ORIGINAL RESEARCH ARTICLES

STRUCTURAL FEATURE STUDY OF QUINOLINES DERIVATIVES WITH THERMODYNAMIC AND OTHER DESCRIPTORS: A QSAR APPROACH

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(Received 10 February 2020) (Accepted 24 May 2021)

ABSTRACT

Quantitative structure activity relationship analysis was performed on a series of thirty-three quinoline derivatives to establish the structural features required for angiotensin II receptor activity. QSAR models were derived by stepwise multiple regression analysis employing the method of least squares, using quantum chemical, thermodynamic, electronic and steric descriptors. Model showed best predictability of activity with cross validated value (q^2) =0.7485, coefficient of determination (r^2) =0.8734 and standard error of estimate (s) = 0.2690. These guidelines may be used to develop new antihypertensive agents based on the quinoline analogues scaffold.

Keywords: QSAR, Multiple linear regressions, AT_1 Receptor, antihypertensive agents

INTRODUCTION

The potent vasoactive octapeptide hormone angiotensin II acts through the AT_1 and the AT_2 receptors, both of which belong to the G-protein-coupled receptor super family. The AT_1 receptor mediates most of the known actions of angiotensin II, such as vasoconstriction, aldosterone release, and sodium and water retention[1,2]. Recently it has been established that the AT_2 receptor has a physiologic role in the brain and in cardiovascular and renal functions in adults, as well as in the modulation of various processes associated with cell differentiation and tissue repair[3]. Renin-angiotensin system activity begins with the rate-limiting step of renin synthesis and release from the juxtaglomerular cells of the kidney[4].

Quantitative structure–activity relationship (QSAR) studies leading to models in terms of chemical structures and their biological activities produce useful information for drug design and medicinal chemistry[5]. QSAR can be regarded as a computer-derived rule that quantitatively describes biological activity in terms of chemical descriptors. Once a QSAR is known, prediction or generation of new compounds with better activity is promising. The most popular 3D QSAR methods are comparative molecular field analysis (CoMFA) and comparative molecular similarity analysis (CoMSIA)[6,7]. The present study was aimed to elucidate the structural features of 2-alkyl-4-(biphenylmethoxy) derivatives[8] required for AT_1 receptor antagonists and to obtain predictive two dimensional QSAR models to guide the rational synthesis of novel antihypertensive activity.

MATERIALS AND METHODS

The biological data used in this study reported are the angiotensin II receptor (IC_{50}) of a series of 2-alkyl-4-(biphenyl methoxy) quinoline derivatives[8]. The guinea pig adrenal membrane activities (IC_{50}), converted to pIC_{50}, were considered as QSAR values and were used as dependent variables in the QSAR analysis. The data set was split randomly into a training set (25 molecules) to build the quantitative model and the remaining molecules (test set) were used to test the performance of the proposed model. An optimal model for the training set with significant statistical quality was established. The general structure of these analogues is shown in Fig. 1 (lead compound) and Table I lists the structural features and antihypertensive activity of the respective compounds under study.

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https://doi.org/10.53879/id.58.09.12322

Table I: Chemical and biological data of 2-alkyl-4-(biphenyl methoxy) derivatives

