PDEAS International Journal of Research in Ayurved & Allied Sciences
Volume 2 Issue 1 ; 29th February 2020

PDEAS International Journal of Research in Ayurved & Allied Sciences

Review Article

ANTIMICROBIAL ACTIVITY OF VARIOUS SULFONE DERIVATIVES: A REVIEW

Jayashri R. Jagtap[1,*], Pooja A. Petkar[2], Pranali A. Jadhav[3], Meenakshi N. Deodhar[4], Rajashree S. Chavan[5]
Department of Chemistry
PDEA's Seth Govind Raghunath Sable College of Pharmacy, Saswad, Pune, Maharashtra, India-412301

Article Received on: 31/01/2020; Accepted on: 13/02/2020.
***Corresponding Author:** *Mrs. Jayashri R. Jagtap*, **E-mail:** jayarjagtap@rediffmail.com

ABSTRACT:
Sulfones are the organo sulfur compounds containing sulfonyl functional group attached to two carbon atoms. Sulfone derivatives have wide range of biological and pharmacological properties. Due to the wide range of applications chemistry of sulfones has been explored. Most of the sulfone analogues are studied for their antimicrobial activity. The use of drugs containing sulfones extends from the treatment of chronic and acute Gram-positive and Gram - negative bacterial infections, through malaria, trachoma, leprosy, dermatitis herpetiformis, *pneumocystis carinii pneumonia* (PCP), nocardiosis, coccidiosis to toxoplasmosis. The present review includes rigorous literature survey on the sulfone derivatives as an antimicrobial agent and offer prospective in the development of new sulfone derivative as antimicrobial agent.

KEY WORDS: Sulfone, Antimicrobial, Antibacterial.

INTRODUCTION:

Sulfone is a chemical compound containing sulfonyl group having general structural formula R-S(O_2)-R', where R and R' can be hydrocarbon substituents' including cyclic ones, or any combination. They are used as synthetic intermediates for the production of variety of chemically and biologically active molecules. In addition to antimicrobial activity sulfones are also reported to possess many therapeutic activities, including cysteine protease inhibitor, anti-inflammatory activity, anti-HIV, anti-proliferative, anti-cancer, protein phosphatase methylesterase-1 inhibitors, thyroid receptor antagonist, 11β-hydroxy steroid dehydrogenase type -1 inhibitors, γ-secretase inhibitors, β-lactamase inhibitors and gelatinase inhibitors, etc[1,2].

Mode of action:

Like sulfonamides, the sulfones, are structural analogues of para-aminobenzoic acid that interfere with folic acid metabolism and act as bacteriostatic. This is accomplished by acting as competitive inhibitors of dihydropteroate synthetase. They have broad range of activity against Gram +ve and Gram -ve cocci and bacilli, mycobacteria, some viruses and protozoa such as *Streptococcus pyogenes, Staphylococcus aureus, Bacillus anthracis, Mycobacterium tuberculosis, Neisseria meningitidis, Haemophilus influenzea, Plasmodium malariae, Actinomyces bovis, Escherichia coli, Lymphocytic choriomeningitis virus*, etc.[3] Dapsone , also called as 4, 4'-diaminodiphenylsulfone (DDS), is a prototype compound of this class mainly used as antibacterial antibiotic for the treatment of leprosy. It is also used for the treatment of *pneumocystis pneumonia* (PCP), toxoplasmosis, acne, *dermatitis herpetiformis* and as a powerful antimicrobial agent.[4]

Numerous derivatives of sulfones have been synthesized to improve upon its activity. A mechanism for the antimalarial action of DDS involving inhibition of glucose utilisation by the intraerythrocytic parasite; this inhibition was shown to be antagonized by raising glucose concentration of the medium.[5]

Structure activity relationship:

As like sulfonamides, a *p*-aminobenzene-sulfonyl moiety as such, or carrying groups, which can generate it *in vivo* seems important for activity. The 4, 4' – diaminodiphenyl-sulfoxide showed significant antileprotic activity during clinical trial but later was found to be more toxic. Its activity possibly due to its *in vivo* oxidation to DDS, sulfoxide and its N-methyl derivatives shown to undergo *in vivo* oxidation to sulfones.

