Modeling of cytochrome P-450 enzyme inhibitors activities using 2D/3D QSAR

Farahmand Asadi¹ · Mohammad Hossein Fatemi¹Received: 13 April 2020 / Accepted: 10 August 2020 / Published online: 28 August 2020
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Abstract

In this research, quantitative structure–activity relationship (QSAR) studies were carried out on the inhibitory activities of a set of nicotine derivatives against the cytochrome-p450 2A6 (CYP2A6) enzyme. Two-dimensional quantitative structure–activity relationship (2D-QSAR) models were developed using multiple linear regression (MLR) and linear square-support vector machine (LS-SVM) methods. The result of statistical parameters of the MLR method show that the correlation coefficient (R^2) and standard error (SE) for the training set respectively are $R^2 = 0.702$, $SE = 0.49$ and for the test set $R^2 = 0.689$, $SE = 0.52$ and the results of statistical parameters of the LS-SVM method for the training set $R^2 = 0.993$, $SE = 0.10$ and for the test set $R^2 = 0.977$, $SE = 0.20$. The obtained results reveal the superiority of LS-SVM over MLR model. Then three-dimensional quantitative structure–activity relationship (3D-QSAR) model was developed using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) on the same dataset of nicotine derivatives. The acquired statistical parameters of the CoMFA model for the training set are $R^2 = 0.884$, $SE = 0.316$ and for the test set $R^2 = 0.847$, $SE = 0.33$, $F = 41.27$, $Q^2 = 0.581$, while the statistical values of CoMSIA model for the training set are $R^2 = 0.889$, $SE = 0.31$ and for the test set $R^2 = 0.670$, $SE = 0.54$, $F = 39.049$, $Q^2 = 0.554$. The results of this study revealed that the CoMFA model was more predictive and could be helpful in designing novel potent nicotine derivatives with enhanced inhibitory activity.

Keywords CoMFA · CoMSIA · Cytochrome P-450 2A6 · Inhibitory activity · LS-SVM · MLR

1 Introduction

Tobacco contains a package of harmful and addictive compounds [2] that its all forms rise the health problems in humans [47]. Long-term is speaking of lung cancer, heart disease, stroke and other fatal and non-fatal diseases [7, 23, 33]. Tobacco is the common cause of premature death compared to other consumer products [37]. It kills more people in developing countries than in industrialized countries [18]. The principal ingredient of tobacco leaves is nicotine which is highly addictive [3]. Even though numerous smoking-related diseases are preventable but due to the dependency of a smoker to nicotine, only a small

number of smokers manage to quit perfectly. Researchers have developed different nicotine replacements like nicotine gum and patch, to lower the addiction liability and to assist in smoking cessation [44]. The metabolism of nicotine leads to several metabolites [26]. In humans, the major product of this conversion is cotinine [4]. Hepatic Cytochrome P-450 2A6 (CYP2A6) is widely considered to be the principal catalyzing enzymes of nicotine metabolism via the intermediacy of aldehydes-catalyzed iminium ion [24, 36]. The addiction liability of nicotine is closely related to the efficiency of the CYP2A6-mediated metabolism of nicotine and a specific concentration of nicotine in the bloodstream. Individuals with inactive CYP2A6

✉ Farahmand Asadi, farahmand361@gmail.com | ¹Chemometrics Laboratory, Faculty of Chemistry, University of Mazandaran, Babolsar 47416-97445, Iran.

alleles displayed a significantly decreased dependency on smoking [34, 38]. Since nicotine primarily oxidation by the CYP2A6 is a rate-limiting step, obstructing this enzymatic reaction by a chemical inhibitor would increase nicotine oral bioavailability and decrease smoking [40]. Until today, a variety of compounds have been tested as CYP2A6 inhibitors with strong inhibitory results. To be used as a CYP2A6 inhibitory ligand, the best possible candidate of the drug must be an extremely potent and selective agent to avoid undesirable side effects. In this study, a series of nicotine derivatives with noun inhibitory properties were used as potent inhibitors of CYP2A6 enzyme [15]. The reported compounds were used as the database for performing two-dimensional quantitative structure–activity relationship (2D-QSAR) and three-dimensional quantitative structure–activity relationship (3D-QSAR) studies. Denton and co-workers was mentioned the inhibitory activity (IC₅₀) of a large number of nicotine analogue that highly selective for the inhibition of CYP2A6 versus the other isoforms of CYP contains CYP2E1, CYP2B6, CYP2C9, CYP2C19 and CYP2D6; Also, there is no effects of nicotine on activity of human CYP2E1 [Hukkanen, 2010 #458] and CYP1A2 [Hukkanen, 2011 #457]. 2D-QSAR study applied in a search for aminooxadiazole derivatives as PIM1 inhibitors [Aouidate, 2018 #521], N-substituted oseltamivir derivatives as potent avian influenza virus H5N1 inhibitors [Chtita, 2020 #524] and investigation of a class of acetylcholinesterase inhibitors being pyridazine derivatives as Anti-Alzheimer drugs [Zerroug, 2019 #525]. Also, 3D-QSAR applied for designing of new Kinase-related apoptosis-inducing kinase 2 (DRAK2) inhibitors [Aouidate, 2018 #520] and investigation of Furanone derivatives as new inhibitors of Cell division cycle 7 (CDC7) kinase [Aouidate, 2018 #522] and pyrazolopyrimidine derivatives as Ca²⁺/calmodulin-dependent protein kinase II (CAMKII δ) kinase inhibitors [Aouidate, 2018 #523]. 2D-QSAR models were developed using multiple linear regression (MLR) and linear square-support vector machine (LS-SVM) methods. The purpose of this study was to extract a good correlation between the biological activity of nicotine derivatives and their 3D structure with the eventual aim of predicting and developing a potent and specific inhibitor of CYP2A6 enzyme. 3D-QSAR models consisting of comparative molecular field analysis (COMFA) [32] and comparative molecular similarity indices analysis (COMSIA) [5, 31] were used to forecast activities of these inhibitors successfully and to provide areas in space where various interactive fields may affect the activity. The predictive inhibitory activity values could be anticipated by each generated 3D-QSAR models. Moreover, the subsequent partial least squares (PLS) analysis of the data was used to construct a linear correlation coefficient between experimental versus calculated inhibitory activities [49]. Finally, COMFA and COMSIA contour maps are used to

