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Efficient Computational Analysis of 4-(butan-2-ylideneamino)-N'-ethylidenebenzohydrazide Derivatives for Design of Anti microbial agents

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Abstract

QSAR studies were performed on selected series of 4-(butan-2-ylideneamino)- N'-ethylidenebenzohydrazide derivatives. The best quantitative structure activity relationship models were further validated by LOO method of cross-validation. The study of best model shows that the steric property like Radius (Rad) contributed negatively and thermodynamic descriptors torsion energy (ToE), Vander waal 1,4 energy (VDWE) contributes positively and molar refractivity (MR) contributed negatively. The equation obtained were validated and resulting data studied. The study suggested that substitution at R_1, R_2, R_3, R_4 and R_5 on 4-(butan-2-lideneamino)benzohydrazide nucleus by certain functional groups which increase the vander waal energy and Torsion energy may lead to enhancement of the Antimicrobial activity. Attempts are made to minimize molar refractivity and radius for better biological activity. The current quantitative structure activity relationship study provides important structural insights in designing of potent Antimicrobial agents.

Keywords: Antimicrobial resistance, statistical Analysis, molar refractivity, cross validation

Contents

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1. Introduction

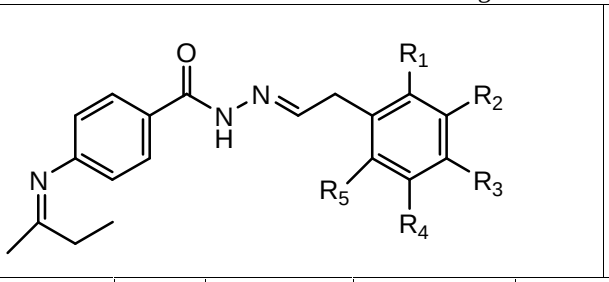
The infectious diseases are widely managed by the antimicrobial agents but increase in the resistance of microorganisms towards antimicrobial agents in the past few years have become a problem, and this has lead to the necessity of deigning of some novel, potent and safe antimicrobial agents against the resistant microbial strains. Major concern is the development of antibiotic resistance in *Staphylococcus aureus*, primarily because *S. aureus* is frequently associated with hospital and community-acquired infections. Infections with multi-drug resistant *S. aureus* have become responsible for huge healthcare costs and are projected to be responsible for more deaths this year in the United States than HIV/AIDS. Despite this increasing problem of antibiotic resistance, the number of different antibiotics available is dwindling and there are only a handful of new antibiotics in the drug development

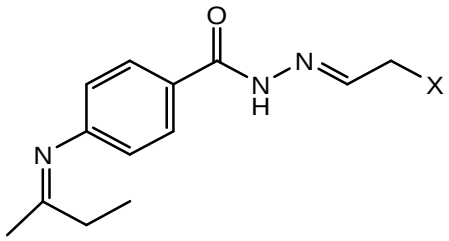
pipeline. Therefore, there is an urgent need for new antibacterial drugs preferably with new modes of action to potentially avoid cross-resistance [2-4]. QSARs are being applied in many disciplines for example risk assessment, toxicity prediction, and regulatory decisions in addition to drug discovery and lead optimization. Obtaining a good quality QSAR model depends on many factors, such as the quality of biological data, the choice of descriptors and statistical methods. Any QSAR modeling should ultimately lead to statistically robust models capable of making accurate and reliable predictions of biological activities of new compounds [5]. In the present work, we describe the QSAR studies from multiple linear regression analysis (MRA) in order to investigate the quantitative effect between the various physicochemical parameters of 4-(butan-2-lideneamino) benzohydrazide on their antibacterial activity again staphylocoocus aureus.

