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Synthesis, Antibacterial Activity and Preliminary QSAR Studies of Diaryl Sulfones

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ABSTRACT

Sulfones are known to possess various biological activities. Their great potential as bioactive compounds, combined with the easy method of synthesis, make this class a strong candidate for the production of medicines economically. This article deals with the synthesis of a series of ten diaryl sulfones, their antibacterial activity, individually, synergistic antibacterial activity with trimethoprim against *E. coli* and preliminary QSAR studies. The antibacterial activity was performed by *agar diffusion method*, against Gram positive and Gram negative bacteria. Few derivatives exhibited antibacterial activity comparable to or better than the standard, sulphamethoxazole, against Gram negative organisms (*E. coli* and *S. dysentrae*). Sulfones being folic acid inhibitors, their synergistic effect was checked with trimethoprim on *E. coli*. Most of the compounds exhibited synergistic effect with trimethoprim, which was better than the combination of trimethoprim and sulfamethoxazole (1:5). Quantitative structure activity relationships studies were performed by multiple linear regression analysis. The antibacterial activity of sulfones was found to correlate well with their dipole moment and ionization potential.

Keywords: Diaryl sulfones, Antimicrobial activity, Synergistic effect, QSAR

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INTRODUCTION

Chemotherapy is one of the most important tools for the management of diseases since the 19th century. However, emergence and spread of parasites, resistant to almost all the existing drugs, is of great concern. Resistance to antibiotics has led to wide ranging consultation at National and International levels as to how to address this issue. Resistance has become a growing menace to a world that expects to have effective drugs available for every disease. This expectation is no longer being fully met by the marketed anti-infective agents. In addition to attempting to limit the spread of resistance, there is a growing consensus that a cornerstone requirement is the development of new antibiotics to help redress the balance of resistance versus available antibiotics[1]. Therefore, resistance remains an important driving force for antibiotic drug discovery efforts.

As an alternative, a number of combinations of drugs are being recommended and implemented for the treatment of bacterial diseases, but the cost and adequacy of the supply necessitate the need to identify novel agents. Nowadays, about 70 per cent of the bacteria that cause infections in hospitals are resistant to at least one of the drugs most commonly used for the treatment. Few organisms are resistant to all the approved antimicrobials and can only be treated with experimental and potentially toxic drugs[2]. Microbial developments of resistance as well as economic incentives have resulted in research and development in the area of new antimicrobials in order to maintain a pool of effective drugs at all times. The use of combinations of antimicrobial agents is a common practice during clinical therapy. Sulfones possess various valuable biological activities such as antimalarial[3], antileprotic[4], antitubercular[5], insecticidal, ascaricidal, analgesic, hypnotic[6], etc. There are several reasons why combination therapy is used or should be used, but all have intention of increasing efficacy and decreasing resistance. One of the major reasons is the proposed synergistic action between two antimicrobial agents. Studies have shown that bacterial resistance develops more slowly with the combination of the two drugs than with either of the drugs alone [6]. The combination of trimethoprim and sulfonamide has been demonstrated to be synergistic in affecting cell growth. The synergism between sulfonamide and trimethoprim has been attributed to the fact that the drugs inhibit different enzymes in the same biosynthetic pathway[7]. Hence, the present research work is based on the synthesis of diaryl sulfones and screening them for antibacterial activity, individually, and in combination with trimethoprim. The QSAR study was performed to identify the physicochemical parameter/s contributing towards the antibacterial activity of diaryl sulfones.

MATERIALS AND METHODS

Materials

The chemicals were purchased from Aldrich. The melting points of compounds were recorded using Expo-Hitech melting point apparatus. The R_f values from thin layer chromatography (TLC) were determined using silica gel pre-coated plates. Various combinations of solvents were tried to standardize the mobile phase. Compounds were purified by column chromatography and purity was confirmed by reverse phase HPLC. The structures of the synthesized derivatives were characterized from the IR spectra using JASCO FTIR 5300 spectrometer. Potassium bromide pellet method was used to record the IR spectra. The structures of the compounds were confirmed by recording their ^{1}H NMR spectra on VNMRS-300 spectrometer. Dimethyl sulfoxide was used as a solvent and tetramethylsilane was used as the reference standard for recording the NMR spectra.

