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Prediction of antibacterial and antifungal activity of 4 –benzylideneamino –benzene sulfonamides series by 2D QSAR studies

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Abstract

A series of thirty one molecules substituted 4-benzylideneamino benzene sulphonamides derivatives compounds displaying variable inhibition of microbial activity were selected to develop models for establishing 2D QSAR by multiple linear regressions. The compounds in the selected series were characterized by spatial, molecular and electro topological descriptors using QSAR model of molecular design suite (V-Life MDS 3.5). Correlations between inhibitory activities and calculated predictor variables were established through partial least square regression method. The whole dataset was divided into training set (22 compounds) and test set (09 compounds). The statistically significant best 2D QSAR model having correlation coefficient r2 = 0.8482and cross validated squared correlation coefficient q2 = 0.8094with external predictive ability of pred_r2 = 0.0947 coefficient of correlation of predicted data set (pred_r2se) 0.0879 was developed by stepwise PLSR method with the descriptors like T_2_N_5, T_2_N_3, SsssNE-index, SssOH Eindex Count, SsBrcount and Xlogp. These results should serve as a guideline in designing more potent and selective antimicrobial molecules.

Keywords: QSAR, 4 –benzylideneamino-benzene sulfonamides; Antimicrobial activity and multiple linear regression analysis

1. Introduction

Quantitative structure activity relationship (QSAR) is one of the major tools in drug discovery to explore ligand– receptor/enzyme interactions, especially when the structural details of the target are not known. 2D-QSAR does not involve complex alignment or assumptions on conformations; therefore they can easily be applied to large compound sets, both in model building and in model application to new compounds. The QSAR approach helps to correlate the specific biological activities or physical properties of a series of compounds with the measured or computed molecular properties of the compounds, in terms of descriptors. A number of quantitative structure–activity relationship (QSAR) studies related to design 4-benzylideneamino benzene sulfonamides drugs have also been reported. The development of a quantitative SAR with the aid of various physicochemical parameters has been an important task in lead optimization. The present study aimed to elucidate the structural features of 4-benzylideneamino benzene sulfonamides derivatives required for antimicrobial activity and to obtain predictive two-dimensional quantitative structure– activity relationship (2D QSAR) models, which may guide the rational synthesis of antimicrobial activity of novel molecules.

2. Materials and Methods

2.1. Methodology

The antibacterial and anti fungal activity data substituted at the 4-benzylideneaminobenzenesulphonamides moiety which was taken from the reported work. A data set of 31 compounds for antimicrobial activity was used for the present QSAR study. The molar concentrations of the compounds required to produce binding at receptor site (in nm) converted to negative logarithm MIC values for undertaking the QSAR study. The biological activity data (IC_{50} in nm) were converted to their molar units and then further to negative logarithmic scale (pIC50) and subsequently used as the dependent variable for the QSAR analysis. Table 1 shows the structure of thirty one such compounds along with their biological activity values. The molecular modeling was carried out on Compaq PC having Pentium IV processor and windows XP operating system, using the software namely: V-life MDS (Molecular Design Suite) 3.5 (www.Vlifesciences.com). All the structures were constructed using the 2D draw application provided as a tool of main MDS window. The 2D structures were converted to 3D structures by sending them to MDS. Energy minimization and geometry optimization were conducted using Merck Molecular Force Field (MMFF) method with Root Mean Square (RMS) gradient set to 0.01 kcal/mol A° and iteration limit to 10 000. The 2D descriptors (physicochemical and alignment independent) were calculated for the optimized com- pounds on QSAR plus work sheet. The invariable descriptors (the descriptors that are constant for all the molecules) were re- moved, as they do not contribute to QSAR. Monto Carlo con- formational search method is similar to the RIPS method that generates a new molecular conformation by randomly perturbing the position of each coordinate of each atom in molecule, followed by energy minimization and optimization is a necessary process for proper alignment of molecules around the tem- plate. Most stable structure for each compound was generated after energy minimization and used for calculating various physicochemical descriptors like thermodynamic, steric and electronic. The energy-minimized geometry was used for the calculation of the various descriptors (retention index, atomic valence connectivity

