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Research Article

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2D-QSAR Study of Indole Derivatives for Anti-Microbial Study

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ABSTRACT

A series of methyl 3-(2-amino-2-oxoacetyl)-6-chloro-1-methyl-1H-indole-5-carboxylate were screened for their anti-microbial activity against bacteria S.aureus. These compounds have showed moderate and very good antimicrobial activity. The Quantitative Structure Activity-Relationships (QSAR) study on the indole series was made using lipophilic, electronic and steric parameters. Several statistical expressions were developed and best models were validated. The studies confirm that the antimicrobial activity is dependent on selected lipophilic, electronic and steric parameters.The QSAR study provides important structural insights in designing of potent antimicrobial agents.

Keywords: QSAR; Antimicrobial agents; Indole derivatives; Multiple linear regression

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INTRODUCTION

The development of new antibacterial agents has been a very important step for researchers. Most of the research programme efforts are directed toward the design of new drugs, because of the unsatisfactory status of present drugs side effects and the acquisition of resistance by the infecting organisms to present drugs. The resistance of common pathogens to standard antibiotic therapy is rapidly becoming a major health problem throughout the world [1,2].

The investigation of the quantitative structure activity/property relationships (QSAR/QSPR) of substances is an important aspect of modern chemistry, biochemistry, medicinal chemistry, and drug discovery. The data or results that are obtained from the QSAR study consist of mathematical equations which relate the chemical structure of compounds to a wide variety of their physical, chemical, electronic and biological properties. Once a correlation between structure and activity/property is found, any number of compounds, including those not synthesized yet, can readily be screened in silico for selection of structures with desired properties. Hence, it is possible to select the most promising compounds for synthesis and testing in the laboratory [3,4].

A new approach called the Hansch approach is a new extra thermodynamic approach in the analysis of quantitative structure activity relationships (QSAR). It has been most widely and effectively used for theoretical drug design. This method works by assuming that the potency of a certain biological activity exerted by a series of congeneric compounds can be expressed in terms of a function of various physicochemical (electronic, steric and hydrophobic) effects.

This equation below helps to obtain relationships between functions and activity of compounds:

f (biological activity) =f (electronic) +f (steric) +f(hydrophobic) +[f (structural) +f (theoretical)]

If these functions could be formulated in an equation showing certain effects favorable for the activity, structural modifications that enhance such properties would be expected to generate potent active compounds [5-7].

Anti-bacterial Agents

Antimicrobial agents that can serve as replacements to conventional pharmaceutical antibiotics are disclosed. The antimicrobial agents comprise conjugatively transmissible plasmids that kill targeted pathogenic bacteria, but are not harmful to donor bacteria.

METHOD AND RESULTS

Firstly 20 indole deravatives were selected of wide diverse functional group substituents. Using the Chem Draw software all the structures were made, based on the structure physic-chemical properties were calculated in the same software. The results obtained were tabulated in the excel sheet and then multiple linear regression was performed and various QSAR models were generated (Figures 1 and 2). Based on model obtained the best model was selected. 20 indole derivatives were selected for the QSAR study. Out of 16 were chosen as training set compounds and4 were taken as test set compounds [8] (Tables 1-7, Figures 3-12).

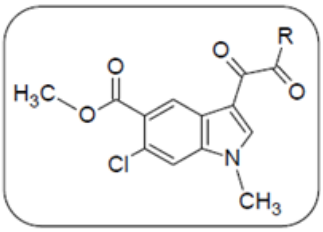

Figure 1: Methyl 6-chloro-3-[(N,N-dialkylamino)(oxo)acetyl 1-methyl-1H-indole-5-carboxylates

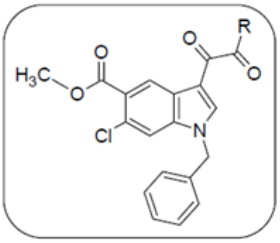

Figure 2: Methyl 1-benzyl-6-chloro-3-[(N,N-dialkylamin)(oxo)acetyl]-1H-indole-5-carboxylates