Methods

Synthesis of diaryl sulfones:

Aromatic substrate (0.05 mol) and aromatic sulfonyl chloride (0.05 mol) were taken in a round bottom flask. Anhydrous aluminium chloride (0.8 g) was added to it slowly with continuous shaking. The reaction mixture was then heated at 90 ºC for 7-8 h **(Scheme 1)**. The reaction was monitored by TLC. After the completion of a reaction, the reaction mixture was cooled and poured into the mixture of water and concentrated HCl. The precipitate obtained was recrystallized from ethanol. For few compounds, instead of precipitate, an oily layer was obtained. In such cases, an oily layer was extracted with diethyl ether. Ether layer was washed with water and passed through anhydrous Na_2SO_4. Ether was then recovered and the solid crude product was recrystallized to get pure, crystalline product. **Table 1** provides the structural details of the synthesized diaryl sulfones. The physical and spectral characterstics of all the compounds are mentioned below.

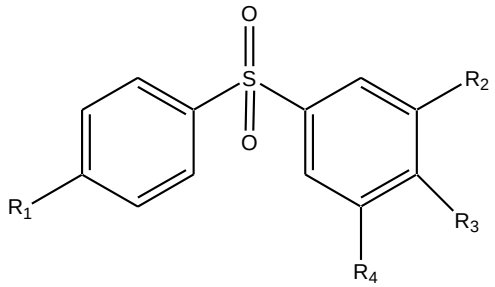


Table 1: Substituents on diarylsulfones

Compounds	R_1	R_2	R_3	R_4
1	H	H	C_2H_5	H
2	CH3	H	C_2H_5	H
3	H	H	Br	H
4	CH3	H	Br	H
5	CH3	CH3	H	CH3
6	H	H	OCH3	H
7	H	H	Cl	Cl
8	CH3	H	Cl	Cl
9	H	H	C_6H_5	H
10	CH_3	H	C_6H_5	H

4-Ethyldiphenyl sulfone (1). Yield 72 %; m.p. 79-85 °C; HPLC purity 97.96 %; IR (cm^{-1}): 2972 (C-H str), 1408, 1446, 1494 (C=C str), 1307, 1166 (O=S=O str); ^{1}H-NMR δ: 7.4-7.8 (m, 9H, Ar), 2.6 (q, 2H, CH_2), 1.1 (t, 3H, CH_3).

4-Ethyl-4'-methyldiphenyl sulfone (2). Yield 74 %; m.p. 106-109 °C; HPLC purity 97.76 %; IR (cm^{-1}): 2970 (C-H str), 1410, 1458, 1491(C=C str), 1304, 1186 (O=S=O str); ^{1}H-NMR δ: 7.78-7.83 (q, 4H, Ar), 7.3-7.4 (q, 4H, Ar), 2.5 (q, 2H, CH_2), 2.3 (s, 3H, CH_3), 1.15 (t, 3H, CH_3).

4-Bromodiphenyl sulfone (3). Yield 80 %; m.p. 94-97 °C; HPLC purity 99.75 %; IR (cm^{-1}): 3063 (C-H str), 1444, 1469, 1572 (C=C str), 1321, 1157 (O=S=O str); ^{1}H-NMR δ: 7.2-7.9 (m, 9H, Ar).

4-Bromo-4'-methyldiphenyl sulfone (4). Yield 86 %; m.p. 129-132 °C; HPLC purity 99.55 %; IR (cm^{-1}): 2949 (C-H str), 1446, 1469, 1572 (C=C str), 1321, 1166 (O=S=O str); ^{1}H-NMR δ: 7.2-7.8 (m, 8H, Ar), 2.4 (s, 3H, CH_3).

3,5,4'-Trimethyldiphenyl sulfone (5). Yield 82 %; m.p. 71-74 °C; HPLC purity 85 %; IR (cm^{-1}): 2970 (C-H str), 1408, 1448, 1493(C=C str), 1313, 1163 (O=S=O str); ^{1}H-NMR δ: (m, 7H, Ar) 7-8, 2.4 (s, 6H, 2 x CH_3), 2.35 (s, 3H, CH_3).