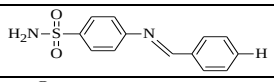
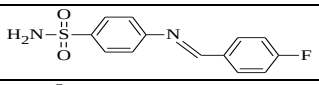
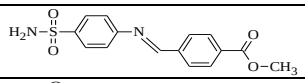
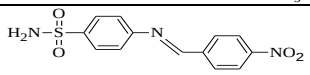
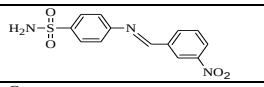
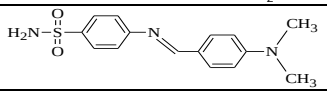
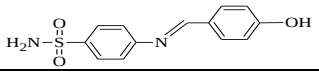
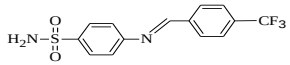
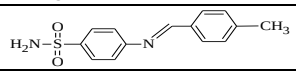
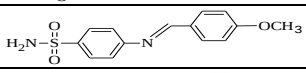
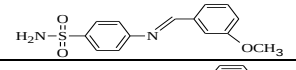
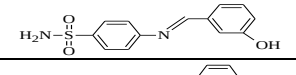
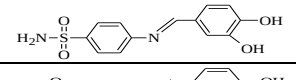
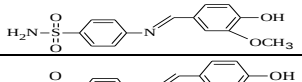
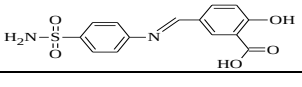
index, path count, chi chain, chiV chain, cluster, path cluster, kappa, element count, estate numbers, estate contributions, information theory index, and polar surface area) that were considered as independent variables in the present study. The pre-processing of the independent variables (i.e., descriptors) was done by removing invariable (constant column), which resulted in total 246 descriptors to be used for QSAR analysis and descriptors used in QSAR models with values (Table 2). The calculated descriptors were gathered in a data matrix. First, the descriptors were checked for constant or near constant values and those detected were discarded from the original data matrix. Then, the descriptors were correlated with each other and with the activity data. Finally, different regression analysis with stepwise selection and elimination of variables was applied to the development of QSAR models using software. The resulting models were validated by leave- one-out cross-validation procedures to check their predict activity and robustness. The antimicrobial activity data and various parameters (Physiochemical and alignment independent) were taken as dependent and independent variables respectively and correlation were established between them by employing multiple linear regression (MLR) method. In the generation of QSAR model we have selected eleven test and twenty one training set. In classical sphere-exclusion algorithm the molecules are selected whose similarities with each of the other selected molecules are not higher than addend threshold. Each selected molecule generates a hyper-sphere around itself, so that any molecule inside the sphere is excluded from the selection in the training set and driven toward the test set. Sphere exclusion method was adopted for division of training and test set. Sphere exclusion method is used for creating training and test set from the data. This is a rational selection method which takes into consideration both biological and chemical space for division of dataset. Dissimilarity value provides handle to vary train/test set size. It needs to be adjusted by trial and error until a desired division of train and test set is achieved. As a rule, increase in dissimilarity value will lead to increase in the number of molecules in the test set. The number of compounds selected and the diversity among them can be determined by adjusting the radius of the sphere.

2.2 A brief review on sulfonamides

The medicinal importance, synthesis and use of sulfonamides as synthetic tools in organic chemistry. The sulfonamide functionality is much more widespread in pharmaceuticals than just in an early class of antibiotics and antifungal. Sulfonamides have been the subject of pharmaceutical interest as a result of their potent biological activities such as antihypertensive agent, antiviral HIV protease inhibitor, anticancer, anti-inflammatory and antiviral agents.