Compounds with replacement of one benzene ring by a 2- or 4-pyridyl, 2- or 5-thiazolyl or 8-quinolyl moiety, preferably carrying an amino group, retains significant activity, but replacement of both benzene rings by these heterocycles results in inactive compounds. None of these derivatives of sulfones with mono -heterocyclic substitution, however, offer any distinct advantages over DDS. A number of mono-N-alkyl sulfones with lower alkyl substituents have been shown to possess significant antitubercular activity in guinea-pigs and mice.[6]

Antimicrobial activity of sulfones:

Wadher *et al*[7] reported the synthesis of Schiff's base (Fig.-1) and 2-azetidinones (Fig.-2) of 4, 4'–diaminodiphenylsulfone (Dapsone) (Fig-1) and these compounds were evaluated for their *in vitro* antimicrobial activity. against *E. coli* and *Staphylococcus aureus* and antifungal activity against *Candida albicans* and *Aspergilus niger*. using reference standard ciprofloxacin and fluconazole.

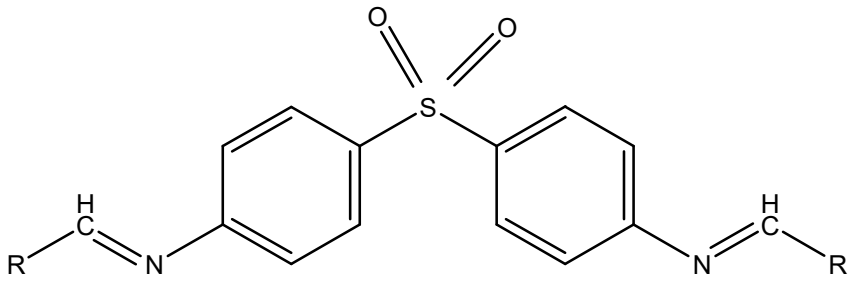


Fig.-1

R= $-C_6H_4F$, $-C_6H_4-OCH_3$, $-C_6H_4Cl$

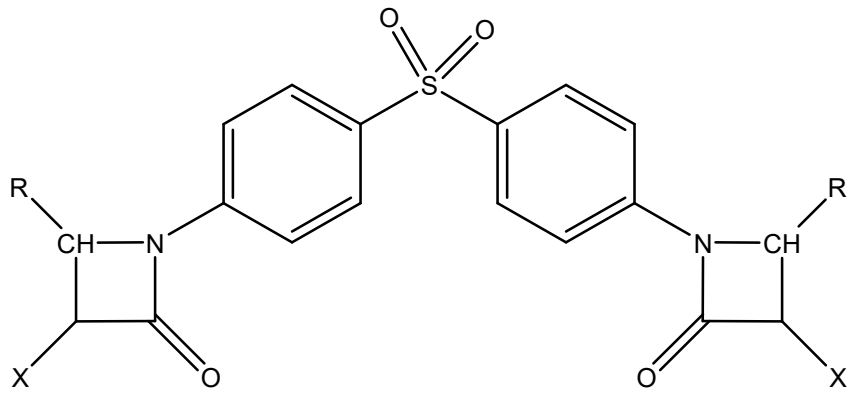
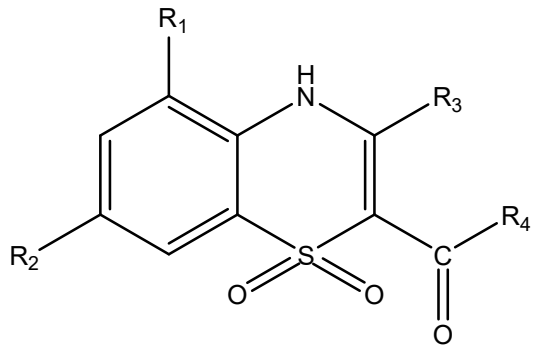