4-Methoxydiphenyl sulfone (6). Yield 71 %; m.p. 75-77 °C; HPLC purity 95.19 %; IR (cm^{-1}): 2947 (C-H str), 1415, 1446, 1466, 1479 (C=C- str), 1315, 1151 (O=S=O str); ^{1}H-NMR δ: 7.2-7.9 (m, 9H, Ar), 3.8 (s, 3H, OCH_3).

3,4-Dichlorodiphenyl sulfone (7). Yield 78 %; mp. 117-120 °C; HPLC purity 97.21 %; IR (cm^{-1}): 3003 (C-H str), 1410, 1450, 1477 (C=C str), 1369, 1138 (O=S=O str); ^{1}H-NMR δ: 7.2-7.7

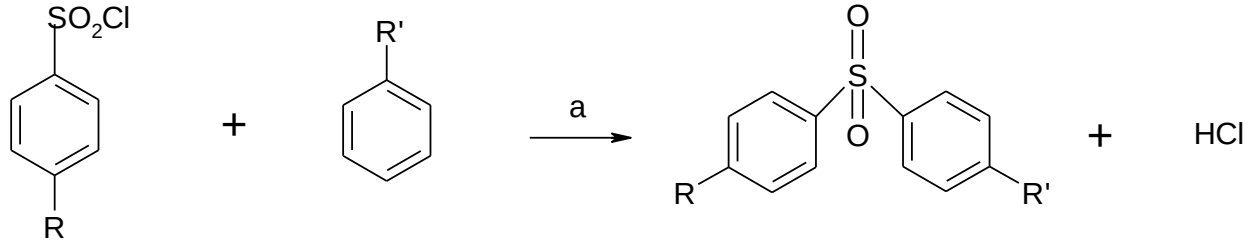
(m, 8H, Ar).

3,4-Dichloro-4'-methyldiphenyl sulfone (8). Yield 76 %; m.p. 100-103 °C; HPLC purity 99.95 %; IR (cm^{-1}): 2922 (C-H str), 1400, 1448, 1493 (C=C str), 1323, 1159 (O=S=O str); ^{1}H-NMR δ: 7.2-7.8 (m, 7H, Ar), 2.4 (t, 3H, CH_3).

Phenyl biphenylyl sulfone (9). Yield 68 %; m.p. 138-141°C; HPLC purity 99.35 %; IR (cm^{-1}): 3061 (C-H str), 1446, 1479, 1562 (C=C str), 1319, 1155 (O=S=O str); ^{1}H-NMR δ: 7.2-8 (m, 14H, Ar).

4-Methylphenyl biphenylyl sulfones (10). Yield 65 %; m.p. 104-106 °C; HPLC purity 88.81 %; IR (cm^{-1}): 2970 (C-H str), 1394, 1446, 1479 (C=C str), 1319, 1153 (O=S=O str); ^{1}H-NMR δ: 7-7.6 (m, 13H, Ar), 2.3 (t, 3H, CH_3)

Scheme 1: Synthesis of diaryl sulfones



R = H, -CH_3

R' = halide, alkyl or aryl substituents

a = $AlCl_3$, 90 ºC

Antibacterial evaluation of diaryl sulfones

The synthesized diaryl sulfones were evaluated for antibacterial activity by agar diffusion method, against Gram positive bacteria (*S. aureus, B. subtilis) and* Gram negative bacteria (*E. coli, K. pneumoniae, S. dysentrae, S. typhi).* Sulphamethoxazole was used as the positive control and DMSO was used as vehicle control.

Synergistic antibacterial activity of diaryl sulfones with trimethoprim

Sulfones being folic acid inhibitors, their synergistic antibacterial activity was checked in combination with trimethoprim, on *E. coli*. The ratio of trimethoprim: sulfone used was 1:5. The results were compared with the standard, i.e., trimethoprim (TMP): sulphamethoxazole (SMX) (1:5).

