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QSAR STUDIES AND INHIBITION OF PNEUMOCYSTIS CARINII DIHYDROPTEROATE SYNTHETASE BY SULFONAMIDES

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ABSTRACT
Sulfanilamide sulfa drugs have been shown to inhibit dihydropteroate synthetase (DHPS) isolated from Pneumocystis carinii. In order to develop a pharmacophoric model for this inhibition, quantitative structure-activity relationships (QSAR) for sulfa drugs active against DHPS have been studied by regression analysis which is done with topological indices, later inhibitory activity is correlated with topological properties. QSAR studies of the sulfonamides is attempted using the Wiener Index (w), Balaban index, connectivity indices, χ_{eq} and indicator parameters. The regression analysis of the data employing the multiple regression analysis has indicated that Wiener index and zero order connectivity index are most suitable indexes for this purpose.

KEYWORDS: QSAR, sulfonamides, DHPS**.**

INTRODUCTION
Pneumocystis carinii can be considered a protozoan organism, but it shares many characteristics with fungi.[1] As one of the more common AIDS-defining illnesses, P. carinii pneumonia is often the ultimate cause of morbidity for immune compromised individuals. As such, treatment and long-term prophylaxis of P. carinii pneumonia continue to be active areas of study. Currently, the most effective treatment is co-trimoxazole, a synergistic combination of the sulfanilamide sulfamethoxazole and the dihydrofolate reductase inhibitor trimethoprim. The use of co-trimoxazole, however, produces adverse side effects in 20 to 57% of patients, resulting in discontinuation of treatment.[2] Other combination treatments, including pyrimethamine and either sulfadiazine or sulfadoxine, are also plagued with side effects which limit their use and give rise to the need for more effective treatments.[3]

Pneumocystis carinii pneumonia (PCP) is a major cause of morbidity and mortality in AIDS patients. Even though the PCP incidence in AIDS patients has declined in recent years, PCP remains the most common AIDS-defining opportunistic infection.[4]

Sulfa drugs are among the most effective agents used in the treatment of PCP. Co-trimoxazole, which is sulfamethoxazole in combination with trimethoprim, is the most effective of the currently available agents for both the prophylaxis and treatment of PCP. Unfortunately, approximately 30% of AIDS patients experience side effects, necessitating the use of alternative agents. Other sulfa drugs, including dapsone and sulfadoxine, are also in use, but they are all also limited by a high incidence of drug intolerance.[5]

Sulfa drugs act by inhibiting the enzyme dihydropteroate synthetase (DHPS), the folate biosynthesis enzyme that catalyzes the linkage of 7,8-dihydro-6-hydroxymethylpterin pyrophosphate (H2PtCH2OPP) with p-aminobenzoic acid (PABA) to form dihydropteroate. The P. carinii DHPS has recently been cloned by Volpe and coworkers and expressed in a baculovirus vector.[6,7] The P. carinii DHPS is located on a multifunctional protein along with two other folate biosynthesis enzymes, dihydroneopterin aldolase and hydroxymethyldihydropterin pyrophosphokinase.[6]

The antimetabolite sulfa drugs function by inhibiting dihydropteroate synthetase (DHPS), an enzyme catalyzing a crucial step in the biosynthesis of tetrahydrofolate and, ultimately, nucleotides. The lack of a mechanism for uptake of preformed folate in P. carinii and the absence of a DHPS pathway in mammals make this enzyme an ideal target for drug therapy. As noted in a recent paper by Hong et al.[8] of the many sulfa drugs that have been synthesized, few have been tested against P. carinii. Given that sulfa drugs differ in their ability to elicit adverse effects, an exploration of the structure-activity relationships (SAR) of a variety of sulfa drugs could lead to more effective treatments.

Sulfa drugs are known to vary in the frequency of their association with adverse effects.[9] Thus, it is possible that other sulfa drugs might be as effective as sulfamethoxazole without eliciting adverse effects. Very few of the approximately 15,000 sulfa drugs that have been synthesized[10] have ever been tested against P. carinii in vitro.[11,12] or in vivo.[13,15] This low rate of testing is due, in part, to the inability to culture these organisms continuously in vitro[16] and to the complexities of the various animal models.[17] Therefore, an enzyme based screen represents a more practical approach to the identification of effective sulfa drugs. Two small enzyme-based screens measuring DHPS activity in homogenates of isolated organisms have been carried out.[11,12] Both studies were limited by difficulties in obtaining large amounts of organisms. There are no such limitations when a recombinant enzyme is used. In this study, the recombinant DHPS enzyme was used to compare the relative efficacies of 33 sulfa drugs.