Table 1: Compounds taken as training set

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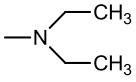
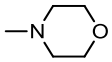
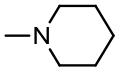
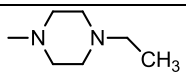
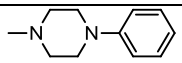
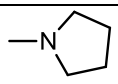
1	
2	
3	
5	
6	
8	

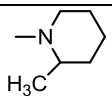
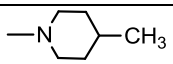
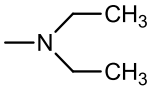
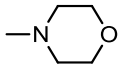
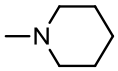
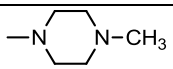
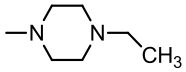
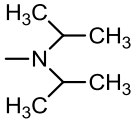
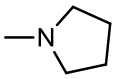
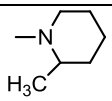
9	
10	
11	
12	
13	
14	
15	
17	
18	
19	

Table 2: Table showing calculation of physicochemical properties done for training set compounds

Sr No	Compound	Log P	Index of refraction	parachor	Polarizability (*10-24)	MIC *S. aureus*	pMIC
1	1	1.78	1.579	704.3	36.27	200	2.3
2	2	0.7	1.63	683.7	35.96	25	1.4
3	3	1.83	1.629	703.1	37.24	62.5	1.8
4	5	1.19	1.622	768.3	40.56	100	2
5	6	2.93	1.644	875.5	46.93	250	2.4
6	8	1.42	1.639	664.5	35.41	62.5	1.8
7	9	2.15	1.621	734.2	38.99	250	2.4
8	10	2.16	1.621	734.2	38.99	250	2.4
9	11	3.51	1.595	888.7	46.3	500	2.7
10	12	2.43	1.636	868.1	45.99	62.5	1.8
11	13	3.57	1.635	887.5	47.26	500	2.7
12	14	0.86	1.636	914.1	48.76	25	1.4
13	15	2.93	1.629	952.7	50.58	250	2.4
14	17	4.15	1.586	950.9	49.81	750	2.88
15	18	3.15	1.643	848.9	45.43	200	2.3
16	19	3.89	1.628	918.6	49.02	250	2.4

Table 3: Compounds taken as test set

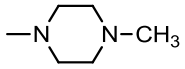
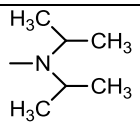
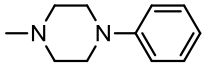
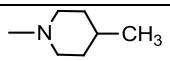
Sr No.	R
4	
7	
16	
20	

Table 4: Table showing calculation of physicochemical properties done for test set compounds

Sr No	Compound	Log P	index of refraction	parachor	Polarizability (*10-24)	MIC *S. aureus*	pMIC
1	4	0.86	1.631	729.7	38.73	25	1.4
2	7	2.41	1.571	766.5	39.78	500	2.7
3	16	4.66	1.646	1059.9	56.96	750	2.88
4	20	3.9	1.628	918.6	49.02	400	2.6

Table 5: Comparison of predicted value and observed value for training set

Sr No	Compound	pMIC	Predicted value
1	1	2.3	2.29
2	2	1.4	1.48
3	3	1.8	1.99
4	5	2	1.75
5	6	2.4	2.24
6	8	1.8	1.83
7	9	2.4	2.25
8	10	2.4	2.26
9	11	2.7	2.58
10	12	1.8	1.94
11	13	2.7	2.45
12	14	1.4	1.5
13	15	2.4	2.19
14	17	2.88	2.99
15	18	2.3	2.31
16	19	2.4	2.7