Preliminary QSAR Studies

The Quantitative Structure Activity Relationships (QSAR) studies were carried out on diaryl sulfones in order to establish correlation between physicochemical parameters and their

antibacterial activity. The structures of diaryl sulfones were fed to a computer using the software *LigPrep* from Schrodinger. Physicochemical properties of compounds were obtained using the software *QikProp* from Schrodinger. The correlation of antibacterial activity of diaryl sulfones against *E. coli*, with their physicochemical parameters, was carried out using the software *Strike* from Schrödinger. Simple (one physicochemical parameter at a time) and multiple (more than one physicochemical parameter at a time) linear regression analysis were performed considering zone of inhibition as dependent variable. The significance of correlation of antibacterial activity with physicochemical parameters of sulfones was determined based on the F-ratio and correlation coefficient value. The antibacterial activity was expressed as –log (zone of inhibition) produced by sulfones against *E.coli.*

RESULTS AND DISCUSSION

Antibacterial Activity

None of the synthesized diaryl sulfones showed activity against *B. subtilis*.

E. coli (Figure. 1): Compounds 1, 2, 3 and 4 showed antibacterial activity higher than that of the standard at 100 µg/ml, but on increasing the concentration up to 1000 µg/ml, the corresponding increase in the activity was not observed. Compounds 6 and 7 did not show activity at 100 µg/ml. Compound 9 did not show any activity against *E. coli* at all the four tested concentrations.

S. aureus (Figure. 2): Out of ten compounds, only 5 compounds, viz., 1, 2, 3, 4 and 8, were active at all the four tested concentrations. Rest of the 5 compounds were either inactive or showed activity only at 500 or 1000 µg/ml. Overall activity of sulfones was found to be less than that of the standard, sulfamethoxazole.

S. dysenteriae (Figure. 3): All the sulfones, except for compounds 6 and 7 were found to possess good activity against *S. dysenteriae.* Compounds 2, 3, 4, 8 and 9 were found to be highly active. Activity of these compounds was more than that of standard at all the concentrations, except for 100 µg/ml.

S. typhi (Figure. 4): Compounds 1-7 were active against *S. typhi* but compounds 8, 9 and 10 did not show any activity. All the compounds showed increase in activity with increase in concentration, but activity of all these compounds was less at all the concentrations as compared to the standard, sulfamethoxazole.

K. pneumoniae (Figure. 5): All the compounds were found to be active against *K. pneumoniae*, but activity was less as compared to the standard, sulfamethoxazole.

Sulfones were found to be more active against Gram negative organisms than Gram positive organisms.

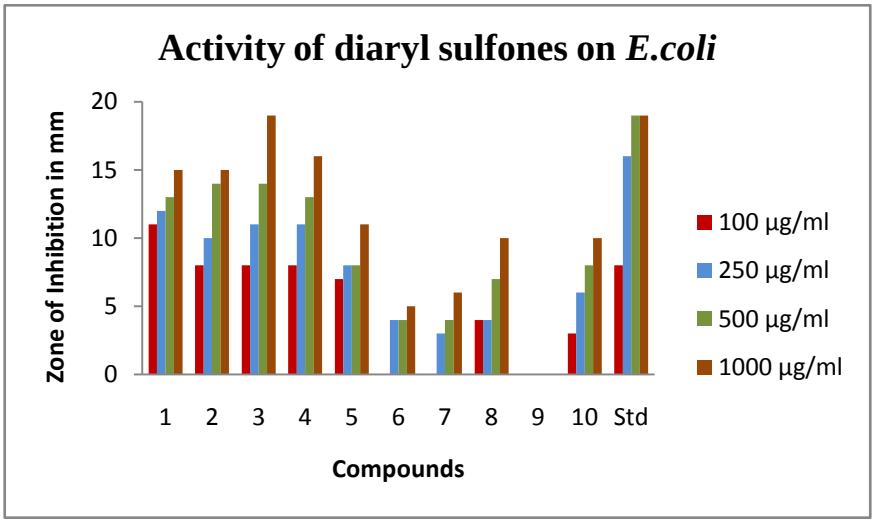


Figure 1: Activity of diaryl sulfones against *E. coli* at various concentrations