2. Experimental

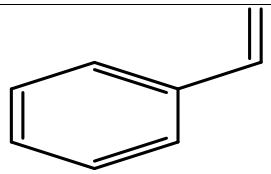
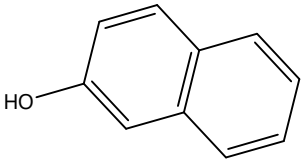
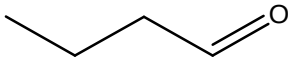
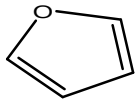
The Table 1 shows the structural features of given derivatives along with their biological activities (MIC µg/ml). The biological activity data MIC (minimum inhibitory concentration in µg/ml) were converted to negative logarithmic dose in moles (pMIC) for QSAR analysis. The correlations were sought between inhibitory activity and various substituent constants at position R1, R2, R3, R4, R5 or X of the molecule. The series was subjected to molecular modeling using CS Chem-Office 8.0. Structures of all the compounds were sketched using builder module of the programmed. 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.[6] The descriptor values for all the molecules were calculated using software. Statistical analysis was performed on the observed descriptors using VALSTAT.[7]

Table 1: Structural features of given derivatives along with their biological activities





Comp	R1	R2	R3	R4	R5	X	OBSERVED ACTIVITY (pMIC)
C1	H	H	CH_3	H	H	-	8.26
C2	H	OCH_3	OCH_3	H	H	-	8.31
C3	H	H	H	H	H	-	8.36
C4	H	Cl	$N(CH_3)_2$	H	H	-	8.29
C5	H	OCH3	OCH_3	OCH_3	H	-	8.43
C6	H	H	Br	H	H	-	8.40
C7	H	H	OCH_3	H	H	-	8.36
C8	H	H	Cl	H	H	-	8.36
C9	H	H	H	H	H	-	8.32
C10	H	H	OCH_3	OH	H	-	8.39
C11	H	H	OC_2H_5	OH	H	-	8.39
C12	H	H	OH	H	H	-	8.33
C13	Cl	H	H	H	H	-	8.37
C14	H	H	H	H	H	-	8.34
C15	OH	H	H	H	H	-	8.34

C16	-	-	-	-	-		8.34
C17	-	-	-	-	-		8.41
C18	-	-	CHO	-	-	-	8.37
C19	-	-	-	-	-		8.33
C20	-	-	-	-	-		8.31

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.[8-9]

3. Results and Discussion

By the QSAR Statistical Analysis Several Models Were Obtained. Among them the best Model (Model 1) shows four physicochemical Descriptors (Table 2) that correlates with Anti- bacterial activity. The internal validation parameters which conforms the acceptability of Model 1 (Statistical analysis) are shown in table 3. With the help of statistical equation Calculated BA was compared with Observed BA and LOO Predicted BA (Table 4).

Table 2: Physicochemical Descriptors for given compound [Method: -Statistical Analysis]

Derivative Number	Molar Refractivity (in cm.cm.cm/mol)	Torsion Energy (Kcal/mol)	1,4- Dihedral Vander Waal Energy (Kcal/mol)	Radius (cm)
c1	94.28	-5.40	13.03	8.00
c2	102.17	0.57	16.90	9.00
c3	94.04	-3.64	12.52	8.00
c4	103.67	-5.90	15.26	9.00
c5	108.63	3.45	18.45	9.00
c6	96.86	-3.87	12.63	8.00
c7	95.70	-0.27	14.14	9.00
c8	94.04	-3.46	12.44	8.00
c9	89.24	-1.30	12.18	8.00
c10	97.40	-1.93	14.25	9.00
c11	102.15	-2.67	16.15	9.00
c12	90.93	-1.20	12.44	8.00
c13	94.04	-3.00	13.06	8.00
c14	96.86	-3.69	12.99	8.00
c15	90.93	7.38	11.82	8.00
c16	98.93	-6.17	13.47	8.00
c17	107.38	-10.91	15.68	8.00
c18	95.83	-1.79	12.88	9.00
C19	82.88	7.77	11.55	8.00
c20	81.66	4.54	8.06	7.00

Equation obtained (Statistical) were also validated by using the Test & Training set analysis. Derivatives C1, C3, C6, C7 and C17 were randomly inbuilt put for Test set and remaining fifteen derivatives were for training set. The physicochemical descriptors upon which the test and training equation was Compute, are shown in table 5. The validation parameters for acceptability of test and training equation are showing in table 6. The comparison of Predicted (LOO for training set), Observed and Calculated Biological activity of Test set and Training Set are Shown in table 7 and table 8 respectively.

