QSAR Study of Sulphonamides with Anti-bacterial Activity Against Pseudomonas aeruginosa

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***Abstract*- In the present study, we have made efforts to investigate Anti-bacterial activity of Mannich bases against Pseudomonas aeruginosa. The results have shown that Anti-bacterial activity of these compounds can be modeled excellently in tri-parametric models in which Weiner index W, Balaban index F and Topological index T played a dominating role. The predictive ability of the model is discussed on the basis of cross-validation method. The superiority of these indices over several other molecular descriptors is critically examined. The values obtained for the best model are- R^2 = 0.6278, Adjusted R^2= 0.4417, Coefficient of variation= 0.2811 and F-ratio= 3.374.**

Keywords*- QSAR, Mannich bases, Topological indices, Weiner Index, Balaban Index, Regression analysis.

I. INTRODUCTION

One of the key objectives of organic and medicinal chemistry is to design and synthesize molecules that possess potent therapeutic values. The rapid development of resistance to existing antimicrobial drugs generates a serious challenge to the scientific community. Consequently, there is a vital need for the development of new antimicrobial agents with potent activity against drug resistant microorganisms[1](Malhotra et al., 2011).

QSAR is a tool which is used to design libraries of various ligands targeted toward particular receptors and to ensure increase in the probability of synthesizing therapeutically active drugs. In the present paper, we have done QSAR study of a series of Sulphonamides, in which different substituents are substituted on a parent compound. Sulphonamide is a type of Mannich base. A mannich base is a beta-amino-ketone, which is formed in the reaction of an amine, formaldehyde (or an aldehyde) and a carbon acid[2]. In this paper, the different topological indices are calculated which are correlated with the anti-bacterial activity of Sulphonamides against Pseudomonas aeruginosa. Sulphonamides are any of a class of organic compounds that are amides of sulphonic acids containing the group $-SO_2NH_2$or a group derived from this. An important class of sulphonamides is the sulfa drugs.

Sulfonamide or sulphonamide 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. The sulfonylureas and thiazide diuretics are newer drug groups based on the antibacterial sulfonamides[3].

In our previous study[4], we have synthesized Mannich bases through condensation of some aromatic and heteroaromatic amides with sulphonamides and various secondary amines. They were screened for their antibacterial properties.

In the present paper, we have done the QSAR studies on the Anti-bacterial activity of Sulphonamides against P. aruginosa. The antibacterial activities of these compounds are correlated with their structures using various topological indices. The topological indices[5-13] which are taken into consideration are- Weiner index[14]; Platt's index[15-17]; Schultz molecular topological index[18,19]; Balaban indices[20]- J, F & G and Zagreb group indices- ZM_1 & ZM_2[21].

II. RESULTS AND DISCUSSION

The structural details of the series of Sulphonamides which are taken into consideration in this paper are given in Table-1. The calculated values of topological indices of these compounds are presented in Table-2. The details of the abbreviations are given in the footnotes of this table. The selection result section is given in Table-3. Since the mono- and bi-parametric models do not give appropriate results, hence only tri-parametric models are considered and are given in Table-4.

The best tri-parametric model is model no. 7, containing W, F and T indices. The best estimated model is given by equation 1.

Best Estimated Model

Anti-bacterial activity against P. aruginosa= -74.4889 - 2.1557 * T + 1.9227E-02 * W + 30.3551 * F (1)

R2	0.6278
Adj R2	0.4417
Coefficient of Variation	0.2811
F-ratio	3.374

The predicted values with confidence limit of means obtained from model no. 7, equation 1 are given in Table-5 and a straight line graph (Figure-1) is plotted between Actual and Predicted Anti-bacterial activity on X- and Y-axes respectively, using ORIGIN software, on the basis of table-5

III. EXPERIMENTAL SECTION

1) *The Anti-bacterial Activity:* The anti-bacterial activity of the series of compounds is taken from the thesis work of one of our authors[4].

2) *Topological descriptors:* The structure of compounds is drawn by using ACD-labs Chem-sketch Software[22]. The various topological descriptors used in the present study were calculated from the Hydrogen Suppressed molecular graphs of Isoniazide derivatives by using Dragon software[23].

