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# A REVIEW: BIOLOGICAL SIGNIFICANCE OF SULFONAMIDES

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## ABSTRACT

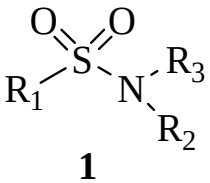
Sulfonamide drugs were the first antibiotics to be used systemically, and paved the way for the antibiotic revolution in medicine. Sulfonamide derivatives are well known pharmaceutical agents since this group has been the main functional part of the most of the drug structures due to stability and tolerance in human beings. Sulphonamides possess various types of pharmacological activities such as antibacterial, diuretic, antithyroid, anti-inflammatory, antitumor, carbonic anhydrase inhibitors, antiglaucoma, antidepressant, antihypertensive, cyclooxygenase inhibitors, that act by competing with tissue factors such as *p*-aminobenzoic acid. They have a wide range of activity. They are effective against some protozoa, including *Toxoplasma* and Coccidia. Sulphonamides diffuse well into body tissues. They are partly inactivated in the liver. The acetylated derivatives are relatively insoluble in acid urine and can precipitate in renal tubules, leading to crystalluria and renal failure. Rabbits excrete alkaline urine and are therefore less likely to develop crystalluria and subsequent renal damage as a result of sulphonamide therapy. However, kidney function is a consideration when selecting any therapeutic agent, including sulphonamides and good hydration should be maintained.

**KEYWORDS:** Antibacterial, Antithyroid, Anti- inflammatory, Antileishmanial, Antimalarial, Antiepileptic, Protease inhibitors, Antitumor, Carbonic anhydrase inhibitors, Antiglaucoma, Antidepressant, Antihypertensive, Cyclooxygenase inhibitors.

## GENERAL INTRODUCTION

Sulfonamide or Sulphonamide **(1),** 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.[1] They are first used as

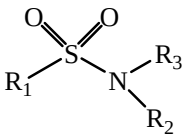
antibacterial/antibiotic agents, but their applications have been extended to treat other diseases. They possess various types of pharmacological activites such as antibacterial,[2] antithyroid,[3] anti-inflammatory,[4] antidepressant,[5] diuretic,[6] protease inhibitors.[7]



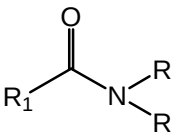
**1**

**Chemistry of sulfonamide nucleus**

Sulfonamides **(1),** are synthetic derivatives of sulfanilamide. Sulfonamides are amide **(2),** analogs in which the carbonyl moiety is replaced with an Isosteric $SO_2$ group.[8]

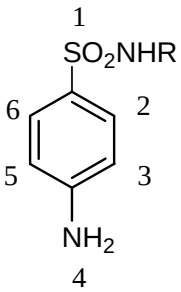


**1**



**2**

Structurally, sulfonamides **(3),** are close to *p*-aminobenzoic acid[9] (PABA) **(4)**.



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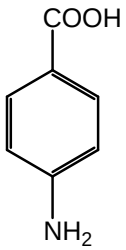
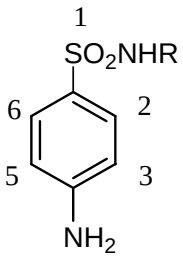


**4**

Chemically sulfa drugs are amphoteric. They behave as weak organic acid with pKa 4.79 to 8.56. Though they are weakly soluble in water, their solubility is increased at alkaline pH. Sodium salts are however easily soluble in water. Systemic sulfa drugs are evolved by substitution at $N^1$ position whereas gut active sulfa drugs are produced by substituting $N^4$ position. By substitution at $N^1$ and $N^4$ positions number of compounds are synthesized. The lipophilicity of the $N^1$ group has the largest effect on protein binding and, generally, the more lipid soluble a sulfonamide is, the more of it will be protein bound.[8]

