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QSAR STUDY OF INDOLYLPYRIMIDINES DERIVATIVES AS ANTIBACTERIAL ACTIVITY

[1] Priyanka Dahiya [1] , Shailja sachan [2], Sukhendra singh patel [3]

[1]Department of Chemistry 1st, A.P.S. University , Rewa (M.P.) ,INDIA – 486001

[1]Department of Chemistry 1st , M. S. Golvalkar College, Rewa (M.P.) ,INDIA – 486001

Abstract: QSAR analysis on a set of indolylpyrimidine derivatives compounds for (PA) antibacterial activity was performed by using multiple regression procedure. The activity contributions of these compounds were determined from regression equation and the validation procedure to analyze the predictive ability of QSAR model was described. The best QSAR model with good correlation coefficient (r^2=0.8360), Q-ratio= 0.341, F-ratio =30.593 and N = 22. The leave-one-out (LOO) cross validation method using Ridge regression analysis was used in the future to confirm this model.

Keywords **- QSAR analysis, Inhibitory Activity, QSAR, LOO.**

I. INTRODUCTION

An important contributor to hospital acquired infections and antimicrobial resistance is gram-negative bacterium *Pseudomonas aeruginosa* (PA).[1,2] *Pseudomonas aeruginosa* is in charge of a variety of infectious cases, including nosocomial pneumonia, urinary tract infections, surgical wound infections, and bloodstream infections.[3] Gram-positive and gramme-negative bacteria have different cell walls in terms of structure. Antibiotics side effects, digestive enzymes, reactions, and heavy metal toxicityare all protected from by the outer membrane. Many chemical substances function as antibacterial agents by preventing the DNA synthesis of cell wall by blocking enzymes like DNA gyrase and dihydrofolate reductase and even by inhibiting enzymes processing the growth of peptidoglycan layer.[4,5] In the current work, we have made an effort to use QSAR molecular descriptors, which explains surface phenomenon, to distinguish between how chemical entities behave towards gramme positive and gramme negative bacteria. The goal of the current study was to examine the of utility of QSAR in the anticipation of indolylpyrimidine derivatives antibacterial activity against *Pseudomonas aeruginosa* (PA) and *Staphylococcus aureus* (SA). Learn how multiple linear regression (MLR) equations can be used to describe the correlation between the distinct behavior of activity against both gramme positive and gramme negative strains. Multiple downstream signaling cascades are recruited, phosphorylated,and activated as a result of this metabolic activity. Numerous cancers, including non-small cell lung cancer (NSCLC), osteosarcoma, breast cancer, acute myeloid leukemia, prostate cancer, and colorectal cancer, have been found to overexpress AXL.[6] Pyrimidine compounds are important in medicine because they work well as analgesic, the release of anti-inflammatory mediators such as histamine from mast cell, which are responsible for inflammatory and hypotension.[7] Anticonvulsant, insecticidal, herbicidal, antitubercular, anti-cancer and antidiabetic agents. The indole ring is recognized to have anti-inflammatory, antimicrobial and antifungal activities.[8–12] The fused ring system of substituted indolylpyrimidines is remarkably effective as antitumor and anti bacterialactivity.[13,14]The chemical structures were designed using ACD/ChemSketch 2021 and were saved as mol. files. The Dragon program was used to calculate the values of 28 descriptors shown.[15, 16]

11. BIOLOGICAL ACTIVITIES

In a series of indolylpyrimidines-based selective *Pseudomonas aeruginosa* (PA)and *Staphylococcus aureus* (SA)derivatives tests, each compound was examined for its ability to inhibit the growth of bacteria. The results are presented in the form of *Pseudomonas aeruginosa* (PAantibact), which was first established as converted to the 100 μg/mL and distance unit, value, millimeters (mm). This is directly collected from the work and used as the dependent variable in the QSAR study Panda and coworker's.[17-21]

