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NOVEL RESEARCH STRATEGIES OF SULFONAMIDE DERIVATIVES

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ABSTRACT

Sulfonamide plays a vital role in medicinal chemistry which is used as an antimicrobial, diuretic, oral hypoglycaemic agent for discovery of novel therapeutic agents. Substitution of sulfonamide nucleus is a significant synthetic strategy in drug discovery process. Therapeutic properties of sulfonamides related drugs have motivated the medicinal chemists to synthesize novel therapeutic agents. In this review, sulfonamide derivatives with different pharmacological activities are reported on the basis of substitutions on the nucleus with an aim to help medicinal chemists for the development of SAR on sulfonamides for each activity. This article main object is to review the work done, chemistry and pharmacological activities of sulfonamide derivatives during past years. 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.

KEYWORDS: Sulfonamides, pharmacological activities, novel therapeutic agents etc.

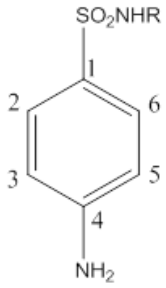
INTRODUCTION

The sulfonamides were the first effective chemotherapeutic agent used for the prevention and the treatment of pyogenic bacterial infections in humans.[1] In 1935 a German scientist, Domagk discovered Prontosil, an azo dye which is the first commercially available antibiotic possessing para amnio benzene sulfonamide group. He was awarded Nobel Prize of Medicine in 1939 for his outstanding contribution.[2] The sulfonamide drugs are used to treat urinary tract infections, bacterial respiratory infections and gastrointestinal infections. Sulfonamide

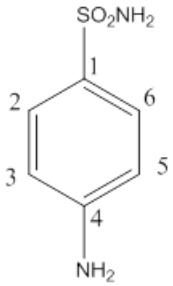
derivatives such as sulfadoxine and sulfamethopyrazine are used for malaria and toxoplasmosis when combined with pyrimethamine. Sulfonamide derivative such as sulfamethoxazole is used for many bacterial infections when combined with trimethoprim.[3-5] They are also used as an oral hypoglycaemic, diuretic agents etc. Sulfonamides are bacteriostatic antibiotics against many gram -positive and gram- negative bacteria. Microorganisms that may be susceptible to sulfonamides are Streptococcus pyogenes, H. influenzae, H. ducreyi, Vibrio cholerae, Calymmatobacterium granulomatis and Chlamydia trachomatis.[6-7]

CHEMISTRY

The sulfonamide exists as a white powder, mild acidic in nature and form water-soluble salts with bases.



Sulfonamide



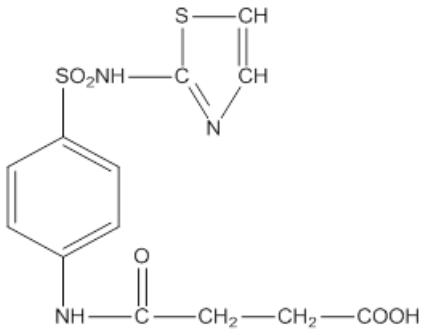
Sulfanilamide

A free amino group in the para position (N^4) is required for antibacterial activity. Sulfonamides can be considered as derivative of para amino benzene sulfonamide (Sulfanilamide).

