Research Article

QSAR: EXPLORATION OF OXADIAZOLE DERIVATIVES AS A POTENT ANTIMICROBIAL AGENT

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ABSTRACT

A quantitative structure activity relationship study on a series of 2-substituted-1H benzimidazole, 1, 3, 4-oxadiazole analogues (derivatives) was made using combination of various descriptors. Several statistical expressions were developed using multiple liner regression analysis. The best quantitative structure activity relationship models were further validated by Loo method of cross-validation. The study revealed that the Thermodynamic property, i.e., steric property like Shape Coefficient and Molecular Topological Index (MIT), contributed positively and Electronic property like Dipole (DPL) and Electronic Energy (EE) contributed negatively. The study suggested that substitution of group at R & R1 on oxadiazole ring by those groups which increase the Shape Coefficient and Molecular Topological Index which enhances the antimicrobial activity. Attempts are made to minimise Dipole and Electronic Energy for better biological activity. The quantitative structure activity relationship study provides important structural insights in designing of potent antimicrobial agents.

Keywords: Oxadiazole, antimicrobial, QSAR, descriptors.

INTRODUCTION

Aim is focussing on successful synthesis and antimicrobial activity of new derivatives. The antimicrobial activity study revealed that all the compounds can be show moderate to good antibacterial activities against microorganisms. With proper designing and structure activity relationship studies of compounds having oxadiazole nucleus, prospective compounds can be synthesized for a particular biological activity.

Antimicrobials are one of most significant molecules in fighting bacterial infections. They have extremely benefited the health-related quality of human life. Over the past few decades, these health benefits are under threat as many commonly used antibiotics have become less effective against certain illnesses because of their toxic reactions and due to emergence of microbial resistance. Therefore, it is essential to investigate newer drugs with lower resistance[1,2].

Benzimidazoles are remarkably effective compounds both with respect to their inhibitory activity and their favourable selectivity ratio. Extensive biochemical and pharmacological studies have confirmed that benzimidazole molecules are effective against various strains of microorganisms. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities[3,4].

Oxadiazole is a heterocyclic aromatic chemical compound with the molecular formula $C_2H_2N_2O$. Oxadiazole derivatives are well known to have a wide range of biological activities. In addition, 1, 3, 4-oxadiazole is a versatile lead molecule for designing potent bioactive agents. This interesting group of compounds possesses diverse biological activity such as antimicrobial, anti-inflammatory, antitubercular, anticonvulsant, anticancer, anti-HIV, hypoglycaemic and genotoxic activities. In light of these interesting biological activities, it was our interest to synthesize some new 1, 3, 4-oxadiazole derivatives bearing different types of derivatives and evaluate their antimicrobial potential.

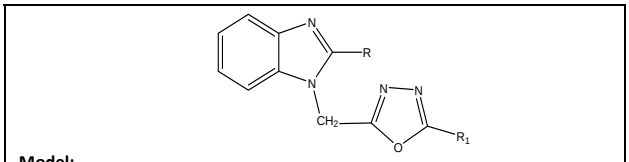
Hence, there is a need to analyze the correlation present in between antimicrobial activity and physico-chemical parameters using the QSAR methods. QSAR enables the investigators to establish reliable quantitative structure-activity and structure-property relationships to derive an in QSAR model to predict the activity of novel molecules prior to their synthesis. In order to study and deduce a correlation between structure and biological activity of 2-substituted-1H benzimidazole, 1, 3, 4-oxadiazole benzoic acid derivatives as antibacterial agents, we have developed QSAR models. Together with these models derived it revealed the significance of some steric, electrostatic, hydrophobic parameters with biological activity[5]. Structural variations in the molecular fields of particular regions can be studied and QSAR models can be used to give an insight for the design of potent antibacterial agents.