3) *Regression Analysis:* The correlation-regression analysis of the data was done by using NCSS-8 software[24] as well as Origin-6 software.

CONCLUSION

The best estimated model shows that with the decrease in the value of Topological Index T and increase in the values of Weiner Index W and Balaban Index F, the Anti-bacterial activity of Sulphonamides against P. aruginosa increases.

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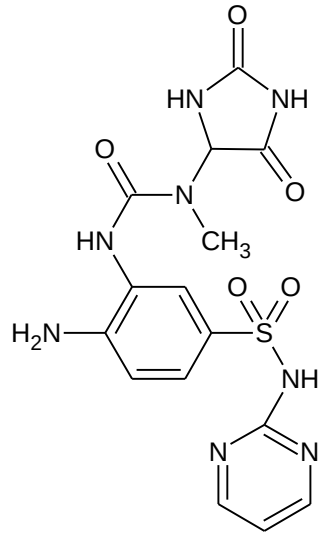
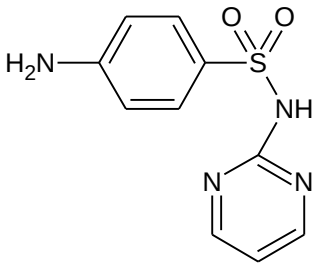
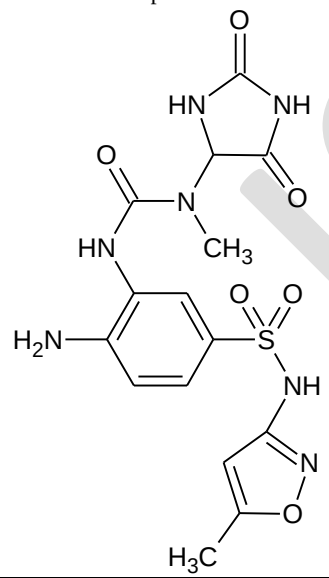
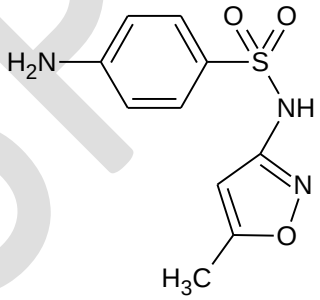
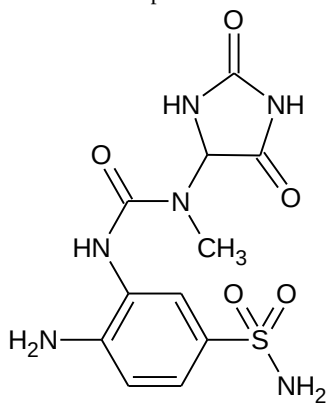
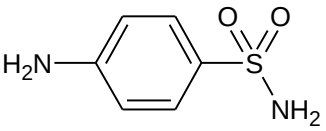
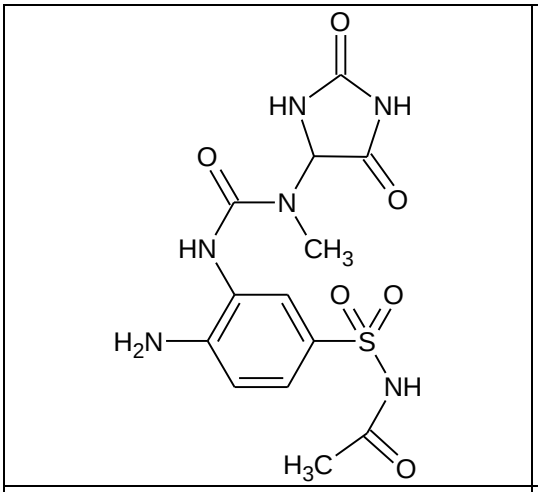
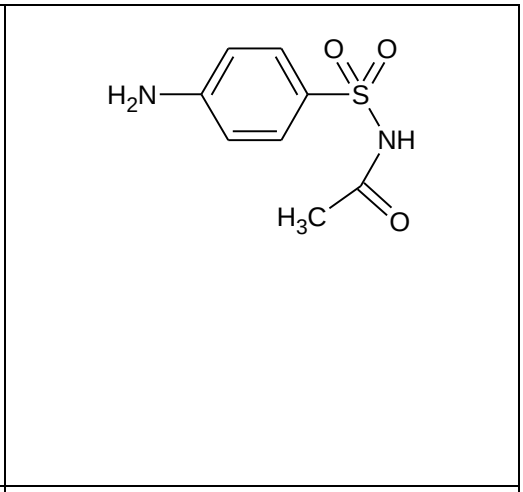
TABLE-1: STRUCTURE OF COMPOUNDS- SULPHONAMIDES