describe different structural necessities for the inhibitors in the active site of CYP2A6. Contour results can be helpful in testing the new designed analogues before their synthesis.

2 2D-QSAR study

2.1 Dataset and molecular modeling for 2D-QSAR

A substituted pyridine analogues of nicotine with well-expressed inhibitory activity (IC₅₀) against the CYP2A6 enzyme were used for the current study [15]. The IC₅₀ value is the minimum concentration of a compound that results in a 50% reduction in the activity of CYP2A6 enzyme that were transformed into the corresponding form of the logarithm (pIC₅₀). The molecular structure of the studied compounds with the corresponding pIC₅₀ is shown in Table 1. Based on the measured values, compounds numbered 6, 18 and 60 possess inhibitory activity values greater than 67 μ m, so these compounds were excluded from the current QSAR modeling. All the remaining compounds then randomly divided into two independent subsets; a training set (49 compound) for the generation of QSAR models and a test set (8 compound) for evaluating the quality of the models. The training set was selected manually based on the diversity of structures possessing a wide range of activity. As shown in this table, compounds marked with (*) symbol represents the test set and the rest are the training set. The selection of the test set was in such a way that their values lie between the maximum-minimum values of the training set.

2.2 Principal component analysis (PCA)

The principal component analysis (PCA) [48] is a powerful way to reduce the dimensions of a set of multivariate data. The number of employed descriptors represents the dimensions of the data set which are often related to each other. This analysis is used to depict multivariate data through diversity plots and reduce the number of variables in a series of non-related variables which is most commonly used for sample analysis in the applicability domain. Using molecular descriptors, primary PCA was carried out on the remaining 57 compounds with diverse molecular structures. As can be seen in Fig. 1, the results of PCA show well- distribution of chemicals in the structural space except for compounds numbered 36, 38 and 39 which were then excluded from the consequent 2D-QSAR modeling and the remaining compounds were used in the current study.

Table 1 Structure and experimental inhibitory activities of nicotine analogues on CYP2A6 enzyme

Compound	Structure	IC ₅₀ (μM)	pIC ₅₀ (μM)
1		4.40	−0.64
2		1.20	−0.08
3		3.20	−0.51
4		0.10	1.00
5		0.21	0.68
6		≥67	−1.83
7		1.50	−0.18
8		0.79	0.10
9		1.40	−0.15
10		19.70	−1.29
11		0.22	0.66
12		0.97	0.01
13		9.70	−0.99
14		4.50	−0.65
15		0.25	0.60
16		2.60	−0.41
17		6.60	−0.82
18		≥67	−1.83
19		7.70	−0.89
20		43.70	−1.64
21		5.10	−0.71
22		2.70	−0.43

2.3 Descriptors calculation and selection

Initially, the structure of the compounds was drawn using hyperchem software [27]. Then, its three-dimensional structure was optimized using the AM1 semi-empirical

method. The resulting output files functioned as input for Dragon [35], MOPAC [42], CODESSA [28] and PADEL [50] software to calculate the molecular descriptors. But only a few of them have an effective correlation with the inhibitory activity of CYP2A6 enzyme. Besides, there is a

Table 1 (continued)