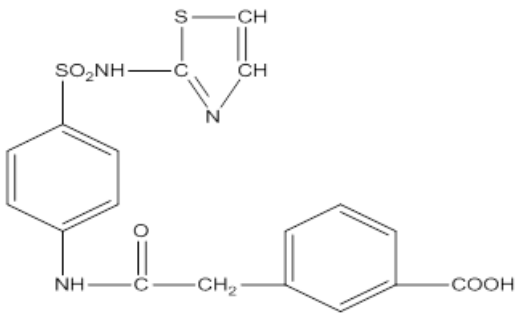
CLASSIFICATION

1. **Based on chemical structure**

(i) Both N^1 and N^4 Substituted sulfonamides



Succinyl Sulfathiazole

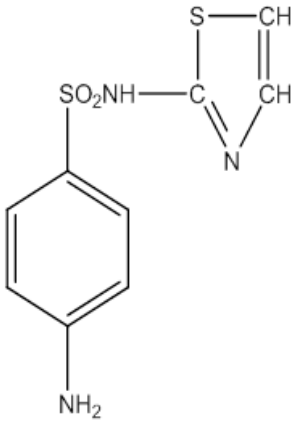


Phthalyl Sulfathiazole

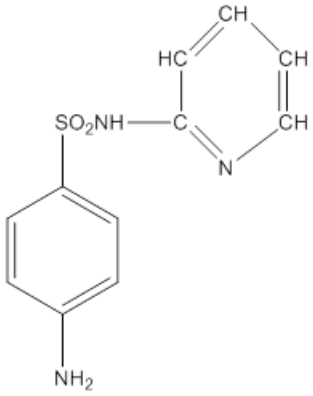
Succinyl Sulfathiazole: It is a sulfonamide. It is also called as succinyl sulphathiazole. It is a white or yellow-white crystalline powder. It dissolves in aqueous solutions of alkali hydroxides and carbonates but is very slightly soluble in water. It comes under ultra long acting drug.[8]

Phthalyl Sulfathiazole: It belongs to the group of drugs called sulfonamides. The drug is a broad-spectrum antimicrobial that can treat intestinal infection. The drug is used in the treatment of dysentery, colitis, gastroenteritis and intestinal surgery.[9]

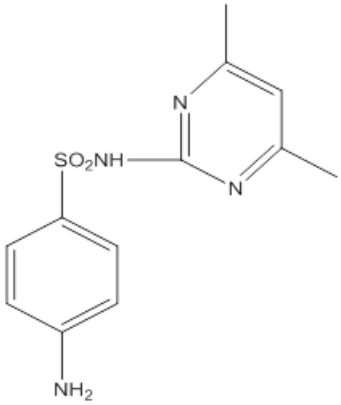
(ii) N^1 Substituted sulfonamides



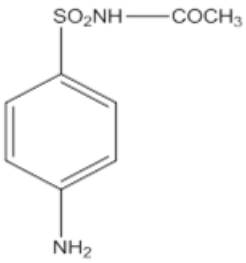
Sulfapyridine



Sulfathiazole



Sulfadimidine



Sulfacetamide

Sulfapyridine: It is a sulfanilamide antibacterial medication. It was also referred as M&B 693. However, it may also be used to treat linear IgA disease and has use in veterinary medicine. It is a good antibacterial drug, but its water solubility is very pH dependent.[10]

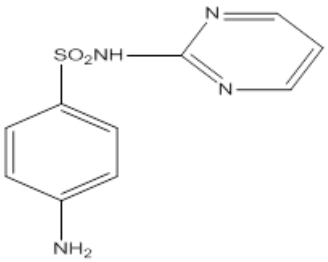
Sulfathiazole: Sulfathiazole is an organosulfur compound used as a short-acting sulfa drug. Formerly, it was an oral and topical antimicrobial agent.[11]

Sulfadimidine: Sulfadimidine is a sulfonamide antibacterial. They are more commonly SDD. Other names of Sulfadimidine are or sulfamethazine, sulfadimerazine, sulfadimezine, and sulphadimethylpyrimidine.[12]

Sulfacetamide: It is a sulfonamide antibiotic. Sulfacetamide has antibacterial activity and is used to control acne. There are several prescription topical products containing sulfacetamide, such as foams, shampoos, sunscreens, creams and washes.[13]

2. Bases on duration of Action

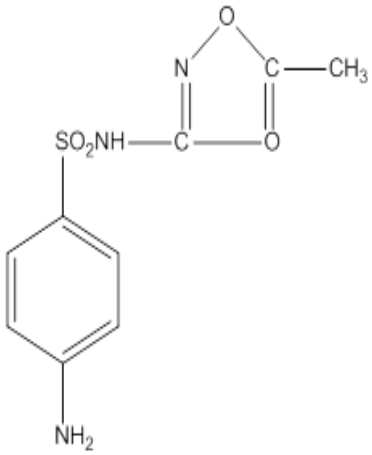
(i) Short duration of action



Sulfadiazine

Sulfadiazine: It is an antibiotic which is used together with pyrimethamine; it is the treatment of choice for toxoplasmosis. It is a second-line treatment for the prevention of rheumatic fever, chancroid, chlamydia. It is taken by mouth.[14-15]