A number of 31 compounds 4-benzylideneamino-and 4-phenyliminomethyl- benzene sulfonamides derivatives having antimicrobial activity were considered in the present study. The 4-benzylideneamino-and 4-phenyliminomethyl- benzene sulfonamides derivatives were taken from the reported work (Lin et al., 2008). Biological activity expressed in terms of IC_{50} was converted in to pIC_{50} (pIC_{50}= log $1/IC_{50}$).

Table 1: Series of 4-benzylideneamino-and 4-phenyliminomethyl-benzenesulfonamides derivatives with their biological activity

Serial no.	Compound code	Structure	IC_{50}	Log1/IC_{50}
01	DS01		2.87	-0.4579
02	DS02		2.22	-0.3463
03	DS03		2.73	-0.4361
04	DS04		3.00	-0.4771
05	DS05		6.75	-0.8293
06	DS06		3.36	-0.5263
07	DS07		3.42	-0.5340
08	DS08		4.60	-0.6627
09	DS09		4.94	-0.6937
10	DS10		9.88	-0.9947
11	DS11		5.45	-0.7363
12	DS12		2.78	-0.4440
13	DS13		2.85	-0.4548
14	DS14		2.95	-0.4698
15	DS15		0.74	0.1307

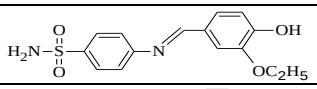
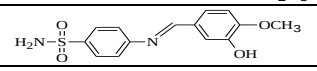
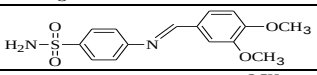
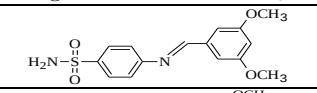
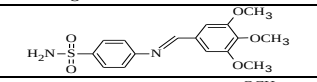
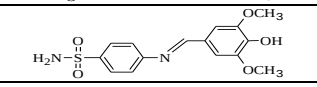
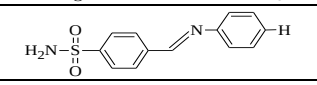
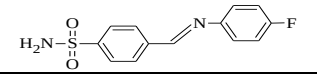
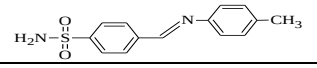
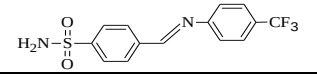
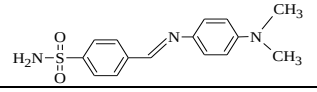
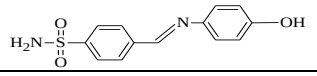
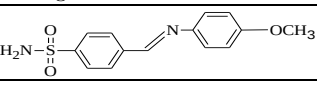
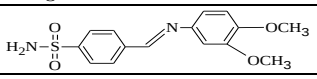
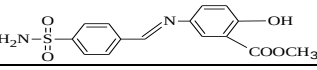
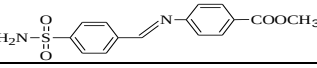
16	DS16		3.69	-0.5670
17	DS17		3.50	-0.5440
18	DS18		3.09	-0.4899
19	DS19		3.40	-0.5314
20	DS20		2.39	-0.4668
21	DS21		2.71	-0.4329
22	DS22		3.11	-0.4927
23	DS23		4.38	-0.6414
24	DS24		4.62	-0.6646
25	DS25		6.54	-0.8155
26	DS26		1.95	-0.2900
27	DS27		5.09	-0.7067
28	DS28		4.14	-0.6170
29	DS29		4.28	-0.6314
30	DS30		3.13	-0.4955
31	DS31		3.72	-0.5705

Table 2: 2D descriptors required for 2D QSAR models for antibacterial and antifungal activity

