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Insight into the Structural Requirement of 2-Alkyl-4-(biphenylmethoxy)quinolines as Nonpeptide Angiotensin II Receptor Antagonists: A QSAR Approach

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Abstract

In the current study a quantitative structure activity relationship approach using sequential multiple linear regression analysis was applied to a series of 2-alkyl-4-(biphenylylmethoxy)quinolines as angiotensin II (Ang II) receptor antagonists by using Chem 3D and Dragon Software. The studies, carried out on 33 analogs, give statistically significant correlations of selective Ang II antagonistic activity with physical properties concerning size, symmetry, shape and distribution of molecule atoms. Among several 2D quantitative structure activity relationship models, one model gave good statistical significance ($r > 0.81$, F-test = 10.47, $S < 0.30$, chance correlation < 0.01). 3D QSAR studies show that Hennery's law constant, Dipole and VDWE play a significant role in Ang II antagonistic activity. These QSAR studies help us in the design and prediction of novel substituted benzimidazole Ang II receptor antagonists.

Keywords

QSAR • Angiotensin II antagonists • Hypertension • AT1 and AT2 receptor

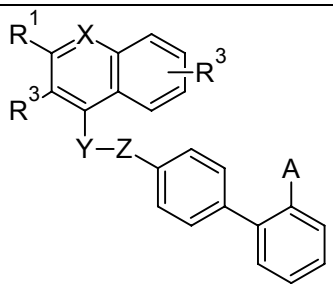
Introduction

The renin-angiotensin-aldosterone system (RAAS) is known to play an important role in electrolyte homeostasis and in the regulation of blood pressure and congestive heart failure [1]. The octapeptide angiotensin II (Ang II) is produced by the renin angiotensin system (RAS) and is a potent vasoconstrictor and thus plays an important role in the pathophysiology of hypertension [2, 3]. This directed many researchers toward the designing of drugs to block the effect of Ang II either by inhibiting the angiotensin converting enzyme (ACE) or renin or by blocking the Ang II receptor [4, 5]. Two distinct subtypes of Ang II receptors [type 1(AT1) and type 2 (AT2)] have been identified, and belong to the G-protein-coupled receptor family (GPCRs). AT1 and AT2 are seven-transmembrane-spanning receptors, comprising an extra cellular glycosylated region connected to the seven transmembrane-alfa-helices, which are linked by three intracellular and three extracellular loops. The carboxy-terminal domain of the protein is cytoplasmic and is a regulatory site. AT1 is a 359-amino acids protein, while AT2 is made up of 363 amino acids and is 30% homologous with AT1. Both receptors are N-linked glycosylated post-translationally [6, 7]. To gain insight into the structural and molecular requirement influencing the AII antagonistic activities, we herein describe the QSAR analysis of 2-alkyl-4-(biphenylylmethoxy)quinolines and a QSAR Model has been obtained for Ang II antagonistic activity. The relevance of the model for the design of novel derivatives should be assessed not only in terms of predictivity, but also in terms of their ability to provide a chemical and structural explanation of their binding interaction. Here we propose a general model for the antagonist and present minimal structural requirement for an Angiotensin II antagonist. These results should serve as a guideline in designing more potent and selective Ang II antagonist.

Methodology

The Ang II receptor antagonistic activity data of 2-alkyl 4-(biphenylylmethoxy)quinolines were taken from the reported work of Bradbury *et al* [8] (Table 1). The biological activity data (IC_{50} in μM) was converted to negative logarithmic mole dose (pIC_{50}) for quantitative structure activity relationship (QSAR) analysis. Initially, series was subjected to Fujita-Ban analysis using regression technique in order to estimate the *de novo* contribution of substituents to the activity of the molecules. Then Hansch approach was carried out to establish the correlations between Ang II antagonistic activity and various substituents constants at position R_1, R_2, R_3, A, X and Y–Z of the key molecule. Values of the substituents constants like hydrophobic (π), steric (Molar refractivity or MR), hydrogen acceptor (HA), hydrogen donor (HD) and electronic (field effect or F, resonance effect or R and Hammett's constant or σ), were taken from the reported work of Hansch *et al* [9]. The series was further subjected to molecular modeling studies using CS Chem-Office Software version 8.0 (Cambridge Soft) [10] and DRAGON [11] running on P-IV processor and regression analysis program VALSTAT [12].