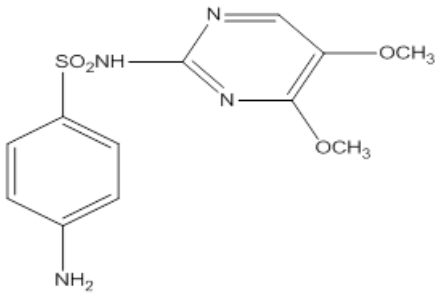
(ii) Intermediate acting sulphonamide



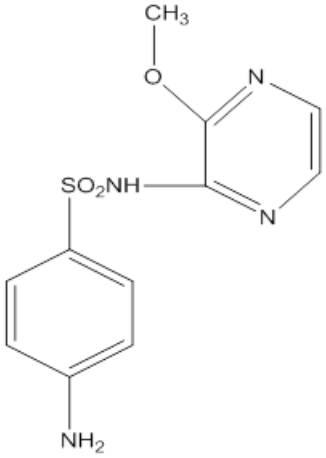
Sulfamethoxazole

Sulfamethoxazole: It has intermediate duration of action due slower oral absorption and urinary excretion. It is combined with trimethoprim (Cotrimoxzole) as the $t^{1/2}$ of both is same i.e. 10 hours. Sulfamethoxazole is 65% bound to plasma membrane.[16-17]

(iii) Long acting sulphonamides



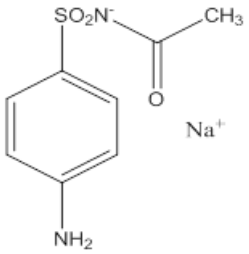
Sulfadoxine



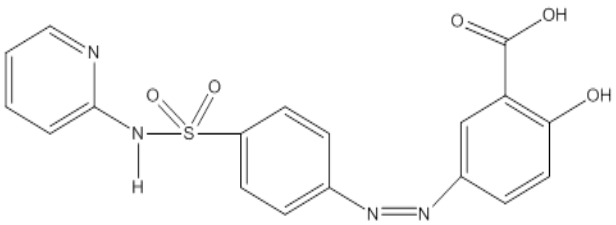
Sulfamethopyrazine

Sulfadoxine and sulfamethopyrazine both are intermediate acting sulfonamides acting > 1 week because of high plasma protein binding. $t^{1/2}$ is 5-9 days. They attain low plasma concentration but are used in the combination of pyrimethamine in the treatment of malaria.[18]

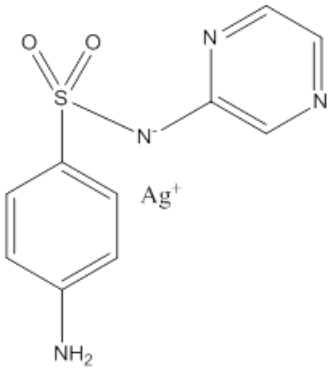
(iv) Special purpose sulfonamides



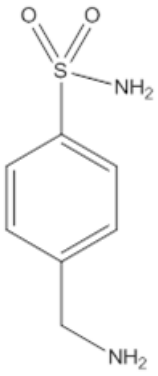
Sulfacetamide sodium



Salfasalazine



Silver Sulfacetamide



Mafenide

Sulfacetamide Sodium: It is highly soluble compound yielding neutral solution. It is used topically for ocular infections due to susceptible bacteria and Chlamydia, including ophthalmia neonatorum caused by Ch. oculogenitalis. After topical instillation it attains high concentrations in anterior segment and aqueous humour.[19]

Sulfasalazine: It is also called salicylazosulfapyridine which is a compound of 5-aminosalicylic acid (5-ASA) with sulfapyridine linked through an azo bond and has a specific therapeutic effect in inflammatory bowel disease (IBD). It is also used in ulcerative colitis and rheumatoid arthritis.[20]

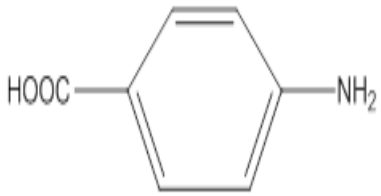
Silver Sulfacetamide: It is used topically as 1% cream, it is active against a large number of bacteria and fungi, even those resistant to other sulfonamides, e.g. Pseudomonas. It slowly releases silver ions which appear to be largely responsible for the antimicrobial action. It is considered to be the most effective drug for preventing infection of burnt surfaces and chronic ulcers and is well tolerated.[21]

Mafenide: It is used topically that inhibits a variety of gram -positive and gram- negative bacteria. It is active in the presence of pus and against Pseudomonas, clostridia. It has been mainly employed for burn dressing to prevent infection.[22]

