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QSAR Study on N- Substituted Sulphonamide Derivatives as Anti-Bacterial Agents

Aradhana Singh[1], Anil Kumar Soni[2] and P. P. Singh[1]
[1]Department of Chemistry, M.L.K. P.G. College, U.P., India
[2]Corresponding Author, Department of Chemistry, Shia P.G. College, Lucknow, U.P., India
Email: anilsony82@gmail.com

Abstract

Sulfonamides exert their anti-bacterial action by competiting with of p-aminobenzoic acid in the sequencial pathway of folate synthesis in bacteria. In the QSAR study the predictive model of forty one N-substituted sulfonamides has been buildup with the help of molecular property descriptors, heat of formation; molecular weight; total energy; eigen value of higest occupied molecular orbital; eigen value of lowest unoccupied molecular orbital; absolute hardness and electronegativity. For QSAR prediction, the 3D modeling and geometry optimization of all the derivatives have been done with the help of PCMODEL software using the semiempirical PM3 Hamiltonian. The first QSAR model has been made for eighteen N-substituted sulfonamides include the molecular weight; total energy; eigen value of highest occupied molecular orbital and eigen value of lowest unoccupied molecular orbital as best descriptors as the model has cross validation coefficient and correlation coefficient 0.795181 and 0.854468 respectively. The second QSAR model has been made for twenty-three N-phenyl substituted sulfonamides include the heat of formation, molecular weight, eigen value of highest occupied molecular orbital and eigen value of lowest unoccupied molecular orbital as best descriptors as the model has cross validation coefficient and correlation coefficient 0.74232 and 0.856631respectively. The predicted activity of the N-substituted sulfonamides as calculated from first and second models has also correlated with observed activity and correlation result is also good. On the basis of statistical quality of result it is clear that one can use these equations to predict the antibacterial activity of a hypothetical compound of similar series.

Keywords: QSAR, Sulfonamides, molecular descriptors, PM3.

1. Introduction

In the sequencial pathway of folate synthesis in bacteria, the incorporation of p-aminobenzoic acid (PAB) into dihydropteroic acid is mediated by dihydropteroate synthetase enzyme (*Brown, 1971*). It has been established that sulfonamides exert their anti-bacterial action by competiting with PAB, hence a series of sulfonamides have been taken from literature for quantitative structure activity relationships (QSAR) study with the help of reactivity indeces: heat of formation (ΔH_f), molecular weight (MW), total energy (TE), eigen value of HOMO (εHOMO), eigen value of LUMO (εLUMO), absolute hardness (η) and electronegativity (χ) (*Gupta, 1987*). QSAR are predictive tools for a preliminary evaluation of the activity of chemical compounds by using computer-aided models (*Hansch, 1969*). The survey of the literatures indicates that no QSAR study of N^l-Substituted Sulfonamides and N^l-phenylsulfonamides have been made with these reactivity indices. Based on these reactivity indices, the QSAR study of eighteen N^l-substituted sulfonamides and twenty-three N^l-phenylsulfonamides is presented in this paper.

2. Materials and Methods

The study materials of this paper are N^l-Substitutedsulfonamides and N^l-phenylsulfonamides and are presented in Tables-1 and 2 (*Seydel, 1971*). Table-1 includes derivatives of N^l-substitutedsulfonamides and Table-2 includes derivatives of N^l-phenylsulfonamides. The biological activity of these derivatives has been measured in term of inhibitory activity. For QSAR

prediction, the 3D modeling and geometry optimization of all the derivatives have been done with the help of PCMODEL software using the semiempirical PM3 Hamiltonian (*Stewart, 1989*). The MOPAC calculations have been performed with Win MOPAC 7.21 software by applying key words PM3 Charge = 0 Gnorm = 0.1, Bonds, Geo-OK, Vectors Density, and all the values required for the determination of the value of various descriptors have been obtained from this software. The results are also reported in Tables 1-2.

