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QSAR Study on Sulfonylcarbamate Derivatives: An Insight into the Structural Requirement for the Angiotensin II Receptor Antagonist

Mukesh Chandra Sharma and Dharm Veer Kohli

Department of Pharmaceutical Sciences, Drug Research Laboratory,
Dr. H.S. Gour University, Sagar (M.P.) 470 003, India

Abstract: Quantitative Structure Activity Relationship (QSAR) represents an attempt to correlate 2D descriptors of compounds with activity. In order to get the relation between various physicochemical descriptors with biological activity, a QSAR study for the angiotensin II activity of 16 compounds was established with the VLifeMDS 3.5 (VLife sciences Molecular Design Suit Version 3.5. Statistical regression expressions were obtained with 2D-QSAR study using multiple linear regression (MLR) analysis and two statistical significant models were generated (r2 = 0.7615, 0.7965 and pred_r^{2}0.7267 0.7430 for model 1 and 2, respectively) indicating that biological activity is influenced by the descriptors SssNHE-index, SaaCHcount, T_2_F_1 and SsOH count, T_2_Cl_6. QSAR model was to design and predict accurately the modelled properties of the newly synthesized compounds as antihypertensive.

Key words: Ang II · Sulfonyl carbamate · 2D QSAR · AT_1 · Antihypertensive

INTRODUCTION

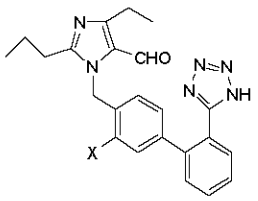
The renin-angiotensin system (RAS) plays an important role in blood pressure regulation and electrolyte homeostasis [1]. Angiotensin II (Ang II) is the biologically active component of the RAS and is responsible for most of the peripheral effects of this system. The octapeptide angiotensin II (Ang II) 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]. 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 [3]. Renin, an enzyme produced primarily by the juxtaglomerular cells of the kidney, catalyzes the conversion of angiotensinogen into an inactive substance, angiotensin I (Ang-I). Angiotensin-converting enzyme (ACE) then converts Ang -I to the physiologically active angiotensin II (Ang-II), which causes potent vasoconstriction, aldosterone secretion and sympathetic activation. All of these actions contribute to the development of hypertension [4-5]. A number of quantitative structure-activity relationship (QSAR) studies related to design of antihypertensive drugs have also been reported [6-10]. The present study aimed to elucidate the structural features of sulfonylcarbamate isostere derivatives required for angiotensin II receptor antagonists and to obtain predictive two-dimensional QSAR models to guide the rational synthesis of novel antihypertensive molecules.

MATERIALS AND METHODS

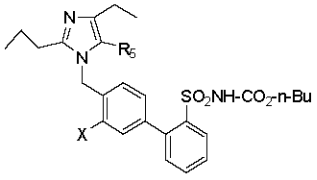
The Angiotensin II antagonist activity data of synthesized sulfonylcarbamate isostere derivatives were taken from the reported work [11]. The biological activity data (IC_{50} in nm) were converted to negative logarithmic dose (pIC_{50}) for quantitative structure activity analysis (Table 1). These models provide great relevance in design of novel Ang II antagonist not only in terms of predictivity, internally or externally, but also in terms of their ability to provide a chemical and structural explanation of their binding interaction and using descriptor 2D QSAR model describe (Table 2). All modelling studies (2D) were performed using the Molecular Design Suite (Vlife MDS software package, version 3.5; supplied by VLife Sciences, Pune, India) [12] on a Compaq PC with a Pentium IV processor and a Windows XP operating system. Structures were sketched using the 2D draw application and converted to 3D structures. Three-dimensional structures were drawn for each molecule and the molecular geometries optimized

Corresponding Author: M.C. Sharma, Department of Pharmaceutical Sciences, Drug Research Laboratory, Dr. H.S. Gour University, Sagar (M.P.) 470 003, India. E-mail: mukeshcsharma@yahoo.com.

