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Quantitative structure activity relationship analysis of a series of antibacterial 3-bromo-4-(1-*H*-3-indolyl)-2, 5-dihydro-1*H*-2, 5- pyrroledione derivatives

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Abstract

The use of quantitative structure–activity relationships, since its advent, has become increasingly helpful in understanding many aspects of biochemical interactions in drug research. This approach was utilized to explain the relationship of structure with biological activity of antibacterial. For the development of new fungicides against, the quantitative structural–activity relationship (QSAR) analyses for fungicidal activities of Pyrroledione Derivatives were carried out using multiple linear regression (MLR) Quantitative structure–activity relationship (QSAR) analysis was performed on a series of 3-Bromo-4-(1-H-3-Indolyl)-2, 5-Dihydro-1H-2, 5-Pyrroledione Derivatives.QSAR investigations were based on Hansch's extra thermodynamic multi-parameter approach. QSAR investigations reveal that steric and electrostatic interactions are primarily responsible for enzyme–ligand interaction. These studies produced good predictive models and give statistically significant correlations of selective COX-2 inhibitory with physical property, connectivity and conformation of molecule. Also when available COX-1 inhibitory data was analyzed with descriptors obtained from chem. Office 2007, partial charge descriptor, van der Waal's surface area and solvation energy gave statistically significant results. The results obtained by combining these methodologies give insights into the key features for designing more potent analogs antibacterial.

Keywords : 2D QSAR, Antibacterial, Staphylococcus aureus.

Introduction

The acquisition of a micro organism by a host is called microbial infection[1-2]. These can be caused by viruses, bacteria, micro fungi and protozoa.Despite the extensive use of antibiotics and

vaccination programmes, infectious diseases continue to be a leading cause of morbidity and mortality worldwide. Widespread antibiotic resistance, the emergence of new pathogens in addition to the resurgence of old ones, and the lack of effective new therapeutics exacerbate the problems. Antibacterial[3-4] may be defined as anything that destroys bacteria or suppresses their growth or their ability to reproduce. Heat, chemicals such as chlorine, and antibiotic drugs all have antibacterial properties. In its broadest definition, an antibacterial is an agent that interferes with the growth and reproduction of bacteria. The incidence of invasive microbial infections caused by opportunistic pathogens, often characterized by high mortality rates, has been increasing over the past two decades. Patients who become severely immuno compromised because of underlying diseases such as leukemia or recently acquired immunodeficiency syndrome or patients who undergo cancer chemotherapy or organ transplantation are particularly susceptible to opportunistic microbial infection [5]. Almost all of the major classes of antibiotics have encountered resistance in clinical applications [6]. The emergence of bacterial resistance to ß-lactam antibiotics, macrolides, quinolones and vancomycin is becoming a major worldwide health problem [7]. A matter of concern in the treatment of microbial infections is the limited number of efficacious antimicrobial drugs. Many of the currently available drugs are toxic, enable recurrence because they are bacteriostatic/fungistatic and not bactericidal/fungicidal or lead to the development of resistance due in part to the prolonged periods of administration [8]. There is a real perceived need for the discovery of new compounds that are endowed with antibacterial and antifungal activities, possibly acting through mechanism of actions, which are distinct from those of well known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant [9].

Materials and Methods

Experimental

1.1 Data set

The antibacterial activity data of 3-Bromo-4-(1-H-3-Indolyl)-2, 5-Dihydro-1H-2, 5- Pyrroledione Derivatives having 55 compounds out of which 49 compounds having well defined biological activity reported by Mahboobi.S.et al[10] (Table1).. The biological activity data (IC_{50} in μm) were converted to negative logarithmic dose (pIC_{50}) for quantitative structure activity analysis.

1.2 Geometry optimization

The molecular structures of all 49 compounds were sketched using the Chemdraw Ultra (Version 8.0) software & energy minimized via MOPAC with energy tolerance value of root mean square gradient 0.001 kcal/mol & maximum number of iteration set to 1000. Conformational search of each energy-minimized structure was performed using the stochastic approach which is similar to the RIPS Method. All conformers generated for each structure were analyzed in conformational geometrics panels with great care, and the lowest energy conformation of each structure was selected & added to a molecular database to compute various physicochemical properties. The descriptor values used in the model generation are shown in the table.

