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Research Article

An approach to design antimicrobial agents by 2D QSAR studies on series of 5, 5-diphenylimidazolidine-2, 4-dione derivatives

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Abstract

A series of twenty two molecules substituted 5,5-diphenylimidazolidine-2,4-dione derivatives displaying variable inhibition of microbial activity were selected to develop models for establishing 2D QSAR by multiple linear regression analysis. 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 multiple linear regression method. The whole dataset was divided into training set (17 compounds) and test set (05 compounds). The statistically significant best 2D QSAR model having correlation coefficient r^2 = 0.8686 and cross validated squared correlation coefficient q^2 = 0.7994 with external predictive ability of pred_r^2 = 0.6791 coefficient of correlation of predicted data set (pred_r^2se) 0.0999 was developed by stepwise MLR method with the descriptors like $SSCH_3$, SdSE-index, SsssN Count and Xlogp. These results should serve as a guideline in designing more potent and selective antimicrobial and antifungal molecules.

Keywords: QSAR, Multiple linear regressions, Antibacterial and antifungal

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 5, 5-diphenylimidazolidine-2,4-dione 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 5,5-diphenylimidazolidine-2,4-dione derivatives required for antimicrobial and antifungal 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.[1,3]

1.1 A brief review on 5, 5-diphenylimidazolidine-2, 4-dione derivatives

5, 5-diphenylimidazolidine-2, 4-dione derivatives are five-member heterocyclic system containing very reactive cyclic urea and thiourea cores. Imidazolidine-2,4-dione derivatives are found in many area of medicinal chemistry (serotonin and fibrinogen receptor antagonists, inhibitors of the glycine binding site of the NMDA receptor, antagonists of leukocyte cell adhesion, acting as allosteric inhibitors of the protein–protein interaction. In particular, several reports present interest in cancer research. A imidazolidine-2,4-dione series including some whose anticonvulsant activities have already been reported in the literature.

A number of 22 compounds 5, 5 diphenylimidazolidine-2, 4-dione derivatives having antimicrobial activity were considered in the present study. The 5, 5 diphenyl imidazolidine-2, 4-dione derivatives were taken from the reported work (Liton et al., 2014). Biological activity expressed in terms of IC_{50} was converted in to pIC_{50} (pIC_{50}= log $1/IC_{50}$).

2. Materials and Methods

2.1. Methodology

The antibacterial and anti fungal activity data substituted at the 5,5-diphenylimidazolidine-2,4-dione moiety. A data set of 22 compounds for antimicrobial and antifungal 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 (pIC_{50}) and subsequently used as the dependent variable for the QSAR analysis. Table 1 shows the structure of twenty two 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 removed, 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 physico-chemical 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