Chemical Sample	Mol. Wt.	H-Acceptor Count	H-Donor Count	Rotatable Bond Count	XlogP	slogp	smr	chi2	Nitrogens Count	log1/IC_{50}
DS01	260.3	5	1	4	0	2.5	71	8.1650	2	-0.4579
DS02	278.3	6	1	4	0	2.6	71	8.7869	2	-0.3463
DS03	318.3	7	1	7	0	2.3	82	9.8273	2	-0.4361
DS04	307.3	8	3	7	0	2.0	77	9.6858	3	-0.4771
DS05	307.3	8	3	7	0	2.0	77	9.6977	3	-0.8293
DS06	303.3	6	1	7	0	2.5	85	9.6977	3	-0.5263
DS07	276.3	6	2	5	0	2.2	72	8.7869	2	-0.534
DS08	328.3	8	1	5	1	3.4	76	10.744	2	-0.6627
DS09	274.3	5	1	5	1	2.8	76	8.7869	2	-0.6937
DS10	290.3	6	1	6	0	2.5	77	8.9560	2	-0.9947
DS11	290.3	6	1	6	0	2.5	77	8.9679	2	-0.7363
DS12	276.3	6	2	5	0	2.2	72	8.7988	2	-0.444
DS13	292.3	7	3	6	0	1.9	74	9.2946	2	-0.4548
DS14	306.3	7	2	7	0	2.2	79	9.4857	2	-0.4698
DS15	320.3	8	3	7	0	1.9	79	10.225	2	0.1307
DS16	320.3	7	2	8	0	2.6	84	9.8661	2	-0.567
DS17	306.3	7	2	7	0	2.2	79	9.4857	2	-0.544
DS18	320.3	7	1	8	0	2.5	84	9.6767	2	-0.4899

DS19	320.3	7	1	8	0	2.5	84	9.7827	2	-0.5314
DS20	350.3	8	1	10	0	2.5	90	10.407	2	-0.4668
DS21	336.3	8	2	9	0	2.2	86	10.194	2	-0.4329
DS22	260.3	5	1	4	0	2.5	71	8.1650	2	-0.4927
DS23	278.3	6	1	4	0	2.6	71	8.7869	2	-0.6414
DS24	274.3	5	1	5	1	2.8	76	8.7869	2	-0.6646
DS25	328.3	8	1	5	1	3.4	76	10.744	2	-0.8155
DS26	303.3	6	1	7	0	2.5	85	9.6858	3	-0.29
DS27	276.3	6	2	5	0	2.2	72	8.7869	2	-0.7067
DS28	290.3	6	1	6	0	2.5	77	8.9560	2	-0.617
DS29	320.3	7	1	8	0	2.5	84	9.6767	2	-0.6314
DS30	334.3	8	2	8	0	2.0	84	10.366	2	-0.4955
DS31	318.3	7	1	7	0	2.3	82	9.8273	2	-0.5705

2.3. Creation of training and test set

The sphere exclusion method was adopted for division of training and test data set comprising twenty nine and eleven molecules, respectively, with dissimilarity value of 8.1 where the dissimilarity value gives the sphere exclusion radius. In order to assess the similarity of the distribution pattern of the molecules in the generated sets, statistical parameters (with respect to the biological activity), i.e., mean, maximum, mini- mum and standard deviation were calculated for the training and test sets. Nine compounds, namely DS1, DS3, DS5, DS7, DS18, DS19, DS21, DS24 and DS30 were used as test set while the remaining molecules were used as the training set.

2.4. Multiple linear regression and model validation

MLR is a generalization of regression, which can handle data with strongly correlated and/or noisy or numerous X variables. It gives a reduced solution, which is statistically more robust than PLS. The linear MLR model ‘‘new variables’’ (latent variables or X scores) which are linear combinations of the original variables. To avoid overtting, a strict test for the significance of each consecutive MLR component is necessary and then stopping when the components are not significant. Cross-validation is a practical and reliable method for testing this significance. This is done to test the internal stability and predictive ability of the QSAR models. Internal validation is carried out using ‘leave-one-out’ (LOO) method.