Model 1: (Statistical analysis)

BA= [1.33678 (± 0.115415)] + MR [-0.000155775(± 0.000147167)] + ToE[0.0154203(± 0.00531667)] + VDWE [0.0257099 (± 0.0139529)] + Rad [-0.00154777 (± 0.00125372)]

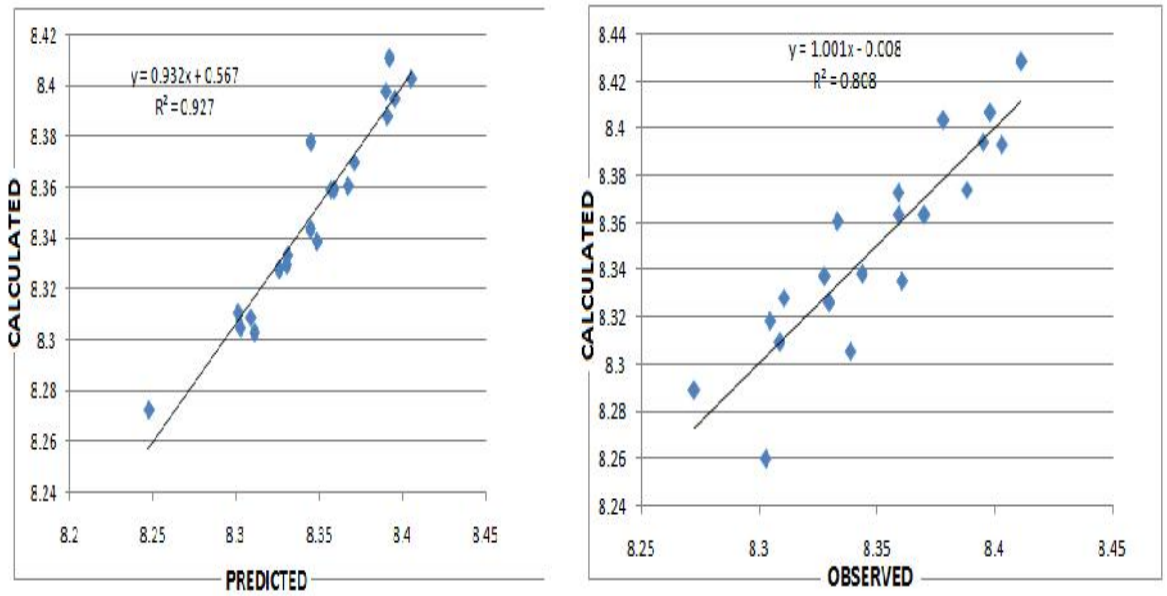


Figure 3: Calculated BA verses Observed BA and Calculated BA verses Predicted BA

Table 3: Shows the Values Related Model 1 (Statistical analysis)

S.No	Parameters	Values
1	N	21
2	R	0.933969
3	r^2	0.872298
4	Variance	0.002116
5	Std	0.046007
6	F	27.3228
7	FIT	295.382
8	Bootstrapping r2	0.900042
9	Q^2	0.700666
10	S press	0.0704376
11	S dep	0.061483

Table 4 : Comparison of Calculated BA, Observed BA and LOO Predicted BA (Statistical analysis)

S. No	Derivatives name	Observed	Loo predicted	Calculated
1	C1	8.2598	8.31093	8.30281
2	C2	8.3053	8.3485	8.3388
3	C3	8.3633	8.35884	8.35928
4	C4	8.2889	8.24712	8.27228
5	C5	8.4284	8.39226	8.41127
6	C6	8.4035	8.34485	8.37807
7	C7	8.3605	8.33095	8.33328
8	C8	8.3633	8.37108	8.37001
9	C9	8.3182	8.30241	8.30469
10	C10	8.3940	8.39541	8.3951

11	C11	8.3930	8.40542	8.40299
12	C12	8.3261	8.33034	8.32958
13	C13	8.3726	8.35695	8.35917
14	C14	8.3351	8.36734	8.36068
15	C15	8.3382	8.34461	8.34376
16	C16	8.3372	8.32576	8.32771
17	C17	8.4067	8.39014	8.39803
18	C18	8.3737	8.39094	8.38824
19	C19	8.3279	8.30089	8.31057
20	C20	8.3093	8.30857	8.30869

Out of four parameters half contributed negatively and half contributed positively to the BA, the above result shows that subsituent with less molar refractivity and radius, more torsion energy and I,4 dihedral vander waal energy be responsible for the activity of compound. For activity, the most influencing descriptor would be torsion energy; 1,4 dihedral vander waal energy and molar refractivity. Torsion energy is a thermodynamic parameter, which represent the energy associated with deforming torsion angles in the molecule from their ideal values.