1.3. Statistical methods and molecular descriptors

The series was divided in to a training set of 37 compounds & a test set of 12 compounds carried out automatically by the VALSTAT software (Table 4 and 5). The sequential multiple linear regression analysis method was employed. In sequential multiple linear regression, the program searches for all permutations & combinations sequentially for the data set. The ± data with in the parentheses are the standard deviations associated with the coefficient of descriptors in regression equations. The best model was selected from the various statistically significant equations on the basis of the observed squared correlation coefficient (r^2), variance (v), standard

deviation (std.) the sequential Fischer test (F), the Bootstrapping r^2, chance, Q^2 value, S_{press} value, standard deviation of error prediction (SDEP) & the predictive squared correlation coefficient of the test set (r^2 pred.)[11]

1.4 Multiple Linear Regression Analysis

The stepwise multiple regression analyses were carried out using the statistical software openstat2, version 6.5.1, designed and standardized by Bill Miller and Stat Val. Correlation matrix was obtained to justify the use of more than one variable in the study. The variables used were with maximum correlation to activity and minimum inter-correlation with each other. From the statistical viewpoint, the ratio of the number of samples (N) to the number of variables used (M) should not be very low; usually it is recommended that N/M≥5.

The QSAR equations were constructed for efficacy data of both species of malarial parasite with the physcio-chemical descriptors and indicator variables. The statistical quality of the equations[12] was judged by the parameters like correlation coefficient (r), explained variance (r^2), standard error of estimate(s) and the variance ratio or overall significance value (F).The accepted equations are validated for stability and predictive ability using "leave –one-out" and cross validation technique. The statistical parameters used to access the quality of the models are the predictive sum of squares (PRESS) of validation. Finally, the standard cross-validation correlation coefficient r^2 and q^2 are also calculated.

$$PRESS = \Sigma (Ypred - Y\ obs)^2$$

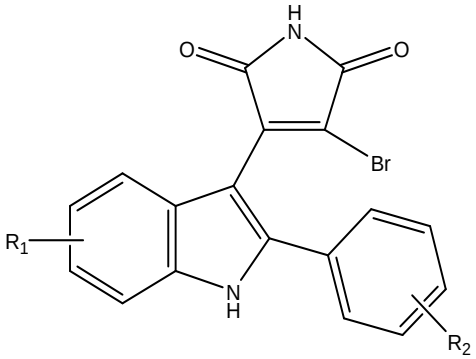
$$S_{press} = \sqrt{} PRESS/ (n-k-1)$$

n= no. of compounds used for cross-validation

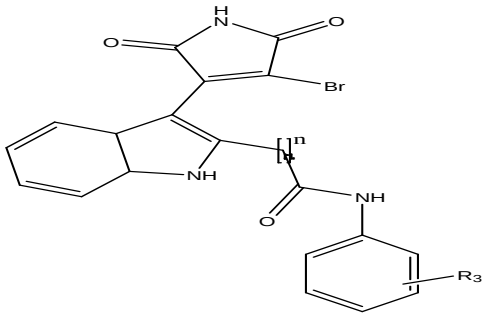
y_i= experimental value of the physic-chemical property for the ith sample

y= value predicted by the model built without the sample i

Table 1: **Activity of 3-bromo-4-(1-*H*-3-indolyl)-2,5-dihydro-1*H*-2,5-pyrroledione derivatives against *Staphylococcus aureus* 134/93**



(7a-28h)



(34a-h)

Sr.	R1	R2	MIC*10^{-6}	pMIC
7a	H	4-Ome	0.32	6.5
7b	H	4-Obu	0.45	6.3
7c	H	4-Open -	0.88	6.1
7d	H	4-Ooct	50	4.3
7f	H	4-Obzl	0.21	6.7
7g	H	4-Onaph	1.5	5.8
12a	5-Ome	H	1.00	6.0
12b	5-Oet	H	3.80	5.4
12c	5-Opr	H	0.95	6.0