Fig.-2

R= $-C_6H_4F$, $-C_6H_4-OCH_3$, $-C_6H_4Cl$, X=Cl

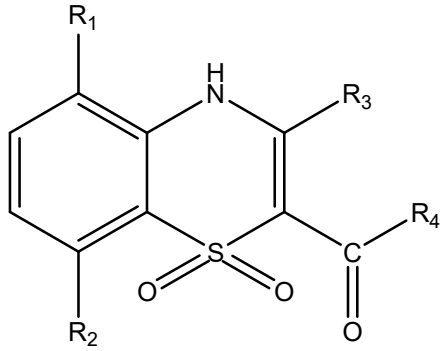
Gautam *et al*[8] synthesized a series of sulfone derivatives of 4*H*-1,4-benzothiazines (Fig.-3) by condensation followed by oxidative cyclization of substituted 2-aminobenzenethiols with compounds containing active methylene groups and evaluated for their *in vitro* antimicrobial activity against *Micromonospora sp.* MTCC 3296 and *Zymomonas mobilis* MTCC 88 and against fungi *Aspergillus solani* MTCC 2101 and *Fusarium culmorum* MTCC 349 and few synthesized sulfone compounds showed promising results as compared to parent compound.



R_1= CH_3, H, R_2= CH_3, C_4H_9, F, R_3= C_3H_7, CH_3, C_2H_5,
R_4= -OC_2H_5, *p*-C_6H_4-Br, -C_2H_5, -$OCH(CH_3)_2$

Fig.-3

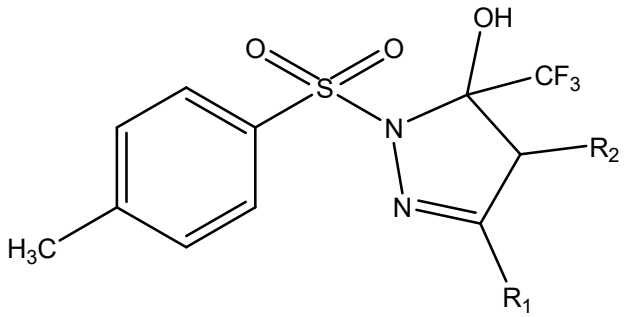
Khandelwal et al[9] synthesized substituted 8-chloro- 5- methoxy/ 8-chloro-4H-1,4-benzothiazines, their sulfones (Fig.-4) and ex-amined for antibacterialactivity against the four strains of bacteria Gram−ve bacteria (*E.coli*, *Pseudomonas aeruginosa)* and Gram+ve bacteria (*Bacillus subtilis*, *Staphylococcus aureus*) and antifungal activity against the two s trains of fungi *C. albicans* and *A. niger*. The sulfones shown significant antibacterial and antifungal activities as compared to their benzothiazines and this activity possibly due to electron withdrawing effect of oxygen.



R_1= OCH_3, Cl, R_2= Cl, H, R_3= CF_3, C_3H_7, C_2H_5,
R_4= CF_3, OC_2H_5, OCH_3, C_2H_5

Fig.-4

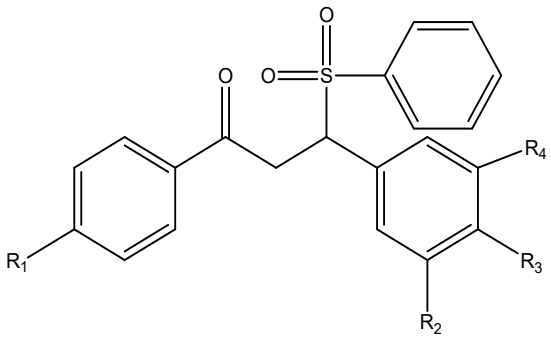
Synthesis of series of trifluoromethyl-containing pyrazolinyl (*p*-tolyl) sulfones (Fig.-5) as a promising antimicrobial agents was achieved by H. G. Bonacorso *et al*[10]. The pyrazolinyl sulfone possessing 4-fluorophenyl and a trifluoromethyl substituent linked at the carbon-3 and -5 of the pyrazoline ring (2h), respectively exhibited best activity against strains of *Staphylococcus aureus* ATCC 25923.