Tab. 1. Structure and activities of 2-alkyl-4-(biphenylmethoxy)quinolines used in QSAR.



Cpd.	R^1	R^2	R^3	Y–Z	X	A	IC_{50}[a]	pIC_{50}[b]
1	Me	H	H	OCH_2	COOH	N	0.18	6.74
2	Et	H	H	OCH_2	COOH	N	0.17	6.76
3	Pr	H	H	OCH_2	COOH	N	0.60	6.22
4	Bu	H	H	OCH_2	COOH	N	3.1	5.5
5	H	H	H	OCH_2	Tetrazol-5-yl	N	6.3	5.2
6	Me	H	H	OCH_2	Tetrazol-5-yl	N	0.016	7.79
7	Et	H	H	OCH_2	Tetrazol-5-yl	N	0.031	7.5
8	Me	H	H	OCH_2	Tetrazol-5-yl	CH	90	4.04
9	Me	Me	H	OCH_2	Tetrazol-5-yl	N	4.6	5.33
10	Me	H	H	$OCH(CH_3)$	Tetrazol-5-yl	N	0.040	7.39
11	Me	H	H	SCH_2	Tetrazol-5-yl	N	0.37	6.43
12	Me	H	H	CH=CH	Tetrazol-5-yl	N	1.3	5.88
13	Me	H	H	CH_2CH_2	Tetrazol-5-yl	N	0.27	6.56
14	Et	H	5-Me	OCH_2	Tetrazol-5-yl	N	0.013	7.88
15	Et	H	5-Cl	OCH_2	Tetrazol-5-yl	N	0.12	6.92
16	Et	H	5-CN	OCH_2	Tetrazol-5-yl	N	0.060	7.22
17	Me	H	6-Me	OCH_2	Tetrazol-5-yl	N	0.47	6.32
18	Me	H	6-Cl	OCH_2	Tetrazol-5-yl	N	1.2	5.92
19	Et	H	6-CN	OCH_2	Tetrazol-5-yl	N	0.36	6.44
20	Et	H	6-CF_3	OCH_2	Tetrazol-5-yl	N	0.86	6.06
21	Et	H	6-COOMe	OCH_2	Tetrazol-5-yl	N	0.066	7.18
22	Et	H	6-OMe	OCH_2	Tetrazol-5-yl	N	0.022	7.65
23	Et	H	6-O-*i*-Pr	OCH_2	Tetrazol-5-yl	N	0.026	7.58
24	Et	H	6-CH_2CH_2 F	OCH_2	Tetrazol-5-yl	N	0.007	8.15
25	Et	H	6-CH_2CF_3	OCH_2	Tetrazol-5-yl	N	0.026	7.58
26	Et	H	7-Me	OCH_2	Tetrazol-5-yl	N	0.14	6.85
27	Et	H	7-Cl	OCH_2	Tetrazol-5-yl	N	0.16	6.79
28	Et	H	7-CN	OCH_2	Tetrazol-5-yl	N	0.46	6.33
29	Et	H	7-OMe	OCH_2	Tetrazol-5-yl	N	0.22	6.65
30	Me	H	8-Me	OCH_2	Tetrazol-5-yl	N	0.31	6.5
31	Et	H	8-Cl	OCH_2	Tetrazol-5-yl	N	0.14	6.85
32	Et	H	8-CF_3	OCH_2	Tetrazol-5-yl	N	2.0	5.69
33	Et	H	8-OMe	OCH_2	Tetrazol-5-yl	N	0.96	6.01

[a] Concentration of 50 percent antihypertensive activity data against Angiotensin II receptor antagonist
[b] Negative logarithm of IC_{50}