2.5. Models on the basis of two dimensional QSAR

Table 3: Observed and predicted biological activity for series of sulfonamide derivatives:

Compound no.	Observed activity	Predicted activity
DS01	0.4579	0.4671
DS02	0.3463	0.4618
DS03	0.4361	0.3959
DS04	0.4771	0.4999
DS05	0.8293	0.9312
DS06	0.5263	0.5734
DS07	0.5340	0.6312
DS08	0.6627	0.5931
DS09	0.6937	0.7012
DS10	0.9947	0.8120
DS11	0.7363	0.6219
DS12	0.4440	0.5312
DS13	0.4548	0.4748
DS14	0.4698	0.5102
DS15	0.1307	0.2101
DS16	0.5670	0.6178
DS17	0.5440	0.6192
DS18	0.4899	0.7812
DS19	0.5314	0.4214
DS20	0.4666	0.3912
DS21	0.4329	0.3810
DS22	0.4927	0.4311
DS23	0.6414	0.8194
DS24	0.6646	0.7219
DS25	0.8155	0.9901
DS26	0.2900	0.1212
DS27	0.7067	0.5916
DS28	0.6170	0.4211
DS29	0.6314	0.5612
DS30	0.4955	0.5194
DS31	0.5705	0.7104

Several regression equations were obtained in this study. Among the regression results, three equations were selected as models. The generated QSAR models leave one out (LOO) method was used indicated as value of q^2 (cross validated explained variance) which is a measure of internal predictive ability of the model. The cross-validation run returns the optimum number of components for which it has maximum coefficient correlation r^2 values and minimum standard error of prediction pred_rse^2. The low standard error of r^2_se demonstrates accuracy of the model, Crossvalidated squared correlation coefficient q^2 of this model shows good internal prediction power of this model. The F-test value shows the overall statistical significance level of the model, which means that the probability of failure for model is 1 in 10,000. Another parameter for predict activity of test set compounds is high pred_r^2, which shows good external predictive power of the model.

2.6. Observed and predicted activity

The above-mentioned model is validated by predicting the biological activities of the all molecules, as indicated in Table 3 it is evident that the predicted activities of all the compounds are in good agreement with their corresponding experimental activities and optimal fit is obtained. The plot of actual versus predicted activities for the test compounds is represented in Fig.1 and Fig 2.

The sphere exclusion method was adopted for division of training and test data set comprising twenty two and nine molecules, respectively, with dissimilarity value of 8.1 where the dissimilarity value gives the sphere exclusion radius. In order to assess the similarity of the distribution pattern of the molecules in the generated sets, statistical parameters (with respect to the biological activity), i.e., mean, maximum, mini- mum and standard deviation were calculated for the training and test sets. Nine compounds, namely DS1, DS3, DS5, DS7, DS18, DS19, DS21, DS24 and DS30 were used as test set while the remaining molecules were used as the training set. Test and training sets are reported in Table 4 and Table 5 respectively.

Table 4: Observed and predicted activities for test set of compounds

Compound No.	Observed Activity	Predicted Activity
DS01	0.4579	0.5179
DS03	0.4361	0.4412
DS05	0.8293	0.9214
DS07	0.5340	0.4612
DS18	0.4899	0.3912
DS19	0.5314	0.6121
DS21	0.4329	0.5917
DS24	0.6646	0.7107
DS30	0.4955	0.5214

Table 5: Observed and predicted activities for training set of compounds

Compound No.	Observed Activity	Predicted Activity
DS02	0.3463	0.4924
DS04	0.4771	0.5643
DS06	0.5263	0.4850
DS07	0.5340	0.4534
DS08	0.6627	0.7285
DS09	0.6937	0.5442
DS10	0.9947	0.4952
DS11	0.7363	0.7312
DS12	0.4440	0.4534
DS13	0.4548	0.4570
DS16	0.5670	0.6182
DS17	0.5440	0.4988
DS19	0.5314	0.5406
DS21	0.4329	0.5442
DS22	0.4927	0.5704
DS24	0.6646	0.5648
DS25	0.8155	0.8490
DS26	0.2900	0.6056
DS27	0.7067	0.5748
DS28	0.6170	0.6157
DS29	0.6314	0.6611
DS31	0.5705	0.6269