Table 1: Structure and biological activities of Sulfonyl carbamate ring derivatives



Compound [1-4]



Compound [5-16]

Comp	X	R_5	IC_{50}(nM)	pIC_{50}
1	F	-	7.0	0.84500
2*	Cl	-	10.0	1.00000
3	Br	-	20.0	1.30100
4	CH_3	-	40.0	1.60200
5	H	CHO	2.0	0.30100
6*	CH_3	CHO	3.0	0.47710
7	F	CHO	0.7	-0.15400
8	H	CO_2CH_3	2.0	0.30100
9*	NO;	CO_2CH_3	7.0	0.84500
10	Br	CO_2CH_3	2.0	0.30100
11	CH_3	CO_2CH_3	3.0	0.47710
12	Cl	CO_2CH_3	3.0	0.47710
13	F	CO_2CH_3	0.6	-0.22100
14*	H	$COCH_3$	2.0	0.30100
15	CH_3	$COCH_3$	2.0	0.30130
16	Cl	$COCH_3$	6.0	0.77815

*test compounds

Table 2: Description of descriptor used in the 3D QSAR study

SssNHE-index	SaaCHcount	T_2_F_1	SsOH	Chlorine count	SsClE-index
8.764215	6.832039	5.743211	15	14	12
8.357239	6.867747	5.261804	15	14	12
7.779401	6.496211	4.946430	13	11	10
7.889282	6.607828	4.995651	14	11	10
8.367835	6.825966	5.132612	15	12	11
8.087505	6.685801	5.077476	14	12	10
8.511149	6.881843	5.183055	14	13	10
9.633694	7.911901	5.890747	16	13	12
8.116743	6.956188	5.366814	15	12	10
8.120674	6.870494	5.310702	15	12	10
8.595297	7.174327	5.115051	16	13	11
8.314967	7.034162	5.209765	15	13	10
9.022132	7.417413	5.442838	17	13	12
9.025801	7.785235	5.614838	17	13	12
9.671578	8.044195	6.051356	17	14	12
9.155715	7.659546	5.714768	16	14	12

using Monte Carlo conformational search [13], MMFF [14] fields and charges. Optimal training and test set were generated using the sphere exclusion algorithm [15]. Various 2D descriptors (a total of 230) like element counts, molecular weight, molecular refractivity, log *P*, topological index, Baumann alignment independent topological descriptors *etc*., were calculated using VlifeMDS software. The pre-processing of the independent variables (i.e., descriptors) was done by removing invariable (constant column) and cross-correlated descriptors (with r = 0.99) which resulted for MLR to be used for QSAR analysis.

Multiple Linear Regression (MLR) Analysis and Model Validation: Multiple regressions are the standard method of regression estimates the values of the regression coefficients by applying least squares curve fitting method. For getting reliable results, dataset having typically 3 times as many data points (molecules) as independent variables (descriptors) is required.

$$Y = b1*x1 + b2*x2 + b3*x3 + c$$

Where Y is the dependent variable, the 'b's are regression coefficients for corresponding 'x's

(independent variable), 'c' is a regression constant or intercept. In the present study QSAR model was developed using multiple regression by forward-backward variable selection method with pIC_{50} activity field as dependent variable and 132 physico-chemical descriptors as independent variable.

The cross-validated r^2 (q^2) value was calculated [16], where *yi* and *yi* are the actual and predicted activities of the i^{th} molecule, respectively and y_{mean} is the average QSAR activity of all molecules in the training set. Both summations are over all molecules in the training set. Since the calculation of the pair wise molecular similarities and hence the predictions, were based upon the current trial solution, the q^2 obtained is indicative of the predictive power of the current model.