Tab. 2. Physicochemical properties of 2-alkyl-4-(biphenylmethoxy)quinolines used in 3D QSAR

Cpd.	CAA	PMI_Y	HLC	MR	D2	VDWE	nRO-RPh	Mor 03v	Mor 18u	Mor 28u
1	348.93	8398.6	389.62	10.921	2.239	16.679	1	-2.731	-1.973	-0.271
2	367.38	9606.0	412.55	11.385	1.945	17.742	1	-2.987	-2.353	-0.470
3	383.85	10111	435.48	11.848	1.237	18.506	1	-3.189	-2.318	-0.352
4	401.93	11861	458.41	12.312	0.529	20.174	1	-3.196	-2.582	-0.552
5	353.91	9204.8	391.78	11.112	3.965	12.560	1	-2.993	-1.617	-0.112
6	363.4	9277.4	416.57	11.576	4.519	17.011	1	-2.489	-2.182	-0.414
7	381.75	10195.	439.50	12.039	4.416	18.222	1	-2.559	-2.419	-0.484
8	367.98	9389.1	420.12	11.787	2.466	17.590	0	-2.824	-2.323	-0.391
9	375.56	9580.1	441.36	12.039	4.617	17.984	1	-2.47	-2.466	-0.483
10	376.07	9364.2	440.01	12.039	3.618	18.014	1	-2.633	-2.303	-0.710
11	370.11	9505.3	422.25	12.22	3.958	16.238	0	-3.22	-2.032	-0.473
12	364.62	9790	413.55	12.224	1.359	17.010	0	-3.126	-2.333	-0.284
13	369.93	9947.4	424.43	11.886	3.924	16.512	0	-3.296	-2.119	-0.812
14	395.54	10351	464.29	12.503	5.084	19.064	1	-2.55	-2.336	-0.559
15	392.38	10549	454.73	12.531	2.733	18.627	1	-2.823	-2.229	-0.289
16	394.22	9695.9	464.43	12.517	3.912	18.487	1	-2.606	-2.281	-0.350
17	393.40	10515	441.36	12.039	3.728	13.400	1	-3.333	-1.730	-0.387
18	379.39	10132	431.80	12.067	4.702	17.643	1	-2.798	-2.287	-0.343
19	399.43	11224	464.43	12.517	3.144	18.488	1	-2.898	-2.166	-0.468
20	413.81	12808	488.85	12.550	2.918	17.297	1	-3.392	-2.631	-0.787
21	428.77	11125	503.13	13.156	4.823	22.122	1	-2.639	-2.479	-0.540
22	410.14	11227.	479.36	12.656	4.785	19.943	2	-2.877	-2.640	-0.837
23	455.56	11399	525.74	13.584	4.161	21.424	2	-3.287	-2.603	-0.837
24	442.74	11399	510.62	13.136	5.748	22.510	2	-3.308	-1.925	-0.578
25	437.13	10845	502.29	13.120	7.436	21.751	2	-3.1	-2.483	-0.872
26	400.64	10927	464.29	12.503	4.177	19.073	1	-2.539	-2.671	-0.576
27	396.69	12519	454.73	12.531	4.591	18.500	1	-2.959	-2.576	-0.665
28	398.3	12170	464.43	12.517	3.569	18.272	1	-2.802	-2.340	-0.407
29	410.52	11331	479.36	12.656	6.514	20.957	2	-2.723	-2.247	-0.438
30	382.18	10556	441.34	12.039	3.828	17.559	1	-3.043	-2.407	-0.747
31	397.48	12395	454.73	12.531	5.938	19.180	1	-3.042	-2.266	-0.412
32	415.51	13698	488.85	12.550	9.586	18.694	1	-3.437	-2.358	-0.475
33	408.25	11977	479.36	12.656	3.982	20.624	2	-3.437	-2.358	-0.475