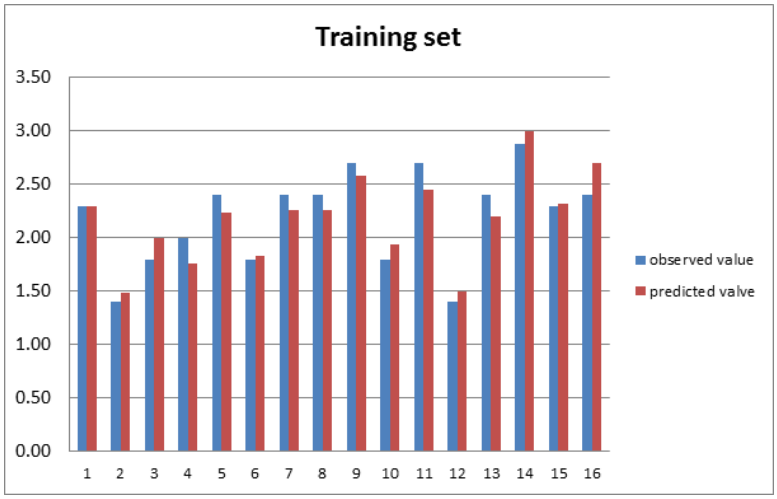


Figure 3: Chart of comparison between observed and predicted PMIC value for training set

Table 6: Comparison of predicted value and observed value for test set

Sr No	Compound	pMIC	Predicted value
1	4	1.4	1.63
2	7	2.7	2.68
3	16	2.88	2.76
4	20	2.6	2.7

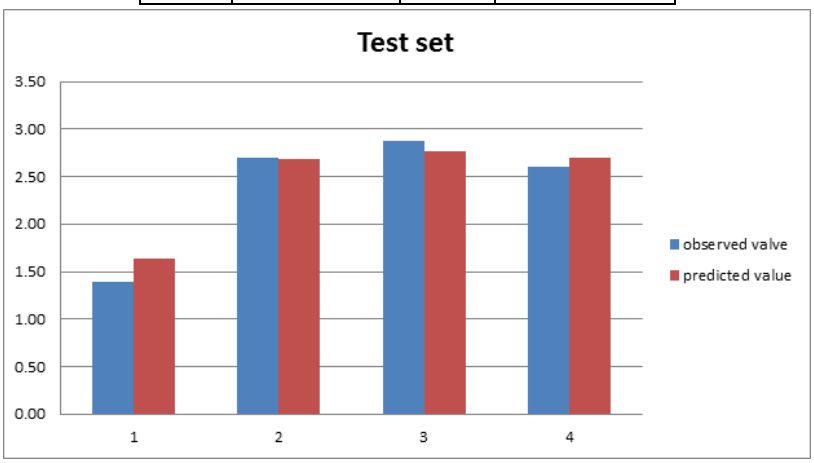


Figure 4: Chart of comparison between observed and predicted PMIC value for test set

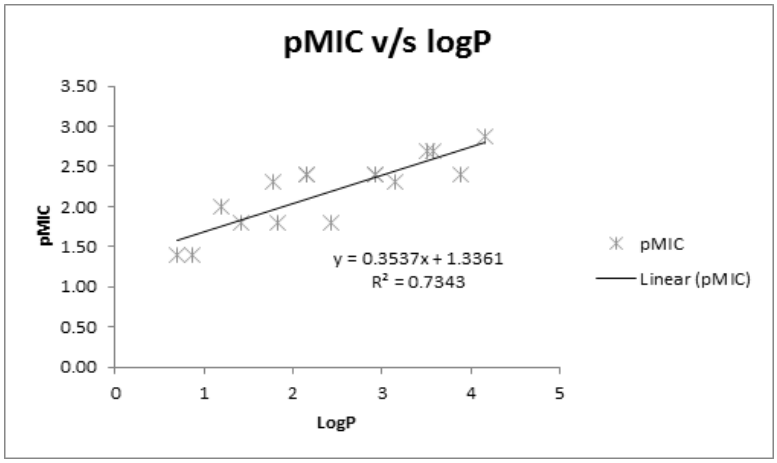


Figure 5: Chart of comparison between parameter (Log P) and pMIC values for training set

