



Scheme 1.6

CONCLUSION

In conclusion, sulfonamides can be prepared in the laboratory in many ways. For example, by the reaction of sulfonyl chlorides with amines in the synthesis of sulfonylmethylamide. A readily available sulfonyl chloride source is tosyl chloride. Triflimide or triflimidic acid $HN(Tf)_2$ (bis(trifluoromethane)sulfonimide) is the formal adduct of triflic acid and ammonia. Phenyl triflimide is a

triflating reagent. The related metal triflimidates are used as catalysts. The anion bistriflimide is hydrophobic.

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REFRENCES

1. Locuson, C. W.; Gannett, P. M.; Ayscue, R.; Tracy, T. S. Use of simple docking methods to screen a virtual library for heteroactivators of cytochrome P450 2C9. *J. Med. Chem.*, 50(6):1158-1165,(2007)
2. Boison, J. O.; Nachilobe, P.; Cassidy, R.; Keng, L.; Thacker, P. A.; Peacock, A.; Fesser, A. C.; Lee, S.; Korsrud, G. O.; Bulmer, W. S. Determination of trimethoprim and sulphadoxine residues in porcine tissues and plasma. *Canadian J. Vet. Res.*, 60(4):281-287,(1996)
3. O'Shea, R.; Moser, H. E. Physicochemical properties of antibacterial compounds: Implications for drug discovery. *J. Med. Chem.*, 51(10): 2871-2878,(2008)
4. Bailey, S. W.; Ayling, J. E. The extremely slow and variable activity of dihydrofolatereductase in human liver and its implications for high folic acid intake. *PNAS US*, 106 (36): 15424-15429,(2009)
5. Weinstein, S. J.; Hartman, T. J.; Stolzenberg-Solomon, R.; Pietinen, P.; Barrett, M. J.; Taylor, P. R.; Virtamo, J.; Albanes, D. Null association between prostate cancer and serum folate, vitamin B_6, vitamin B_{12}, and homocysteine (PDF). *Cancer Epidemiol. Biomarkers Preven.*, 12(11): 1271-1272,(2003)
6. Maren, T. H. Relations between structure and biological activity of sulfonamides. *Annual Rev. Pharmacol. Toxicol.*, 16, 309-327, (1976)
7. Renzi, G.; Scozzafava, A.; Supuran, C. T. Carbonic anhydrase inhibitors: Topical sulfonamide antiglaucoma agents incorporating secondary amine moieties. *Bioorg. Med. Chem. Lett.*, 10(7): 673-676 ,(2000)
8. Li, J. J.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Collins, J. T.; Garland, D. J.; Gregory, S. A.; Huang, H. C.; Isakson, P. C. 1,2-Diarylcyclopentenes as selective cyclooxygenase-2 inhibitors and orally active anti-inflammatory agents. *J. Med. Chem.*, 38(22):4570-4578,(1995)
9. Yoshino, H.; Ueda, N.; Niijima, J.; Sugumi, H.; Kotake, Y.; Koyanagi, N.; Yoshimatsu, K.; Asada, M.; Watanabe, T. Novel sulfonamides as potential systemically active antitumor agents. *J. Med. Chem.*, 35(13): 2496-2497,(1992)
10. Chiou, C. T.; Chen, G. S.; Chen, M. L.; Li, H.; Shi, L.; Huang, X. H.; Dai, W. M.; Chern, J. W. Synthesis of anti-microtube *N*-(2-arylindol-7-yl)benzene sulfonamide derivatives and their antitumor mechanisms. *ChemMedChem.* 5(9):1489-1497,(2010)
11. Singh, U. K.; Pandeya, S. N.; Sethia, S. K.; Pandey, M.; Singh, A.; Garg, A.; Kumar, P. Synthesis and biological evaluation of some sulfonamide schiff's bases. *International J. Pharm. Sci. Drug Res.*, 2(3),:216-218, (2010)
12. Dogruer, D. S.; Urlu, S.; Onkol, T.; Ozcellik, B.; Sahin, M. F. Synthesis of some pyridazine derivatives carrying urea, thiourea, and sulfonamide moieties and their antimicrobial activity. *Turkey J. Chem.*, 34(1): 57-65,(2010)
13. Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Alikarami, M. Copper-catalysed *N*-arylation of arylsulfonamides

with aryl bromides and aryl iodides using KF/Al_2O_3. *J. Chem. Sci*., 122(2): 143-148,(2010)

14. Zuo, H.; Jose, G.; Li, Z.-B.; Moon, B.-H.; Shin, D.-S.; Ghate, M. Microwave-assisted synthesis of fluorinated coumarino sulfonamides. *ARKIVOC*, (ii): 183-189,(2008)
15. Jiao, Z.-G.; He, H.-Q.; Zeng, C.-C.; Tan, J.-J.; Hu, L.-M.; Wang, C.-X. Design, synthesis and anti-HIV integrase evaluation of *N*-(5-chloro-8-hydroxy-2-styrylquinoline-7-yl) benzenesulfonamide derivatives. *Molecules*, 15(3): 1903-1917,(2010)
16. Argyropoulou, I.; Geronikaki, A.; Vicini, P.; Zani, F. Synthesis and biological evaluation of sulfonamide thiazole and benzothiazole derivatives as antimicrobial agents. *ARKIVOC*, (vi):89-102,(2009).