3. Results and Discussion

The discussion has been made in two sets, the first comprises the derivatives of N^1-substituted sulfonamides and the second set comprises of derivatives of N^1-pheny substituted sulfonamides. The compounds of both the sets are presented in Tables-1 and 2 respectively along with their observed activity (*Seydel, 1971*). The values of heat of formation, molecular weight, total energy, HOMO energy, LUMO energy, absolute hardness and electronegativity, of both the sets are also presented in Tables-1 and 2. The values of various descriptors of these compounds have been evaluated with the help of MOPAC2002 associated with CAChe (*Soni et al., 2011*). The values of various descriptors, in different combinations have been used for MLR analysis. The MLR equation (eqn.-1) giving the best result has been chosen as QSAR model shown below

$$A_{pred}=0.20805*\Delta H_f^0-0.112678*M_W+0.0106054*E_T+231.476*\varepsilon HOMO-214.665*\varepsilon LUMO +458.567*\eta+70.2947 \quad (1)$$

rCV^2=0.808016, r^2=0.902548, n= 41, DC= 6

This model includes the ΔH_f^0, M_W, E_T, εHOMO, εLUMO and η. All the values are molecular property and we already have tested these parameters as molecular descriptors in our previous communications (*Singh and Sahu, 2007*). The predicted activity (pI_{50}/s and pI_{50}) from Eq.1 is also reported in Table-1 and 2. MLR analysis of this set using regression, Eq.1 indicates good prediction result for predicted activity. On the basis of statistical quality of result it is clear that one can use this equation to predict the activity of a hypothetical compound of similar series.

4. Conclusions

1. The first QSAR model shows high degree of predictive power as the model has high values of cross validation coefficient and correlation coefficient, which are 0.795181 and 0.854468 respectively. Molecular weight, total energy, eigen value of highest occupied molecular orbital and eigen value of lowest unoccupied molecular orbital are as the best descriptors.
2. The second QSAR model model also shows high degree of predictive power as it also has high cross validation coefficient (0.74232) and correlation coefficient and (0.856631) respectively. The model shows that, heat of formation, molecular weight, eigen value of highest occupied molecular orbital and eigen value of lowest unoccupied molecular orbital are found as best descriptors
3. The predicted activity of the N-substituted sulfonamides as calculated from first and second models has good correlation with observed activity.

On the basis of statistical quality of result it is clear that one can use these models to predict the antibacterial activity of a hypothetical compound of similar series.

5. Acknowledgement

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References

1. Brown, G. M. 1971; *Adv. Biochem.* 35, 35.

2. Gupta, S. P. 1987; *Am. Chem. Soc.* 87, 1183.
3. Hansch, C. 1969; Chem. Res. 2, 232.
4. Seydel. J. K. 1971; *J. Med. Chem.* 14, 24.
5. Stewart, J. J. P. 1989; *J. Comp. Chem.* 10, 209.
6. Singh, P. P. and Sahu, V. K. 2007; *Mat. Sci. (I. J.)* 3, 55.
7. Soni, A.K., Sahu, V. K., Singh, P. P. 2011; *Asian J. Chem.* 23, 671.

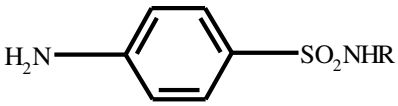

Fig.-1 Skleton structure of Nl-subsituted sulfonamide

Table-1. N^1-Substituted Sulfonamides and Their Cell-Free Inhibition Index (l_{50}/s)

S. No.	Compound	l_{50}/s	Descriptors							pl_{50}/s
			ΔH_f	MW	E_T	εHOMO	εLUMO	η	χ	
1	N^1-ethylsulfanilamide	28.00	-53.36	200.26	-104.54	-9.20	-0.56	4.32	-4.88	7.17
2	N^1-methylsulfanilamide	21.00	-47.27	186.23	-97.39	-9.21	-0.57	4.32	-4.89	9.92
3	Sulfanilamide	10.00	-45.17	172.20	-90.28	-9.31	-0.66	4.32	-4.98	8.19
4	N^1-phenylsulfanilamide	1.90	-17.57	248.30	-126.44	-8.96	-0.69	4.13	-4.82	5.30
5	Sulfapyridine	0.67	-11.17	249.29	-128.60	-9.08	-0.79	4.15	-4.93	9.36
6	Sulfisomidine	0.45	-22.20	278.33	-145.15	-9.32	-0.83	4.24	-5.07	-2.08
7	Sulfamethazine	0.51	-23.29	278.33	-145.15	-9.15	-0.75	4.20	-4.95	1.53
8	Sulfathiazole	0.34	3.39	255.31	-125.28	-9.06	-0.96	4.05	-5.01	7.01
9	Sulfamoxole	0.27	-57.02	267.30	-142.63	-8.67	-0.90	3.89	-4.79	-3.07
10	Sulfadiazine	0.78	-4.55	250.28	-130.79	-9.26	-0.80	4.23	-5.03	7.77
11	Sulfadimethozine	0.27	43.48	328.35	-171.21	-9.15	-0.74	4.21	-4.94	11.94
12	Sulfamethoxazole	0.25	-14.93	253.28	-135.32	-9.13	-1.04	4.05	-5.08	4.29
13	Sulfaethylathiadiazole	0.43	22.78	270.32	-134.60	-9.32	-1.13	4.09	-5.23	3.91