The structure of the corresponding 2-alkyl-4-(biphenylmethoxy)quinoline was drawn in Chem draw ultra 8 and was copied to Chem 3D ultra to create 3D model, which served as a template model. For every compound the template compound was suitably modified considering its structural feature keeping the same sequence of atoms for every compound. These structures were then subjected to energy minimization using molecular mechanism (MM2) until the root mean square (RMS) gradients value became less than 0.1 kcal/mol Å. The minimized molecules are then subjected to re-optimization via AM1 method using closed shell (restricted) wave function of MOPAC module until the RMS

gradient attained a value less than 0.0001 kcal/mol Å. The geometric optimization of the lowest energy structure was carried out eigenvector (EF) routine. The energy-minimized geometry was used for the calculation of descriptor and extended Hückel charges of different atoms. The descriptor values were calculated using the "computed properties" module of the program. The descriptor values used in model generation are shown in table 1. The data was transferred to a statistical program in order to establish a correlation between physicochemical parameters as an independent variable and the Ang II antagonistic activity as a dependent variable using a sequential multiple linear regression analysis method (in sequential multiple regression the program searched for all permutation and combination sequentially for the data set). The ± data within the parentheses represent the standard deviation, associated with the coefficient of descriptors in regression equations. The best model was selected from the various statistically significant equations on the basis of observed squared correlation coefficient (r^2), standard error of estimate (SE), sequential Fischer test (F), bootstrapping squared correlation coefficient (r^2_{bs}), bootstrapping standard deviation (S_{bs}), cross validated squared correlation coefficient using leave one out procedure (r^2_{cv}), 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), outliers (on the basis of Z-score value).

Results and Discussion

In order to develop 2D QSAR, the data set was subjected to a stepwise multiple linear regression analysis. This resulted into several correlation equations between the pIC50 values as a dependent variable and several quantifying parameters as an independent variable. Equation 1 was considered as model for antagonistic activity on Ang II. This model shows a better correlation coefficient (r = 0.813) with low standard error of estimation. Eqn. 1 accounts for 66% variance in the biological activity.

$$pIC_{50} = [4.04\ (\pm 1.131)] + R^1\_Et\ [0.901(\pm 0.437)] + R^2\_H\ [2.014\ (\pm 1.181)] + \ldots$$
$$\ldots\ Y\text{-}Z\_OCH(CH_3)\ [1.335(\pm 1.181)] + R^3\_6\text{-}OCH_2CF_3\ [1.194\ (\pm 1.164)] + \ldots$$
$$\ldots\ R^3\_8\text{-}CF_3\ [-1.265\ (\pm 1.164)]$$

Eqn. 1. n = 33, r = 0.813, r^2 = 0.66, SE = 0.30, F = 10.476, ICPA < 0.165

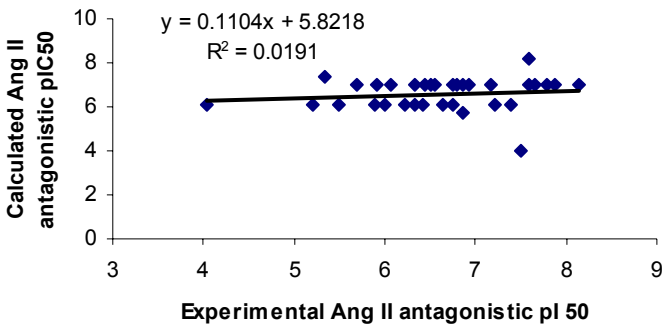


Fig. 1. Plot between calculated and experimental Ang II antagonistic pIC_{50} for model-1

The eqn. 1 shows overall internal statistical significance level better than 99.9% as it exceeds the tabulated F (5.20) $_{27,5}$ = 10.47. The Inter-correlation among the parameter (ICPA) is significantly low which suggests the non-dependency of the parameters. Equation 1 suggested that all the parameters in the quinoline ring contributed positively and linearly to the antagonistic activity.