RESULT AND DISCUSSION

It is an established fact that excellent QSAR models can aid in understanding the mechanism of the action of drugs and may save the cost and time in the course of developing a new drug as compared with empirical procedure.[18-20] It is helpful experimental chemists in synthesizing more effective drugs in lesser time.

Presentation of data

The present study contains 33 sulfonamides. The inhibitory activity (IC_{50}) of these compounds is taken from the work of Hong Y.Lee et al.[21] The common structure of compounds used in this study of sulfa drugs is as below.

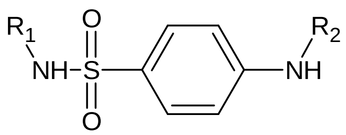


Figure I: Structure of sulfa drugs.

In obtaining QSAR models for modeling the activity, we have used the maximum R^2 method. For deciding the model we have used Pogliani's quality factor Q[22-23] as one of the parameters apart from investigating relative predictive power of the model and finally confirmation by using cross-validation[24] techniques. The structural details of 33 sulfonamides used in the present study and their inhibitory activity ($logIC_{50}$) against Pneumocystis carinii Dihydropteroate Synthetase are reported in Table I. The topological and indicator parameters calculated for these compounds are presented in Table II.

The correlation of the used parameters and their correlation with the activity is shown in Table III. The cross validated parameters are given in Table IV while calculation of observed and predicted log IC_{50} using best model is shown in Table V. The graph between observed and predicted log IC_{50} is represented in Figure-2.

Indicator parameters

In the present study we have used two indicator variables, IR_1 and IR_2. IR_1 is taken as unity when aromatic ring is present at R_1 otherwise it is zero and IR_2 is 1 if ketonic group is present at R_2 otherwise its value is zero. Multiple regression analysis for correlating activities of sulfonamide derivatives with molecular descriptors has been carried out using NCSS software.

RESULT AND DISCUSSION

A perusal of Table III reveals collinearity exists among the calculated descriptors. The correlation matrix represented in Table III shows that W and IR_2 show some good correlation with activity. Strong autocorrelation is present between (i) W and Randic (ii)$^0\chi^V$ and Randic (iii) W and $^0\chi^V$. Comparatively poor autocorrelations exist between (i) χ_{eq} and $^0\chi^V$ (ii) IR_1 and IR_2. The models obtained and the quality of these models are given in Table IV.

Table I: Structure of Sulphonamides with their inhibitory activity.