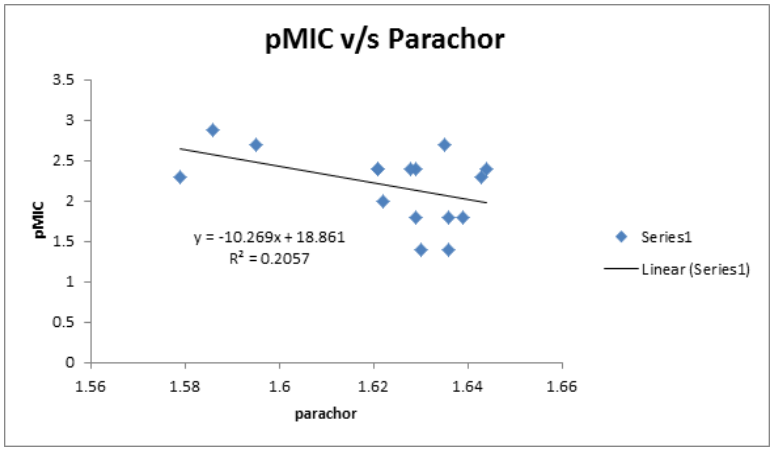


Figure 6: Chart of comparison between parameter (Parachor) and pMIC values for training set

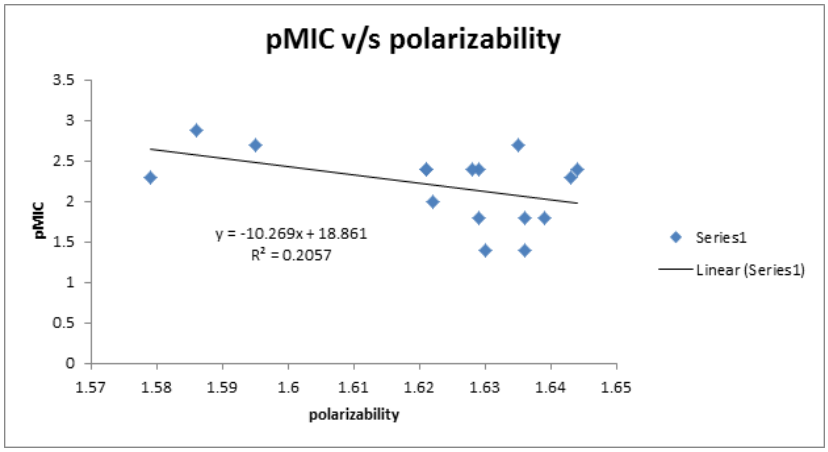


Figure 7: Chart of comparison between parameter (polarizabilty) and pMIC values for training set

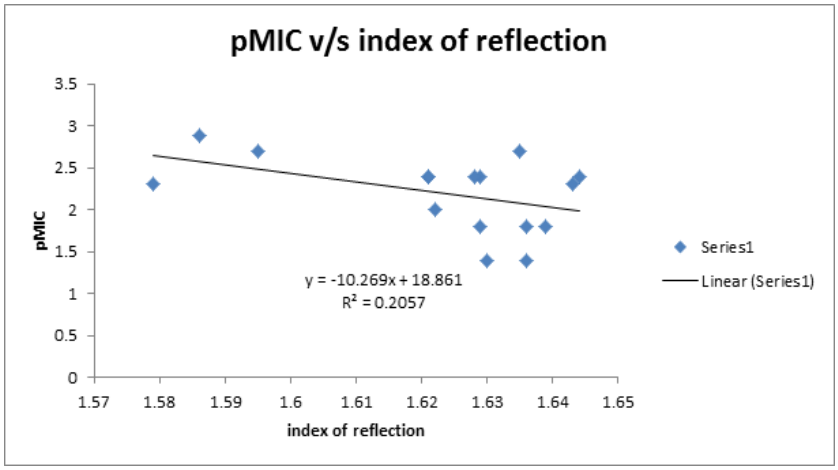


Figure 8: Chart of comparison between parameter (index of reflection) and pMIC values for training set