Compound	Structure	IC ₅₀ (μM)	pIC ₅₀ (μM)
23		9.80	−0.99
24		1.80	−0.26
25		27.40	−1.44
26		1.10	−0.04
27		6.30	−0.80
28		44.50	−1.65
29		0.25	0.60
30		6.20	−0.79
31		0.24	0.62
32		0.24	0.62
33		0.71	0.15
34		13.70	−1.14
35		0.02	1.70
36		1.20	−0.08
37		0.04	1.40
38		1.50	−0.08
39		2.80	−0.45
40		0.18	0.74
41		0.28	0.55
42		22.20	−1.35
43		47.20	−1.67

high intercorrelation between many descriptors. Thus, descriptors, having zero, constant or almost constant values were removed from the pool of descriptors because they could not link the differences in molecule structure to the differences in activity. The correlation coefficient

between the remaining descriptors was calculated and those having $r^2 > 0.9$ were considered as intercorrelated because contain the same information or effect on activity and utilization of one of them is sufficient for modeling. Afterward, forward stepwise variable selection

Table 1 (continued)

Compound	Structure	IC ₅₀ (μM)	pIC ₅₀ (μM)
44		5.60	−0.75
45		35.20	−1.55
46		0.09	0.05
47		0.89	0.05
48		22.70	−1.36
49		1.40	−0.15
50		11.00	−1.04
51		0.17	0.77
52		0.59	0.23
53		0.13	0.89
54		0.52	0.28
55		0.23	0.64
56		0.17	0.77
57		0.25	0.60
58		0.62	0.21
59		64.80	−1.81
60		≥67	−1.83

was used to further reduce non-significant descriptors. The selected descriptors served as inputs for establishing multiple linear regressions (MLR) and least-squares support vector machine (LS-SVM) models. The correlation coefficient matrix between the selected descriptors is depicted in the Table 2. As shown in this table, the selected descriptors are completely independent of each other.

2.4 Multiple linear regression

The most common method utilized in QSAR modeling is multiple linear regression [1, 14]. Indeed, MLR is referred to be the classic and standard technique for analysis of multivariate data. The main aim of multiple regression is to quantify a linear relationship between a dependent variable (inhibitory activity) and a number of independent

Fig. 1 The plot of accomplished PCA analysis

variables (descriptors). This method of regression utilizes the least square curve fitting strategy to determine the values of regression coefficients. The multivariate analysis applies statistical methods to analyze metrics of multidimensional data such as dependent and/or independent variables. The multiple linear regression equation is shown below;

$$\hat{y} = b_0 + b_1x_1 + b_2x_2 + b_px_p \quad (1)$$

where $\hat{y}$ is the dependent variable and b_1 and b_2 represent the regression coefficients and b_0 is a regression constant and x_1 to x_p are independent variables.

2.5 Least-squares support vector machine

Support vector machine (SVM), developed by Curtis and Vapnik [11] obtained popularity in a variety of academic works due to its many attractive characteristics and

remarkable empirical performance. Later an alternative version of SVM through the implementation of the least-squares supplement, was developed by Suykens and Vandewalle [43]. The main advantage of LS-SVM is its capacity for dealing with problems of linear and nonlinear multivariate capacity in a rather fast way. Further comprehensive studies of LS-SVM approach could be found in references [9, 13, 19]. On the whole, a linear relationship between the dependent variable (y) and the regressors (x) are always fitted by LS-SVM as following:

$$y = \sum_{i=1}^N \alpha_i k(x_i, x) + b \quad (2)$$

$$\alpha_i = 2\gamma e_i \quad (3)$$

where α_i represents Lagrange multipliers, $k(x_i, x)$ is the kernel function, b represents the bias term and γ (gamma) parameter denotes the relative weight of the error term. A polynomial or Gaussian form of kernel function is utilized to delineate the input vectors into a higher dimensional feature space. The radial basis function (RBF) is considered the most common kernel function:

$$k(x_i, x) = \exp\left(-\frac{\|x_i - x\|^2}{2\sigma^2}\right) \quad (4)$$

where σ^2 represents the width of the RBF function. Generalizability potential of SVM relies on the appropriate choice of its parameters. The most careful attention in the LS-SVM algorithm concerns the choice of kernel function and its respective parameters. Since they clarify the spread of training set samples in the high dimensional feature space. Subsequent to training the predictability power of the machine is utilized to foresee or estimate unknown target values of objects. In this study, LS-SVM was established by RBF kernel function and MATLAB (v.7.6) was used to carry out all the calculations related to this work.

Table 2 Correlation matrix among selected descriptors

	Hy	Mor21m	MATS8m	Mor18u	BEHm2	AlogP	L2u	Mor20u
Hy	1	-0.072	0.344	0.024	-0.146	0.106	0.201	0.202
Mor21m		1	-0.407	0.300	0.132	-0.177	0.416	0.295
MATS8m			1	-0.233	0.345	0.152	0.222	0.388
Mor18u				1	-0.231	0.461	0.122	-0.150
BEHm2					1	0.062	0.162	-0.120
AlogP						1	-0.046	0.001
L2u							1	0.198
Mor20u								1

3 3D-QSAR study

3.1 Datasets

The same selected training and test set in 2D-QSAR modeling was applied for developing the 3D-QSAR models.