Com.	R^1	R^2	R^3	Y–Z	A	X	IC_{50} [a]μM	pIC^b_{50}
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[c]	Pr	H	H	OCH_2	COOH	N	0.60	6.22
4	Bu	H	H	OCH_2	COOH	N	3.10	5.50
5	H	H	H	OCH_2	Tetrazol-5-yl	N	6.30	5.20
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	7.50
8	Me	H	H	OCH_2	Tetrazol-5-yl	CH	90.0	4.04
9	Me	Me	H	OCH_2	Tetrazol-5-yl	N	4.6	5.33
10[c]	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	1.30	5.88
13	Me	H	H	CH_2CH_2	Tetrazol-5-yl	N	0.27	6.56
14	Et	H	5-Me	OCH_2	H	H	0.013	7.88
15[c]	Et	H	5-Cl	OCH_2	H	H	0.12	6.92
16	Et	H	5-CN	OCH_2	H	H	0.060	7.22
17	Me	H	6-Me	OCH_2	H	H	0.47	6.32
18[c]	Me	H	6-Cl	OCH_2	H	H	1.20	5.92
19	Et	H	6-CN	OCH_2	H	H	0.36	6.44
20	Et	H	6-CF_3	OCH_2	H	H	0.86	6.06
21[c]	Et	H	6-COOMe	OCH_2	H	H	0.066	7.18
22	Et	H	6-OMe	OCH_2	H	H	0.022	7.65
23	Et	H	6-O-*i*-Pr	OCH_2	H	H	0.026	7.58
24[c]	Et	H	6-CH_2CH_2 F	OCH_2	H	H	0.007	8.15
25	Et	H	6-CH_2CF_3	OCH_2	H	H	0.026	7.58
26	Et	H	7-Me	OCH_2	H	H	0.14	6.85
27[c]	Et	H	7-Cl	OCH_2	H	H	0.16	6.79
28	Et	H	7-CN	OCH_2	H	H	0.46	6.33
29	Et	H	7-OMe	OCH_2	H	H	0.22	6.65
30	Me	H	8-Me	OCH_2	H	H	0.31	6.50
31	Et	H	8-Cl	OCH_2	H	H	0.14	6.85
32[c]	Et	H	8-CF_3	OCH_2	H	H	2.00	5.69
33	Et	H	8-OMe	OCH_2	H	H	0.96	6.01

[a] IC_{50} or inhibition of specific binding of [^{125}I] AII to a guinea pig adrenal membrane preparation

[b] -log IC_{50} to generate equation

[c] Indicates the compounds considered in the test set in 2D QSAR

Table II: Comparative observed and predicted activities of 2-alkyl-4-(biphenyl methoxy) derivatives

Comp	pIC_{50}	2D Model-I		2D Model-II	
		Pred.	Res.	Pred.	Res.
1	6.74	6.16	0.58	6.82	-0.08
2	6.76	6.42	0.34	6.66	0.1
3	6.22	5.79	0.43	6.02	0.2
4	5.5	5.18	0.32	5.31	0.19
5	5.2	4.81	0.39	5.03	0.17
6	7.79	7.33	0.46	7.07	0.72
7	7.5	7.09	0.41	7.66	-0.16
8	4.04	3.7	0.34	4.28	-0.24
9	5.33	5.03	0.3	5.49	-0.16
10	7.39	7.15	0.24	7.18	0.21
11	6.43	6.25	0.18	6.35	0.08
12	5.88	5.7	0.18	5.62	0.26
13	6.56	6.29	0.27	6.88	-0.32
14	7.88	8.17	-0.29	8.13	-0.25
15	6.92	6.63	0.29	7.09	-0.17
16	7.22	7.05	0.17	7.15	0.07
17	6.32	5.84	0.48	6.21	0.11
18	5.92	5.59	0.33	5.68	0.24
19	6.44	6.14	0.3	6.94	-0.5
20	6.06	6.48	-0.42	6.18	-0.12
21	7.18	7.69	-0.51	7.03	0.15
22	7.65	7.49	0.16	7.96	-0.31
23	7.58	7.44	0.14	7.22	0.36
24	8.15	8.53	-0.38	8.41	-0.26
25	7.58	7.17	0.41	7.39	0.19
26	6.85	6.63	0.22	6.97	-0.12
27	6.79	6.9	-0.11	6.55	0.24
28	6.33	5.89	0.44	6.08	0.25
29	6.65	6.57	0.08	6.86	-0.21
30	6.5	6.79	-0.29	6.11	0.39
31	6.85	6.58	0.27	6.68	0.17
32	5.69	5.32	0.37	5.38	0.31
33	6.01	5.65	0.36	6.44	-0.43