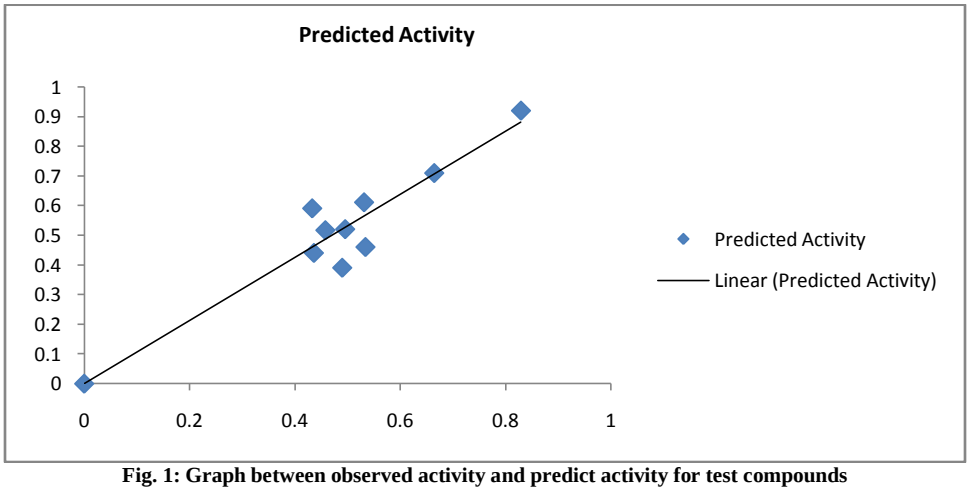


Fig. 1: Graph between observed activity and predict activity for test compounds

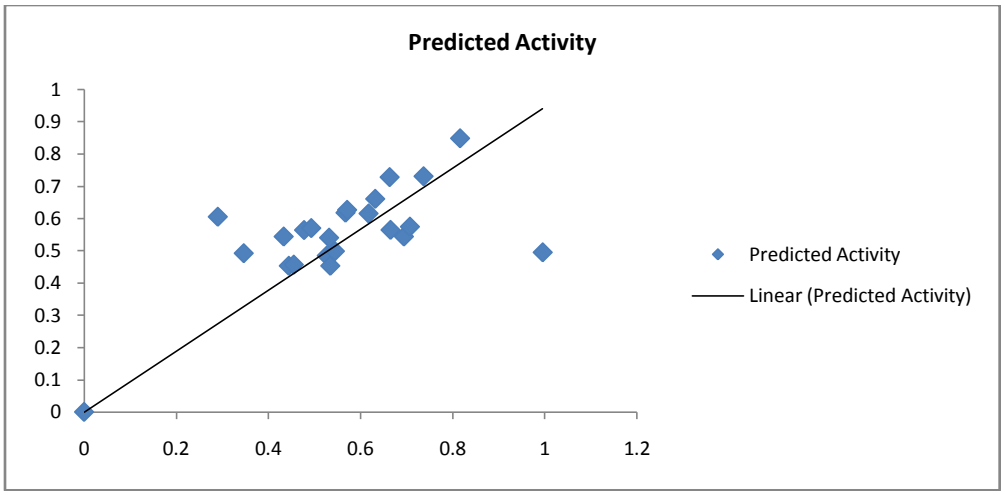


Fig. 2: Graph between observed activity and predict activity for training compounds

The correlation matrixis of Imidazolidine 2,4-dione derivatives shown in Table 6 which shows good correlation of selected parameters with biological activity.