3.2 Molecular modeling

The three-dimensional structures of 57 nicotine derivatives were built by using Sybyl (x.2.1.1) programming package of Tripos, Inc [6]. The whole compounds were subjected to structural energy minimization by using Sybyl energy minimizer (Tripos Force Field) and the atomic charge was assigned by Gasteiger-Huckel method, with Powell conjugate gradient algorithm with $0.005 \text{ kcal.mol}^{-1} \text{ \AA}^{-1}$ convergence criterion.

3.3 Molecular alignment

The most sensitive parameter in CoMFA and CoMSIA studies is the alignment of 3D structures of the compounds to be analyzed in accord with an appropriate conformational template. The prediction power and accuracy of CoMFA and CoMSIA models and the creditability of contour maps directly rely on the suitable alignment molecule. In this study, the most active compound 35 was employed as a template for alignment and other compounds were superimposed on it, the resulting alignments are depicted in Fig. 2. As can be seen from this figure, the common fragment for all compounds is a pyridine ring with 3-substituted heteroaromatics.

3.4 CoMFA and CoMSIA analyses

In CoMFA method [32] the biological activity of a series of compounds are related to their steric and electrostatic

fields which are derived by putting the aligned compounds one by one into a 3D grid box with regularly grid spacing of $2 \text{ \AA}$ and expanding beyond $4 \text{ \AA}$ in all directions from the coordination of each compound [30]. The Tripos force field approach is then used to calculate the van der Waals potentials and Coulombic terms which respectively stand for steric and electrostatic fields. A sp^3 carbon atom having a $+1$ charge and a van der Waals radius of $1.52 \text{ \AA}$ was employed as a probe atom to compute the electrostatic and steric fields at each grid intersection. The threshold values of column-filtering was adjusted to $2.0 \text{ kcal.mol}^{-1}$ to enhance signal-noise ratio by deleting those grid points having a energy values lower than this threshold. It is needed to truncate the energy values of steric and electrostatic fields to 30 kcal mol^{-1} to prevent the energy values within the molecules from stretching into infinity [10, 12].

In CoMSIA [31] method which is an extension of the CoMFA method, five descriptors including steric, electrostatic, hydrophobic, hydrogen bond donor and hydrogen bond acceptor were computed with the same grid box and probe atom utilized in CoMFA calculations [5]. Gaussian type functional distance dependence was applied in CoMSIA which can avoid a sharp change of potential energies adjacent to the molecular surface using a default value of 0.3 as the attenuation Factor [40]. The equation for the calculation of similarity indices (A_F) between the molecules and the probe atom can be shown as below:

$$A_{F,K}^q(j) = \sum_i \omega_{\text{probe},k} \omega_{ik} e_{iq}^{-\alpha r_{iq}^2} \quad (5)$$

where $\omega_{\text{probe},k}$ represents probe atom, ω_{ik} represents the real value of the physiochemical property k of atom i , α denotes the attenuation factor and r_{iq} represents the mutual distance between each atoms i of the molecule j and the probe atom at lattice point q .

3.5 Partial least square analysis and model validation

After the calculation of all CoMFA and CoMSIA descriptors, partial least squares (PLS) analysis, supposed to be an extension of the multiple regression analysis, was carried out to produce a 3D-QSAR model [8, 41]. The PLS regression algorithm was employed to construct a linear relationship between inhibitory activity values (pIC_{50}) as dependent variables and CoMFA and CoMSIA fields as independent variables. Before performing the PLS analysis, column filtering was employed to filter CoMFA and CoMSIA columns to a limit smaller than 20 kcal mol^{-1} to lower the noise. In order to achieve the excellent model, the cross-validation process was done using the

Fig. 2 Structural alignment of the training set molecules for establishing the 3-D QSAR models

leave-one-out (LOO) approach to investigate the predictability of the generated model and to determine the optimal number of components (ONC) giving rise to the utmost cross-validated r^2 (r_{cv}^2) [22]. The LOO methodology is based on omitting one molecule from the dataset and then, driving a model using the remaining molecules. Afterwards, the generated model is employed to predict the activity of the deleted molecule. The ONC achieved from cross-validation techniques was subsequently employed in the regression model. The PLS analysis based on non-cross validation was then utilized to create final models of CoMFA and CoMSIA. To further appraise the robustness and statistical reliance of the accurate model, a bootstrap analysis for 100 cycles was done. In this technique, n chance selections among n objects of the original set are executed several times to achieve an excellent statistical result (100 times are needed). In each selection,

$$\begin{aligned} \text{PIC}_{50} = & 4.892(\pm 2.426) + 0.998(\pm 0.209) \times \text{Hy} + 2.738(\pm 0.793) \times \text{MATs8m} \\ & - 0.502(\pm 0.265) \times \text{L2u} + 0.446(\pm 0.149) \times \text{AlogP} - 1.601(\pm 0.705) \times \text{BEHm2} \\ & - 0.763(\pm 0.450) \times \text{Mor20u} + 2.738(\pm 0.793) \times \text{Mor21m} - 1.984(\pm 0.398) \times \text{Mor18u} \end{aligned} \quad (7)$$