Torsion energy contributes positively to QSAR model which suggest that absence of conjugation would be conductive for inhibitory activity of compound. 1,4 dihedral vander waal energy term is defined as sum of pair wise vander waal interaction energy for the atoms exactly separated by three chemical bonds which explains depth of attraction potential energy well and how easy it to push atoms together. Positive contribution of this indicate that the substitution which increases the energy for this interaction generally leads to higher activity.[10] For the increase in descriptors like vander waal energy one should have more emphasis on functional groups that increases dipole dipole interaction that increases the vander waal energy.[11] By using Lorentz Lorentz equation, reduction in the molecular weight reduces molar refractivity.[12] This all collectively may enhance the Anti- bacterial activity.

Model 1: (Test and Training analysis)
BA= [9.09608 (± 1.12059)] + Ovality [-1.03834 (± 0.735397)] + ElcE [-0.0000138445 (±0.00000610274)] +Homo [-0.0623172 (± 0.0254403)]

Table 5 : Physiochemical descriptors for given compound.[method: - test And training analysis]

Derivative Number	Ovality (unit less)	Electronic Energy (in eV)	HOMO Energy (in eV)
C1	1.60	-24891.00	-8.86
C2	1.67	-31130.10	-8.58
C3	1.59	-25050.00	-9.24
C4	1.63	-28616.80	-8.08
C5	1.68	-35833.60	-9.14
C6	1.60	-24894.20	-9.13
C7	1.62	-26865.90	-8.92
C8	1.59	-24929.10	-9.24
C9	1.60	-23059.00	-8.80
C10	1.62	-29042.60	-9.03
C11	1.65	-30917.30	-9.15
C12	1.60	-24928.50	-8.57
C13	1.58	-25412.20	-9.02
C14	1.59	-24994.20	-9.17
C15	1.60	-25316.50	-8.87
C16	1.61	-26428.20	-8.99
C17	1.62	-31648.70	-8.46
C18	1.60	-26139.90	-9.30
C19	1.60	-22693.70	-9.38
C20	1.58	-22146.00	-8.62

Table 6: Shows the Values Related Model 1(Test and Training analysis)

S.No	Parameters	Values
1	N	15
2	R	0.939631
3	r^2	0.882906
4	Variance	0.00204809
5	Std	0.0143111
6	F	27.6471
7	FIT	345.589
8	Bootstrapping r2	0.902266
9	Q^2	0.744778
10	S press	0.0211284
11	S dep	0.0180932

Table 7: Comparison of Calculated, Predicted and Observed Biological Activity (Test set)

S. No	Derivatives	Calculated	Predicted	Observed
1	C3	8.35928	8.36774	8.3633
2	C6	8.37807	8.34835	8.4035
3	C1	8.30281	8.33148	8.2598
4	C17	8.39803	8.37934	8.4067
5	C7	8.33328	8.34179	8.3605