R1= H, Me, Ph, 4-MePh, 4-OmePh, 4-BrPh, 4-ClPh, 4-FPh, R2= H, Ph

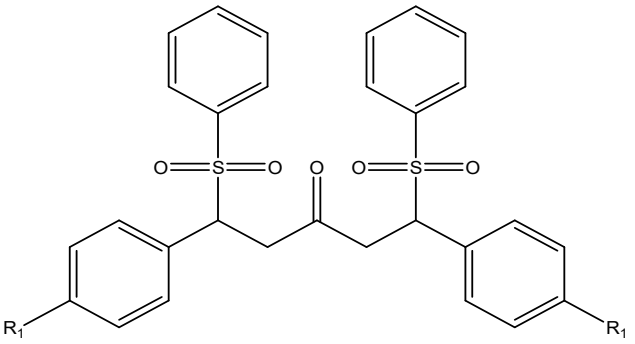
Fig.-5

N. K. Konduru *et al*[11] reported synthesis and antibacterial and antifungal evaluation of some chalcone based sulfones (Fig.-6) and bisulfones (Fig.-7). Antimicrobial activity of sulfones and bisulfones were assessed by microdilution method against yeast (*Aspergillus niger* and *Candida albicans*), Gram-positive bacteria (*Bacillus subtilis*, and *Staphylococcus aureus*) and Gram-negative bacteria (*Pseudomonas aeruginosa* and *Salmonella typhimurium*).



R_1= H, Cl, Br, R_2= H, OMe, NO_2, R_3= H, Cl, OMe, R_4= H, OMe

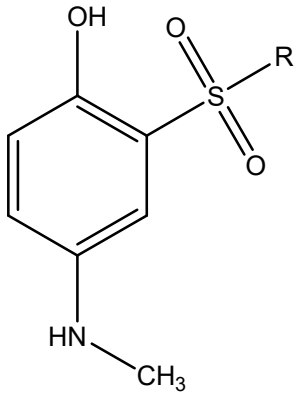
Fig.- 6



R_1= H, Cl, Me, OMe

Fig.-7

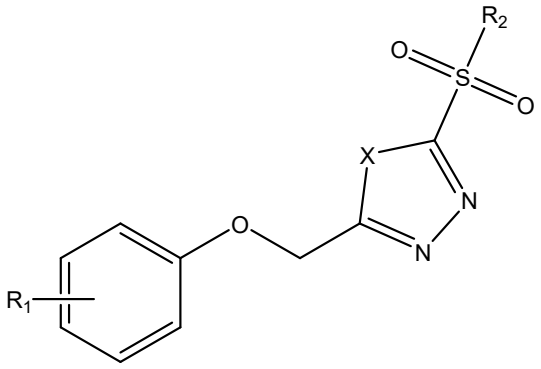
D. Nematollahi *et al*[12] synthesized and perfomed antibacterial activity of sulfone derivatives of *p*-methylaminophenol (Fig.-8). Against Gram +ve (*Staphylococcus aureus*) and Gram-ve (*Escherichia coli*) strains. The compounds were tested by Kirby-bauer disk diffusion method. They found that the antimicrobial activity varied in the order R= CH_3> *p*- tolyl> phenyl > *p*-ClPh.



R= Me, p-ClPh, p- tolyl, phenyl

Fig.- 8

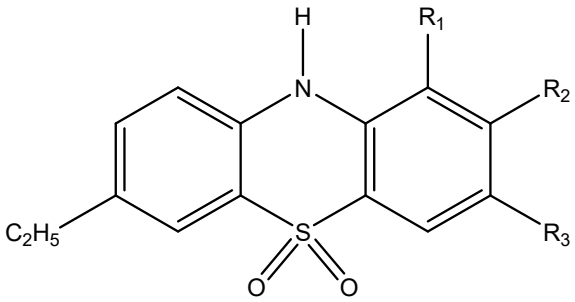
Synthesis and SAR studies of series of sulfone derivatives containing 2-Aroxymethyl-1,3,4-Oxadiazole/ Thiadiazole moiety (Fig.-9) was done by Shihu Su *et* al[13]. The antibacterial activities of all synthesized compounds were evaluated against Pathogens *X. oryzae, R. solanacearum* and *X.* axonopodis via the turbidimeter tests. All the sulfone analogs exhibited remarkably higher *in vitro* bactericidal activity and few compounds showed excellent *in vivo* inhibitory effect as compared to Bismerthiazol, Bismerthiazol, one of the major bactericides for the control of rice bacterial leaf blight. Structure-Activity Relationship studies revealed that, the derivatives of 1,3,4-oxadiazole sulfones showed more potent anti-bacterial activity as compared to their 1,3,4-thiadiazole derivatives.