The series was further subjected to Hansch approach in order to develop 2D-QSAR between inhibitions of Ang II receptor against hypertension, which account for more than 66% variance in activity.

$$pIC_{50} = [3.745\ (\pm\ 1.455)] + X\_HA\ [2.449\ (\pm\ 1.393)] + R^1\_F\ [-12.659\ (\pm\ 12.204)] + \ldots$$
$$\ldots\ R^2\_MR\ [-0.251(\pm\ 0.301)] + R^3\_MR\ [0.0448\ (\pm\ 0.060)]$$

Eqn. 2. n=33, r=0.724, r^2=0.524, SE= 0.441, F=7.646, ICPA < 0. 2

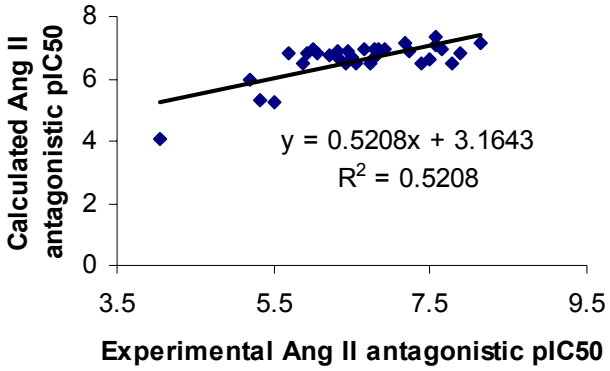


Fig. 2. Plot between calculated and experimental Ang II antagonistic pIC_{50} for model-2

This model has a coefficient of correlation (r=0.72) that explains 52% variance in the activity. The model showed an overall internal statistical significance level better than 99.5 % as it exceeded the tabulated F (5.11) $_{4,28}$ = 7.60. The intercorrelation among the parameter is less than 0.2 suggesting the absence of interdependency of substituent constants. The model was further tested for outliers by Z-score method and no compound was found to be such an outlier. Eqn. 2 shows that Molar refractivity (MR_R^2, MR_R^3), which is representative of bulkiness or molar volume of substituents, Hydrogen acceptor effect of substituents contributed positively to the equation and they are conducive for Ang II antagonistic activity.

Followed by 2D-QSAR analysis, the series was further subjected to molecular modeling studies in order to explore the three dimensional properties of the molecules which are responsible for the interaction of molecules with Ang II inhibitory activity. All the descriptor values were calculated from the program (Chem 3D 8, DRAGON) were considered as independent variable. Stepwise linear regression analysis method was used to develop multi-variant QSAR equation.

$$pIC_{50} = [6.737 (\pm 2.810)] + HLC [0.018 (\pm 0.190)] + PMI\_Y [-0.001 (\pm 0.001)] \ldots$$
$$\ldots + VDWE [0.182 (\pm 0.097)] + D\_2 [0.128 (\pm 0.121)]$$

Eqn. 3. n = 31, r = 0.758, r^2 = 0.574, SE = 0.482, F = 8.74

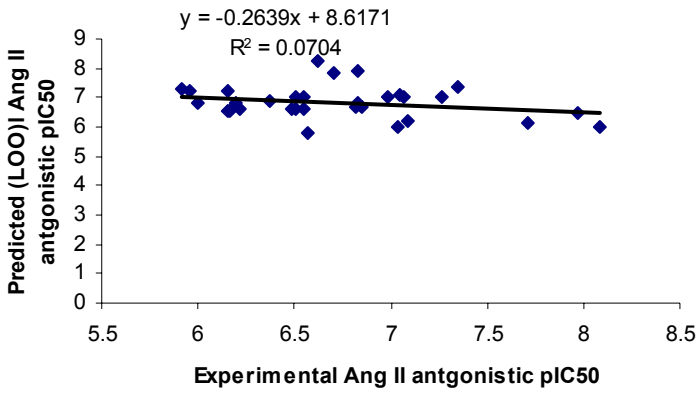


Fig. 3. Plot between observed pIC_{50} and predicted (LOO) pIC_{50} with residual presentation using model-3

Eqn. 3 explains for more than 57% variance in activity. The equation 4 was considered as 3D-model for the data set. The model is used for internal predictivity, the value of leave one out cross validation squared correlation coefficient (q^2 = 0.358) suggested goodness of the prediction.