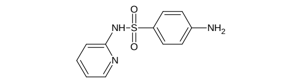
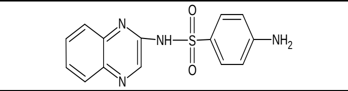
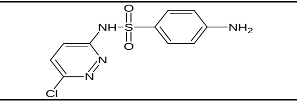
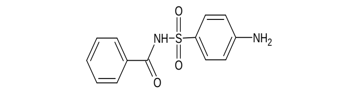
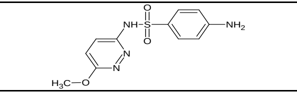
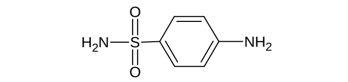
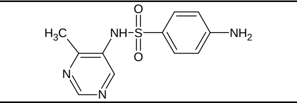
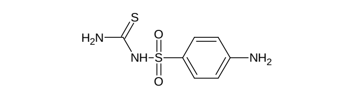
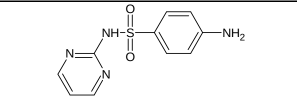
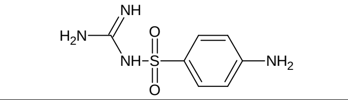
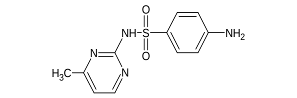
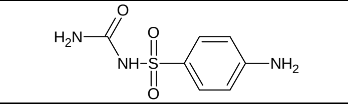
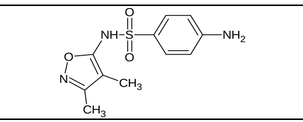
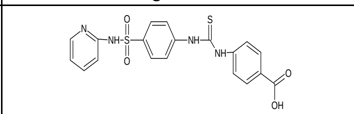
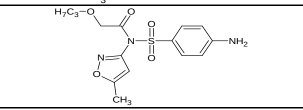
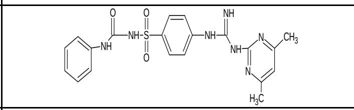
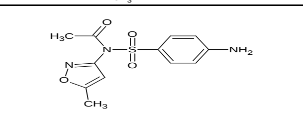
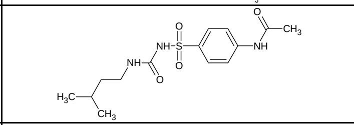
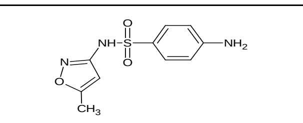
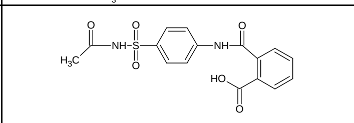
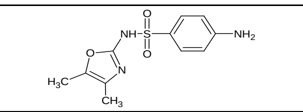
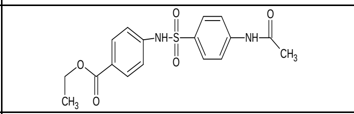
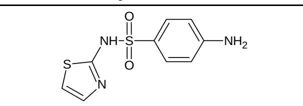
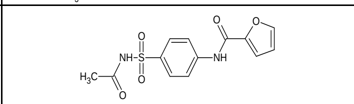
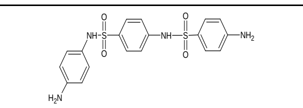
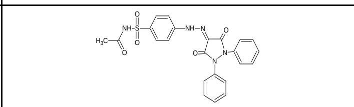
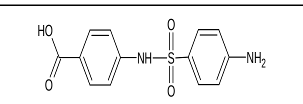
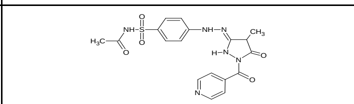
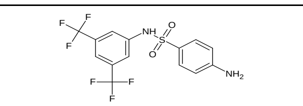
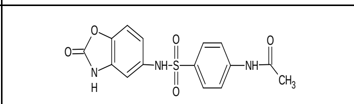
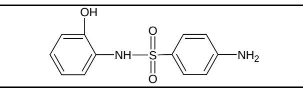
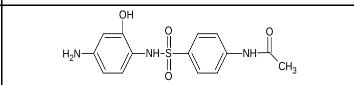
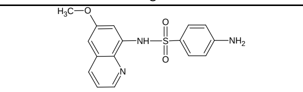
S.N0.	Compound	$LogIC_{50}$	S.N0.	Compound	$LogIC_{50}$
1		-0.7447	18		-1.5229
2		-1.7447	19		-0.4949
3		-1.7696	20		0.6232
4		0.4314	21		-1.6576
5		-0.7212-	22		0.5051
6		-1.1079	23		-0.5229
7		-1.3979	24		0.7709
8		-1.6383	25		2.7124
9		-1.6990	26		2.8941
10		-1.6383	27		2.0373
11		-1.0506	28		2.3766
12		-1.8861	29		3.1169
13		-0.7447	30		2.6575
14		-0.5850	31		3.3233
15		-0.0969	32		2.7793
16		-0.6383	33		1.7316
17		-0.4202			

Table II: Calculated molecular descriptors.