$n = 46$ $R^2 = 0.702$ $\text{SE} = .49$ $F = 10.896$

some objects may be excluded from the PLS analysis, while some objects may be incorporated more than one time. Bootstrap r^2 (r_{boot}^2) stands for the mean correlation coefficient. To validate the obtained models of CoMFA and CoMSIA, the predictability power for the compounds of the test set (represented as r_{pred}^2) is verified by employing the following formula:

$$r_{pred}^2 = (\text{SD} - \text{PRESS}) / \text{SD} \quad (6)$$

where SD represents the sum of the squared deviations found between the activities of the external test set and training set molecules and PRESS represents the sum of the squared deviations found between the actual and predicted activities of the external test set molecules.

4 Results and discussion

4.1 2D-QSAR statistical analyses

The technique of the stepwise multi linear regression was used to choose the most related descriptors from the pool of the descriptors which rely on the compounds of the training set. Based on the calculation outcomes of the correlation matrix in Fig. 2 no intense correlation was found among the chosen descriptors. Moreover, the MLR approach was employed to construct linear models of QSAR to foresee the inhibitory activities of nicotine derivatives. The selected descriptors were employed as independent variables and pIC_{50} values were employed as dependent variables. Specification of the achieved MLR model with these descriptors is depicted in the following equation:

where throughout this study, n stands for the number of compounds, R^2 depicts the square of correlation coefficients, SE represents the estimated standard error and F represents the F-ratio between the variances of computed and observed activities. Also, the values shown in the parenthesis depict the standard errors related to the regression coefficient. Definition and categories of the 8 selected descriptors were appeared in Table 3. Further detailed studies of these descriptors can be acquired in the handbook of molecular descriptors [45].

The Hy stands for hydrophilic index descriptor and is related to the hydrophilicity of the compound. It is calculated as below:

Table 3 Definition and categories of selected descriptors

Descriptor	Definition	Category
Hy	Hydrophilicity factor	Molecular properties
Mor18u	3-D MoRSE signal – 18/unweighted	3-D MoRSE
Mor20u	3-D MoRSE signal – 20/unweighted	3-D MoRSE
Mor21m	3-D MoRSE signal – 21/weighted by atomic mass	3-D MoRSE
MATS8m	Moran autocorrelation - lag 8/weighted by atomic mass	2-D autocorrelation
BEHm2	Highest eigen value no.2 of Burden matrix/weighted by atomic mass	BCUT descriptors
AlogP	Ghose-Crippen octanol–water partition coefficients. (logP)	Molecular properties
L2u	2nd component size directional WHIM index/unweight	WHIM descriptors

$$Hy = \frac{(1 + N_{Hy}) \cdot \log_2(1 + N_{Hy}) + N_c \cdot \left(\frac{1}{A} \cdot \log_2 \frac{1}{A} \right) + \sqrt{\frac{N_{Hy}}{A^2}}}{\log_2^{(1+A)}}$$

where N_{Hy} depicts the number of hydrophilic sets (–OH, –SH, –NH), N_c defines the number of carbon atoms and A depicts the number of atoms disregarding hydrogen atoms [44]. The negative coefficient of H_y descriptor signifies that presence of hydrophilic groups in aromatic rings decreases pIC_{50} . It is important to mention that a low value of pIC_{50} shows a low inhibitory activity of inhibitors. Mor18u and Mor20u are 3D-MorSE (3D- molecular representation of structure based on electron diffraction) un-weighted descriptors and encode information of structural features like mass and number of branching in substituted benzene derivative [17]. The negative sign in the regression coefficients of these descriptors reveals that the addition of substituents in the aromatic ring decrease the value of pIC_{50} . The fourth descriptor is Mor21m, 3D-MorSE – signal 21/weighted by atomic masses [20, 39]. The positive sign in the regression coefficient of this descriptor reflects positively the role of atomic masses on the inhibitory activity of inhibitors. The fifth descriptor is MATs8m, Moran autocorrelation- lag8 which is weighted by atomic mass and is 2D- autocorrelation [16]. The positive sign in the regression coefficient of this descriptor denotes positively increased value of pIC_{50} . The sixth descriptor is BEHm2, highest eigen value NO. 2 of Burden matrix, which is weighted by atomic mass [29]. Encoding of this descriptor is accompanied by descriptor of Burden eigen values and is computed using hydrogen involved molecular graph. As shown in Eq. (7), the regression coefficient of this descriptor has a negative sign which indicates a negative effect of adding hydrogen in molecular graph on the pIC_{50} value. The next descriptor is AlogP, Ghose-Crippen octanol–water partition coefficient, which denotes the lipophilicity of the molecule [21]. The positive coefficient of this descriptor in Eq. (7) shows that as the hydrophobic groups of the molecule increase the inhibitory activity becomes stronger. The last descriptor is L2u, 2nd component size directional WHIM index/unweight, which uses molecular size to gain related molecular 3D information [46]. According to Eq. (7), this descriptor has a negative coefficient which means it is inversely related to the pIC_{50} . These selected descriptors were employed as inputs to drive linear and non-linear 2D-QSAR models respectively by MLR and LS-SVM methods.