R_1= H, 4-F, 4-Cl, 4- Br, 2,4- diCl, 2-CH_3-4-Cl, R_2= CH_3, CH_2CH_3, CH_2Ph
X= O, S

Fig.-9

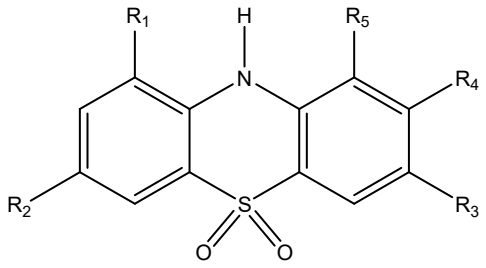
Gautam *et al*[14] synthesized a series of novel fluorinated 7-ethyl-10*H*-phenothiazines via Smiles rearrangement and their sulfones on refluxing phenothiazines with 30% H_2O_2 in glacial acetic acid (Fig.-10). The antimicrobial activity of newly synthesized compounds were screened by the liquid dilution method using Gram +ve (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram -ve (*Escherichia coli* and *Pseudomonas aeruginosa*) strains. Among them, few of compounds showed good antibacterial and antifungal activities. They concluded that the activity was mainly due to electron withdrawing effect of oxygen in sulfones.



R_1= NO_2, CF_3, H, R_2= H, Cl, R_3= CF_3, NO_2, F, CF_3

Fig. 10

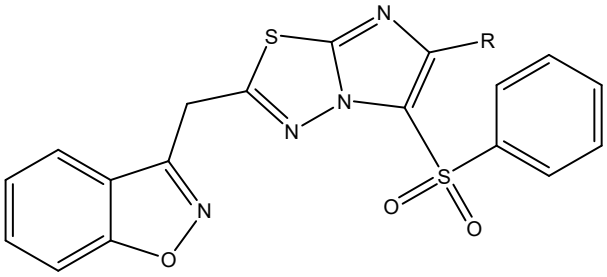
Dixit *et al*[15] reported synthesis of bioactive fluorinated 10*H*-Phenothiazines and their sulfone derivatives (Fig.-11). Antibacterial activity of newly synthesized compounds was estimated by Kerby Bauer procedure against *Staphylococcus aureus* and *Pseudomonas flueroscence* strain using Streptomycin as a standard drug. Antifungal activity was determined against *Aspergillus flavus* and *Aspergillus niger* using Flukanozole as a standard drug. The results showed that all synthesized compounds showed moderate to good activity against the microbes.



R_1=H, F, $(CH_3)_2CH$, R_2= H, $(CH_3)_2CH$, R_3= H, NO_2, R_4= H, F, R_5= H, F

Fig.-11

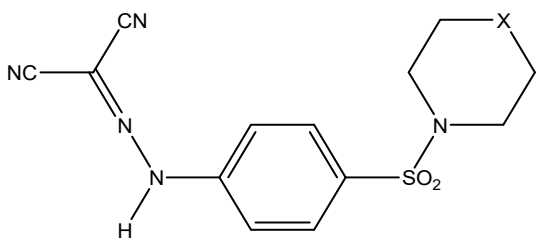
A various sulfides and sulfones of methylene-bridged benzisoxazolylimidazo[2,1-b][1,3,4]thiadiazoles (Fig.-12) have been synthesized and evaluated for their antibacterial and antifungal activity by Belavagi *et al*[16]. The sulfide derivatives were obtained by the nucleophilic substitution of bromo derivatives with thiophenols, and sulfone derivatives were obtained by the oxidation of sulfides.These novel sulfide and sulfone derivatives were screened for their antibacterial and antifungal activities against various microorganisms using ampicillin and clotrimazole as a reference standard respectively.