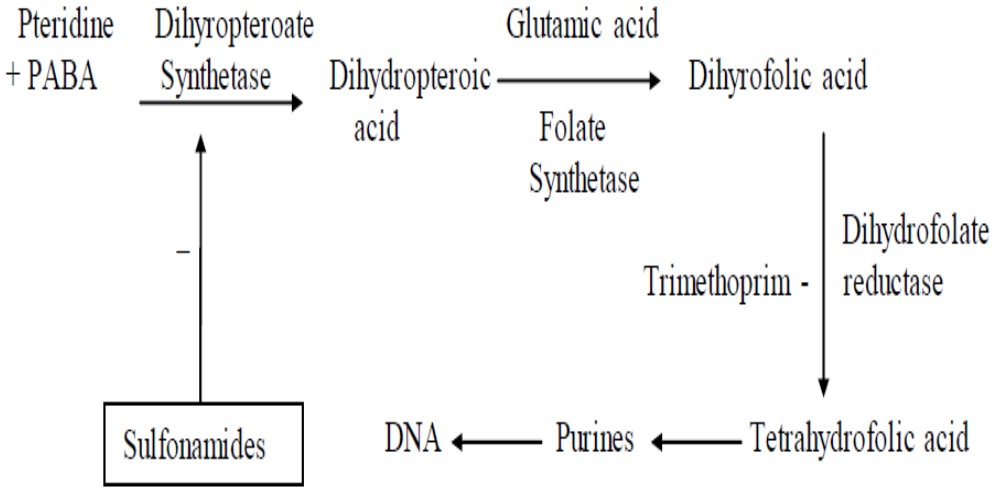
PHARMACOLOGICAL ACTIVITIES

1. ANTIMICROBIAL ACTIVITY

Antimicrobial activities of the sulfonamides depend on substituent and their position in the benzene ring. Sulfonamides are bacteriostatic in nature. Bacteria synthesize their own folic acid with PABA (Para amino benzoic acid) is essential for the synthesis of RNA and DNA. Sulfonamides being structural analogue of PABA inhibit bacterial folate synthetase so that folic acid is not formed preventing bacterial growth and cell division.[23-25]

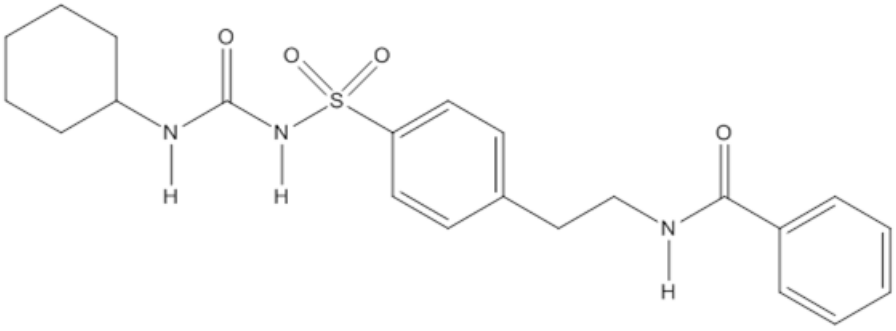


Para amino benzoic acid

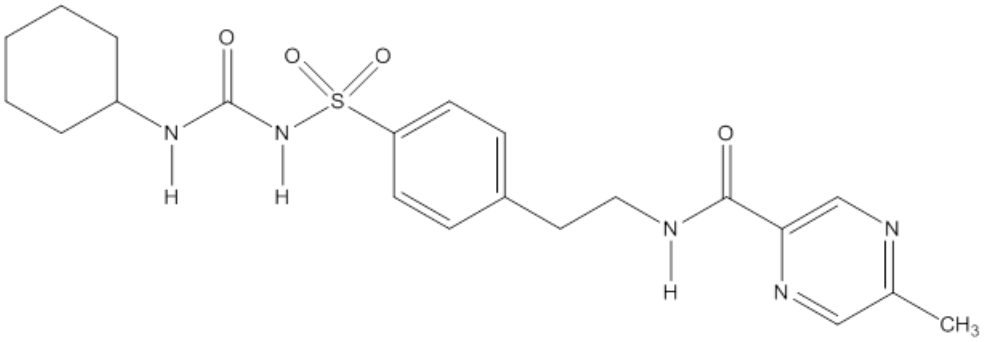


2. ORAL HYPOGLYCAEMIC ACTIVITY

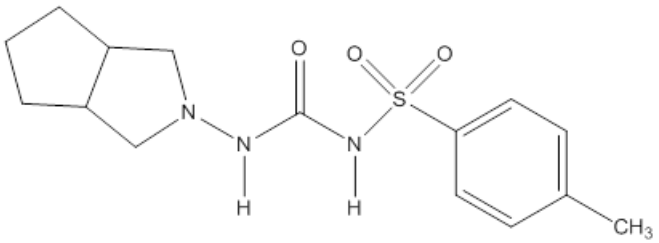
Sulfonyl ureas such as glibendamide, glipizide, glicrazide are used as oral hypoglycemic agents. It is used in the management of diabetes mellitus type-2.