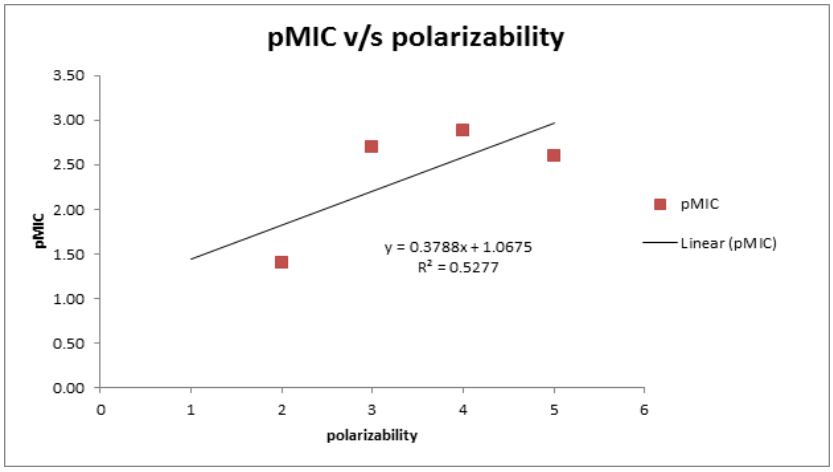


Figure 9: Chart of comparison between parameter (polarizabilty) and pMIC values for test set

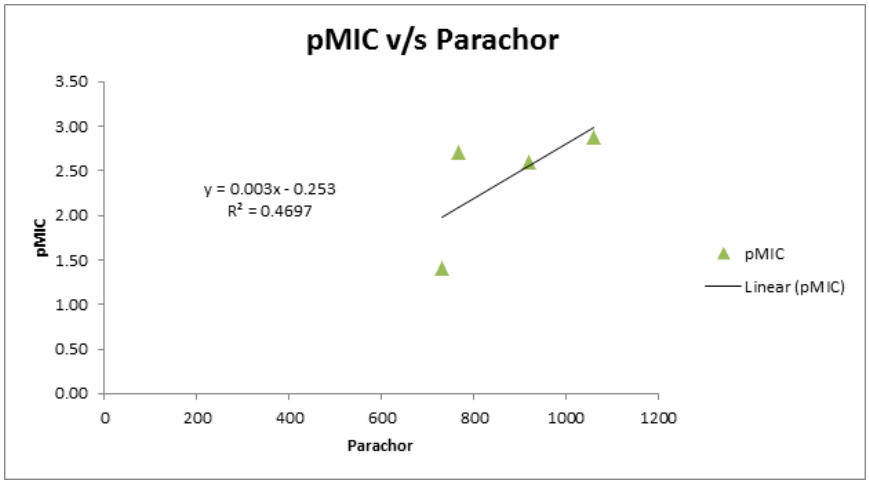


Figure 10: Chart of comparison between parameter (parachor) and pMIC values for test set

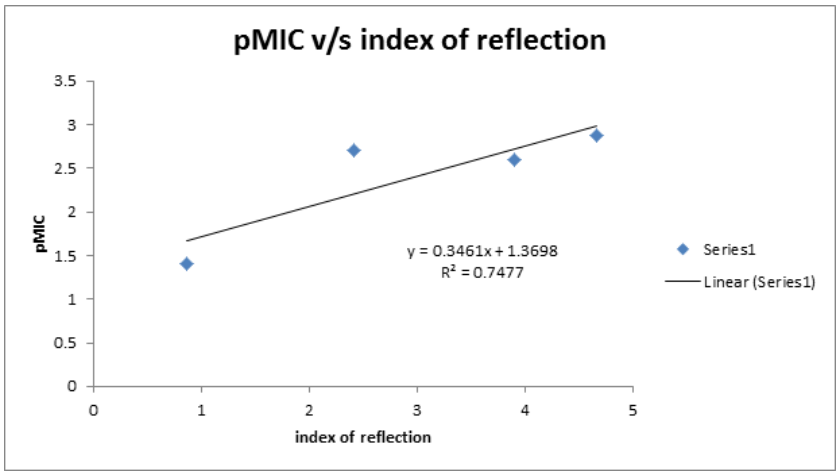


Figure 11: Chart of comparison between parameter (index of reflection) and pMIC values for test set