R= Ph, *p*-Cl-Ph, *p*- NO_2-Ph, *p*- Br-Ph, *p*-OMe-Ph,3-Coumarinyl

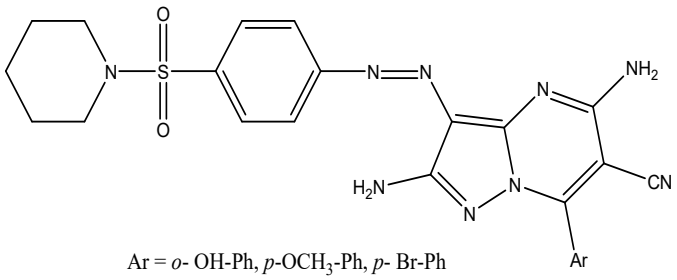
Fig.-12

Saleh *et al*[17] reported synthesis of hydrazones of sulfones by coupling of diazonium salts of sulfones with malononitrile (Fig. 13) and pyrazolo[1,5-*a*] pyrimidine containing piperidinyl sulfone moiety by reaction of aminopyrazole with chalcones, arylidenemalononitriles (Fig. 14). *In vitro* antibacterial activities of synthesized sulfones were estimated against Gram +ve (*Staphylococcus aureus* and *Bacillus cereus*) and Gram -ve (*Serratia marcesens* and *Proteus merabitis*) bacteria by the filter paper disk method. Most of the synthesized compounds exhibited antibacterial activity towards all the microorganisms used.



X= CH_2, O

Fig.-13



Ar = *o*- OH-Ph, *p*-OCH_3-Ph, *p*- Br-Ph

Fig.-14

Padmavathi *et al*[18] synthesized series of sulfone linked bisheterocycles (Fig.-15) and screened for antimicrobial activity against Gram +ve (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram -ve (*Escherichia coli* and *Klebsiella pneumoniae*) using chloramphenicol as a reference drug. Among them, compounds (Fig. 15 and 16) exhibited greater antimicrobial activity.

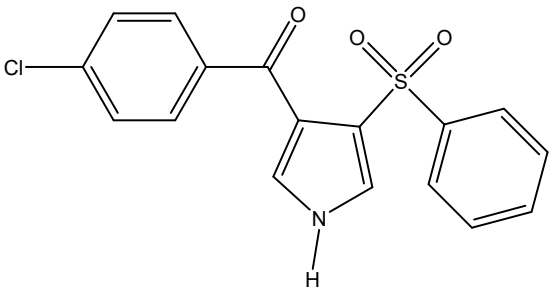


Fig.- 15

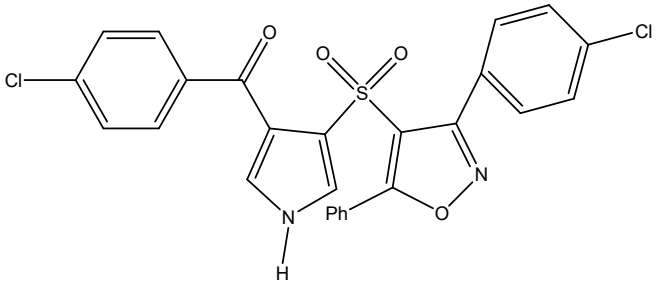


Fig.-16

CONCLUSION:

Sulfones are important class of organo sulfur compounds that possesses a variety of biological actions. In this review, we have summarized antimicrobial activity of various sulfone derivatives along with recent advancement in this field during past two decades. Variety of sulfones have been reported in literature having good antimicrobial activities. We can conclude that this review will help researchers further to design and synthesis new sulfones with promising antimicrobial activities.

REFERENCES:

[1] I. Ahmad, Shagufta. 2015. Sulfones: An important class of organic compounds with diverse biological activities. International Journal of Pharmacy and Pharmaceutical Sciences. 7(3):19-27.

[2] J. Xiang, M. Ipek, V. Suri et al. 2007. β-Keto sulfones as inhibitors of 11β-hydroxysteroid dehydrogenase type I and the mechanism of action. Bioorganic & Medicinal Chemistry. 15(13): 4396-4405.

[3] 4. Corcoran, J.W., Hahn, F.E., Snell, J.F., Arora, K.L; 'Mechanism of Action of Antimicrobial and Antitumor Agents', vol 3, 1975, 668-698.

[4] G. Wozel, C. Blasum. 2014. Dapsone in dermatology and beyond. Archives of dermatological research. 306 (2):103-124.

[5] R. J. Cenedellaand, J. J.Jarrell. 1970. Suggested new mechanisms of antimalarial action for DDS involving inhibition of glucose utilization by the intraerythrocytic parasite. The American Journal of Tropical Medicine and Hygiene. 19, 592-598.