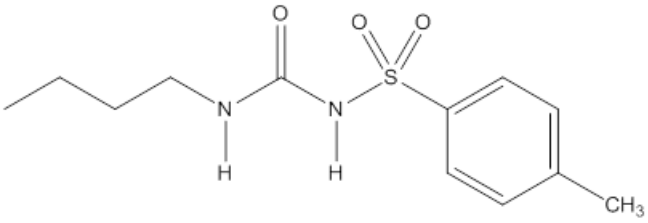
Glibenclamide



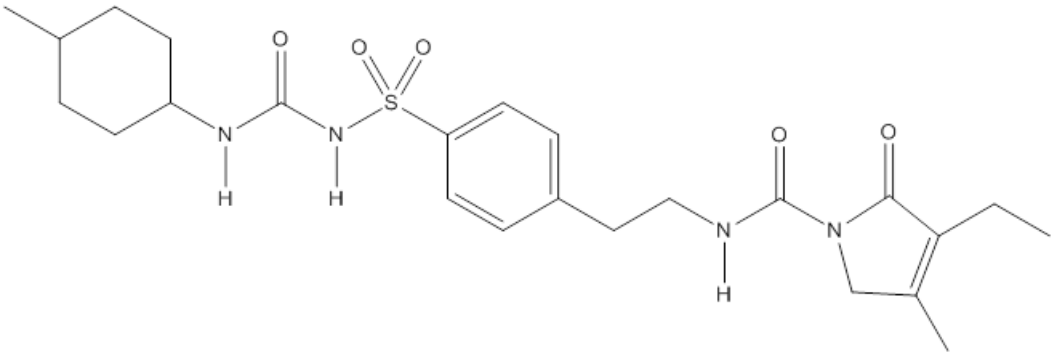
Glipizide



Gliclazide



Tolbutamide

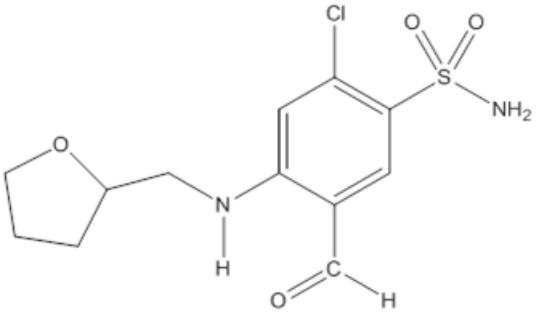


Glimepiride

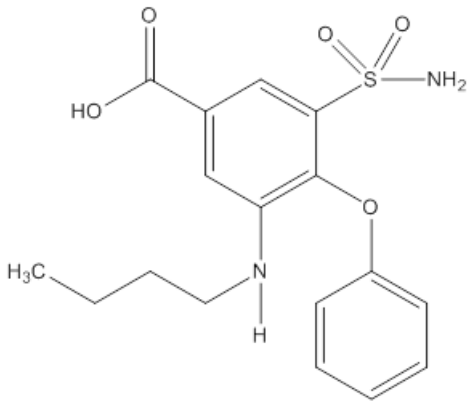
It is used in the management of diabetes mellitus type-2. The sulfonyl ureas bind to sulfonyl urea receptor (SUR1) and form a subunit of ATP sensitive K^+ channels in the membrane of pancreatic β cells, blocking the outward flow of K^+ ion resulting in the high intracellular K^+ concentration. It causes partial depolarization of membrane which activates the Ca^{++} channels. The Ca^{++} ion promotes fusion of insulin containing intracellular granules with the plasma membrane which results in exocytotic release of insulin.[26]