12d	5-Obu	H	0.11	6.9
12e	5-Open	H	27	4.6
13a	5-Oet	4-Ome	2.0	5.7
13b	5-Opr	4-Ome	0.44	6.4
13c	5-Obu	4-Ome	0.10	7.0
18a	5-Ohex	H	0.13	6.9
18b	5-Et	H	0.13	6.9
18c	5-Pr	H	0.50	6.3
18d	5-Bu	H	0.24	6.6
18e	5-Pen	H	0.91	6.0
19a	5-Me	4-Ome	0.12	6.9
19b	5-Et	4-Ome	0.23	6.6
19c	5-Pr	4-Ome	0.45	6.3
19d	5-Bu	4-Ome	0.44	6.4
19e	5-Pen	4-Ome	0.85	6.1
24a	7-Me	H	3.98	5.4
24b	7-Et	H	2.51	5.7
24c	7-Bu	H	0.25	6.6
24d	7-Pen	H	0.50	6.3
25a	7- Me	4-Ome	2.00	5.7
25b	7- Et	4-Ome	0.50	6.3
25c	7- Pr	4-Ome	0.50	6.3
25d	7- Bu	4-Ome	0.25	6.6
25e	7- Hex	4-Ome	0.40	6.4
28a	5-Ome	3- Ome	1.90	5.7
28b	5-Oet	3- Ome	3.50	5.5
28c	5-Obu	3- Ome	3.30	5.5
28d	5-Ohex	3- Ome	12.60	4.9
28e	5-Me	3- Ome	0.20	6.6
28f	5-Et	3- Ome	0.50	6.3
28g	5-Bu	3- Ome	3.40	5.5
28h	5-Hex	3- Ome	26.00	4.6
Nr	**n**	**R^3**	**MIC*10^{-6}**	**pMIC**
34a	2	H	0.18	6.7
34b	3	H	1.7	5.8
34c	4	H	1.7	5.8
34d	5	H	0.10	7.0
34e	6	H	0.10	7.0
34f	3	4-Me	1.58	5.8
34g	3	3-Me	0.79	6.1
34h	3	2-Me	0.32	6.5
ciprofloxacin			38.1	4.4

Table 2: Calculated values of independent variables

MR	CAA	Gibb's energy	Tot.Eng	MSA	ovality	DDE	Log P	SBE	NDEW	DPL
6.221	5.0032	133.2795	51.52081	53.568	23.49299	16.63536	14.71616	12.6966	11.93902	10.04118
6.221	5.0032	133.2795	51.52081	53.568	23.49299	16.63536	14.71616	12.70348	11.70306	9.75099
6.967	5.9277	127.5067	49.09488	51.189	21.91564	15.72468	13.81723	11.97542	11.19859	9.53579
6.967	5.9277	127.5067	49.09488	51.189	21.91564	15.72468	13.81723	11.9823	10.89584	9.408625
6.221	5.0032	133.2795	51.52081	53.568	23.49299	16.6522	14.65128	12.62385	12.01926	10.56465
4.139	4.7276	132.2225	49.35908	52.689	24.41564	16.95284	15.70621	12.87315	12.62978	11.20823
4.139	4.7276	132.2225	49.35908	52.689	24.41564	16.936	15.77501	12.93798	12.18346	10.2189
4.139	4.7276	132.2225	49.35908	52.689	24.41564	16.936	15.77501	12.94485	11.95263	9.872439
4.139	4.7276	132.2225	49.35908	52.689	24.41564	16.95284	15.71593	12.82781	12.17676	10.83936