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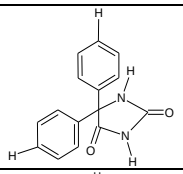
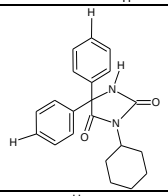
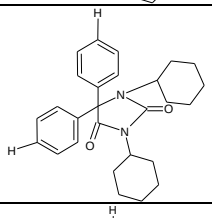
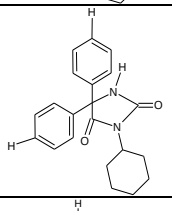
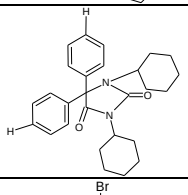
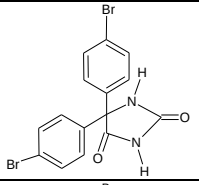
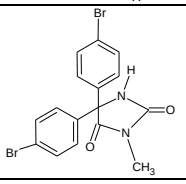
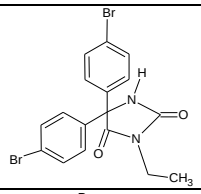
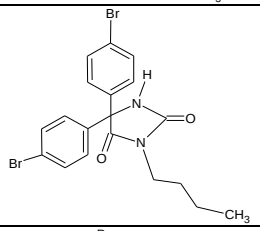
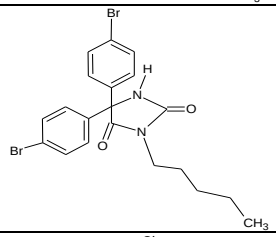
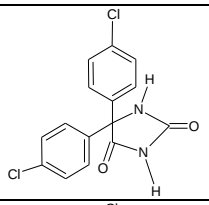
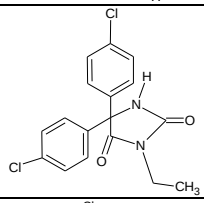
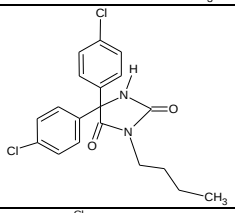
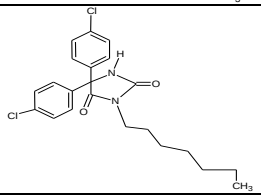
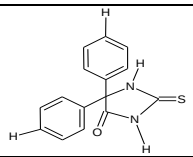
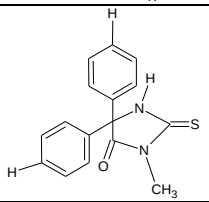
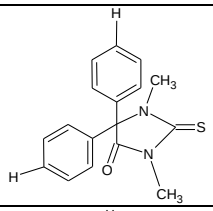
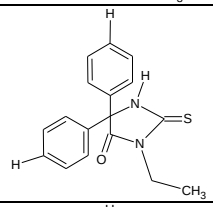
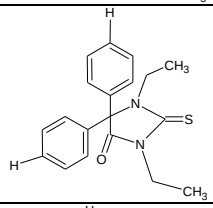
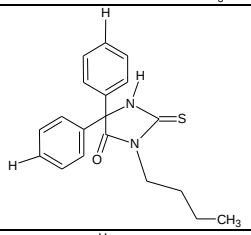
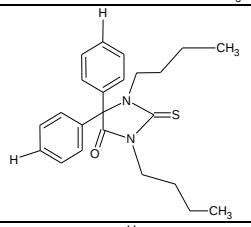
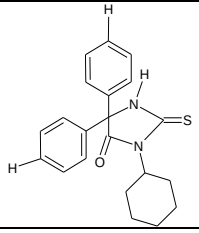
count, chi chain, chiV chain, cluster, path cluster, kappa, element count, estate numbers, estate contributions, information theory index, and polar surface area) that were considered as independent variables in the present study. The pre-processing of the independent variables (i.e., descriptors) was done by removing invariable (constant column), 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 method (MLRM). In the generation of QSAR model we have selected five test and seventeen 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. [4, 6, 9]

Table 1: Series of 5, 5, diphenyl imidazolidine 2, 4-dione with biological activity

Comp. No	Structure	IC50	Log $1/IC_{50}$
NS01		35.9	-1.98
NS02		31.50	-1.50
NS03		1.60	-0.20
NS04		86	-1.93
NS05		1.90	-0.28
NS06		82	-1.91
NS07		40	-1.6

NS08		34	-1.53
NS09		3.10	-0.43
NS10		2.10	-0.32
NS11		91.25	-1.96
NS12		9.40	-0.97
NS13		3.55	-0.55
NS14		1.30	-0.11
NS15		43.82	-1.64
NS16		63.60	-1.8

NS17		76.30	-1.88
NS18		18.75	-1.27
NS19		6.50	-0.81
NS20		11.20	-1.05
NS21		3.52	-0.55
NS22		3.24	-0.51

2.2. Creation of training and test set

The sphere exclusion method was adopted for division of training and test data set comprising seventeen and five 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. Five compounds, namely1, NEWNS01, NEWNS05, NEWNS11, NEWNS17 and NEWNS21 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.

2.3. Multiple linear regression and 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 17 compounds and test set of 5 compounds 1, 5, 11, 17 and 21. 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.

$Log(1/IC_{50})$= 0.907 (±0.069)T_C_N_7 -0.070 (±0.095)SssCH2count+0.003 (±0.008) Xlogp-0.09 (±0.009)$SsCH_3$+0.221 (±0.630)

n = 22 r = 0.956, s = 0.3093, F = 18.09, r^2 = 0.913

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.