In LS-SVM modeling, the values of parameters of σ^2 and the relative weight of the regression error (γ) were optimized to gain the maximum root mean square errors (RMSE). Consequently, the optimum values of σ^2 and γ were found 8 and 98, respectively. The experimental and

Table 4 Dataset and corresponding experimental and calculated pIC_{50} values for MLR and LS-SVM models

Compound	$pIC_{50\text{ exp}}$	MLR		LS-SVM	
		$pIC_{50\text{ PRED}}$	Residual	$pIC_{50\text{ PRED}}$	Residual
1	−0.64	−0.57	−0.07	−0.61	−0.03
2	−0.08	0.01	−0.09	−0.03	−0.05
3	−0.51	0.28	−0.79	−0.47	−0.04
4*	1.00	0.32	0.68	0.51	0.49
5	0.68	0.37	0.31	0.68	0.00
7	−0.18	−0.13	−0.05	−0.18	0.00
8	0.10	0.39	−0.29	0.08	0.02
9	−0.15	−0.74	0.59	−0.19	0.04
10	−1.29	−0.87	−0.42	−1.35	0.06
11	0.66	0.41	0.25	0.63	0.03
12*	0.01	−0.21	0.22	−0.15	0.16
13	−0.99	−0.59	−0.40	−0.98	−0.01
14	−0.65	−0.71	0.06	−0.64	−0.01
15*	0.60	−0.05	0.65	0.06	0.54
16	−0.41	−0.39	−0.02	−0.40	−0.01
17	−0.82	−0.89	0.07	−0.82	0.00
19*	−0.89	−0.61	−0.28	−0.90	0.01
20	−1.64	−1.33	−0.31	−1.59	−0.05
21	−0.71	−0.91	0.20	−0.69	−0.02
22	−0.43	−0.32	−0.11	−0.29	−0.14
23	−0.99	−0.46	−0.53	−0.99	0.00
24*	−0.26	−0.28	0.02	−0.77	0.51
25	−1.44	−0.63	−0.81	−1.11	−0.33
26	−0.04	−0.75	0.71	−0.43	0.39
27	−0.80	−1.07	0.27	−0.74	−0.06
28	−1.65	−1.40	−0.25	−1.65	0.00
29	0.60	0.49	0.11	0.48	0.12
30	−0.79	0.06	−0.85	−0.52	−0.27
31	0.62	−0.22	0.84	0.40	0.22
32	0.62	0.16	0.46	0.66	−0.04
33	0.15	−0.35	0.50	0.11	0.04
34	−1.14	−0.24	−0.90	−1.14	0.00
35	1.70	0.92	0.78	1.54	0.16
37	1.40	−1.02	0.38	1.36	0.04
40	0.74	0.15	0.59	0.74	0.00
41	0.55	−0.31	86.0	0.48	0.07
42	−1.35	−1.32	−0.03	−1.33	−0.02
43	−1.67	−1.99	0.32	−1.67	0.00
44	−0.75	0.01	−0.76	−0.63	−0.12
45*	−1.55	−0.40	−1.15	−1.52	−0.03
46	1.05	1.00	0.05	1.03	0.02
47	0.05	0.02	0.03	0.05	0.00
48	−1.36	−1.67	0.31	−1.35	−0.01
49	−0.15	0.53	−0.68	−0.14	−0.01
50	−1.04	−0.51	−0.53	−1.05	0.01
51	0.77	0.67	0.10	0.77	0.00
52	0.23	1.00	−0.77	0.37	−0.14
53*	0.89	0.66	0.23	0.60	0.29

Table 4 (continued)

Compound	pIC ₅₀ exp	MLR		LS-SVM	
		pIC ₅₀ PRED	Residual	pIC ₅₀ PRED	Residual
54	0.28	0.58	−0.30	0.30	−0.02
55	0.64	0.18	0.46	0.62	0.02
56	0.77	0.25	0.52	0.62	0.15
57	0.60	0.28	0.32	0.58	0.02
58*	0.21	0.27	−0.06	0.05	0.16
59	−1.81	−1.58	−0.23	−1.80	−0.01

*Compounds of the test set

Table 5 Statistical results for MLR and LS-SVM models

Model	Train set		Test set	
	R ²	SE	R ²	SE
MLR	0.702	0.49	0.689	0.53
LS-SVM	0.993	0.10	0.977	0.20