I11. RESULTS AND DISCUSSION

In order to understand the experimental biological activity data of 28 indolylpyrimidines derivatives antibacterial activity as selective *Pseudomonas aeruginosa*, regression equation the most significant in contribution to inhibitory activity, we established a QSAR study between their in antibacterial activity and descriptors coding for molecular descriptors; Burden eigenvalues SpMax5_Bh(e), and SpMin7_Bh(i), Information(Yindex), Topological(DECC), Constitutional(MW), Edge(SpAD_EA(bo), Eta (Eta_betaS),descriptors of the molecules under consideration using Hansch and Fujita.[22-23] Pearson's correlation matrix has been performed on all descriptors by using NCSS statistical Software.[24] The analysis of the matrix revealed six descriptors for the development of MLR model. The value of descriptors selected for MLR model are presented in Table3 the correlation coefficient from 0.8360. The QSAR equation is supposed to be good if the *F*-test is above a threshold value. The statistical quality of the resulting models, as depicted in Table 6, is determined by r, standard error (std error), and randomization test. (ran $r2$) [25-26]

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Table 1: Structure and Activity of compounds

Com. no	R1	R2	*Pseudomonas aeruginosa*(PA) Antibacteria
1	OH	H	13
2	OH	p-NH_2	24
3	OH	p-Br	19
4	OH	P-Cl	18
5	OH	O,p-OH	14
6	OH	P-F	17
7	OH	P-CH_3	13
8	OH	P-OCH_3	17
9	OH	p-OH	11
10	OH	p-NO_2	23
11	SH	H	12
12	SH	p-NH_2	18
13	SH	p-Br	15
14	SH	P-Cl	16
15	SH	P-F	14
16	SH	P-CH_3	10
17	SH	P-OCH_3	13
18	SH	p-NO_2	19
19	NH_2	H	11
20	NH_2	p-NH_2	10
21	NH_2	p-Br	17
22	NH_2	P-Cl	15
23	NH_2	O,p-OH	13
24	NH_2	P-F	23
25	NH_2	P-CH_3	13
26	NH_2	P-OCH_3	25
27	NH_2	p-OH	13
28	NH_2	p-NO_2	24

Detailed Name of Descriptors

Name of Descriptors	Detailed Name of Descriptors
MW	molecular weight
Y index EA	Balaban Y index
DECC	Eccentric
SpMax5_Bh(e)	largest eigenvalue n. 5 of Burden matrix weighted by Sanderson electronegativity
SpMin7_Bh(i)	smallest eigenvalue n. 7 of Burden matrix weighted by ionization potential
SpAD_EA(bo)	spectral absolute deviation from edge adjacency mat. weighted by bond order
Eta_betaS	eta sigma VEM count

Table.2 Descriptor used in QSAR study

PA	Y index	DECC	MW	SpMax5_Bh(e)	SpMin7_Bh(i)	SpAD_EA(bo)	Eta_betaS
13	0.645	1.227	276.23	2.828	0.346	50.284	14.25
24	0.617	1.365	289.23	2.842	0.345	52.034	15
19	0.617	1.365	355.12	2.843	0.349	52.034	14.75
18	0.617	1.365	310.67	2.85	0.347	52.034	15
14	0.624	1.347	307.22	2.895	0.425	53.722	15.75
17	0.617	1.365	294.22	2.867	0.341	52.034	15
13	0.617	1.365	287.23	2.832	0.35	52.034	14.75
17	0.586	1.469	303.23	2.902	0.367	53.322	15.75
11	0.617	1.365	291.22	2.855	0.346	52.034	15
23	0.566	1.52	321.23	3.021	0.511	57.789	16.5
12	0.645	1.227	292.3	2.813	0.362	50.284	14
18	0.617	1.365	305.3	2.828	0.36	52.034	14.75
15	0.617	1.365	371.19	2.829	0.365	52.034	14.5
16	0.617	1.365	326.74	2.836	0.363	52.034	14.75
14	0.617	1.365	310.29	2.853	0.355	52.034	14.75
10	0.617	1.365	303.3	2.817	0.367	52.034	14.5
13	0.586	1.469	319.3	2.889	0.384	53.322	15.5
19	0.566	1.52	337.3	3.016	0.532	57.789	16.25
11	0.645	1.227	274.24	2.818	0.342	50.284	14.25
10	0.617	1.365	287.24	2.832	0.341	52.034	15
17	0.617	1.365	353.13	2.833	0.345	52.034	14.75
15	0.617	1.365	308.68	2.84	0.343	52.034	15
13	0.624	1.347	305.23	2.888	0.423	53.722	15.75
23	0.617	1.365	292.23	2.857	0.337	52.034	15
13	0.617	1.365	285.24	2.821	0.346	52.034	14.75
25	0.586	1.469	301.24	2.893	0.362	53.322	15.75
13	0.617	1.365	289.23	2.845	0.342	52.034	15
24	0.566	1.52	319.24	3.017	0.505	57.789	16.5

