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QSAR study on the antibacterial activity of some sulfa drugs: building blockers of Mannich bases

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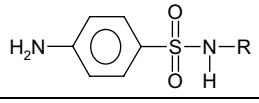
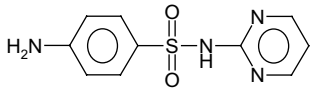
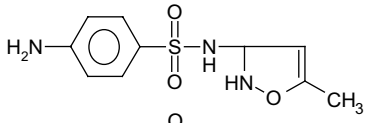
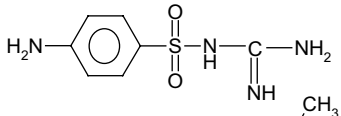
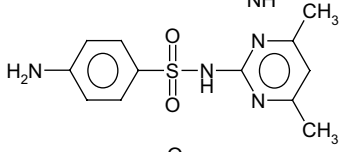
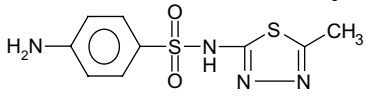
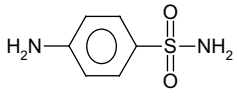
Abstract—Sulfa drugs are building blockers of several types of Mannich bases. Consequently, the antibacterial activities of sulfa drugs are reported in this paper, which will help in explaining and understanding antibacterial activities of Mannich bases. Reported QSAR is carried out using distance-based topological indices and discussed critically on the basis of statistical parameters.

1. Introduction

The importance of sulfa drugs (sulfonamides) is well established in pharmaceutical chemistry and drug design. This class of drugs is well known as antibacterial, carbonic anhydrase inhibitors, anti-cancerous and also as anti-inflammatory agents. Consequent to these physiological activities of sulfa drugs they are used as building blockers for making Mannich bases.[1,2]

In our earlier studies[3–16] several Mannich bases were synthesized from the sulfa drugs and have evaluated for their biological significance and toxicity, in particular antibacterial activity. However, to understand the biological potential of the derived Mannich bases, the same should be known for their building blockers, for example, sulfa drugs. This can be done more efficiently by investigating quantitative structure–activity relationship (QSAR) study using distance-based topological indices.[17–21] Such a study for the sulfa drugs used in the present study (Table 1) are not reported in the literature. Thus, the present work deals with the antibacterial activity of sulfa drugs (Table 1) against *E. coli*, *K. pneumonae* and *B. subtilis*. In doing so we have used distance-based topological indices: Wiener (W);[17] Szeged index (Sz),[20,21] first-order connectivity index ($^1\chi$)[18] and Balaban index (J).[19] The details of these indices are given in Section 4.

Table 1. Molecular structures of the sulfa drugs used in the present study

	General structure	
1	Sulfadiazine (S-1)	
2	Sulfamethoxazole (S-2)	
3	Sulfaguanidine (S-3)	
4	Sulfadimidine (S-4)	
5	Sulfamethiazole (S-5)	
6	Sulfanilamide (S-6)	

Keywords: QSAR; Mannich base; Topological index; Regression analysis; Topological drug design; Antibacterial activity.
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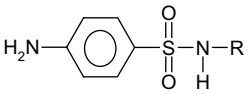

Figure 1. General structure of sulfa drugs used in the present study (see Table 1 for more details).

Before discussing the results obtained in the present study, it is worthy to mention that QSAR methodology is very useful in screening a large library of possible drug candidates for selectivity and potency.[22–27] Mathematical models are formed that correlate molecular structure to an activity or property of interest. Molecular structure is encoded through the generation of descriptors, which are numerical values corresponding to topological, geometric or electronic structural features. The goal of QSAR methodology is to develop several models to predict activity/property/toxicity using correlation analysis employing statistical techniques. In the present study we have used simple as well as multiple regression analysis using maximum R^2 methods[28] for modelling antibacterial activity of sulfa drugs with the general structure as given in Figure 1.