[6] G. A. Ellard. 1996. Absorption, metabolism and excretion of di(*p*-aminophenyl)sulfone (dapsone) and di(*p*-aminophenyl)sulfoxide in man. British Journal of Pharmacology. 26:212-217.

[7] S. J. Wadher, M. P. Puranik, N. A. Karande and P. G. Yeole. 2009. Synthesis and biological evaluation of Schiff base of dapsone and their derivatives as antimicrobial agents. International Journal of Pharm Tech Research. 1(1): 22-33.

[8] N. Gautam, A. K. Bishnoi, A. Guleria, et al. 2013. Synthesis characterization and in vitro antimicrobial assessment of some novel 4*H*-1,4-benzothiazines and their sulfone derivatives. Heterocyclic communications. 19(1): 37-42.

[9] N. Khandelwal, Abhilasha, Naveen Gautam and D. C. Gautam. 2013. An efficient synthesis and biological study of substituted 8-chloro-5-methoxy/8-chloro-4H-1,4-benzothiazines, their sulfones and ribofuranosides. Journal of Chemical sciences. 125(1): 85-93.

[10]H. G. Bonacorso, A. P. Wentz, R. V. Lourega et al. 2006. Trifluoromethyl-containing pyrazolinyl (*p*-tolyl) sulfones: The synthesis and structure of promising antimicrobial agents. Journal of Fluorine Chemistry. 127: 1066-1072.

[11]N. K. Konduru, S. Dey, M. Sajid et al. 2013. Synthesis and antibacterial and antifungal evaluation of some chalcone based sulfones and bisulfones. European Journal of Medicinal Chemistry. 59: 23-30.

[12]D. Nematollahi, S. Khazalpour, M. Ranjbar and S. Momeni. 2017. A green strategy for the synthesis of sulfone derivatives of *p*-methylaminophenol: Kinetic evaluation and antibacterial susceptibility. Scientific reports. 7(4436): 1-11.

[13]S. Shihu, X. Zhou, G. Liao, Q. Puying and J. Linhong. 2017. Synthesis and antibacterial evaluation of new sulfone

derivatives containing 2-aroxymethyl-1,3,4-Oxadiazole/ Thiadiazole moiety. Molecules. 22(1): 64.

[14]N.Gautam, A. Yadav, N. Khandelwal and D. C. Gautam. 2014. Synthesis and evaluation of antimicrobial and anthelmintic activity of novel fluorinated 7-ethyl-10*H*-phenothiazines, their sulfones and ribofuranosides. Journal of Chemical Sciences.126(1): 197-204.

[15]Y. Dixit, R. Dixit, N. Gautam and D. C. Gautam. 2008. Synthesis of bioactive fluorinated 10*H*-phenithiazines and their sulfone derivatives. E-Journal of Chemistry. 5(S1): 1063-1068.

[16]N.S. Belavagi, M. G. Sunagar, R. S. Lamani et al. 2015. Synthesis and antimicrobial activity of novel sulfides and sulfones of methylene-bridged benzisoxazolylimidazo [2,1-b][1,3,4]thiadiazoles. Phosphorus, Sulfur, and Silicon and the Related Elements. 190(10): 1580-1587.

[17]N. M. Saleh, Y. A. Ammar, J.A. Micky, et al. 2004. Novel synthesis and antimicrobial investigation of pyrazolo[1,5-*a*] pyrimidine and pyrazolotriazine containing piperidinyl sulfone moiety. Indian Journal of Chemistry. 43B: 2195-2202.

[18]P. Venkatapuram, R. L. Thunga, C. V. Bhumireddy, M. Konda. 2011. Synthesis and antimicrobial activity of a new class of sulfone linked bisheterocycles. International Journal of Organic Chemistry, 1(3): 78-86.

Cite this article as:

Jayashri R. Jagtap, Pooja A. Petkar, Pranali A. Jadhav, Meenakshi N. Deodhar, Rajashree S. Chavan Antimicrobial activity of various sulfone derivatives: a review , PDEAS Int. J. R. Ayu. & A. Sc., 2(1); Feb 2020, p. 53-60.