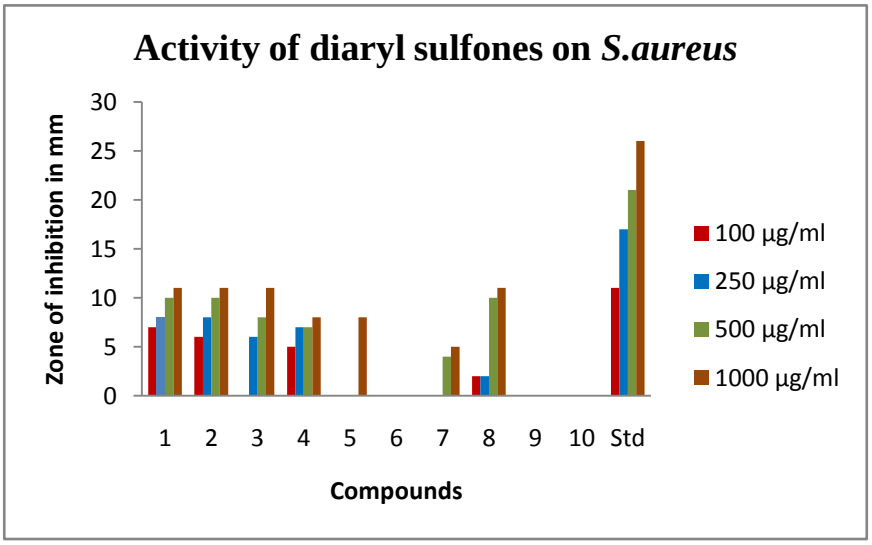


Figure 2: Activity of diaryl sulfones against *S. aureus* at various concentrations

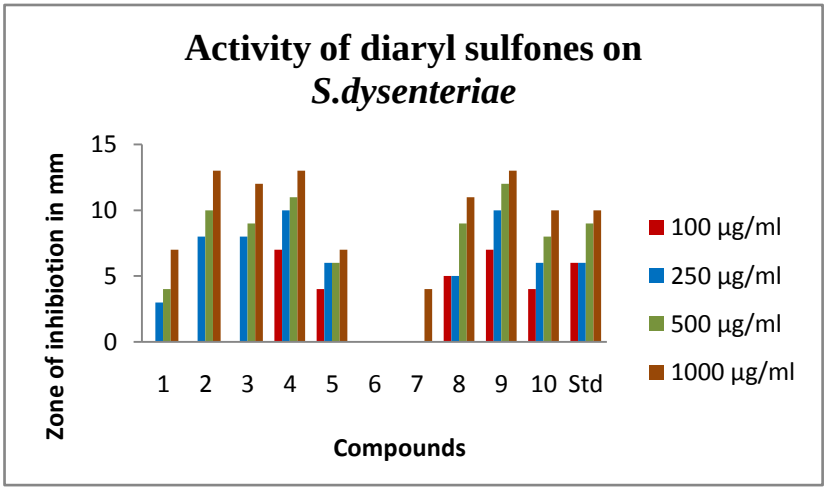


Figure 3: Activity of diaryl sulfones against *S. dysenteriae* at various concentrations