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	smr	chi0	chi1	chi2	Nitrogens Count	log1/ IC_{50}
NS01	260.	5	1	4	0.	2.5	7	71.32	13.	8.5	8.1650	2	-1.98
NS02	278.	6	1	4	0.	2.6	7	71.28	13.	8.9	8.7869	2	-1.50
NS03	318.	7	1	7	0.	2.3	8	82.66	16.	10.	9.8273	2	-0.20
NS04	307.	8	3	7	0.	2.0	7	77.38	15.	9.8	9.6858	3	-1.93
NS05	307.	8	3	7	0.	2.0	7.	77.38	15.	9.8	9.6977	3	-0.28
NS06	303.	6	1	7	0.	2.5	8	85.65	15.	9.8	9.6977	3	-1.91
NS07	276.	6	2	5	0.	2.2	7.	72.99	13.	8.9	8.7869	2	-1.6
NS08	328.	8	1	5	1.	3.4	7	76.48	16.	10.	10.744	2	-1.53
NS09	274.	5	1	5	1.	2.8	7	76.06	13.	8.9	8.7869	2	-0.43
NS10	290.	6	1	6	0.	2.5	7	77.88	14.	9.4	8.9560	2	-0.32
NS11	290.	6	1	6	0.	2.5	7	77.88	14.	9.4	8.9679	2	-1.96
NS12	276.	6	2	5	0.	2.	7	72.99	13.	8.9	8.7988	2	-0.97
NS13	292.	7	3	6	0.	1.9	7	74.65	14.	9.3	9.2946	2	-0.55
NS14	306.	7	2	7	0	2.2	7.	79.54	15.	9.8	9.4857	2	-0.11
NS15	320.	8	3	7	0.	1.9	7	79.95	16.	10.	10.225	2	-1.64
NS16	320.	7	2	8	0.	2.6	8	84.16	16.	10.	9.8661	2	-1.8
NS17	306.	7	2	7	0.	2.2	7	79.54	15.	9.8	9.4857	2	-1.88
NS18	320.	7	1	8	0.	2.5	8	84.43	16.	10.	9.6767	2	-1.27
NS19	320.	7	1	8	0.	2.5	8	84.43	16.	10.	9.7827	2	-0.81
NS20	350.	8	1	10	6	2.5	0.	90.98	17.	11.	10.407	2	-1.05
NS21	336.	8	2	9	3	2.2	6.	86.09	17.	108	10.194	2	-0.55
NS22	260.	5	1	4	0.	2.5	7	71.3	13.	8.5	8.11	2	-0.51

2.4 Observed and predicted activity of 5, 5, diphenyl Imidazolidine 2, 4-dione derivatives

The model is validated by predicting the biological activities of the all molecules, as indicated in Table 3. It was 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 the plot of actual versus predicted activities for the training test compounds is represented in Fig. 2.

Table 3: Observed and predicted biological activity for series of 5, 5, diphenyl Imidazolidine 2,4 dione derivatives

Compound No.	Observed activity	Predicted(LOO) activity
NS01	1.98	2.148
NS02	1.50	1.798
NS03	0.20	0.335
NS04	1.93	1.512
NS05	0.28	0.586
NS06	1.91	2.707
NS07	1.6	2.013
NS08	1.53	2.954
NS09	0.49	1.066
NS10	0.32	1.416
NS11	1.96	2.914
NS12	0.97	0.843
NS13	0.55	0.473
NS14	1.30	2.754
NS15	1.64	1.272
NS16	1.8	0.918
NS17	1.88	2.820
NS18	1.27	2.810
NS19	0.81	1.959
NS20	1.05	2.806
NS21	0.55	1.317
NS22	0.51	1.065

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

Compound No.	Observed Activity	Predicted Activity
NS01	1.98	1.3
NS05	0.28	0.58
NS11	1.96	1.5
NS17	1.88	1.6
NS21	0.55	0.67