Fig. 3 The plot of LS-SVM calculated versus experimental values of pIC₅₀ **Fig. 4** The plot of MLR calculated residuals versus experimental values of pIC₅₀

calculated values of PIC50 by MLR and LS-SVM model and their corresponding residual values for training and test set were reported in Table 4. Also, statistical parameters of 2D-QSAR models were displayed in Table 5. The better

statistical values of this model are fulfilling and reveal the steadiness robustness of LS-SVM model and depict the superiority of LS-SVM over MLR model. Apart from this, the validity of the LS-SVM model was assessed using the cross-validation (Q^2) method and the obtained Q^2 was 0.550. As a result, the relationship between the selected descriptors and pIC₅₀ values should be nonlinear than linear. The plot of predicted pIC₅₀ values against experimental values was demonstrated in Fig. 3 which indicates LS-SVM well fitness with data. The residuals of predicted PIC₅₀ values were plotted against the experimental values in Fig. 4. The scattering of residuals on each side of the zero line indicates the lack of systematic error in the developed LS-SVM model.

4.2 3D-QSAR statistical analysis

The experimental and calculated values of PIC50 by COMFA and COMSIA model and their corresponding residual values for training and test set were reported in Table 6. More obtained statistical parameters of established CoMFA and COMSIA model were listed in Table 7. The results of this table show the higher influence of steric field descriptors than the electrostatic ones. Figure 5 demonstrates the plot of experimental against calculated values of inhibitory activity by the CoMFA model. As shown in this figure, most points, indicating the training and test molecules, are equally dispersed along the line $y=x$ which demonstrates the good quality of CoMFA model. Also, the results of Table 7 show that the steric field has no contribution in CoMSIA modeling while electrostatic field has a larger contribution over the others. The test set statistical results imply that the CoMFA model is more reliable than CoMSIA model and can be helpful in designing novel potent CYP2A6 inhibitors.

4.2.1 CoMFA contour maps

To envision the information elements of the generated 3D-QSAR models, graphical maps of CoMFA model, which showed better predictability power than CoMSIA model, were created to recognize the important areas around the molecules where any alters in electrostatic and steric fields were anticipated to reduce or increase the inhibitory activity [25]. Figure 6a depicts the CoMFA steric field contour map for compound 35, more potent inhibitor in the dataset. The green colored regions of the steric field graphical plot depict an increase of inhibitory activity by bulky substituents while yellow colored regions depict a reduce of inhibitory activity by bulky substituents. As shown in this figure, the green colored contour emerging near amine group ($-NH_2$) indicates that bulky substituents are favorable at this area but the yellow colored contour adjacent

Table 6 Dataset and corresponding experimental and calculated pIC_{50} values for CoMFA and CoMSIA models

Compound	$\text{pIC}_{50 \text{ exp}}$	CoMFA		CoMSIA	
		$\text{pIC}_{50 \text{ Pred}}$	Residual	$\text{pIC}_{50 \text{ Pred}}$	Residual
1	-0.64	-0.63	-0.01	-0.94	0.30
2	-0.08	0.47	-0.55	0.38	-0.46
3	-0.51	-0.42	-0.09	-0.84	0.33
4*	1.00	0.51	-0.95	0.45	0.55
5	0.68	0.71	-0.03	0.66	0.02
7	-0.18	-0.29	-0.11	-0.31	0.13
8	0.10	0.39	-0.29	0.08	0.02
9	-0.15	-0.74	0.59	-0.19	0.04
10	-1.29	-0.87	-0.42	-1.35	0.06
11	0.66	0.41	0.25	0.63	0.03
12*	0.01	-0.21	0.22	-0.15	0.16
13	-0.99	-0.59	-0.40	-0.98	-0.01
14	-0.65	-0.71	0.06	-0.64	-0.01
15*	0.60	-0.05	0.65	0.06	0.54
16	-0.41	-0.39	-0.02	-0.40	-0.01
17	-0.82	-0.89	0.07	-0.82	0.00
19*	-0.89	-0.61	-0.28	-0.90	0.01
20	-1.64	-1.33	-0.31	-1.59	-0.05
21	-0.71	-0.91	0.20	-0.69	-0.02
22	-0.43	-0.52	0.09	-0.76	0.33
23	-0.99	-0.67	-0.32	-0.73	-0.26
24*	-0.26	-0.24	-0.02	-0.63	0.37
25	-1.44	-0.66	-0.78	-0.99	-0.45
26	-0.04	-0.41	0.37	-0.27	0.23
27	-0.80	-0.78	-0.02	-1.12	0.32
28	-1.65	-1.67	0.02	-1.44	-0.21
29	0.60	-0.27	0.33	0.49	0.11
30	-0.79	0.08	-0.87	-1.00	0.21
31	0.62	0.46	0.16	0.61	0.01
32	0.62	0.29	0.33	0.68	-0.06
33	0.15	-0.48	0.63	0.89	-0.74
34	-1.14	-0.92	-0.22	-1.28	0.14
35	-1.70	1.91	-0.21	1.65	0.05
36	-0.08	-0.11	0.03	-0.19	0.11
37	1.40	1.14	0.26	1.48	-0.08
38	-0.18	-0.33	0.15	-0.46	0.28
39	-0.45	0.00	-0.45	-0.29	-0.16
40	0.74	0.54	0.20	-0.27	1.10
41	0.55	0.70	-0.15	0.81	-0.26
42	-1.35	-1.24	-0.11	-0.87	-0.48
43	-1.67	-1.82	0.15	-1.10	-0.57
44	-0.75	-0.99	0.19	-0.81	0.06
45*	-1.55	-1.28	-0.27	-1.29	-0.26
46	1.05	1.13	-0.08	1.12	-0.07
47	0.05	0.04	0.01	0.17	-0.12
48	-1.36	-1.34	-0.02	-0.58	-0.78
49	-0.15	0.04	-0.19	-0.01	-0.14
50	-1.04	-0.94	-0.10	-0.80	-0.24