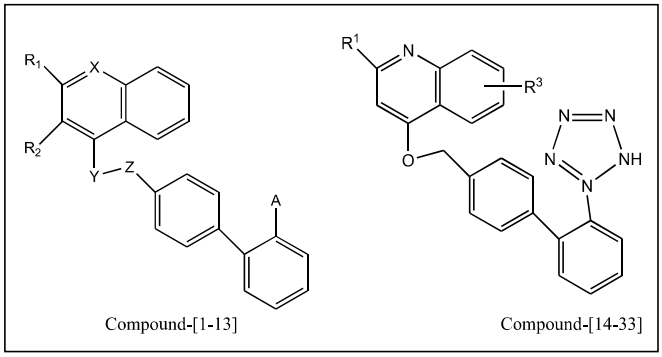

Fig. 1: Lead compound quinoline

Molecular structure generation

The computational studies were performed on a Pentium IV workstation using the molecular modeling software Chemoffice 2004 version 8.0 (Cambridge Software Company, USA[9]). A total of thirty three compounds were selected for the study. All the molecules were sketched using Chem Draw Ultra module and cleaned. The two-dimensional (2D) structures were transformed into three-dimensional (3D) structures by using the Chem3D Ultra module. These molecular geometries were refined using the quantum chemical program package MOPAC 6.0 applying the PM3 parameterization together with eigenvector following geometry optimization procedure. The resulting 3D structures were then subjected to an energy-minimization process by using the semi empirical quantum mechanics module, for each compound with a root-mean-square (RMS) gradient of 0.001 kcal mol^{-1}. The Austin model (AM-1), Hamiltonian method, closed-shell restricted wave function was adopted for the energy-minimization process.

Calculation of structural descriptors

Various physicochemical descriptors, viz., thermodynamic, electronic and steric and indicator variables were used for the QSAR study of each of the molecules. Twenty four physico parameters, available for the series were calculated for each structure, viz. Bend energy (Eb), Connolly accessible surface area (SAS), Connolly molecular surface area (MS), Connolly solvent excluded volume (SEV), dipole (DPL), dipole energy (Ed), Electronic energy(Elec), exact mass (Mass), Highest occupied molecular orbital energy (HOMO), Lowest un occupied molecular orbital energy (LUMO), Henry's law constant (H), Molar reflectivity (MR), non 1,4 van der Waal's energy (Ev), Ovality, Partition coefficient(octanol/ water) (logp), Principle moment of inertia along with X,Y, and Z axes (PMI-x, PMI-y and PMI-z, respectively, Repulsion energy (NRE), Stretch Energy (Es), Torsion

Table III: Correlation matrix inter-correlation between descriptors for QSAR model I

	PC	vdW	PMI-x	CC
PC	1.0000			
Vdw	0.31765	1.0000		
PMI-x	0.54287	0.68964	1.0000	
CC	0.48065	0.62843	0.76421	1.0000

Energy(Et),Total Energy(E), van der Waal's 1,4 Energy and Stretch bend energy (E_{sb}).

The data was transferred to the statistical program in order to establish a correlation between physico-chemical parameters as independent variable and pIC_{50} as dependent variable employing multiple regression analysis method. The data was transferred to the statistical program VALSTAT[10] to establish the correlation between the physicochemical parameters as independent variables and AT_1 receptor activity as dependent variable.

Statistical analysis

The obtained descriptors were used for the development of a mathematical linear model to predict quantitatively the physicochemical effects of substituents on the antihypertensive activity of 2-alkyl-4-(biphenyl methoxy) quinoline derivatives using multiple regression analysis. The study of the multiple linear regression based on the elimination of descriptors until a valid model was obtained was employed to determine the best regression models. The ± data within the parentheses are the t-values at the 95 % confidence interval, associated with the coefficient of the descriptor in the regression equation. The predictability of each model was evaluated by using cross validated correlation coefficient (q^2), the standard deviation of prediction (S_{press}), and the standard error of predictions (S_{DEP}). The sum of the squared prediction errors, called the predictive residual sum of squares (press), is calculated as the sum of squares of the difference between the predicted and observed values of activity. The best model was selected from the various statistically significant equations on the basis of the observed squared correlation coefficient (r^2), the standard error of the estimate (SE), the sequential Fischer test (F), the bootstrap squared correlation coefficient (r^2 bs), the bootstrap standard deviation (Sbs), the cross-validated squared correlation coefficient using the leave one out method (q^2)[11], chance statistics (evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1 % chance of fortuitous correlation), and outliers (on the basis of the Z-score value). The predictive power of the generated model was assessed using leave-one-out (LOO) internal cross validation methods and external validation.