14	Sulfacetamide	3.50	-89.41	214.24	-114.93	-9.39	-0.82	4.29	-5.11	-3.95
15	Sulfaethyl-3,4-xylamide	0.55	-52.85	333.40	-175.76	-9.25	-0.68	4.29	-4.96	-8.06
16	Sulfisoxazole	0.46	-20.91	267.30	-142.51	-8.91	-1.03	3.94	-4.97	-0.28
17	Sulfabenzamide	0.95	-54.23	276.31	-143.95	-9.38	-0.81	4.29	-5.10	-3.76
18	Sulfanilylcyanamide	5.20	21.82	212.23	-112.38	-9.43	-1.05	4.19	-5.24	13.71

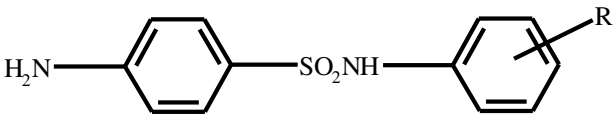

Table-2. Inhibitiory Antibacterial Activities of N^1-Phenylsulfonamides against enzyme dihydropteroat synthetase

S. No.	R(N^1-phenyl)	I_{50}	Descriptors							pI_{50}
			ΔH_f	MW	TE	εHOMO	εLUMO	η	χ	
19	4-OCH_3	58.79	189.21	258.28	-0.05	-8.72	-0.32	4.20	-4.52	56.76
20	H	44.34	117.66	228.25	0.02	-8.94	-0.35	4.30	-4.64	46.63
21	4-CI	33.90	92.21	262.70	0.00	-8.95	-0.43	4.26	-4.69	33.97
22	4-I	16.01	43.53	354.15	0.07	-8.14	-0.41	3.86	-4.27	13.32
23	2-Cl-4-OCH_3	19.00	133.97	292.72	-0.05	-8.82	-0.39	4.21	-4.60	37.86
24	3-CF_3	17.59	36.11	296.25	-0.22	-8.52	-0.51	4.01	-4.52	20.59
25	2-Cl	14.33	3.75	262.70	0.01	-8.97	-0.37	4.30	-4.67	16.40
26	4-$COCH_3$	17.07	19.84	270.29	-0.03	-8.37	-0.48	3.94	-4.42	16.31
27	4-CN	15.13	28.76	253.26	0.07	-9.07	-0.77	4.15	-4.92	16.60
28	4-NO_2	7.00	33.29	273.25	0.16	-8.51	-1.52	3.50	-5.02	7.85
29	2-OCH_3-4-NO_2	9.04	64.19	303.27	0.10	-8.32	-1.55	3.39	-4.94	10.87
30	2-Cl-4NO_2	13.77	93.81	307.69	0.15	-8.57	-1.63	3.47	-5.10	12.53
31	2-NO_2-4-CF_3	5.00	58.49	341.25	-0.09	-8.83	-1.88	3.48	-5.36	-0.54

32	2-Br-4-NO_2	-0.50	51.91	352.14	0.17	-8.63	-1.64	3.49	-5.13	-3.77
33	2-Cl-4-SO_2NH_3	-0.49	39.32	386.22	0.06	-8.97	-1.15	3.91	-5.06	-1.52
34	6-$(C_2H_5)_2N$	107.11	456.64	395.46	0.12	-8.58	-0.36	4.11	-4.47	96.67
35	6-$(CH_3)_2N$	51.63	157.98	271.32	0.01	-8.86	-0.21	4.32	-4.53	47.81
36	6-CH_3O	48.86	146.89	258.28	-0.04	-8.91	-0.30	4.30	-4.61	45.54
37	2-Cl-6-CH_3O	18.50	31.74	292.72	-0.05	-8.89	-0.41	4.24	-4.65	18.43
38	H	16.15	0.27	242.28	0.00	-8.87	-0.34	4.27	-4.61	20.93
39	6-CH_3S	13.97	15.77	274.34	0.03	-8.85	-0.53	4.16	-4.69	15.52
40	6-Cl	14.10	4.60	262.70	0.01	-8.89	-0.41	4.24	-4.65	16.17
41	2-Cl	14.10	3.70	262.70	0.01	-8.97	-0.39	4.29	-4.68	16.10

Fig.-2 Skleton structure of N^1-phenylsubsituted sulfonamide