4.42	5.03602	136.9595	51.19386	54.524	25.28588	17.34669	16.3616	13.09919	12.43001	11.34562
4.758	5.381	137.2325	51.26941	54.617	25.28588	17.34669	16.3616	13.09919	12.43001	11.34562
4.42	5.03602	136.9595	51.19386	54.524	25.28588	17.36352	16.25895	13.1813	12.55441	10.89955
5.072	3.8995	131.7929	50.80608	53.21	23.49299	16.6522	14.64156	12.67253	12.35766	10.87569
4.589	5.1177	136.8395	51.19386	54.524	25.12275	17.5135	15.69204	13.63044	12.34031	10.93536
5.489	5.8979	146.0735	54.8649	58.194	26.53696	18.5135	16.44204	13.89388	12.74671	11.09401
5.92	4.9725	129.456	49.75177	51.819	23.49299	16.6522	14.64156	12.67253	12.35766	10.87569
5.92	4.9725	129.456	49.75177	51.819	23.49299	16.63536	14.71616	12.6966	11.93902	10.04118
5.92	4.9725	129.456	49.75177	51.819	23.49299	16.63536	14.71616	12.70348	11.70306	9.75099
5.92	4.9725	129.456	49.75177	51.819	23.49299	16.6522	14.65128	12.62385	12.01926	10.56465
6.201	5.28092	134.193	51.59095	53.654	24.36323	17.04605	15.29695	12.89113	12.30613	10.99805
6.539	5.6259	134.466	51.63319	53.747	24.36323	17.04605	15.29695	12.89113	12.30613	10.99805
6.201	5.28092	134.193	51.59095	53.654	24.36323	17.06288	15.18851	13.02489	12.2972	10.6361
6.144	5.7924	116.2843	45.35547	46.107	20.21697	14.16904	12.38295	10.49085	9.906599	8.664729
7.01	6.8255	130.9923	50.67255	51.42	22.66456	15.4904	13.85076	11.47482	10.97378	9.940897
0	6.0107	134.211	49.35908	52.689	24.41564	16.99815	15.41052	13.20402	12.51732	10.90441
7.818	6.1107	159.7502	61.84944	64.22	27.73563	19.6902	16.58744	14.26146	13.1893	11.37784
6.038	5.0868	127.8842	49.14573	51.182	22.62275	16.27952	13.91174	12.37932	11.84372	10.23162
4.912	5.7977	135.6777	50.5662	53.887	24.41564	16.95284	15.71593	12.82781	12.17676	10.83936
6.527	5.2319	140.1424	53.89011	56.243	24.03696	17.27952	14.64572	12.78341	12.17053	10.53092
6.629	5.58272	127.2337	49.08759	51.096	21.91564	15.74152	13.72069	12.05223	11.65174	9.7742
6.9	5.8525	143.1645	55.27005	57.324	25.77745	18.10089	15.72338	13.64519	13.48094	10.88769
5.974	4.9799	124.1615	47.83918	49.898	21.91564	15.74152	13.72069	12.05223	11.65174	9.7742
6.021	4.9014	133.8365	51.59095	53.654	24.2001	17.13536	15.13304	12.6291	12.24792	10.49149
6.348	5.2743	122.4967	47.24556	49.261	21.0454	15.33083	13.18347	11.63988	10.95208	9.288485
6.348	5.2743	122.4967	47.24556	49.261	21.0454	15.33083	13.18347	11.63988	10.95208	9.288485
6.221	5.0032	133.2795	51.52081	53.568	23.49299	16.63536	14.71616	12.6966	11.93902	10.04118

Table 3: Predicted biological activity and LOO predicted activity with their variance in comparison to the observed biological activity of equation

Sr.No.	Comp.no.	Actual act. (MIC)	Obs.act (-PMIC).	Pred. act Model-1	Pred. act Model-2	Pred. act Model-3
1	7a	0.32	6.49	6.35	6.23	6.45
2	7b*	0.45	6.34	6.27	6.33	6.21
3	7c	0.88	6.05	6.09	6.14	6.29
4	7d	50	4.3	6.35	5.61	6.15
5	7f	0.21	6.67	6.67	6.87	6.57
6	7g*	1.5	5.82	5.92	5.74	5.89
7	12a	1	6	6.27	617	6.17
8	12b	3.8	5.42	6.07	6.37	6
9	12c	0.95	6.02	6.2	589	6.11
10	12d*	0.11	6.95	6.52	6.82	6.87
11	12e	27	4.56	4.39	4.49	4.49
12	13a	2	5.69	6.25	6.15	5.79
13	13b	0.44	6.35	6.4	6.14	6.43
14	13c	0.1	7	6.71	6.51	7.09
15	18a*	0.13	6.88	6.59	6.89	6.79
16	18b	0.13	6.88	6.65	6.75	7.01
17	18c	0.5	6.3	6.59	6.39	6.45
18	18d	0.24	6.62	6.39	6.69	6.79
19	18e	0.91	6.04	6.18	6.08	6.13
20	19a	0.12	6.92	6.77	697	6.98
21	19b*	0.23	6.63	6.76	656	6.51
22	19c	0.45	6.34	6.69	6.49	6.19