Compound-1 	Compound-2 
Compound-3 	Compound-4 
Compound-5 	Compound-6 
Compound-7	Compound-8





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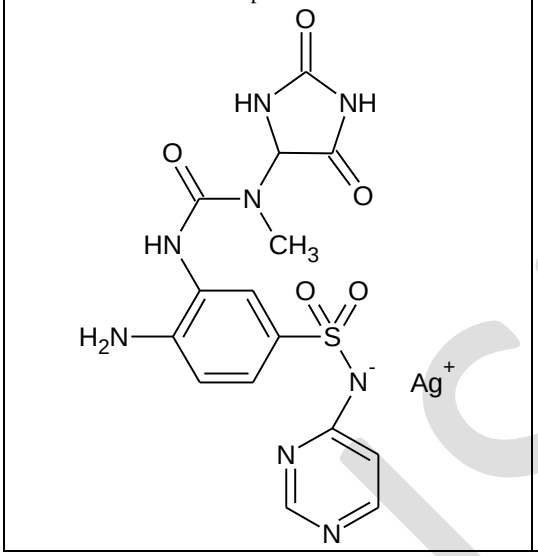

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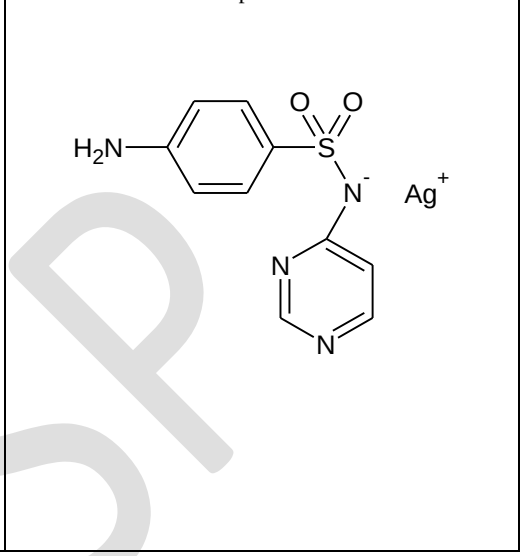

TABLE-2: CALCULATED TOPOLOGICAL INDICES OF THE SERIES OF COMPOUNDS

S. No.	Compound no.	Antibacterial activity	W	P	M	J	F	G	T	ZM1	ZM2
1	1.1	7.33	2415.5	43	809	1.4213	5.6852	144.881	62	140	177
2	1.2	10.17	533	23	287	1.6704	5.0112	1623.628	36	86	97
3	1.3	14.83	2387	43	811	1.4035	5.614	143.0719	62	154	177
4	1.4	20.5	535	22	289	1.7658	5.295	76.51	36	88	100
5	1.5	8	1227.5	34	515	1.7656	5.296	107.753	47	120	134
6	1.6	18.33	152	13	121	2.2467	4.4934	41.8231	22	54	59
7	1.7	9	1977.5	37	652	1.7955	5.3865	125.561	54	134	155
8	1.8	10.67	307	18	194	2.3121	4.6242	56.6464	28	68	75
9	1.9	11.17	2386	43	813	1.4407	5.7629	146.866	62	140	167
10	1.10	9.17	536	22	283	1.6698	5.0094	72.3853	36	86	92

Where W= Weiner index; P= Platt's index; M= Schultz Molecular Topological Index; J, F & G= Balaban Indices; ZM_1 & ZM_2= Zagreb's group Indices.