MATERIALS AND METHODS

The table 1 shows the structural features of given derivatives along with their biological activities (MIC µg/ml). The biological activity data MIC (minimum inhibitory concentration in µg/ml) were converted to negative logarithmic dose in moles (pMIC) for QSAR analysis. The correlations were sought between inhibitory activity and various substituent constants at position R & R1 of the molecule. The series was subjected to molecular modelling using CS Chem-Office 8.0. Structures of all the compounds were sketched using builder module of the programme. These structures were then subjected to energy minimization using force field molecular

mechanics-2 (MM2) until the root mean square (RMS) gradient value became smaller than 0.1 kcal/mol. Å. Minimized molecules were subjected to optimization by MOPAC method until the RMS gradient attained a value smaller than 0.0001 kcal/mol. Å. The descriptor values for all the molecules were calculated using software. Statistical analysis was performed on the observed descriptors using VALSTAT.

Table 1: Structure, Antimicrobial Activities of Compounds and descriptors used in QSAR



Model:-

S. NO.	Comp. No.	Substitution		MIC	pMIC	Structural descriptors		
		R	R1			D4	EE	Sc
1	5	H	CH_3	16	0.07468	4.2018	-15270.2	0.8
2	6	H	C_2H_5	32	0.14019	5.3299	-16928.4	1
3	7	H	CH_2Cl	32	0.12868	3.23	-17125.5	1
4	8	H	CH_2CH_2Cl	16	0.06090	4.263	-18407.7	0.83333
5	9	H	C_6H_4	16	0.05790	5.9584	-21400.8	1
6	10	H	2-ClC_6H_4	16	0.05148	6.6446	-23483.3	1
7	11	H	4-ClC_6H_4	32	0.10297	4.916	-23188.2	0.85714
8	13	H	4-OHC_6H_4	16	0.05473	5.2307	-23167	0.85714
9	14	H	2-$OCH_3C_6H_4$	16	0.05223	6.2732	-25750.3	1
10	15	H	4-$OCH_3C_6H_4$	32	0.10446	5.6936	-25109.1	1
11	16	CH3	CH_3	4	0.01752	3.9962	-17269.9	0.8
12	17	CH3	C_2H_5	8	0.03301	4.7973	-18845.3	1
13	18	CH3	CH_2Cl	16	0.06090	3.9694	-19056.2	1
14	19	CH3	CH_2CH_2Cl	8	0.02890	3.4057	-20602.1	0.83333
15	20	CH3	C_6H_4	8	0.02755	5.8908	-23447.8	1
16	22	CH3	4-ClC_6H_4	4	0.01231	4.9543	-25187	0.85714
17	23	CH3	2-OHC_6H_4	16	0.05223	6.8403	-25745.8	1
18	24	CH3	4-OHC_6H_4	8	0.02611	5.1913	-25373.8	0.85714
19	25	CH3	2-$OCH_3C_6H_4$	4	0.01248	5.8772	-27904.7	1
20	26	CH3	4-$OCH_3C_6H_4$	8	0.02497	5.8772	-27904.7	1

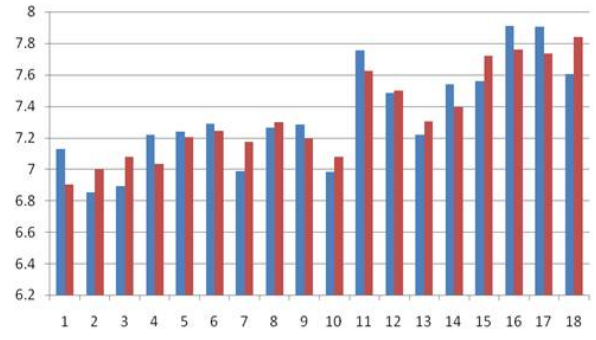


Figure 1

Multiple linear regression analysis method was used to perform QSAR analysis. The best model was selected on the basis of various statistical parameters such as correlation coefficient (r), standard error of estimation (std), sequential Fischer test (F). Quality of the each model was estimated from the cross-validated squared correlation coefficient (Q^2). Calculated root mean square error (SDEP), chance statistics evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation and boot-strapping square correlation coefficient (r^2bs), which confirm the robustness and applicability of QSAR equation.