23	19d	0.44	6.35	6.5	6.45	6.21
24	19e	0.85	6.07	6.28	6.18	5.96
25	24a*	3.98	5.4	5.68	5.58	5.39
26	24b	2.51	5.6	5.75	5.65	5.89
27	24c	0.25	6.6	6.32	6.37	6.69
28	24d*	0.5	6.3	6.43	6.23	6.4
29	25a	2	5.69	5.88	5.788	5.61
30	25b	0.5	6.3	5.93	6.21	6.25
31	25c*	0.5	6.3	6.18	6.24	6.58
32	25d	0.25	6.6	6.48	6.02	6.32
33	25e	0.4	6.39	5.7	5.98	6.11
34	28a*	1.9	5.72	5.9	6.74	5.6
35	28b	3.5	5.45	5.52	5.11	5.61
36	28c	3.3	5.48	5.88	5.02	5.89
37	28d*	12.6	4.9	6.48	3.99	4.71
38	28e	0.2	6.69	5.95	6.12	6.98
39	28f	0.5	6.3	6.07	5.98	6.11
40	28g	3.4	5.46	5.98	5.1	5.9
41	28h	26	4.58	4.37	5.02	4.12
42	34a*	0.18	6.74	6.11	6.21	6.27
43	34b	1.7	5.77	5.21	5.45	6.12
44	34c	1.7	5.77	5.55	6.04	5.6
45	34d	0.1	7	6.88	6.18	6.43
46	34e*	0.1	7	6.95	6.51	6.32
47	34f	1.58	5.8	5.93	6.04	5.67
48	34g	0.79	6.1	5.78	6.42	5.13
49	34h	0.32	6.49	6.07	6.55	5.97

*Obs. Activity: Observed biological activity, Pred. Activity: Predicted biological activity, LOO pred.: Leave one out predicted biological activity. * Test compound*

Table-4: Validated parameters of model-1, 2, 3, 4, 5 and 6

S.No	[a]bsr^2	[b]Q^2	[c]S_{PRESS}	[d]SDEP
Model-1	3.791	0.6891	0.1271	1.6372
Model-2	0.5319	0.7210	0.2193	0.9103
Model-3	0.3027	0.6110	0.2021	0..5261
Model-4	0.3981	0.5901	0.7219	0.5618
Model-5	0.2391	0.5891	0.9103	1.3183
Model-6	0.3392	0.6528	0.5023	0.7610

[a]boot strapped squared correlation coefficient, [b]cross-validated squared correlation coefficient, [c]Standard deviation of sum of squared error of prediction, [d] Standard deviation of error of prediction.

Table 5: correlation matrix of model-1

Parameters	StrE	MR	LogP	Ovality
StrE	1.0000			
MR	0.3612	1.0000		
LogP	0.5130	0.3810	1.0000	
Ovality	0.2160	0.2091	0.3031	1.0000

Table 6: correlation matrix of model-2

Parameters	[a]NVDW	[b]Ovality	[c] LogP	MR
NVDW	1.0000			
Ovality	0.2718	1.0000		
LogP	0.7142	0.3910	1.0000	
MR	0.3619	0.1931	0.5217	1.0000

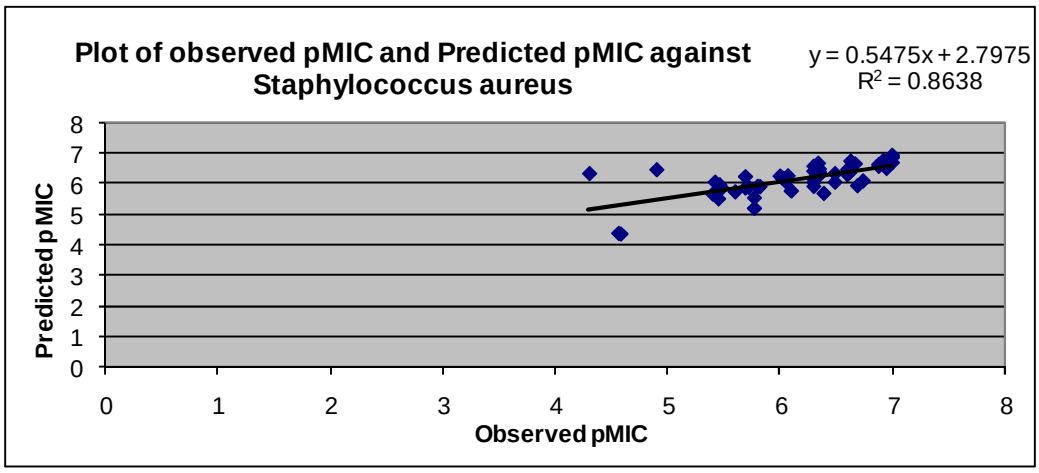


Figure 1: Plot between predicted pIC_{50} and observed pIC_{50} values of compounds of training set for equation 1