**Sulfonamide- A useful pharmacophore**

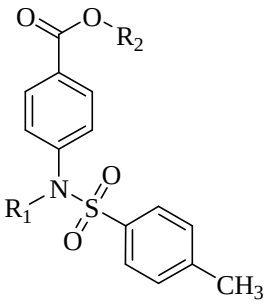
Sulfonamide (3), derivatives are well known pharmaceutical agents since this group has been the main functional part of the most of the drug structures due to stability and tolerance in human beings.[12] These are used in urinary tract infections, meningitis, streptococcal pharyngitis, bacillary dysentery, trachoma, chancroid, malaria, toxoplasmosis, nocardiasis, and conjucnctivis.[13-15] Sulfonamides have a number of biological activities such as antifungal, antibacterial,[16] anti-inflammatory, antitumor,[17] antihypertensive,[18] antviral,[19] anidiabetic, antimicrobial,[20,21] antimalarial, antileishmanial,[22] and cyclooxygenase inhibitor,[23] phospodiesterase-5 inhibitors.[24]




**3**

**Sulfonamide- A useful pharmacophore as anti-inflammatory agent**

New **4-(Tolurene-4-sulfonylamino)-benzoicacids (5)(a-e),** derivatives are investigated against lipooxygenase enzyme and some of these compounds shows good lipooxygenase inhibitory activities.[25]

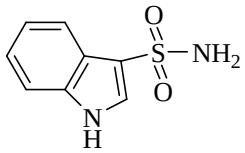



**5**

| Compd no. | $R_1$ | $R_2$ |
|---|---|---|
| **5 a** | $C_4H_9$ | H |
| **5 b** | $C_5H_{11}$ | H |
| **5 c** | $CH_2$-$C_6H_5$ | H |
| **5 d** | $COC_6H_5$ | H |
| **5 e** | $CH_2CH{=}CH(CH_3)_2$ | H |

**Sulfonamide- A useful pharmacophore as antiviral agent**

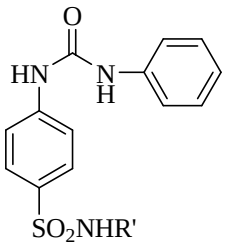
**Indole-3 sulfonamides (6),** are potent HIV non nucleoside reverse transcriptase inhibitors (NNRTIs).[26]



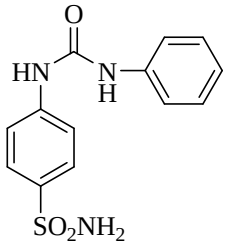
**6**

**Sulfonamide- A useful pharmacophore as antidiabetic agent**

A novel series of **Benzenesulfonamide derivatives (7)(a-b),** are synthesized and evaluated for their antimicrobial and antidiabetic activites. These compound possess marked hypoglycemic activity. The potency of these compounds is more than that of phenformin.[27]



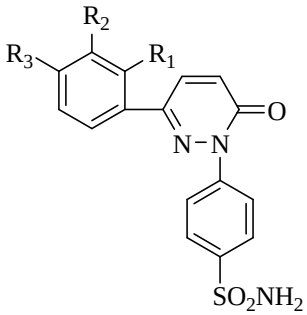
**7 a**



**7 b**

**Sulfonamide- A useful pharmacophore as anticancer agent**

A series of some novel **6-Aryl-2-(*p*-sulfamyl)-pyridazin-3(2*H*)-ones (8)(a-h),** and these derivatives exhibit anticancer activity towards human cancer cell lines.[28]

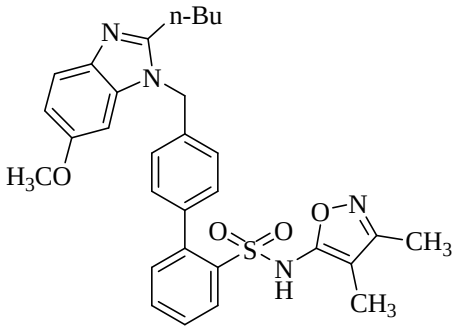


**8**

| Compd no. | $R_1$ | $R_2$ | $R_3$ | Compd no. | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|---|---|---|---|
| **a** | H | H | H | **b** | H | H | Cl |
| **c** | H | H | $CH_3$ | **d** | H | H | $CH_3O$ |
| **e** | H | $CH_3$ | Cl | **f** | $CH_3$ | H | $CH_3$ |
| **g** | H | H | $C_2H_5$ | **h** | H | H | Biphenyl |