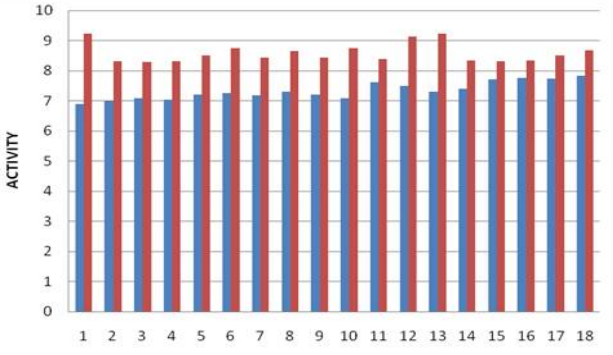


Figure 2

RESULTS

Model no. 1 results are.....

BA = [7.41291 (± 0.228204)] + SC [0.000106956(±3.6883)] - D4 [0.0627517(± 0.045567)] - EE [0.0595078(± 0.0600319)]

Table 2: Shows the Values Related Model no. 1

S.No.	Parameters	Values
1	N	18
2	R	0.906173
3	r^2	0.821149
4	Variance	0.0226586
5	Std	0.150528
6	F	21.4258
7	FIT	238.064
8	Bootstrapping r^2	0.808253
9	Q^2	0.684024
10	S press	0.200077
11	SDEP	0.176451

The model 1 shows that Steric parameter (Shape coefficient) shows positive contribution and electronic parameters (Dipole and Electronic Energy) show negative contribution towards the activity. The model has correlation coefficient (r) of 0. 906. It shows significance level more than 95.0% against tabulated value F=21.4, with a low standard deviation of estimation 0.1505, demonstrating accuracy of the model. The robustness of model was shown by magnitude of the bootstrapping r^2, which was near to conventional r^2. The internal predictivity of model (Q^2=0.684024) was also good. The model once again favoured by the least SPRESS and SDEP values. The table 3 shows the observed, calculated activity for training set of model no. 1, and on the basis of equation some data also shows the comparative predicted activity. After using internal and external validation data was obtained.

Table 3: Training set activity (pMIC) (model: 1)

S.No.	Compd No.	Observed Activity (pMIC)	Calculated Activity (pMIC)	Predicted Activity (pMIC)
1	5	7.126756	6.89978	9.22421
2	6	6.85327	6.99672	8.31364
3	7	6.890479	7.07755	8.29161
4	8	7.21534	7.03472	8.30342
5	9	7.237259	7.20223	8.50232
6	10	7.288283	7.2438	8.75527
7	11	6.987253	7.1727	8.43031
8	13	7.261707	7.29828	8.65485
9	14	7.282064	7.19383	8.44043
10	15	6.981034	7.0778	8.75745
11	16	7.75636	7.62491	8.39662
12	17	7.481231	7.5001	9.13143
13	18	7.21534	7.30446	9.22383
14	19	7.538962	7.39269	8.32951
15	20	7.559796	7.71744	8.30204
16	22	7.909517	7.76109	8.32625
17	24	7.903569	7.7355	8.50923
18	25	7.602539	7.83772	8.67715

DISCUSSION AND CONCLUSION

When data set was subjected to multiple linear regression analysis, in order to develop QSAR between antimicrobial activity as dependent variables and substituent constants as independent variables, several equations were obtained. The statistically significant equations were considered as best model.

The **figure I** shows plot of observed versus calculated pMIC values for training set molecules

And **figure II** is plot of calculated versus predicted pMIC values.

- In **figure I** the line graph of blue line shows data related to the Observed Activity and red line shows data related to the Calculated Activity.
- In **figure II** the line graph of blue line shows data related to the Calculated Activity and red line shows data related to the Predicted Activity.

In conclusion the compound no. 5 to 25 can be synthesized using several substituted 2-substituted-1-[{(5-substituted alkyl/aryl)-1, 3, 4-oxadiazol-2-yl} methyl]-1H-benzimidazoles.

On the basis of model no.1 equation the shape coefficient which is steric properties contributes positively. This suggests that by increasing steric property bulkiness of the molecule increases the shape coefficient also increases hence this enhance the antimicrobial activity.

The dipole and electronic energy are electric properties, which contributes negatively. The dipole is the electrical dipole for a pair of opposite charges of electrons. Polar molecule creates dipole due to separation of charge. Electron donating group decreases the dipole moment. This suggests that by decreasing the dipole moment the activity increases.

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