TABLE-3 SELECTION RESULTS SECTION

Model Size	R-Squared	R-Squared Change	Coded Variables	Decoded Variables
1	0.179879	0.179879	B	P
2	0.391066	0.211187	BC	P, M
3	0.627807	0.236741	AEG	W, F, T
4	0.765755	0.137948	AEGH	W,F,T, ZM_1
5	0.846644	0.080888	ADEGH	W, J, F,T, ZM_1
6	0.964009	0.117365	BCEFGH	P, M, F, G, T, ZM_1

TABLE-4 TRI-PARAMETRIC MODELS

Model No.	Descriptors	R^2	R^2A	Coefficient of Variation	F-ratio	Estimated Model
1	W, J, T	0.2829	0.0000	0.3902	0.789	64.8794 - 1.0847 * T + 1.2211E-02 * W – 11.3799 * J
2	P, F, M_1	0.3964	0.0946	0.3580	1.314	-31.8375 + 0.2194 * M_1 - 1.2047 * P + 10.7668 * F
3	M, G, M_2	0.1950	0.0000	0.4134	0.485	16.8249 - 2.4713E-02 * M_2 -2.7585E-03 * M – 2.1420E-03 * G
4	W, G, M_2	0.1951	0.0000	0.4134	0.485	18.3489 - 5.3804E-02 * M_2 + 5.7405E-04 * W – 2.0110E-03 * G
5	P, J, T	0.2830	0.0000	0.3901	0.789	9.3891E-02 + 1.3414 * T - 1.8249 * P + 3.7237 * J
6	M, F, M_1	0.2185	0.0000	0.4073	0.559	-17.3450 - 0.1105 * M_1 - 4.4479E-03 * M + 8.2806 * F
7	**W, F, T**	**0.6278**	**0.4417**	**0.2811**	**3.374**	**-74.4889 - 2.1557 * T + 1.9227E-02 * W + 30.3551 * F**
8	P, G, M_1	0.3171	0.0000	0.3807	0.929	13.0076 + 0.2672 * M_1 - 0.9790 * P – 2.0156E-03 * G
9	M, J, M_2	0.1527	0.0000	0.4241	0.360	23.6685 - 9.8986E-02 * M_2 + 7.9082E-03 * M – 1.8992 * J

TABLE-5 PREDICTED VALUES WITH CONFIDENCE LIMITS OF MEANS

Row	Actual Antibacterial Activity	Predicted Antibacterial Activity	Standard Error of Predicted
1	7.330	10.873	1.775
2	10.170	10.268	1.848
3	14.830	8.164	1.854
4	20.500	18.921	3.065
5	8.000	8.553	1.785
6	18.330	17.405	2.893
7	9.000	10.630	1.591
8	10.670	11.421	2.037
9	11.170	12.664	1.970
10	9.170	10.271	1.836