Table 6: Final correlation matrix of sulfonamide series

Variable	T_2_N_5	XLogP	T_2_N_3	SssOHE index	SsssNE-in
T_2_N_5	1				
XLogP	0.9865	1			
T_2_N_3	0.8934	0.8789	1		
SssOHE index	0.8791	0.8569	0.8745	1	
SsssNE-index	0.9821	0.9837	0.9385	0.8958	1

3. Results and Discussion

3.1. Model Development

In pursuit of better antimicrobial activity having improved biological activity compared to the existing compounds, a quantitative structure-activity relationship analysis was performed by using modeling software V-life MDS (Molecular Design Suite) 3.5 Step wise-multiple linear regression analysis results three significant QSAR models and their stastically parameter are given in Table 7.

Model-1

pIC50 = +0.878 (±0.2435) T_2_N_5 - 0.8480(± 0.0485) SsssNE-index + 0.7487 (±0.438) T_2_N_3 + 0.0003 (±0.0829) SsBr count +0.7641 (±0.0621) SssOH E indexCount + 0.4987.

n training =22, n test =09, , Degrees of freedom = 21, n=31, r=0.921, S=0.394, F=26.78,r^2=0.8482, q2=0.8094, r^2 se =0.0576, q^2_ se= 0.086, pred_r^2 = 0.7791, pred_r^2se =0.0879, ZScoreQ^2 =1.453, Best Rand Q^2= 0.6243

Model-2

pIC50 = -0.8311(±0.1947) Chain Count+ 0.887(± 0.0329) T_2_N_5 + 0.527(± 0.0205) SsssC count -0.7621(±0.038)

n training =22, n test =09, Degrees of freedom = 24, r=0.884,S=0.456, F=31.75, r^2 = 0.781, q^2 = 0.7638, r^2 se= 0.4711, q2 se = 0.058, pred_r^2 = 0.7642, pred_r^2se= 0.0911, ZScoreQ^2= 5.76419, Best Rand Q^2 = 0.43578.

Model-3

pIC50= +0.7042(±0.0039) SsOH count- 0.4981(±0.0059) SsCl count +0.920(±0.0423) SaaOE-index +0.4687(±0.0907) SsOHE-index+0.74167.

n training = 20, n test = 09, , Degreesof freedom = 20, r=0.879,S=0.512,F=33.54,r^2 = 0.7726, q^2 = 0.750, r^2 se =0.876, q^2_ se= 0.3086, pred_r^2 = 0.7491, pred_r^2se =0.3876, ZScoreQ^2 =1.3265, Best Rand Q^2= 0.6523.

Table 7: Stastical parameter

Model no.	n	R	S	F	r^2	q^2
1	31	0.921	0.394	26.78	0.8482	0.8094
2	31	0.884	0.456	31.75	0.781	0.7638
3	31	0.879	0.512	33.54	0.7726	0.7590

According to model 1 the biological activity of compounds can be increased if :-

(i) T_2_N_5 is increased
(ii) SsssNE-index is decreased
(iii) SssOH E indexCount is increased
(iv) T_2_N_3 is increased
(v) SsBrcount is increased

According to model 2 the biological activity of compounds can be increased if :-

(i) ChainCount is decreased
(ii) SsssCcount is increased
(iii) T_2_N_5 is increased.

According to model 3 the biological activity of compounds can be increased if:-

(i) SsOHcount is increased

(ii) SsClcount is decreased
(iii) SaaOE-index is increased

Among these three models, model 1 was selected as the best model that is statistically significant because it has higher cross validated regression coefficient (q^2) and lower standard error than other models.

This model shows that T_2_N_5, SsssCcount, SsOHcount, T_2_N_3 is positively correlated to activity and SsClcountand ChainCountvalues are negatively correlated to activity. It also shows the greater influence of SsBrcount on biological activity than T_2_N_5, SsssCcount, SsOHcount. Therefore, the groups that impart above-mentioned changes in physicochemical properties included in best model should be attached to the molecules to increase the biological activity.