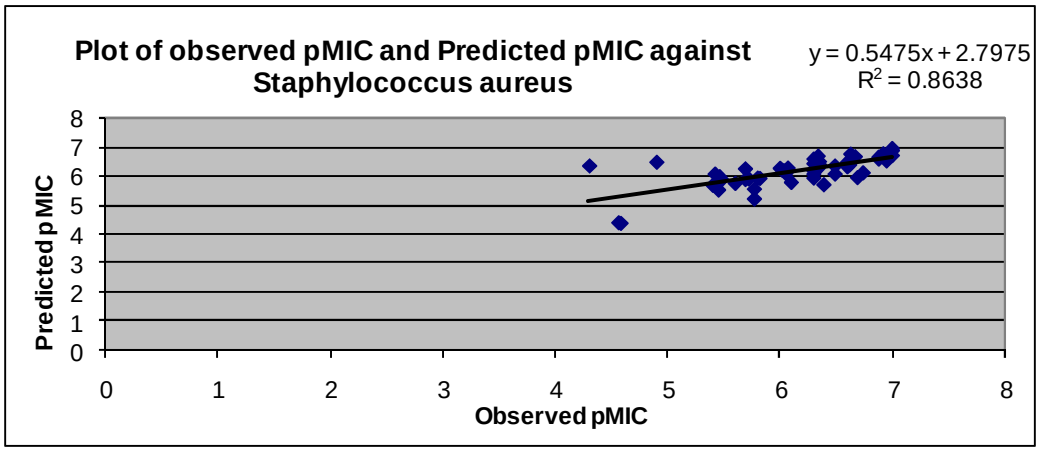


Figure 1: Plot between predicted pIC_{50} and observed pIC_{50} values of compounds of training set for equation 2

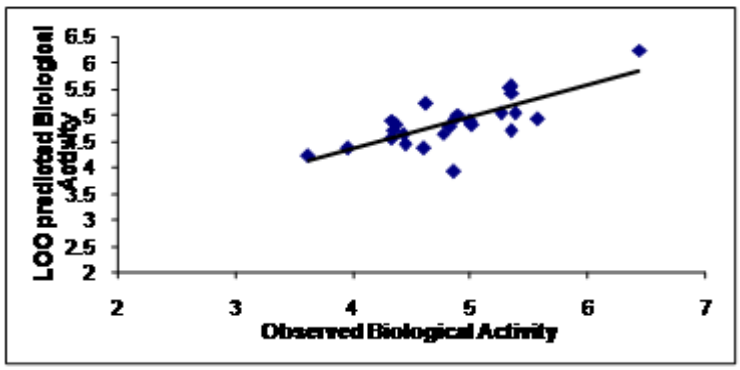


Figure 2: Plot between predicted pIC_{50} and observed pIC_{50} values of compounds of training set for equation 3

Results and Discussion

Biological activity data and various physicochemical parameters were taken as dependent and independent variables respectively and correlations were established using sequential multiple regression analysis. Acceptability of the regression model was judged by examining the correlation coefficient (r), squared correlation coefficient (r^2), fisher's value (F) and standard deviation. Performing multiple linear regression analysis results in

Model-1
BA= [4.04601(± 0.859089)] + StrE [-0.0323814(± 0.0185784)] + MR [0.0203999(± 0.0223441)] + LogP [0.0100504(± 0.00661578)] +Ovality -0.0093099(± 0.0251623)]
n=37, r=0.77687, r^2=0.693527, variance=0.115275, std=0.339522, F=45.7973

Model-1 shows high correlation coefficient (r=0.77687) between descriptors such as thermodynamic Squared correlation coefficient (r^2) of 0.693527, which explains 69.35% variance in biological activity. Model-1 also indicates statistical significance >99.9% with F-values F= 45.7973.Cross-validated Square correlation coefficient of the model was 0.3621, which shows good internal productivity of the model, Fig-1displays a plot between actual activity and predicted activity.

Model-2
BA = [3.74773(± 0.755394)] +NDEW [-0.0287275(± 0.0160425)] +ovality [0.0208738(± 0.0191271)] +log p [0.0125142(± 0.00584014)] +MR [-0.0054298(± 0.0216546)]
n=37, r=0.836961, r^2=0.7604, variance=0.0842067, std=0.290184, F=17.542

Model-2 shows high correlation coefficient (r=0.836961) between descriptors such as thermodynamic (non-Vander walls energy, ovality, total energy and logp). Squared correlation coefficient (r^2) of 0.7604, which explains 76.1% variance in biological activity. Model-2 also indicates statistical significance >99.9% with F-values F= 17.542.Cross-validated Square correlation coefficient of the model was 0.7189, which shows good internal predictivity of the model, Fig-2 displays a plot between actual activity and predicted activity.