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

Compound No.	Observed activity	Predicted(LOO) activity
NS02	1.50	1.45
NS03	1.58	1.94
NS04	1.93	1.76
NS06	1.91	1.87
NS07	1.6	2.43
NS08	1.53	1.95
NS09	0.49	1.11
NS10	0.32	0.57
NS12	0.97	1.12
NS13	0.55	1.47
NS14	0.11	1.75
NS15	1.64	1.91
NS16	1.8	1.98
NS18	1.27	1.81
NS19	0.81	1.31
NS20	1.05	1.51
NS22	0.51	0.71

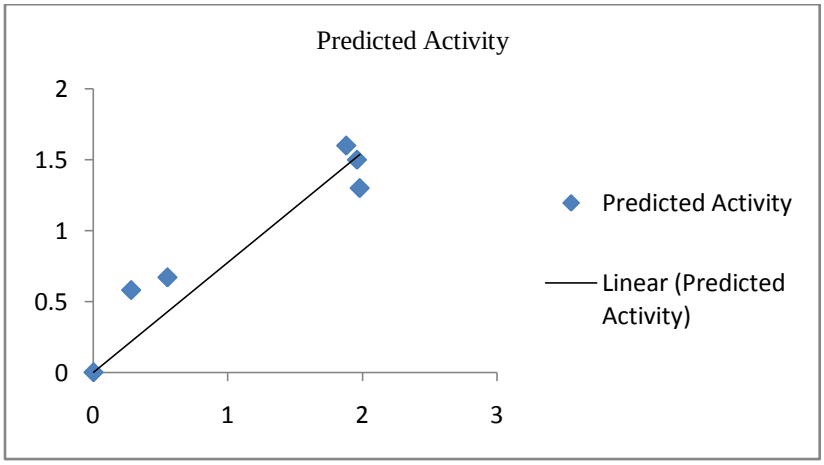


Figure 1: Graph between observed activity and predict activity for test compounds

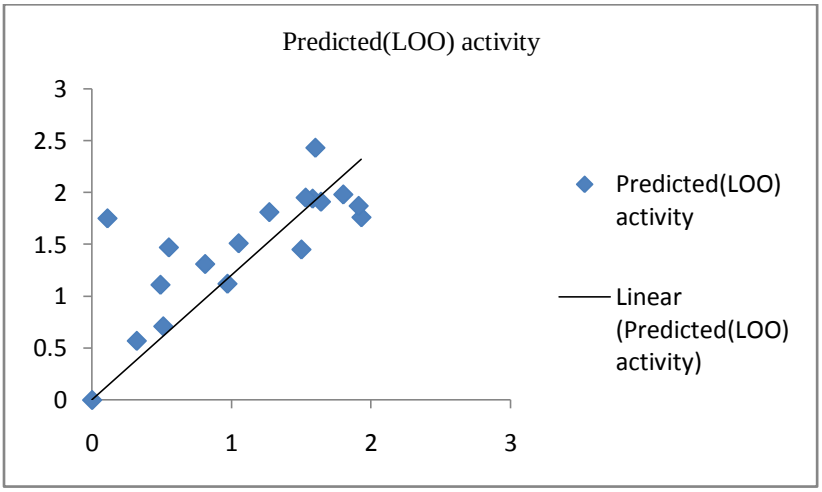


Figure 2: Graph between observed activity and predict activity for training compounds

2.5 Correlation matrix

The final correlation matrix of 5, 5, diphenyl Imidazolidine 2,4 dione derivatives shown in Table 6 which shows good correlation of selected parameters with biological activity.

Table 6: Final correlation matrix

Variable	$SSCH_3$	SdSE-index	Xlogp	$SssCH_2$ count	SssssC count
$SSCH_3$	1.				
SdSE-index	0.986	1			
Xlogp	0.9851	0.9819	1		
$SssCH_2$count	0.9996	0.022	0.9201	1	
SssssCcount	0.9795	0.113	0.9280	0.9391	1

3. Results and Discussion

3.1. Models on the basis of two dimensional QSAR

Several regression equations were obtained in this study. Among the regression results, three equations were selected as models and the statically parameter are given in Table 7. 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; Cross validated 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.