Table 3 Correlation Matrix of different descriptors

	PA	Y index	DECC	MW	SpMax5_ Bh_e_	SpMin7_ Bh_i_	SpAD_ EA_bo_	Eta_beta_S
PA	1.0000							
Y_index	-0.5801	1.0000						
DECC	0.5676	-0.9832	1.0000					
MW	0.2711	-0.3700	0.4006	1.0000				
SpMax5_\Bh__	0.5441	-0.8619	0.8002	0.2640	1.0000			
SpMin7_Bh_i_	0.3632	-0.7209	0.6488	0.3241	0.9226	1.0000		
SpAD_EA_bo_	0.5185	-0.8931	0.8581	0.3546	0.9675	0.9345	1.0000	
Eta_betaS	0.5404	-0.8661	0.8596	0.2093	0.9236	0.8030	0.9270	1.0000

Table 4 result of cross validation

Model No	N	Press	SSY	Press/SSY	R^2	R^2cv	PSE	Spress
1	28	356.834	181.023	1.971	0.336	-0.971	0.674	3.704
2	28	309.000	228.857	1.351	0.425	-0.351	0.627	3.515
3	28	284.128	253.728	1.119	0.471	-0.119	0.602	3.441
4	22	48.265	246.097	0.196	0.836	0.803	0.315	1.637

Model No.1 PA = 90.1201 - 121.0509 Y_index [1]
N= 28, MSE= 13.724, R^2= 0.336, AR^2= 0.311, Q-VALUE= 0.042

Here N is the number of compounds used in the study, MSE is the mean square error of estimation, R^2 is the regression coefficient, AR^2 is the adjusted Regression coefficient, F-ratio and Q= R2/MSE; Pogliani' s Quality factor.[27]
The regression analysis gave many biparametric model follow rule of thumb. The QSAR Model NO.2 has significant.

Model No.2 PA = -259.4234+ 106.1352SpMax5_Bh_e_ - 76.6172SpMin7_Bh_i_ [2]
N= 14, MSE= 12.361, R^2= 0.425, AR^2= 0.379, Q-VALUE= 0.052

The QSAR model no. 1 and model no. 2 has significant importance in which SpMax5_Bh_e_ show positive contribution while Y_index and SpMin7_Bh_i_ show inverse concentration with inhibitory activity.

Model No.3 PA = -280.4490+ 110.1869SpMax5_Bh_e_ - 86.7643SpMin7_Bh_i_ + 0.04294MW [3]
N= 28, MSE= 11.838, R^2= 0.471, AR^2= 0.405, Q-VALUE= 0.057

Various triparametric model have been obtained with similar statistics, out of which one contain SpMax5_Bh_e_ ,SpMin7_Bh_i_,and MW was found to give good result the model obtained is as follows.
Finally in order to confirm which out of the proposed model is the most appropriated for modelling the inhibitory.

Model No.4 PA = -244.7347+ 92.6277SpMax5_Bh_e - 63.1236SpMin7_Bh_i + 0.0592 MW [4]
N= 22, MSE= 2.681, R^2= 0.8360, AR^2= 0.808, Q-VALUE= 0.341

We calculated the pogliani's quality factor Q which is Ratio of R and MSE means square error the these Q-value maximum value is found for, eq. 4 with the highest correlation coefficient (r = 0.9143) with R^2cv = 0.803 was considered to be the best model.