s.n.	χ_{eq}	W	J	$^0\chi^V$	Randic	logP	IR_1	IR_2	Log Ic_{50}
1.	2.4846	536	2.6133	0.28	4.1893	0.03	1	0	-0.7447
2.	2.5439	638	2.3724	0.2636	4.3283	1.02	1	0	-1.7447
3.	2.5114	758	2.5626	0.248	4.6393	0.32	1	0	-1.7696
4.	2.489	616	2.726	0.2726	4.3865	0.25	1	0	0.4314
5.	2.5112	536	2.52	0.28	4.1365	-0.12	1	0	-0.7212-
6.	2.489	627	2.683	0.2683	4.3865	0.34	1	0	-1.1079
7.	2.4861	614	2.8251	0.2734	4.4393	1.01	1	0	-1.3979
8.	2.4789	1311	3.3081	0.2308	5.6629	0.38	1	1	-1.6383
9.	2.5091	765	2.9942	0.2722	4.9129	-0.53	1	1	-1.6990
10.	2.5071	535	2.618	0.2805	4.1893	0.89	1	0	-1.6383
11.	2.4861	625	2.7817	0.2692	4.4393	1.08	1	0	-1.0506
12.	2.5091	448	2.4733	0.2968	3.8475	0.05	1	0	-1.8861
13.	2.4872	2334	2.0056	0.1744	6.9842	0.94	1	0	-0.7447
14.	2.5077	880	2.5237	0.2366	4.9921	1.66	1	0	-0.5850
15.	2.6575	1472	2.562	0.2196	5.8761	4.54	1	0	-0.0969
16.	2.4839	616	2.726	0.2726	4.4921	1.19	1	0	-0.6383
17.	2.4773	1166	2.2353	0.2353	5.9393	3.32	1	0	-0.4202
18.	2.4944	966	1.9503	0.2364	5.3865	1.3	1	0	-1.5229
19.	2.4859	736	2.6298	0.2545	4.7421	1.19	1	0	-0.4949
20.	2.4947	152	3.913	0.4119	2.5185	-0.72	0	0	0.6232
21.	2.5056	307	3.8203	0.3322	3.1698	-0.48	0	0	-1.6576
22.	2.5064	307	3.9864	0.3322	3.1893	-1.22	0	0	0.5051
23.	2.5323	307	3.8203	0.3322	3.2157	-0.7	0	0	-0.5229
24.	2.5031	2754	1.7876	0.1589	7.3142	1.99	1	0	0.7709
25.	2.4819	3288	1.9812	0.1524	7.7281	2.53	1	1	2.7124
26.	2.4469	1250	4.3731	0.2034	5.1629	1.79	0	1	2.8941
27.	2.4605	1660	2.5441	0.1957	6.2157	0.31	1	1	2.0373
28.	2.4787	1752	2.6818	0.1871	6.2157	3.09	0	1	2.3766
29.	2.5284	1043	2.4233	0.2203	5.2157	0.94	1	1	3.1169
30.	2.5069	3705	2.8761	0.1628	8.7601	1.77	1	1	2.6575
31.	2.519	2858.5	1.9644	0.1637	7.4837	-0.13	1	1	3.3233
32.	2.5309	1473.5	1.884	0.2036	6.1629	1.43	0	1	2.7793
33.	2.4923	1148	2.7158	0.2202	5.4393	0.24	0	0	1.7316

χ_{eq} =equalized electronegativity, W=Wiener index, J=Balaban index, $^0\chi^V$= Zero order connectivity, Randic=Randic connectivity index, IR_1 and IR_2 = Indicator parameters

The mono-parameteric model with W, as correlating parameter is as under:

$\log IC_{50}$= -1.2471+0.0012(± 0.0003) W ……..(1)

n =33, R^2=0.3769, Se=1.3852, F-ratio=18.751

Here n is the no. of compounds, R^2 is regression coefficient, Se is standard error of estimation and F-ratio is Fischer test. This model explains only 37% variance in data. Therefore Higher order correlation is desired.

In order to propose statistically more significant model step wise multiple regression analysis has been carried out. Table.4 shows that three significant biparametric correlations are possible in which IR_1 and Randic parameter play important role.

$\log IC_{50}$ = -0.0502+ 0.0014(± 0.0002)W- 1.8612(± 0.4754)IR_1 ……………..(2)

n =33, R^2=0.5876, Se=1.1455, F-ratio =21.375

$\log IC_{50}$=-2.7907 +0.8854(± 0.1496)Randic – 2.1735(± 0.4892)IR_1 ………..(3)

n = 33, R^2= 0.5871, Se= 1.1463, F-ratio= 21.326

In all above models the coefficient of IR_1 is negative showing its negative effect on activity, while coefficient of Randic index has a positive role on inhibitory activity. In a process of step wise regression analysis certain tervariate correlations have also been obtained:

$\log IC_{50}$ = 3.0374+0.0009(± 0.0004)W-9.5679(±6.9946)$^0\chi^V$-2.0380(± 0.4861)IR_1 ………(4)

$\log IC_{50}$=-0.2018+0.0009(±0.0003)W-1.5541(±0.4448)IR_1+1.3497(±0.4905)IR_2

n = 33, R^2= 0.673, Se = 1.0375, F –ratio= 19.896 ……..(5)

In these equations only $^0\chi^V$ is introduced as a new descriptor which shows a negative influence on activity. However statistics shows that one should go for higher order correlations. Therefore two such models have been obtained as under:

$logIC_{50}$=1.6328+0.0007(±0.0004)W-5.6491(±6.6519)$^0\chi^V$–1.6820(±0.4716)IR_1 +1.2462(±0.5077) IR_2
n = 33, R^2= 0.6812, Se= 1.0425, F-ratio= 14.959 …………. (6)

logIC50=1.3426+0.0008(±0.0003)W-0.4320(±0.4061)J-1.8686(± 0.5332)IR_1+1.4644(±0.5011)IR_2
n = 33, R^2= 0.6857, Se = 1.0352, F-ratio = 15.273 ………….(7)

During the process of regression it has been observed that compounds 8 and 29 are serious outliers, therefore they were deleted from the data set. The final models after deletion are as below:

$logIC_{50}$=-0.2156+0.0010(±0.0002)W-1.5944(±0.3740)IR_1+1.2645(±0.4601)IR_2
n=31, R^2 = 0.7764, Se= 0.8308, F-ratio=31.248 ………………..(8)

$logIC_{50}$=0.02227+0.0010(±0.0003)W-0.0665(±0.3462)J-1.6446(±0.4619)IR_1+1.2783(± 0.4741)IR_2
n= 31, R^2= 0.7767, Se= 0.846, F-ratio=22.609 …………………(9)

$logIC_{50}$=0.8513+0.0008(±0.0003)W-3.2855(±5.3952)$^0\chi^V$-1.6668(±0.3966)IR_1+1.2085(± 0.4745)IR_2
n = 31, R^2=0.7795, Se=0.8406, F-ratio=22.982 ………………………(10)

Here it is shown that a marked change in statistics is observed when comp. no. 8 & 29 are considered as outlier. The value of variance 0.673 changes from(eq.5) to 0.7764 (eq. 8) also significant change in variance is observed in tetraparametric correlations 0.7767 (eq. 9) and 0.7795 (eq. 10).

For the best model we performed cross validation and results are reported in Table IV. In this table lower value of PRESS/SSY for eqn. no. 10, and the value of R^2_{CV} (0.7172) suggests that this is the best model.

In order to arrive at a final conclusion we have calculated $logIC_{50}$ values using eqn. 10 and compared them with the observed values of $logIC_{50}$. Finally a graph is plotted between observed and calculated activities.

Table III: Correlation Matrix.

	$LogIC_{50}$	χ_{eq}	W	J	$^0\chi^V$	Randic	LogP	IR_1	IR_2
$LogIC_{50}$	1.0000								
χ_{eq}	-0.0849	1.0000							
W	0.6139	-0.0147	1.0000						
J	-0.0719	-0.1516	-0.4538	1.0000					
$^0\chi^V$	-0.5433	0.0459	-0.8596	0.6046	1.0000				
Randic	0.5615	-0.0150	0.9594	-0.5766	-0.9410	1.0000			
LogP	0.2397	0.2617	0.4586	-0.4112	-0.5924	0.5605	1.0000		
IR_1	-0.3238	0.0693	0.2044	-0.6060	-0.3086	0.3067	0.2168	1.0000	
IR_2	0.6739	-0.1653	0.5611	-0.0216	-0.5489	0.5682	0.1383	-0.0885	1.0000

Table IV: Cross-validation parameters.