Anti-bacterial activity= 4.43541 + 0.62781 x

R= 0.79236 SD= 2.29839 N= 10 P= 0.00628

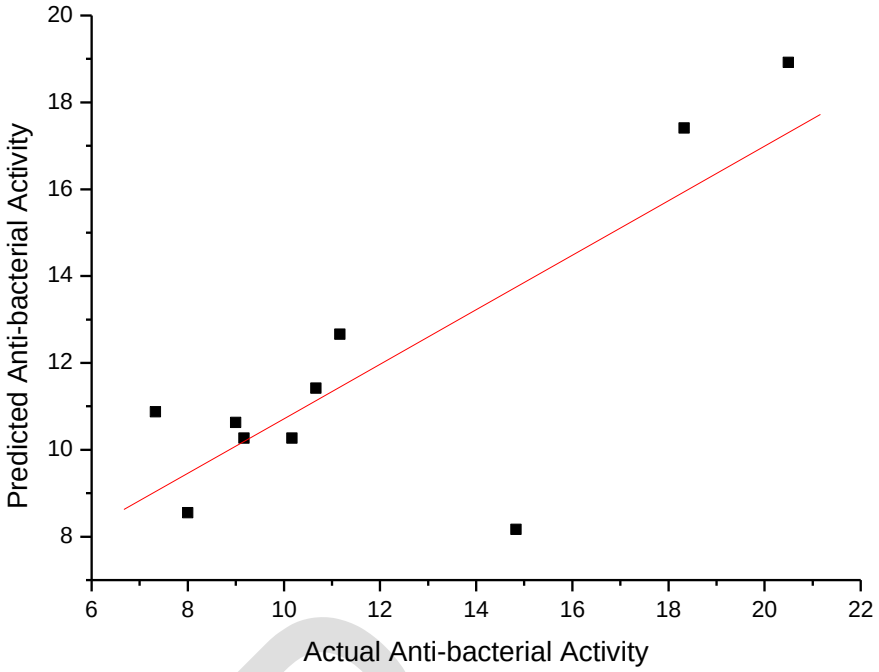

Figure 1 Linear fit of Table-5 based on best estimated model

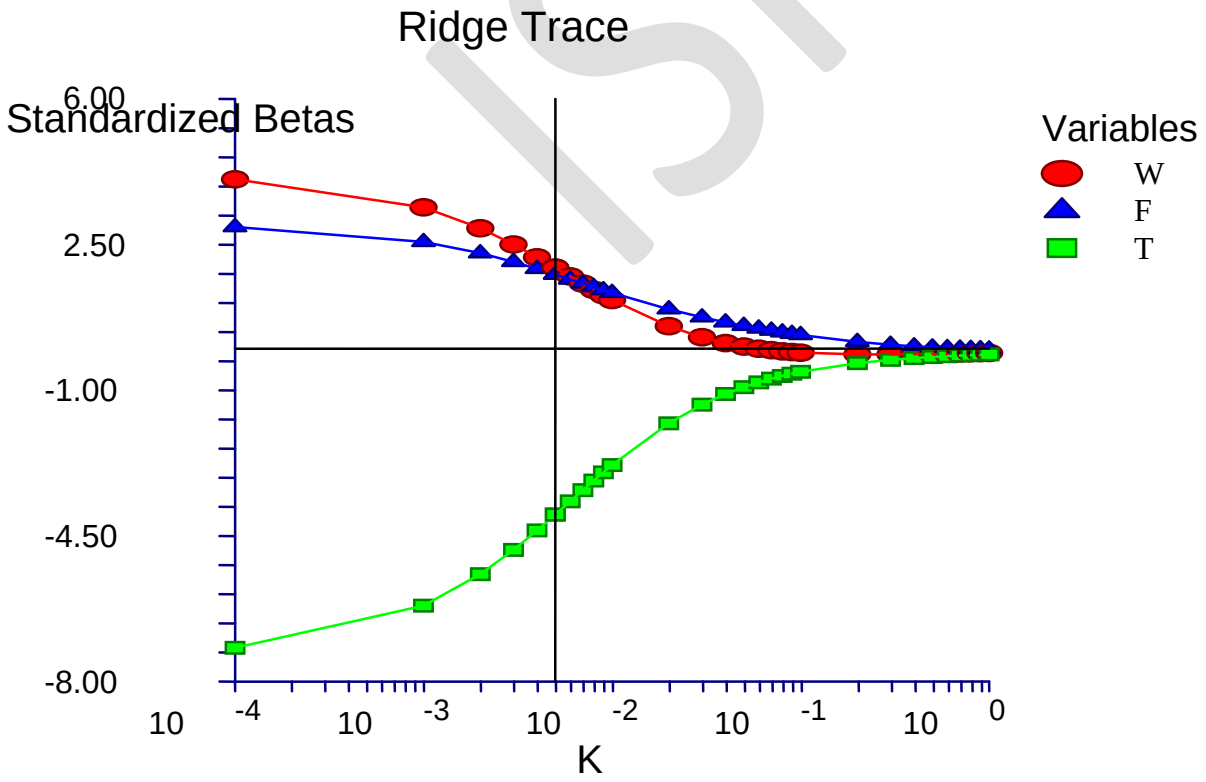

Figure 2 Ridge trace section based on best estimated model