Equation reveals that decreased Chaincount may increases the activity. The negative coefficient of Chaincount shows that volume is deter mental to the activity. Its negative sign also suggest steric hindrance either directly or through a conformational change in the receptor.

In model 1, the positive contribution of Alignment Independent descriptor T_2_N_5 show that the the count of number of double bounded atoms (i.e. any double bonded atom, T_2) separated from Nitrogen atom by 5 bonds. that increase antibacterial and antifungal activity and Alignment Independent descriptor T_2_N_3 show that the count of number of double bounded atoms (i.e. any double bonded atom,T_2) separated from Nitrogen atom by 3 bonds that also increase antimicrobial activity. Make a better fitness of molecules with the receptor binding site, resulting in increase the biological activity. The positive contribution of Estate numbers and Estate Contributions physicochemical descriptors SsssCcount and SsOH count on the biological activity showed that the increase in the values of these parameter lead to better inhibitor properties against the bacteria and fungus.

3.2 *Model validation*

The Model was validated by Internal and External Cross Validation:-

(1) Internal Cross Validation (Leave-One-Out Method):

One compound is removed from the data set and a QSAR correlation obtained for the remaining compounds is used to predict its activity. The compound is then returned to the training set, another one is removed, and a second QSAR correlation is obtained. This procedure is repeated until all the compounds in turn have been removed. The cross validated r^2 value (r^2_{cv} or q^2). It can also be calculated by using following formula:

$$r^2_{CV} = 1 - \frac{\sum_{i=1}^{N} (y_{exp} - y_{pred})^2}{\sum_{i=1}^{N} (y_{exp} - \bar{y})^2}$$

(2) External Cross Validation:

The model was validated by making training set of 22 compounds and test set of nine compounds (1, 3, 5, 7, 18, 19, 21, 24 and 30). The QSAR was performed for training set and a model was developed. This model was used to predict the biological activities of test set of compounds.

Log(1/IC50)= 0.987 (±0.096)SsBrcount+0.370 (±0.075)T_2_N_5 +0.056 (±0.052) SsOHcount- 0.08 (±0.039)SsssNE+0.141 (±0.580)

n = 22, r = 0.902, s = 0.4203, F = 21.79, r^2 = 0.813.

The values of variables present in the model and observed and predicted values of biological activity for test set of compounds show that the prediction of activity by this model is very close to the observed values**.**

Best model shows that T_2_N_5 , SsssCcount, SsOHcount, T_2_N_3 is positively correlated to activity and SsClcount and ChainCount values are negatively correlated to activity. It also shows the greater influence of T_2_N_5, SsssCcount, on biological activity than ChainCount and SsClcount values. Therefore, the groups that impart above-mentioned changes in physicochemical properties included in best model should be attached to the molecules to increase the biological activity.

4. Conclusion

Therefore, obtained data by adequate designed QSAR studies allow observing aspects and essential structural characteristics of sulfonamides related to the increased biological activity, suggesting certain structural requirements for an increased antimicrobial potential. The above study leads to the development of statistically significant QSAR model, which allows understanding of the molecular properties/features that play an important role in governing the variation in the activities. In addition, this QSAR study allowed investigating influence of very simple and easy-to-compute descriptors in determining biological activities, which could shed light on the key factors that may aid in design of novel potent antibacterial and antifungal molecules. The generated models were analyzed and validated for their statistical significance and external prediction power. The physicochemical and alignment-independent descriptors were found to have an important role in governing the change in activity. The present studies were aimed at deriving predictive 2D models capable of elucidating the structural requirements for antimicrobial activity. Our results open very interesting perspectives regarding 4-benzylideneamino benzene sulfonamides derivatives antimicrobial activity.

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