$$q^2 = 1 - \frac{\Sigma(y_i - \hat{y}_i)^2}{\Sigma(y_i - y_{mean})^2}$$

The predicted r^2 (pred_r^2) value was calculated, where y_i and $\hat{y}_i$ are the actual and predicted activities of the i^{th} molecule in test set, respectively and *y* mean is the average activity of all molecules in the training set. Both summations are over all molecules in the test set. The pred_r^2 value is indicative of the predictive power of the current model for external test set.

$$pred\_r^2 = 1 - \frac{\Sigma(y_i - \hat{y}_i)^2}{\Sigma(y_i - y_{mean})^2}$$

To evaluate the statistical significance of the QSAR model for an actual data set, we have employed a one-tail hypothesis testing. The robustness of the QSAR models for experimental training sets was examined by comparing these models to those derived for random data sets. Random sets were generated by rearranging biological activities of the training set molecules. The significance of the models hence obtained was derived based on calculated Z score [17].

$$Z\text{score} = \frac{(h - \mu)}{\sigma}$$

Where h is the q^2 value calculated for the actual dataset, μ the average q^2 and σ is its standard deviation calculated for various iterations using models build by different random data sets. The probability (α) of significance of randomization test is derived by comparing Z_{score} value.

RESULTS AND DISCUSSION

All the sixsteen molecules of the selected series were subjected to regression analysis, the following significant 2D-QSAR models with equations were obtained for angiotensin II activity. Training set of 12 and 4 test set of Sulfonylcarbamate Isostere derivatives having different substitution were employed. QSAR Studies were performed using VLife Molecular Design Suite software [18-21]. The preliminary information obtained from 2D QSAR analysis was used while defining nature of substituent's when the designed and their biological activity were predicted. Following statistical measure was used to correlate biological activity and molecular descriptors; n, number of molecules; k, number of descriptors in a model; df, degree of freedom; r2, coefficient of determination; q^2, cross validated r^2; pred_r^2, r^2 for external test set;pred_r^2se, coefficient of correlation of predicted data set; Z score, calculated by the randomization test; best_ran_r^2; best_ran_q^2, highest q^2 value in the randomization test; α, statistical significance parameter obtained by the randomization test.

Model-1:

pIC50 = 0.8562 (SssNHE-index) + 1.0453 (SsOH count) +0.7432 (SaaCHcount) + 0.10987 (T_2_F_1) + 0.3217 (T_2_Cl_6)

n = 16, degree of freedom = 23, r^2 = 0.7965, q2 = 0.6431, F test =50.4536, r^2 se = 0.1765, q^2 se = 0.6934, pred_r^2 = 0.7430, pred_r2se = 0.8760

Model - 1 developed has a correlation coefficient (r2) of 0.7965, significant cross validated correlation coefficient (q2) of 0.6431, F test of 50.4536, r2 for external test set (pred_r^2) 0.7430, coefficient of correlation of predicted data set (pred_r^2se) 0.8760 and degree of freedom 23. The model developed is validated by an external set of compounds with a predictive correlation of coefficient of 0.5483. The model is validated by α_ran_r2 = 0.00011, α_ran_q2 = 0.01, α_ran_pred_r2 = 0.0000, best_ran_r2 = 0.20986, best_ran_q2 = 0.6896, Z score_ran_r2 = 2.365. The randomization test suggests that the developed model have a probability of less than 1% that the model is generated by chance. The observed and predicted pIC_{50} along with residual values are shown in Table 1. From the plot it can be seen that MLR model is able to predict the activity of training set quite well (all points are close to regression line) as well as external. The major group of descriptors involved sub groups like SssNHE-index, SaaCHcount, T_2_F_1 and SsOH count, T_2_Cl_6 alignment independent descriptors and help in understanding the effect of