Tab. 2. Correlation matrix of descriptors used in model 3

Parameter	HLC	PMIY	VDWE	D_2
HLC	1.000000			
PMIY	0.051654	1.000000		
VDWE	0.173513	0.267632	1.000000	
D2	0.134395	0.329045	0.308559	1.000000

The value of sequential fisher test suggests more than 99.8% internal statistical significance as it exceeds the tabulated value F (5.30) $_{28,4}$ = 8.74. The internal correlations among the parameter (ICAP < 0.32) and suggest that suggests the non-dependency of parameters. This equation was analyzed for search for outlier and two outliers namely compound No. 8 and 9 were identified from their Z score values (absolute difference between the value of model and the activity field divided by the square root of the mean square error of the data set) which are above 2.5. Removal of compound no. 8 and 9 improves the statistical result (eqn. 3). It is clear from the equation (3) that thermodynamic descriptors like Hennery's law constant and VDWE which is sum of pairwise Van der Waals interaction energy term for atom separated by exactly 3 chemical bonds, the electronic descriptor like (D_2) Dipole energy which is the first derivative of the energy with respect to an applied electric field. It measures the asymmetry in the molecular charge

distribution and is reported as a vector in three dimensions were contributed positively to the equation. Steric descriptor like PMI_Y that describes mass distribution over the molecule on Y-component in spatial arrangement, contributed negatively to the activity suggesting that the increase in bulkiness on Y-component of molecule is favourable for the Ang II antagonistic activity. The property values of descriptor were given in Table-1. The reliability of the equation has been further confirmed by internal validation using leave-one-out (LOO) cross validation method to ensure the robustness of the equation. Although equation shows moderate internal consistency (q^2 = 0.358). Bootstrapping technique was used to confirm the independent measure for the stability of the regression equation, r^2_{bsp} > 0.63, and standard error of prediction (S_{DEP} = 0.412).

Parameters were also calculated with DRAGON. Sequential multiple linear regression analysis was carried out for development of the QSAR equations. Conformational and geometrical related physiochemical properties are helpful in understanding the probable binding site of drug with receptor. Correlation were established between physicochemical parameters and angiotensin antagonistic activity using sequential multiple linear regression technique. Best Eq. were selected as a model (Eqn. 4)

$$pIC_{50} = [11.935 (\pm 3.053)] + nRORPh [0.383 (\pm 0.3657)] + Mor18u [1.005 (\pm 0.966)] \ldots$$
$$\ldots + Mor28u [-2.608 (\pm 1.321)] + Mor03v [1.57093 (\pm 0.680308)]$$

Eqn. 4. n = 31, r = 0.778, r^2 = 0.605, F = 9.963, S = 0.492

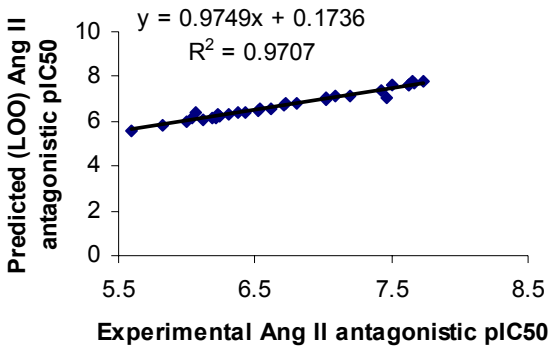


Fig. 4. Plot between observed pIC_{50} and predicted (LOO) pIC_{50} with residual presentation using model-4

A high correlation coefficient is not enough to select the equation as model. The equation screened out on the basis of the validation technique. Internal statistical significance level of equation was confirmed using sequential Fisher test for the equation having significance level more than more than 99.9% as it exceeded the tabulated F (6.12) $_{4,26}$ = 9.963 which suggest that equation are applicable for more than 999 out of 1000 times.