IV. CONCLUSIONS

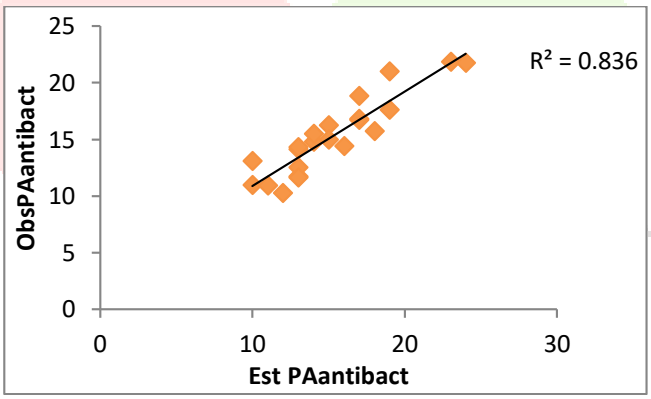
From the result and discussion made above, we conclude that the QSAR study of Indolylpyrimidines derivatives as antibacterial activity were more active against the gram-negative bacteria *Pseudomonas aeruginosa* agents. Linear regression for the total data set of 28 compounds in the present study with Indolylpyrimidines derivatives as antibacterial activity demonstrated that the SpMax5_Bh(e), SpMin7_Bh(i), (MW), molecular descriptors appears to be governing factors for the biological potency of QSAR Study of Indolylpyrimidines derivatives as antibacterial activity**.**

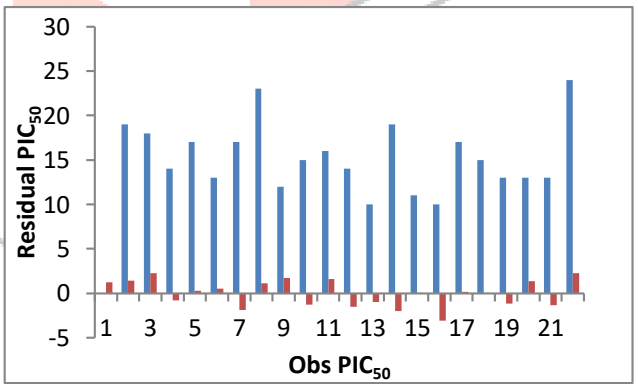
The following conclusions are obtained from this analysis.

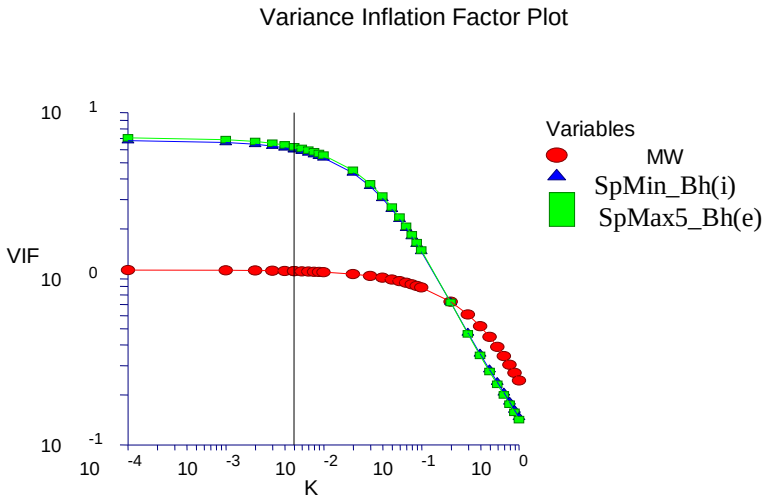
1. The positive coefficient of SpMax5_Bh(e), MW, suggest that these parameters plays a dominating role in deciding the activity of present set of compounds.
2. The negative coefficient of SpMin7_Bh(i), suggest that the low or negative value of SpMin7_Bh(i),will favors the biological activity(Antibacterial).

Table 5: Observed and predicted activity

	Obs.	Predicted	
Com no	PA	PA	Residual
1	13	11.73766	1.26234
2	19	17.61057	1.389434
3	18	15.75232	2.247682
4	14	14.79257	-0.79257
5	17	16.73136	0.268644
6	13	12.50723	0.492765
7	17	18.8658	-1.8658
8	23	21.86488	1.135119
9	12	10.29013	1.709868
10	15	16.25566	-1.25567
11	16	14.39742	1.602582
12	14	15.5027	-1.5027
13	10	10.99658	-0.99658
14	19	21.02801	-2.02801
15	11	10.946	0.053996
16	10	13.07594	-3.07594
17	17	16.81891	0.18109
18	15	14.96066	0.039338
19	13	14.15255	-1.15255
20	13	11.62295	1.377049
21	13	14.33485	-1.33485
22	24	21.75524	2.244761







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