**Sulfonamide- A useful pharmacophore as antihypertensive agent**

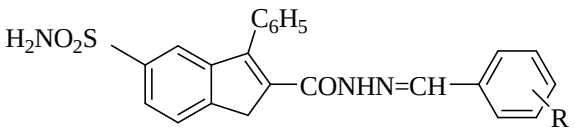
A series of **4'-[(Benzimidazole-1-yl)methyl]-2-sulfonamide (9),** antagonizes both AngII $AT_1$ and endothelin $ET_a$ receptors and are more potent than losartan.[29]




**9**

**Sulfonamide- A useful pharmacophore as antidepressant agent**

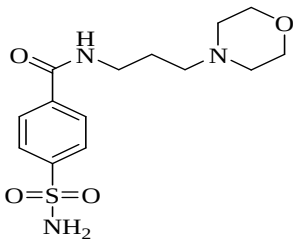
**3-Phenyl-5-sulfonamidoindole derivatives (10-14),** are evaluated for their antidepressant activity by acting as MAO inhibiting agent.[30]



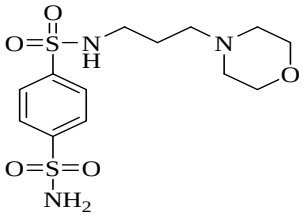

| Compd no. | R | Compd no. | R |
|---|---|---|---|
| **10** | H | **13** | 4-$NO_2$ |
| **11** | 4-$CH_3$ | **14** | 3,4-$OCH_2O$ |
| **12** | - | | |

**Sulfonamide- A useful pharmacophore as antiglaucoma agent**

**4-Sulfamoyl-*N*-(3-morpholinopropyl)benzamide (15), *N*-(morpholinopropyl) benzene-1,4-bis(sulfonamide) (16),** are new aromatic sulfonamide with antiglaucomatic activity.[31]



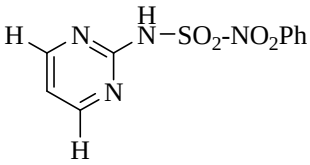
**15**



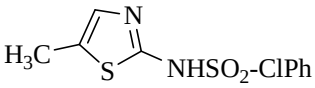
**16**

**Sulfonamide- A useful pharmacophore as antileishmanial agent**

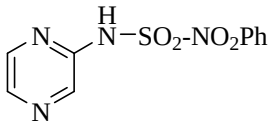
A series of ***N*-benzenesulfonamides of amine substituted aromatic rings,** named **4-Nitro-*N*-pyrimidin-2-yl-benzenesulfonamide (17), 4-Chloro-*N*-5-methyl-thizol-2-yl-benzenesulfonamide (18), 4-Nitro-*N*-pyrazin-2-yl-benzenesulfonamide (19),** are tested against *Leishmania sp.* and *Trypanosome cruzi*.[32]



**17**



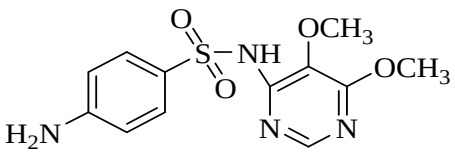
**18**



**19**

**Sulfonamide- A useful pharmacophore as antimalarial agent**

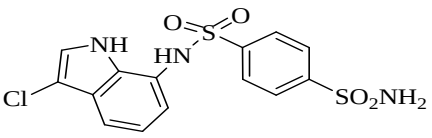
**Sulfadoxine (20),** competitively inhibits dihydropteroate synthase, interfering with folate synthesis. It acts by increasing oxygen in blood**.** It is used in combination with pyrimethamine for treatment of Chloroquinine resistant falciparum malaria.[33]