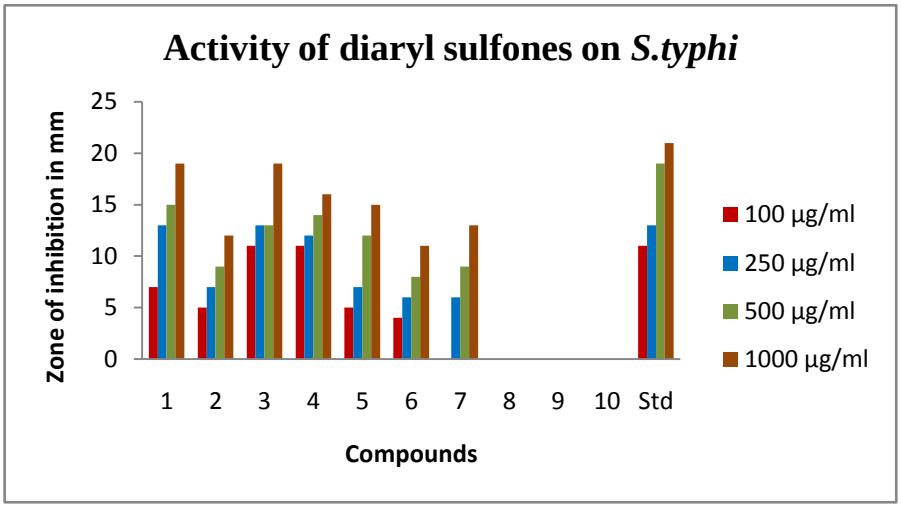


Figure 4: Activity of diaryl sulfones against *S. typhi* at various concentrations

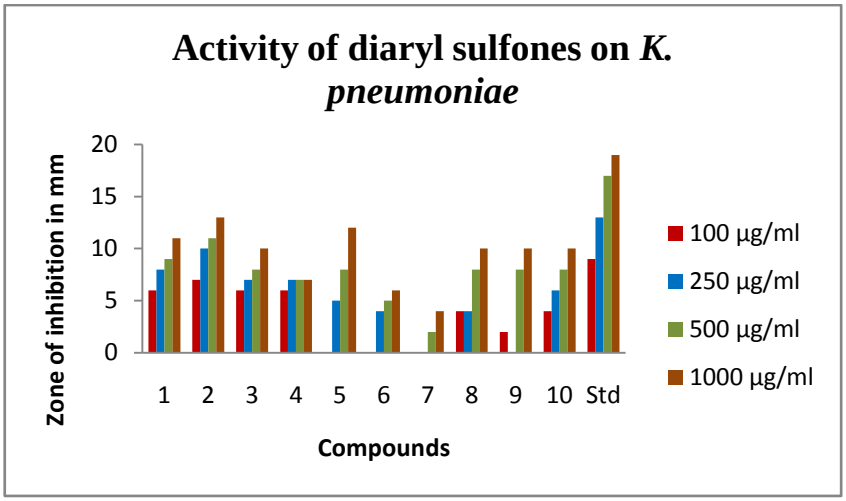


Figure 5: Activity of diaryl sulfones against *K. pneumoniae* at various concentrations

Synergistic Antibacterial Activity of Sulfones with Trimethoprim

From Figure. 6, it is clear that all the sulfones (100 mg) showed synergistic antibacterial activity with trimethoprim (20 mg), against *E. coli*. Except for compound 9, all the compounds showed synergistic effect, better than that of the standard combination, i. e., trimethoprim: sulfamethoxazole (20mg:100mg). Compounds 6, 7 and 9, which did not show activity against *E. coli* at 100 mg/ml when tested individually (Figure. 1), were found to be active, when tested in combination with trimethoprim. Compound 9 did not show activity individually at higher concentrations also, but showed activity in combination with trimethoprim. Synergistic effect of all the compounds, except compound 9, was more than that of the standard combination TMP-SMX. Hence, it can be concluded that combination of all the compounds with trimethoprim was found to be bactericidal.