3.2 Multiple linear regression analysis results following three QSAR models

Model-1

pIC_{50} = +0.8845 (±0.2312) $SSCH_3$ + 0.8579(± 0.0569) SdSE-index + 0.6887 (±0.460) SsssN Count+ 0.0340 (±0.0876) Xlogp +0.8601 (±0.0441)
n training =17, n test =05, , Degrees of freedom = 21, n=22, r=0.932, S=0.243, F=38.46, r^2=0.8686, q^2=0.7994, r^2 se =0.0466, q^2_ se= 0.016, pred_r^2 = 0.6791, pred_r^2se =0.0999, ZScoreQ^2 =1.263, Best Rand Q^2= 0.6673

Model-2

pIC_{50} = -0.7411(±0.1147) K2alpha+ 0.767(± 0.0219) T_C_N_7+ 0.624(± 0.0335) SssCH2count -0.7621(±0.048)chlorlines Count
n training =17, n test =05, Degrees of freedom = 16, r=0.919,S=0.264, F=28.75, r^2 = 0.8445, q^2 = 0.7630, r^2 se= 0.5711, q^2 se = 0.158, pred_r^2 = 0.7642, pred_r^2se= 0.118, ZScoreQ^2= 6.619, Best Rand Q^2 = 0.4750.

Model-3

pIC_{50}= +0.6002(±0.099) SdSEIndex_ 0.6981(±0.079) SssssCcount +0.870(±0.0623) T_2_N_3+0.4540(±0.0870) $SsCH_3$Index+0.8087.
n training = 17, n test = 05, , Degreesof freedom = 19, r=0.912,S=0.672 ,F=22.23,r^2 = 0.8317, q^2 = 0.749, r^2 se =0.986, q^2_ se= 0.4096, pred_r^2 = 0.9491, pred_r^2se =0.4804, ZScoreQ^2 =1.555, Best Rand Q^2= 0.5230.

Table 7: Statistical parameters

Model no.	N	r	S	F	r^2	q^2
1	22	0.932	0.243	38.46	0.8686	0.7994
2	22	0.919	0.264	28.75	0.8445	0.7630
3	22	0.912	0.409	22.23	0.8317	0.7491

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

- $SsCH_3$count is increased.
- SdSE-index is increased
- SsssN Count is increased.
- Xlogpis increased.

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

- K2alphais decreased.
- T_C_N_7 is increased.
- $SssCH_2$count is increased.

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

- SdSE Index is increased.
- SssssC count is decreased
- $SsCH_3$ 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 $SsCH_3$ count, SsssN, Xlogp,T_C_N_7, SssCH2count and SdSE-index is positively correlated to activity and chlorlines Countand ChainCount values are negatively correlated to activity. It also shows the greater influence of $SssCH_2$count on biological activity than T_2_N_5, SssssCcount, SsssN. 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.

In model 1, the positive contribution of Alignment Independent descriptor T_C_N_7 show that the the count of number of double bounded atoms This is the count of number of carbon atoms (single double or triple bonded) separated from nitrogen atom by 7 bond distance in a molecule, that increase antibacterial and antifungal activity and Alignment Estate Numbers descriptor SsCH3 counts. This descriptor defines the total number of $–CH_3$ group connected with single bond.$SssCH_2$count: This descriptor defines the total number of $–CH_2$ group connected with two single bonds that also increase antimicrobial activity SdSE-index: Electrotopological state indices for number of sulphur atom connected with one double bond. 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 SssssCcount and Xlogp on the biological activity showed that the increase in the values of these parameter lead to better inhibitor properties against the bacteria and fungus.

4. Conclusion

In conclusion, the model developed to predict the structural features of 5,5-diphenylimidazolidine-2,4-dione derivatives antimicrobial and antifungal activity, reveals useful information about the structural feature requirements for the molecule. 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 molecules. The present studies were aimed at deriving predictive 2D models capable of elucidating the structural requirements for antimicrobial and antifungal activity. 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.

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