3. DIURETIC ACTIVITY

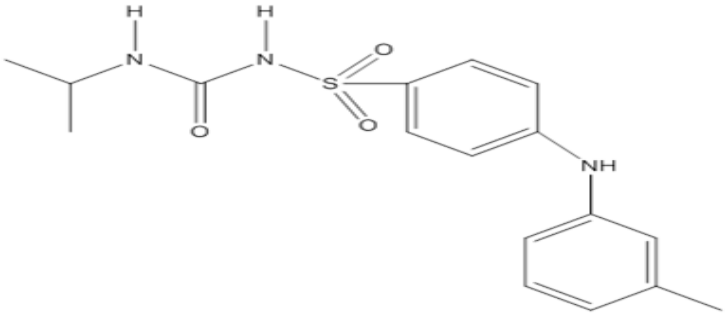
Sulfonamides that are used as diuretics are loop diuretics such as furosemide, bumetanide and torosemide are thiazide diuretics such as chlorothiazide.



Furosemide

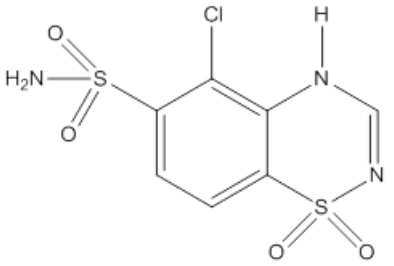


Bumetanide

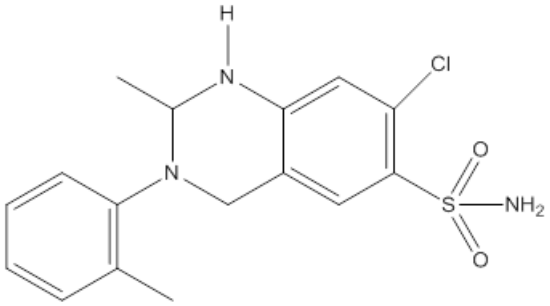


Torosemide

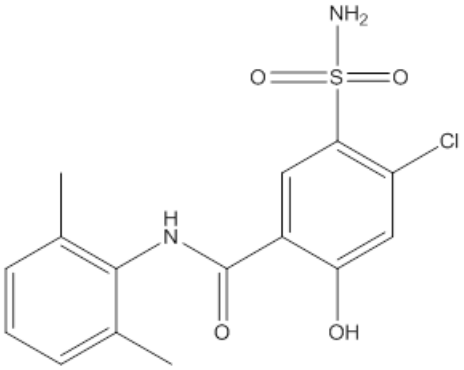
Loop diuretics such as furosemide bumetanide and torosemide inhibits $Na^{+}/K^{+}/2Cl^{-}$ symporter in the thick ascending limb (TAL) of loop of henle.[27]



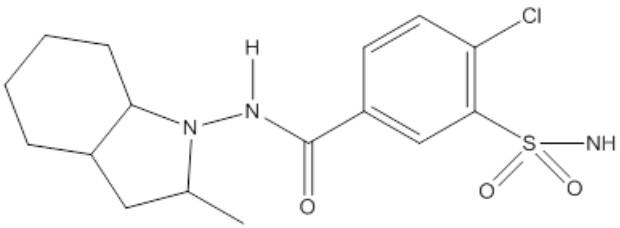
Chlorthiazide



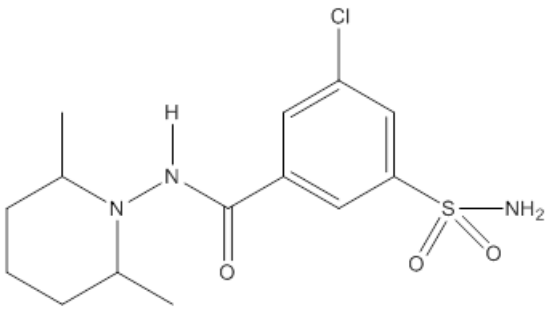
Metolazone



Xipamide



Indapamide



Clopamide

Thiazide diuretics such as chlorthiazide, metolazone, xipamide, indipamide and clopamide inhibits sodium chloride ion in the distal tubule.[28]

CONCLUSION

Sulfonamide nucleus is important in the modern medicinal chemistry research. Various new drug developments in sulfonamide derivatives show better effect and less toxicity which offers better pharmacodynamic characteristics. The new classes of reviewed substituted sulfonamides have a wide variety of biological activities. This article main object is to review the work done, chemistry and pharmacological activities of sulfonamide derivatives during past years. 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.

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