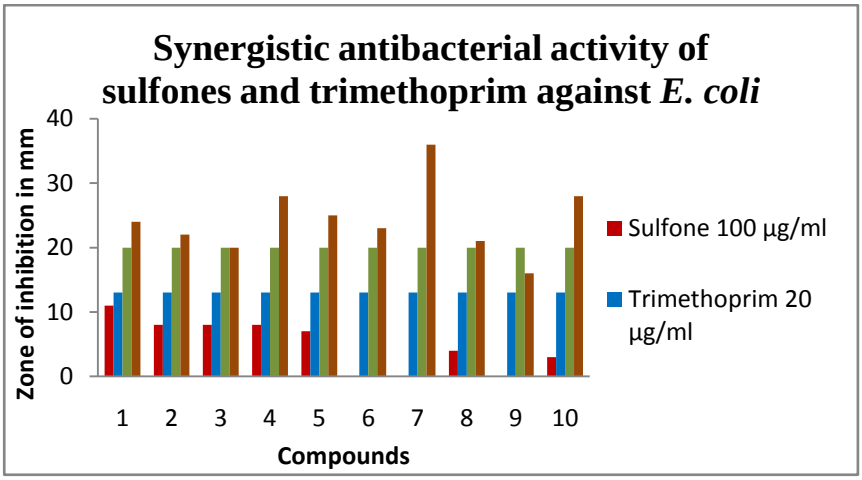


Figure 6: Synergistic antibacterial activity of sulfones and trimethoprim against *E. coli*

Preliminary QSAR study

The QSAR studies were performed by using "*Maestro"* – the molecular modeling software from Schrödinger Inc., USA. The program *LipPrep* was used to get correct conformational structures of sulfones. Different physicochemical parameters, viz., dipole moment, molecular volume, ionization potential, electron affinity and partition coefficient for diaryl sulfones, were obtained by using the software *QikProp* (Table 2).

Antibacterial activity of the synthesized compounds was correlated by simple and multiple linear regression analysis. Results of simple linear regression analysis were not satisfactory.

The best QSAR model was obtained when the antibacterial activity of sulfones against *E. coli* was correlated with dipole moment and ionization potential. Table 3 shows the best QSAR model for ten sulfones. The significance of correlation of antibacterial activity with physicochemical parameters of sulfones was determined based on the F-ratio and correlation coefficient value. From QSAR studies, it can be concluded that new sulfones with higher antibacterial activity can be designed by altering dipole moment and ionization potential. The substituents with low dipole moment and low ionization potential would provide higher antibacterial activity.

Table 2: Physicochemical parameters for diary sulfones

Comp.No.	DM	MW	IP	EA	LogP	PE	MV	PISA
1	7.21467	246.323	10.0467	0.593007	2.67302	36.4346	836.415	297.344
2	7.49523	260.35	9.99847	0.564633	3.00286	36.0893	897.819	241.909
3	7.34459	260.35	9.65767	0.53581	2.95926	36.3548	898.623	197.691
4	6.26708	301.187	9.73988	0.957141	3.25352	34.6698	863.478	224.348

5	5.77924	287.16	9.76038	0.98327	2.92844	35.0454	803.603	280.364
6	7.05998	248.296	9.68964	0.553804	2.03692	51.7731	794.324	307.854
7	7.44008	308.394	9.42033	0.849811	3.98882	68.5806	1015.79	431.273
8	6.25272	311.193	10.1361	1.00538	2.92912	35.2566	836.675	260.85
9	5.79505	297.166	10.1823	1.02351	2.60128	35.621	775.993	316.524
10	8.9065	253.275	8.95503	0.700245	0.145862	7.45101	782.798	189.475

DM = Dipole moment, MW = Molecular weight, IP = Ionization potential, EA = Electron affinity, Log P = Logarithm of partition coefficient, PE = Potential energy, MV = Molar volume and PISA = Pi (π) component of solvent accessible surface area

Table 3: The best QSAR equation obtained by multiple linear regression analysis

PCBA	**Equation**	**n**	**r**	**s**	**F**
DM and IP	-log (ZOI) = 1.2582e + 001 – (4.2382e – 001)DM – (1.1081e + 000)IP	10	0.8395	0.2221	8.4

PCBA = Parameters correlated with biological activity, ZOI = Zones of inhibition, n = number of compounds, r = correlation coefficient, s = standard deviation, F = Fischer's F value

CONCLUSION

Overall, the sulfones showed good antibacterial activity. All the synthesized compounds showed good synergistic activity with trimethoprim. From the QSAR studies, it was concluded that new sulfones with higher antibacterial activity against *E. coli* can be designed by altering the electronic parameters like dipole moment and ionization potential. Low values of dipole moment and ionization potential may increase the antibacterial activity of sulfones against *E. coli*. However, a larger data base would be required for further research on combination of sulfones with trimethoprim as antibacterial agents.

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