Model-3
BA = [3.89782(± 0.674334)] + DDE [-0.0295238(± 0.0154761)] + SBE [0.0130842(± 0.0178486)] + log p [0.0116066(± 0.00508151)]
n=37,r=0.843728,r^2=0.711877,variance=0.081009,std=0.284621,F=18.5305

Model-4
BA = [4.40204(± 0.515426)] + log p [-0.0224323(± 0.0197796)] +MR [0.0105432(± 0.00607993)] + SBE [0.00770263(± 0.0194392)] n=37 ,r=0.806716,r^2=0.650791,variance=0.0981839,std=0.313343,F=13.9771

Model-5
BA = [4.12797(± 0.386667)] + log p [-0.0259112(± 0.0115931)] + CAA [0.0131825(± 0.00439019)] + MSA [0.166785(± 0.112537)]
n=37, r=0.907058,r^2=0.822754,variance=0.0618087,std=0.248614,F=47.9662

Model-6
BA = [4.08856(± 0.351912)] + DPL [-0.0243788(± 0.0105753)] +TotEng [0.0135297(± 0.00399023)] + VDWE [0.175103(± 0.102258)]

n=37, r=0.923075,r^2=0.852067,variance=0.0507033,std=0.225174,F=57.5981

Equations 3, 4, 5 and 6 were quite significant, which showed a bootstrapping squared correlation coefficient values such as 0.741, 0.541, 0.871 and 0.614 respectively. The inter correlation among the parameters of equation 2, 3, and 5 are 0.261, 0.215 and 0.153 respectively. Bootstrapping method and leave one out method were used for the validation of the QSAR models. The descriptor DDE in the models represents the sum of electrostatic terms resulting from the interaction of three dipoles. The descriptor bears a positive coefficient, which suggests significance of dipole–dipole interactions for the antibacterial activity of Pyrroledione derivatives. The Van der Waals energy is a thermodynamic parameter which can be defined as the sum of pair wise Vander Waals interaction energy terms for atoms separated by exactly chemical bonds, related to the structure of the molecule itself. Connolly's solvent accessible area, a steric descriptor, represents the surface area that is in contact with the solvent. The descriptor bears negative coefficient in the model, suggesting increase in the bulk in of the substituents and molecular solvent accessible surface area is not conducive to the activity. The descriptor Ovality in the model bears a negative coefficient thereby it represent the steric hindrance associated with the bulk of the substituents. The observation only reaffirms the conclusion drawn from the descriptor CAA in the model Stretch bend Energy, a Thermodynamic parameter, deals with the stretching and bending or one can say the conformational flexibility of the molecule. The descriptor in the second model bears a positive coefficient, indicating, substituents that increase the flexibility of Pyrroledione derivatives will enhance the antibacterial activity. Equation-1 fulfills many of the statistical validations such as the correlation coefficient; the cross validated squared correlation coefficient, standard deviation, bootstrapping squared correlation coefficient and chance. But the predictive residual sum of square standard error of prediction is less than 0.5 (0.15). The correlation accounted for more than 68.9% of the variance in the activity. The data showed an overall internal statistical significance level better than 99.9% as $F_{(3,\ 16\ \alpha\ 0.001)}$ = 45.7973which exceeds the tabulated $F_{(3,\ 16\ \alpha\ 0.001)}$ = 29.01, the cross validated squared correlation coefficient (Q^2 = 0.689), the predictive residual sum of square S_{PRESS} = 0.579), and the standard error of prediction (S_{DEP} = 0.216) suggested good internal consistency as well as predictive activity of the biological activity with high logP.

Conclusion

QSAR analysis was performed on a series of 3-Bromo-4-(1-H-3-Indolyl)-2, 5-Dihydro-1H-2, 5-Pyrroledione Derivatives using molecular modeling program Chemoffice2001[13]. QSAR models were proposed for antibacterial activity of the Pyrroledione Derivatives using chemSAR descriptors employing sequential multiple regression analysis method. The models also provide valuable insight into the mechanism of action of these compounds. The result of the study suggests involvements of dipole-dipole interaction in the mechanism of microbial action of less bulky substituents are undesirable due to steric hindrance. Additionally, presence of groups contributing to the flexibility of the molecule will increase microbial potency of antibacterial activity.

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