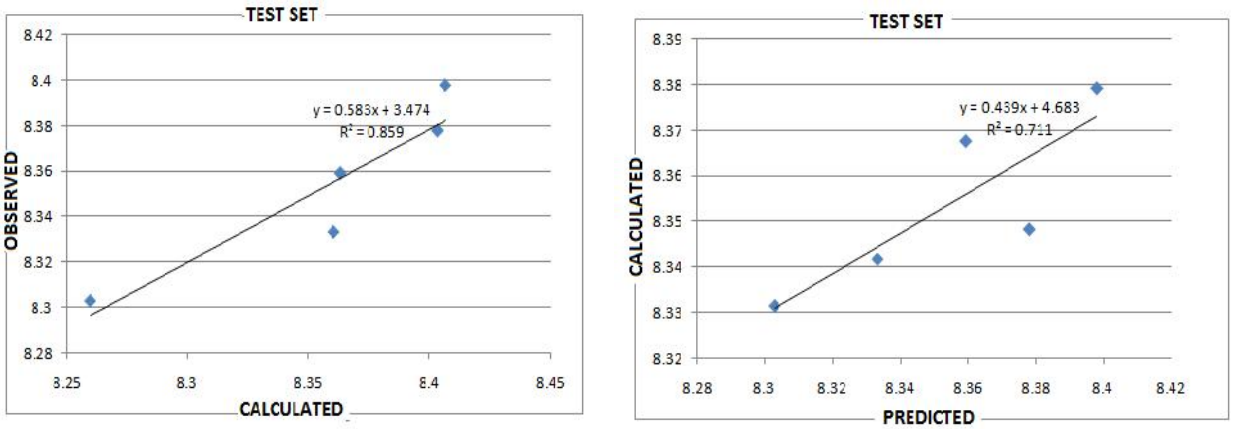


Figure 5: Plot of Cross Validation (Test set)

Table 8. Comparison of Calculated, Predicted and Observed Biological Activity (Training set)

Compound No	Calculated	Predicted	Observed
c5	8.41735	8.40332	8.4284
c8	8.36607	8.36722	8.3633
c19	8.33346	8.33736	8.3633
c9	8.30237	8.29637	8.3182
c15	8.33799	8.33781	8.3382
c20	8.29928	8.29591	8.4035
c10	8.37878	8.37677	8.3940
c16	8.35047	8.35126	8.3372
c18	8.37619	8.37738	8.3737
c14	8.36261	8.36643	8.3351
c13	8.36943	8.36914	8.3726
c4	8.3033	8.31771	8.2889
c12	8.31392	8.31072	8.3261
c2	8.32772	8.34173	8.3053
c11	8.38106	8.37864	8.3930

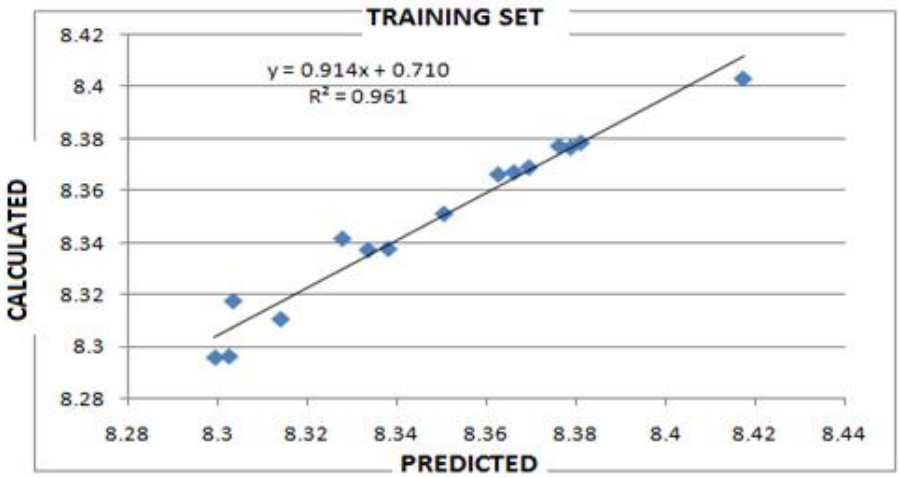


Figure 6: Plot of Cross-validation Calculated Value (Training set)

4. Conclusion

In order to develop QSAR between anti-bacterial activity as dependent variables and substituent constants as independent variables. Multiple linear regression analysis of data was done & several equations were obtained. The statistically significant equations were considered as best model. The challenge in QSAR studies is not only constructing a model that is statistically able to predict the activity within the validation but also developing a model with the capacity to accurately predict the activity of untested chemical. The model testing and training is essential and critical but often neglected component of QSAR development increasing charge in a positive sense on any of these atoms increased the activity of the drug. Phenyl substitution may be effective in this respect [16]. The present study involving study of N- Benzohydrazide Derivatives aims at: Observing the contribution of different descriptors to the biological activity and optimizing those parameters by optimizing the models. The scope for enhancement of selectively of the present class using different substituents, thus the magnitude of the activity can be increased greatly by appropriate selection of same. On the basis of best model the suitable changes on the substitution at R1, R2, R3, R4 and R5 or X on 4 -(butan-2-lideneamino) benzohydrazide by certain functional groups which increase the torsion, 1,4- dihedral vander waal energy and reduces molar refractivity as well as radius which may lead to enhancement of the Anti- bacterial activity.

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