RESULTS AND DISCUSSION

In a search of newer and potent antihypertensive drug, a series of 33 alkyl-4-(biphenyl methoxy) quinoline derivatives were subjected to a quantitative structure activity relationship (QSAR) analysis, for studying, interpreting, and predicting activities and designing new compounds by using multiple linear regression (MLR). In QSAR studies, all physicochemical parameters of each compound from the series were calculated and subjected to multiple linear regressions with respect to biological activity:

pIC_{50}= 3.12212+ 2.6375 (±0.1754) PC +0.3146 (±0.2365) Vdw + 0.5123 (±0.3265) PMI-x - 0.7548 (±2.1756) CC

n=33, r^2=0.8734, q^2= 0.7485, std. =0.4326, Pred_r^2= 0.8496, F=86.3765, SEE = 0.2690, S_{press} = 0.3765, S_{DEP} = 0.1776

The MLR was used to generate the linear QSAR models between pIC_{50} values and molecular descriptors. The tetravariant model I explained 87.34 % of the variance in activity. The observed t values of the descriptors PC, Vdw, PMI-x and CC are greater than the tabulated t value at 95 % confidence interval. The models were found to be robust and having a fairly good predictive ability, as evident from the higher q^2 (0.7485), and low S_{PRESS} and S_{DEP} values. The model is able to explain the structurally diverse analogues and correlation matrix indicating inter-correlation between descriptors for QSAR model I Table II and Table III, respectively. Randomization test data (Chance < 0.001) revealed that the results were not based on chance correlation. Model I revealed that PC is the partition coefficient calculated using atom-based approach and represents the hydrophobicity of the compounds. The positive contribution of PC confirms the hydrophobic binding site of receptor and suggests more hydrophobic molecules for improved activity. Another descriptor vdW contributes positively, that is, increase in vdW causes increased activity. PMI-x, a steric parameter, indicates that the compounds having principle moment in x-axis may show less activity and concerned with the surface area and how that area is distributed about the reference axis of molecules, in this case x-axis. Descriptor CC is cluster count steric parameter, which shows the cluster count of molecules inside the contact surface with receptor during