2. Results and discussion

The details of molecular structures of sulfa drugs used in the present study are given in Table 1 and their antibacterial activities against *E. coli*, *K. pneumonae* and *B. subtilis* are present in Table 2. Here, we have used average zone of inhibition in mm at four different concentrations as antibacterial activity. The best should have been that the activity should have been used as log of ED_{50}. However, earlier also such type of activity were presented. In some cases the activity was reported as '+' or '++'. However, it become essential to make statistical analysis of the data related to the zone of inhibition. The best would be make Student *t*-test. The Student *t*-test can be performed using the following expression:

$$t = \frac{\bar{x} - \mu}{S/\sqrt{n}}$$

The data presented in Table 2 and the above expression indicated that for small sample we are 98% sure that the true mean potency level of the antibacterial activity against each of the bacteria used falls between 8.91 and 9.09. Therefore, *t*-test permits us to use effective zone of inhibition as the antibacterial activity.

The calculated values of distance-based topological indices: W, Sz, $^1\chi$, J, $\log RB$ are summarized in Table 3.

A perusal of Table 2 shows that only five sulfa drugs are effective against *E. coli*; however, against *K. pneumonae* only three viz., **1**, **2** and **5** are effective. In case of *B. Subtilis* sulfa drug **6** is not effective. In obtaining QSAR models we have used average value of zone of inhibition to account for their antibacterial activities against the three bacteria mentioned earlier. Based on these average values we obtained we can propose the following order of antibacterial activity:

Against *E. coli*

$$\mathbf{6} > \mathbf{2} > \mathbf{5} > \mathbf{1} > \mathbf{4} \quad (1)$$

Against *K. pneumonae*

$$\mathbf{5} > \mathbf{1} > \mathbf{2} \quad (2)$$

Against *B. subtilis*

$$\mathbf{2} > \mathbf{1} > \mathbf{4} > \mathbf{5} > \mathbf{3} \quad (3)$$

It is interesting to record that only sulfa drug **3** is active against *B. subtilis* and it is inactive against other two bacteria. Furthermore, these sequences (order) do not establish any quantitative structure–activity (QSAR) relationship. Therefore, we have made such study using topological indices, which encodes the molecular structures of sulfa drugs numerically. Since, different sulfa drugs are found effective against the three bacteria used we have obtained three different correlation matrices (Table 4) for preliminary investigation of correlatedness

Table 2. Antibacterial activity of the sulfa drugs against *E. coli*, *K. pneumonae* and *B. subtilis* adopted from our earlier work[6b]

No.	Compound	Zone of inhibition in mm				
		Concentration in μg/ml				Average
		10	20	40	80	
E. coli						
1	S-1	9.70	17.20	21.20	24.50	18.14
2	S-2	19.63	22.93	23.23	24.03	22.45
3	S-4	15.10	16.90	18.80	18.56	17.34
4	S-5	16.20	17.43	22.20	25.50	20.32
5	S-6	20.43	22.30	22.86	25.55	22.78
						$\bar{x}$ = 20.21
						σ = 2.4566
K. pneumonae						
1	S-1	27.03	29.23	29.53	25.63	27.83
2	S-2	11.63	14.92	22.43	26.46	18.86
3	S-5	30.33	29.86	29.60	27.76	29.39
						$\bar{x}$ = 25.36
						σ = 5.6828
B. subtilis						
1	S-1	20.86	27.23	26.36	25.93	25.10
2	S-2	22.80	25.46	27.43	27.90	25.90
3	S-3	11.23	10.90	17.90	21.76	15.45
4	S-4	15.40	19.96	21.76	22.08	19.80
5	S-5	18.06	19.13	19.46	20.50	19.29
						$\bar{x}$ = 21.11
						σ = 4.3566

Table 3. Distance-based topological indices calculated for sulfa drugs used in the present study

No.	Compound	Topological indices				
		W	Sz	$^1\chi$	J	$\log RB$
1	S-1	536	818	8.0773	1.8372	162.0572
2	S-2	535	731	7.9712	1.8479	161.6517
3	S-3	307	427	6.4155	2.4613	96.2437
4	S-4	722	1092	8.8650	1.8868	215.2262
5	S-5	535	731	7.9712	1.8479	161.6517
6	S-6	152	236	4.9990	2.3936	48.2757