This equation was analyzed for search of outlier and two outliers namely compound No. 8 and 9 were identified from their Z score values. The interdependency of physiochemical properties for equation 4 was checked in order to confirm inimitable contribution of the properties to the expression. The chance of fortuitous correlation was checked with the

help of randomized biological activity test, the value of chance statistic (Chance <0.002) revel that results were not based on the chance correlation.

Tab. 3. Correlation matrix of descriptors used in model 4

Parameter	FDI	Mor18u	Mor28u	Mor03v
FDI	1.000000			
Mor18u	0.393089	1.000000		
Mor28u	0.473813	0.589841	1.000000	
Mor03v	0.062310	0.103728	0.210236	1.000000

Tab. 4. Calculated and Predicted pIC_{50} (by LOO method) with residual and Z-score value using model-3

Cpd.	Calculated pIC_{50}	Residual	Z-value	Predicted pIC_{50} (LOO)	Residual (LOO)
1	6.83076	-0.09076	-0.186201	6.81505	-0.07505
2	6.5462	0.21380	0.438622	7.04318	-0.28318
3	6.48655	-0.26655	-0.546826	6.58285	-0.36285
4	5.95273	-0.45273	-0.928783	7.23206	-1.73206
5	6.15608	-0.95608	-1.961420	6.55011	-1.35011
6	6.98157	0.80843	1.658510	6.99668	0.79332
7	6.84656	0.65344	1.340540	6.68560	0.81440
8	7.0687	0.32130	0.659159	7.02907	0.36093
9	6.57098	-0.14098	-0.289227	5.79756	0.63244
10	6.37685	-0.49685	-1.019300	6.88073	-1.00073
11	6.55133	0.00867	0.017777	6.64436	-0.08436
12	7.04029	0.83971	1.722690	5.98608	1.89392
13	6.7015	0.21850	0.448264	7.80946	-0.88946
14	7.05139	0.16861	0.345904	7.06199	0.15801
15	5.91295	0.40705	0.835060	7.31710	-0.99710
16	6.83084	-0.91084	-1.868610	7.92711	-2.00711
17	6.62461	-0.18461	-0.378732	8.26458	-1.82458
18	5.99351	0.06649	0.136403	6.81744	-0.75744
19	7.70726	-0.52726	-1.081680	6.14954	1.03046
20	7.09217	0.55783	1.144390	6.17366	1.47634
21	7.34566	0.23434	0.480753	7.34589	0.23411
22	7.97419	0.17581	0.360670	6.50236	1.64764
23	8.08245	-0.50245	-1.030790	5.98450	1.59550
24	6.81869	0.03131	0.064240	6.70221	0.14779
25	6.21299	0.57701	1.183740	6.58048	0.20952
26	6.19511	0.13489	0.276720	6.81505	-0.48505
27	7.26852	-0.61852	-1.268900	7.04318	-0.39318
28	6.50227	-0.00227	-0.004653	6.58285	-0.08285
29	6.15087	0.69913	1.434270	7.23206	-0.38206
30	6.15919	-0.46919	-0.962542	6.55011	-0.86011
31	6.50722	-0.49722	-1.020060	6.99668	-0.98668

Bootstrapping technique (r^2_{bsp} = 0.652) was used to confirm the independent measure for the stability of regression equation. On the basis statistical criteria Eqn. 4 was selected as Model. Model has better correlation coefficient (r = 0.778), which accounts for more than 60% variance in the activity. The q^2 value (In the biological activity data of leave one compound) depicted confidence limit grater than 95%, which minimizes the risk of finding significant explanatory equation for the biological activity just by the chance. The cross-validated squared correlation coefficient (q^2 = 0.367) and standard error of prediction, (S_{DEP} = 0.631) further support good internal consistency of the model.