**20**

**Sulfonamide- A useful pharmacophore as carbonic anhydrase inhibitors**

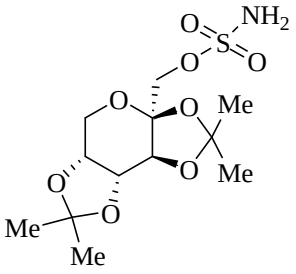
**E7070 [*N*-(3-chloro-7-inolyl)-1,4-benzenedisulfonamide] (21),** is an anticancer drug. But this compound also act as a potent carbonic anhydrase (CA) inhibitors.[34]



**21**

**Sulfonamide- A useful pharmacophore as antiepileptic agent**

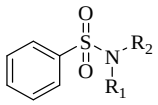
**Topiramate (22),** a sulfamate derivative used as antiepileptic agent.[35]



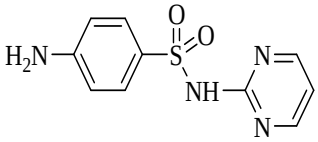
**22**

**Sulfonamide- A useful pharmacophore as antibacterial agent**

**Benzenesulphonicacid-1-methylhydrazide (23), *N*-(3-amino-2-hydroxypropyl) benzenesulfonamides (24),** and ***N*-(2-hydroxyethyl)benzenesulfonamide (25),** have been evaluated for their antibacterial activity. They are active against both gram negative bacteria *P. fluorescens, K. pneumonia, E. coli, P. aeruginosa* and gram positive bacteria *S. aureus, B. cereus, E. aerogens* and also posses antifungal activity against *C. albicans.*[36] Sulfadiazine **(26),** as antibacterial sulfonamide used for many decades. It eliminates bacteria that causes infections by stopping the production of folate inside the bacterial cell. It is commonly used in urinary tract infections (UTIs).[10]



| Compd no. | $R_1$ | $R_2$ |
|---|---|---|
| **23** | $NH_2$ | $CH_3$ |
| **24** | H | $CH_2CH_2OH$ |
| **25** | H | $CH_2CH(OH)CH_2NH_2$ |

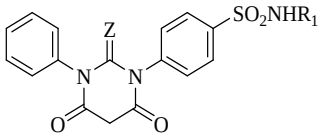


26

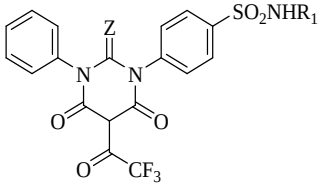
**Sulfonamide- A useful pharmacophore as antibacterial and antifungal agent**

A novel series of **Benzenesulfonamide derivatives of barbituric and thiobarbituric acids (27)(a-b), (28)(a-b), (29)(a-b), (30)(a-b), (31)(a-b),** are tested for antimicrobial and

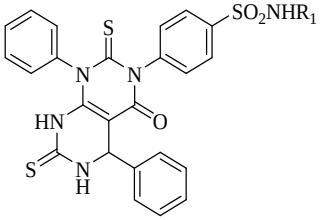
antidiabetic activity. These compounds show better activity profile against gram +ve bacteria (*S. aureus, B. subtillis)* rather than gram –ve strains *(E. coli, P. aeruginosa).* These compounds are able to inhibit growth of two fungal strains *C. albicans, A. niger*.[27]



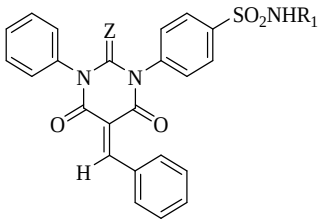
**27 a = Z = S**
**27 b = Z = O**



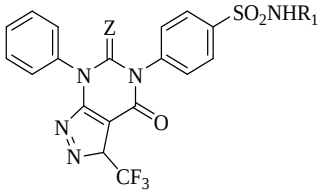
**28 a = Z = S**
**28 a = Z = O**



**29 a = Z = S**
**29 b = Z = O**



**30a = Z = O**
**30b = Z = S**



**31a = Z = O**
**31b = Z = S**

**ACKNOWLDEGEMENT**

I bow my work in the feet of ***"GURU GRANTH SAHIB JI"*** that was with me and led me to actualization of this research work. I am also grateful to all those who directly or indirectly contributed to make my task easier during the whole research work**.**

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