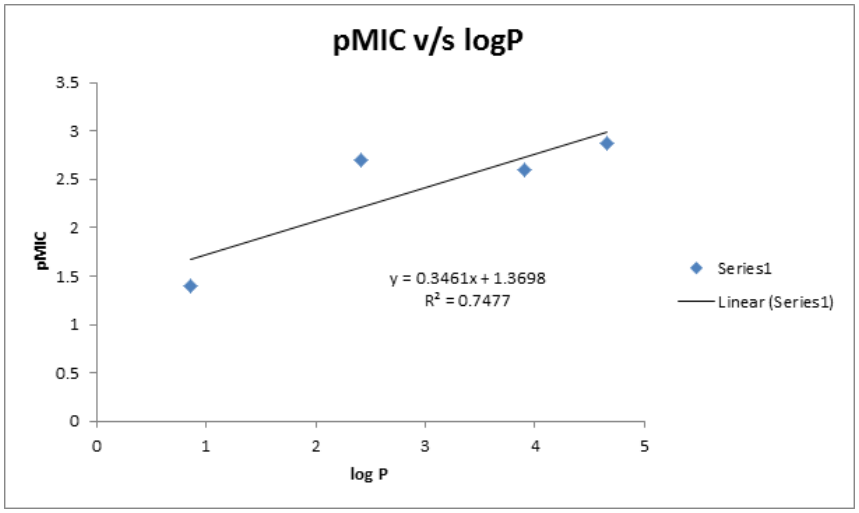


Figure 12: Chart of comparison between parameter (log P) and pMIC values for test set

Table 7: Developed 2D-QSAR models

Model No.	Equation	Observations	R^2	Standard Error	F
1	PMIC=35.764+(0.223*log p)+(0.018*MR)-(21.063*index of reflection)-(0.036*parachor)+(0.647*polarizability)	16	0.875	0.189	14.59
2	PMIC=12.087+(0.334*log p)+(0.008*MR)-(6.424*index of reflection)-(0.001*parachor)	16	0.828	0.209	14.22
3	PMIC=49.725+(0.041*MR)-(30.191*index of reflection)-(0.054*parachor)+(0.965*polarizability)	16	0.838	0.209	14.27
4	PMIC=28.227+(0.351*log p)-(16.065*index of reflection)-(0.026*parachor)+(0.476*polarizability)	16	0.859	0.195	16.78
5	PMIC=1.870+(0.403*log p)+(0.001*MR)+(0.008*parachor)-(0.182*polarizability)	16	0.803	0.231	11.21
6	PMIC=11.105+(0.343*log p)+(0.006*MR)-(5.807*index of reflection)-(0.024*polarizability)	16	0.834	0.211	13.87
7	PMIC=11.317+(0.386*log p)-(0.005*MR)-(5.848*index of reflection)	16	0.819	0.211	18.14
8	PMIC=11.985+(0.329*log P)-(6.523*index of reflection)	16	0.813	0.206	28.4

CONCLUSION

Classical QSAR approach was applied successfully to a 16 training set compounds from series of Methyl 6-chloro-3-[(N,N-dialkylamino)(oxo)acetyl 1-methyl-1H-indole-5-carboxylates with well-expressed antimicrobial activity. The genenerated best equation (No. 1) was validated with 4 test set compounds with same series. Quantitative structure–activity relationship studies revealed that the antimicrobial activities of these synthesized derivatives against the test microorganisms are mainly governed by the logP, Index of reflection, polarizability and parachor parameters. Among four selected parameter index of reflection and parachor produces negative effect on anti-microbial activity while logP and polarizability produces positive effect on antimicrobial activity. Index of reflection has higher impact on antimicrobial activity because their coefficient is higher than rest of all. Thus a proper substitution of the group with lower index of reflection of aromatic ring probably improves the potency of these derivatives as antimicrobial agents. The effect of modification at this site will be the subject of further optimization and investigation.

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