Tab. 5. Calculated and Predicted pIC_{50} (by LOO method) with residual and Z-score value using model-4

Cpd.	Calculated pIC_{50}	Residual	Z-value	Predicted pIC_{50} (LOO)	Residual (LOO)
1	6.61054	0.12946	6.61054	6.59217	0.14783
2	6.18641	0.57359	6.18641	6.13880	0.62120
3	6.11634	0.10366	6.11634	6.09955	0.12045
4	6.04406	-0.54406	6.04406	6.13179	-0.63179
5	6.06245	-0.86245	6.06245	6.42108	-1.22108
6	7.19106	0.59894	7.19106	7.09375	0.69625
7	7.02121	0.47879	7.02121	6.96370	0.53630
8	7.66436	-0.27436	7.66436	7.72580	-0.33580
9	6.30976	0.12024	6.30976	6.29673	0.13327
10	5.59596	0.28404	5.59596	5.53649	0.34351
11	6.72282	-0.16282	6.72282	6.80455	-0.24455
12	7.62170	0.25830	7.62170	7.58592	0.29408
13	6.43224	0.48776	6.43224	6.38413	0.53587
14	7.49835	-0.27835	7.49835	7.58430	-0.36430
15	6.20863	0.11137	6.20863	6.17175	0.14825
16	6.37952	-0.45952	6.37952	6.41861	-0.49861
17	6.80390	-0.36390	6.80390	6.82132	-0.38132
18	6.23261	-0.17261	6.23261	6.27677	-0.21677
19	7.65206	-0.47206	7.65206	7.74693	-0.56693
20	7.42252	0.22748	7.42252	7.38391	0.26609
21	7.62550	-0.04550	7.62550	7.64865	-0.06865
22	7.46618	0.68382	7.46618	7.08086	1.06914
23	7.73876	-0.15876	7.73876	7.77772	-0.19772
24	7.02408	-0.17408	7.02408	7.06159	-0.21159
25	6.52012	0.26988	6.52012	6.48278	0.30722
26	6.53846	-0.20846	6.53846	6.55211	-0.22211
27	7.08293	-0.43293	7.08293	7.11292	-0.46292
28	6.70781	-0.20781	6.70781	6.74585	-0.24585
29	6.24102	0.60898	6.24102	6.20617	0.64383
30	5.82456	-0.13456	5.82456	5.84988	-0.15988
31	5.99409	0.01591	5.99409	5.99086	0.01914

The 3D model suggests that functional group descriptor like nRORPh, which is the number of ethers (aromatic) and Mor03v (3D-MoRSE-signal 03 /weighted by atomic Van der waals volume), Mor18u (3D-MoRSE- signal 18/ unweighted) which were the Morse code (3D molecular representation of structure based on electron diffraction code) [13–16] was calculated by summing atom weights viewed by a different angular scattering function. The values of these code functions were calculated at 32 evenly distributed values of scattering angle(s) in the range of 0–31 $Å^{-1}$ from the three dimensional atomic co-ordinates of a molecule. The 3D-MoRSE code calculated by using following expression;

$$I(s) = \sum_{i=2}^{N} \sum_{j=1}^{i-1} A_i A_j \frac{\sin sr_{ij}}{sr_{ij}}$$

Where, s is scattering angle
r_{ij} is interatomic distance of ith and j^{th} atom
A_i and A_j are atomic properties of ith and j^{th} atom respectively including atomic number, atomic mass, partial atomic charge, residual electro- negativities, and atom polarizability.

The contribution of MoRSE code suggested that the Vander Waals volume is decisive in the interaction with receptor. Functional group descriptors and MoRSE code of AT1 receptor angiotensin II antagonist activity of quinoline derivative bearing acidic heterocycles can be modeled excellently. Some geometric descriptors like FDI (folding degree index) and SPAM (Average Span R) contributed negatively to the equation. QSAR study revels that all models gave insight to some common important structural feature. For the angiotensin II antagonistic activity Electronic, thermodynamic and steric parameters are important.

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Authors' Statement

Competing Interests

The authors declare no conflict of interest.

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