Eqn.l no.	Parameter	PRESS	SSY	PRESS/SSY	R^2_{CV}	R^2_A	R^2	S_{PRESS}
5	W,IR_1,IR_2 (n=33)	31.2169	64.2506	0.4858	0.5142	0.6392	0.673	1.0352
7	W,J,IR_1,IR_2 (n=33)	30.0039	65.4636	0.4583	0.5417	0.6408	0.6857	1.0352
8	W,IR_1,IR_2 (n=31)	23.3264	62.8637	0.3710	0.7004	0.7515	0.7764	0.9127
9	W,J,IR_1,IR_2 (n=31)	22.8537	63.3363	0.3608	0.6932	0.7423	0.7767	0.9200
10	W. $^0\chi^v$ IR_1,IR_2 (n=31)	18.6357	64.7027	0.2880	0.7120	0.7456	0.7795	0.8308

PRESS-Predicted residual sum of squares, SSY-Sum of squares of regression value, R^2_{CV}-Cross- validation correlation coefficient, R^2_A=Adjusted R^2, S_{PRESS}= Uncertainty of prediction

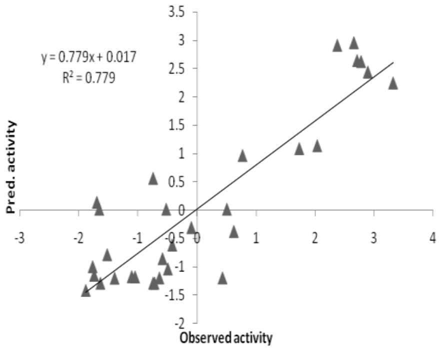


Figure 2: Graph between actual and predicted activity after deletion of outliers (Eq. No. 10).

Table V: Actual and predicted activity after deleting outlier com.no.29 and 8.

Com.no.	Actual	Predicted	Residual
1.	-0.745	-1.287	0.543
2.	-1.745	-1.148	-0.596
3.	-1.77	-0.997	-0.773
4.	0.431	-1.196	1.628
5.	-0.721	-1.287	0.566
6.	-1.108	-1.173	0.065
7.	-1.398	-1.201	-0.197
9.	-1.699	0.138	-1.837
10.	-1.638	-1.29	- 0.348
11.	-1.051	-1.178	0.127
12.	-1.886	-1.416	-0.470
13.	-0.745	0.562	-1.307
14.	-0.585	-0.857	0.272
15.	-0.097	-0.307	0.210
16.	-0.638	-1.196	0.558
17.	-0.42	-0.614	0.194
18.	-1.523	-0.785	-0.738
19.	-0.495	-1.037	0.542
20.	0.623	-0.375	0.998
21.	-1.658	0.016	-1.674
22.	0.505	0.016	0.489
23.	-0.523	0.016	-0.539
24.	0.771	0.964	-0.193
25.	2.712	2.64	0.072
26.	2.894	2.436	0.458
27.	2.037	1.137	0.900
28.	2.377	2.909	-0.533
30.	2.658	2.954	-0.297
31.	3.323	2.244	1.079
32.	2.779	2.622	0.157
33.	1.732	1.087	0.644

CONCLUSION

The aforementioned results and discussion lead us to the following conclusions.

1. Wiener index and zero-order valence connectivity index are useful in modeling the activity of present set of compounds.
2. Branching should be avoided in further developing potent drugs.
3. IR_1 has a negative coefficient suggesting that presence of aromatic ring at R_1 should be avoided.
4. Similarly ketonic group at R_2 will increase the activity hence that group should be preferred.

REFERENCES

1. Edman JC, Kovacs JA, Masur H, Ribosomal RNA sequence shows Pneumocystis carinii to be a member of the fungi. Nature, 1988; 334: 519–522.
2. Safrin S., Finkelstein DM, Feinberg J, Frame P, Simpson G, Wu A, Cheung T, Soeiro R, Hojczyck P, Black J, Comparison of three regimens for