substituent at different position of Sulfonylcarbamate Isostere Derivatives. T_2_F_1: This descriptor means the count of number of double bonded atoms (single, double or triple bonded) separated from any fluorine atom (single or double bonded) by one bond distance. SssNHE-index describes Electro topological state indices for number of -NH group connected with two single bonds. Its negative contribution in the QSAR model implies that secondary or primary amides will lead to reduce potency for the Ang II, instead of COOH group. T_2_Cl_6: This descriptor means the count of number of six bonded atoms (single, double or triple bonded) seprated from any chlorine atom (single or double bonded) by six bond distance. The positive contribution of SaaCHcount i.e. sum of electro topological state indices for unsubstituted aromatic carbons suggest that the presence of more unsubstituted aromatic carbon will be in favor of higher anti-hypertensive activity. An estate number descriptor SsOH count which represents total number of hydroxy group connected with one single bond is inversely proportional to the activity. It reveals that hydroxy group should not be directly attached with Sulfonyl carbamate ring for maximal activity. The observed and predicted pIC50 along with residual values shown in Table 3.

Model-2:

pIC50 = 2.64317 (chlorine count) +0.8742 (SsClE-index) + 1.2986 (SdsNE-index) – 0.6854(polar surface area including P and S) + 6.6729

n = 16, degree of freedom = 23, r^2 = 0.7615, q^2 = 0.6701, F test =38.1765, r^2 se = 0.3125, q^2 se = 0.4012, pred_r^2 = 0.7267, pred_r^2se = 0.5098

The statistically significant model 2 using the analysis method having 0.7615as the coefficient of determination (r^2) was considered. Model 2 can explain 76.15 % of the variance in the observed activity values. It shows an internal predictive power (q^2 = 0.6701) of 67% and a predictivity for the external test set (pred_r^2 = 0.7267) of about 72 % and degree of freedom 23. The model is validated by α_ran_r2 = 0.00017, α_ran_q2 = 0.001, α_ran_pred_r2 = 0.0001, best_ran_r2 = 0.3217, best_ran_q2 = 0.4986, Z score_ran_r2 = 3.7865 and Z score_ran_q2 = 1.2165. The randomization test suggests that the developed model have a probability of less than 1% that the model is generated by chance. The observed and predicted pIC50 along with residual values shown in Table 3. The chlorine count descriptor is directly proportional to the total number of chlorine atom in a molecule. It reveals that presence of electron withdrawing groups over the Sulfonyl carbamate ring is favourable for the activity. An estate contribution descriptor SdsNE-index (17.28%) which represents electro-topological state indices for number of nitrogen atom connected at two double bond and one single bond is directly proportional to the activity. It showed that Nitro group in all Sulfonyl carbamate ring derivatives is essential for the activity. Reduction or any chemical changes made to Nitro group will decrease the activity. The next influential descriptor is Polar Surface area including P and S which signifies total polar surface area including phosphorus and sulphur, is inversely proportional to the activity. This descriptor signifies that less polar group over Sulfonyl carbamate ring derivatives is preferred for having better activity. The SsClE-index is an electro-topological parameter which can define the total number of chlorine atoms connected with one single bond is also contributing immensely to activity.

Table 3: Calculated and Predicted pIC_{50} (by LOO method)

Comp	Observed activity	Model Predict-1	Model Predict-2
1	0.8450	0.641	0.978
2*	1.0000	1.231	0.735
3	1.3010	1.451	1.125
4	1.6020	1.276	1.325
5	0.3010	0.214	0.364
6*	0.4771	0.632	0.564
7	-0.1540	-0.179	-0.126
8	0.3010	0.231	0.312
9*	0.8450	0.795	0.822
10	0.3010	0.318	0.286
11	0.4770	0.451	0.491
12	0.4770	0.496	0.462
13	-0.2210	-0.247	-0.207
14*	0.3010	0.283	0.291
15	0.3010	0.327	0.309
16	0.7780	0.761	0.749

The positive coefficient of the descriptor suggests that Ang II activity of Sulfonyl carbamate derivatives may be increased by increasing the number of chlorine atoms present in the nucleus.In this work, we successfully aligned structures of sulfonylcarbamate derivatives as angiotensin II receptor antagonists.

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