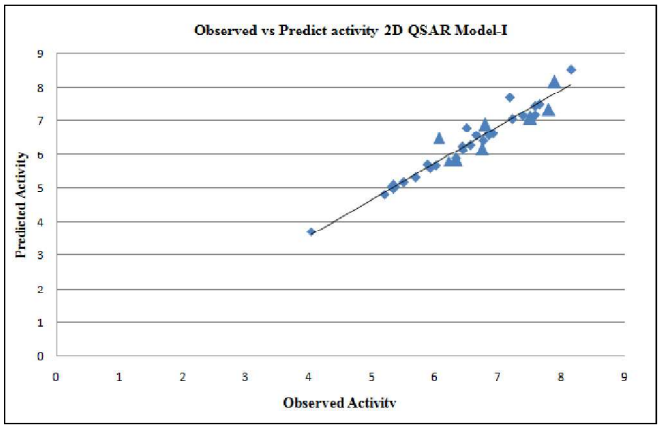

Fig. 2: Graph for observed *vs.* predicted activity of best 2D QSAR model-I

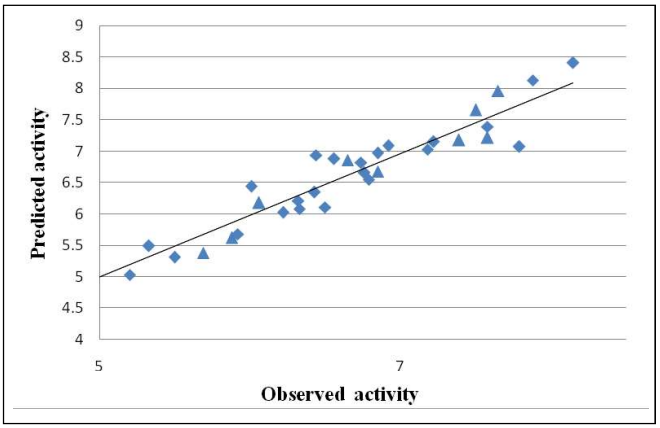

Fig. 3: Graph for observed *vs.* predicted activity of best 2D QSAR model-II

ligand receptor interaction. Negative contribution of these parameters shows that more bulky substituents are not favourable for activity. Graph for Model I for observed versus predicted is shown in Fig. 2.

pIC_{50}= 1.2784 + 1.4534 (±0.3886) LogP +0.6904 (±0.3276) DPL + 1.4354 (±0.8752) Eb - 0.6583 (±1.0965) SE

n=33, r^2=0.8157, *q*2= 0.6358, std. =0.1965, Pred_r^2= 0.6942, F=67.832, SEE = 0.4654, S_{press} = 0.6587, S_{DEP} = 0.3908

Model II is again a tetravariant model with comparatively lesser r^2 value and q^2 value. The model obtained for AT_1 receptor is found to explain 81.57 % of the variance in activity. Positive contributions of LogP indicate favorable hydrophobic interaction is the presence of a lipophillic group. Eb, which is the bend energy, indicates that deformation in the molecule on binding with the receptor is favorable or in other words flexible structures are favorable for the activity. DPL (dipole moment) contributed positively to the activity up to a small extent as suggesting that the moiety, which increases the charge distribution over the molecules, is favorable for the activity and optimizing the hydrophobicity and bulkiness at R_1, and R_2 position. Stretch energy is contributing negatively to biological activity, which indicates that molecules must be flexible enough to fit into the receptor site for ligand-receptor interaction. It is also important in determining the behaviour of the molecule in vicinity of the binding site. Graph for model II for observed versus predicted is shown in Fig. 3.

pIC_{50}= 3.9743 +SE [0.01831(± 0.021447)] +ElcE [1.49e-0083(± 0.311e-0083)] -LUMO energy [0.862(± 0.176)]

n=33, r^2=0.7991, q^2= 0.6931, std. =0.0652, Pred_r^2= 0.7194, F=29.511, SEE = 0.3961, S_{press} = 0.7418, S_{DEP} = 0.4388

The model III shows that thermodynamic parameter stretch energy (SE) contributes negatively and electronic parameters electronic energy (ElcE) and LUMO energy contribute positively and negatively respectively, towards the activity. This model explains 79.91 % of activity for the training set. The model has significance level more than 99 % as the value F=29.511, with a low standard deviation of estimation 0.3961, demonstrate accuracy of the model. The robustness of the model was shown by magnitude of the bootstrapping r^2, which was near to conventional r^2. The internal predictivity of model (q^2=0.6931) was also good. The negative correlation of LUMO with biological activity indicates that the electron withdrawing groups are favorable for the activity. The steric energy of a molecule is the sum of the molecular mechanics potential energies calculated for the bonds, bond angles, dihedral angles, non bonded atoms and so forth. The model shows compounds should have low potential energy for better biological activity.

CONCLUSION

In this work, we studied the antihypertensive activity in a series of alkyl-4-(biphenyl methoxy) quinolines, using electronic descriptors in combination with thermodynamic, and steric parameters to relate them to biological activity. The QSAR model for the AT_1 receptor was able to show predictive power, confirmed by internal and external validation. The findings of QSAR result is consistent with the descriptors, which shows good value of PC and low value of PMI-x, CC and Stretch energy. This indicates that more hydrophobic and less bulky substituents at position R_1 and R_3 of the ring are favorable for interaction

with receptor site. The information obtained in this study provides the tools for predicting the affinity values of structurally similar analogue and we can design new analogues with better potent antihypertensive activity and least toxicity.

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