treatment of mild to moderate Pneumocystis carinii pneumonia in patients with AIDS**.** Ann. Intern. Med, 1996; 124: 792–802.
3. Simonds RJ, Hughes WT, Feinberg J, Navin TR, Human Emerging and Re-emerging Infections Set, Clin. Infect. Dis., 1995; 21(1): S44–S48.
4. Wall PG, Porter K, Noone A, Goldberg DJ, AIDS, 1993; 71: 523–1525.
5. Walker RE, Masur H, In P. Walzer (ed.), Pneumocystis carinii pneumonia, 2nd ed. Marcel Dekker, New York, 1994; 439–466.
6. Volpe F, Ballantine S, Delves C, The multifunctional folic acid synthesis fas gene of Pneumocystis carinii encodes dihydroneopterin aldolase, hydroxymethyldihydropterin pyrophosphokinase and dihydropteroate synthase**,** Eur. J. Biochem., 1993; 216: 449–458.
7. Volpe F, Dyer M, Scaife JG, Darby G, Stammers DK, Delves CJ, The multifunctional folic acid sythesis fas gene of Pneumocystis carinii appears to encode dihydropteroate synthase and hydroxymethyldihydropterin pyrophosphokinase**,** Gene, 1992; 112: 213–218.
8. Hong, YL, Hossler PA, Calhoun DH, Meshnick SR, Inhibition of recombinant Pneumocystis carinii dihydropteroate synthetase by sulfa drugs.**,** Antimicrob. Agents Chemother, 1995; 39: 1756–1763.
9. Bjo¨rkman A, Phillips PA -Howard, Bull. W. H. O., 1991; 69: 297–304.
10. Korolkovas A, Burckhalter JH, Essentials of Medicinal Chemistry**,** John Wiley & Sons, Inc., New York, 1976.
11. Merali S, Zhang Y, Sloan D, Meshnick SR, Inhibition of Pneumocystis carinii dihydropteroate synthetase by sulfa drugs.**,** Antimicrob. AgentsChemother., 1990; 4: 1075–1078.
12. Voeller D, Kovacs J, Andrawis V, Chu E, Masur H, Allegra C, Interaction of Pneumocystis carinii Dihydropteroate Synthase with Sulfonamides and Diaminodiphenyl Sulfone (Dapsone)**,** J. Infect. Dis., 1994; 169: 456–459.
13. Hughes WT, Smith BL, Efficiency of diaminodiphenylsulfone and other drugs in murine Pneumocystis carinii pneumonitis, Antimicrob. Agents Chemother., 1984; 26: 436– 440.
14. Hughes WT, Smith BL., Jacobus DP, Successful treatment and prevention of murine Pneumocystis carinii pneumonitis with 4,4'-sulfonylbisformanilide, Antimicrob. Agents Chemother, 1986; 29: 509–510.
15. Walzer PD, Kim KC, Foy JM, Linke MJ, Cushion MT, Inhibitors of folic acid synthesis in the treatment of experimental Pneumocystis carinii pneumonia, Antimicrob. Agents Chemother., 1988; 32: 96–103.
16. Sloand E, Laughon B, Armstrong M, Bartlett M, Blumenfeld W, Cushion M, Kalica A, Kovacs J, Martin W, Pitt E, Pesanti E, Richards F, Rose R, Walzer P, The challenge of Pneumocystis carinii culture, J. Eukaryot. Microbiol., 1993; 40: 188– 195.
17. Walzer P, P. Pneumocystis carinii: surface reactive carbohydrates detected by lectin probes, J. Protozool., 1991; 38: 122–123.
18. Santos- Filhoo A ,Hopfinger AJ, A search for sources of drug resistance by the 4D-QSAR analysis of a set of antimalarial dihydrofolate reductase inhibitors, J Comput Aided Mol Des, 2001; 15: 1-12.
19. Nanbo A, Nanbo T, Mechanistic study on N-demethylation catalyzed with P-450 by Quantitative structure activity relationship using electronic properties of 4-substituted N, N-dimethylaniline, Quant Struct Act Relat, 2002; 21: 613-616.
20. Wang XD, Lin ZF, Yin DQ, Liu SS, Wang LS, Mechanistic study on N-demethylation catalyzed with P450 by quantitative structure activity relationship using electronic properties of 4-substituted N, N-dimethylaniline, Sci. China Ser B-Chem., 2005; 48(3): 246-252.
21. Pogliani L, Antimicrobial Agents and Chemotherapy, Amino Acids, 1994; 6: 141.
22. Pogliani L, Modelling with special descriptors derived from a medium sized set of connectivity indices, J. Phys. Chem., 1996; 100: 18065-18077.
23. Chaterjee S, Hadi AS, Price B, Regression Analysis by Examples, 3rd Edn., Wiley, New York, 2000.
24. Chaterjee S, Hadi AS, Price B, Regression Analysis by Examples, 3rd Edn., Wiley, New York, (2000).