Table 6 (continued)

Compound	$\text{pIC}_{50 \text{ exp}}$	CoMFA		CoMSIA	
		$\text{pIC}_{50 \text{ Pred}}$	Residual	$\text{pIC}_{50 \text{ Pred}}$	Residual
51	0.77	0.12	0.65	0.77	0.00
52	0.23	0.24	-0.01	-0.14	0.37
53*	0.89	0.31	0.58	0.29	0.60
54	0.28	0.17	0.11	-0.01	0.29
55	0.64	0.70	-0.06	0.55	0.09
56	0.77	0.32	0.45	0.48	0.29
57	0.60	0.17	0.43	0.39	0.21
58*	0.21	-0.14	0.35	0.48	-0.27
59	-1.81	-1.82	0.01	-1.63	-0.18

*Compounds of the test set

Table 7 Statistical results of CoMFA and CoMSIA model

	CoMFA	CoMSIA
<i>Components</i>		
R^2	0.884	0.889
SE	0.32	0.31
R^2_{pred}	0.874	0.670
SE_{pred}	0.33	0.54
F values	41.276	39.49
n	8	8
Q^2	0.581	0.554
<i>Fraction</i>		
Steric	0.605	0.00
Electrostatic	0.395	0.505
Hydrophobic	-	0.145
Hydrogen bond donor	-	0.269
Hydrogen bond acceptor	-	0.81

Fig. 5 The plot of CoMFA calculated versus experimental values of pIC_{50}

to this area indicates that increasing the number of bulky substituents at this area would decrease the inhibitory activity which may be due to the hindrance effect of bulky

Fig. 6 **a** Steric field contour map and **b** electrostatic field contour map produced by CoMFA model

substituents on the activity of sulfur or oxygen atom at the thiophene and furan ring, respectively.

A comparison between compounds 35 ($pIC_{50} = 1.70$) and 37 ($pIC_{50} = 1.40$) shows that as the larger sulfur atom in thiophene ring replaces with a smaller oxygen atom in furan ring, inhibitory activity decreases. Also, this trend can be seen between compounds 40 ($pIC_{50} = 0.74$) and 41 ($pIC_{50} = 0.55$) and between compounds 42 ($pIC_{50} = -1.35$) and 43 ($pIC_{50} = -1.67$). The results of these comparisons reveal that as the thiophene ring attached to the amide group ($-CH_2-NH_2$) replaces with furan ring, inhibitory activity decreases due to the smaller size of oxygen than sulphur atom. In contrast, increased bulky substituents to the nitrogen of amine decrease the biological activity. It may be due to the proximity of yellow colored contour to green colored contour that makes these bulky substituents unfavorable. For example, comparison between compounds 35 ($pIC_{50} = 0.74$) and 36 ($pIC_{50} = -0.08$) reveals that compounds 36 have an increased steric bulky substituent and as a result, its inhibitory activity dramatically drops. The same activity trends are observed among compounds 37 ($pIC_{50} = 1.40$), 38 ($pIC_{50} = -0.18$) and 39 ($pIC_{50} = -0.45$) and between compounds 40 ($pIC_{50} = 0.74$) and 42 ($pIC_{50} = -1.35$) and finally between compounds 41 ($pIC_{50} = 0.55$) and 43 ($pIC_{50} = -1.67$). Figure 6b displays the CoMFA electrostatic field graphical plot for compound 35, having the highest inhibitory activity in the dataset. Blue colored graphical plots depict areas where electrostatic groups are favorable whereas red colored ones depict regions where electronegative groups are favorable. As shown in this figure, the blue electrostatic contour near 3 and 4-position of thiophene ring reveals that any electropositive groups at these positions would increase the inhibitory activity. For example, the inhibitory activity of compound 4 ($pIC_{50} = 1.00$) is more than 10-fold higher than the inhibitory activity of compound 2 ($pIC_{50} = -0.08$), due to the electropositive CH_3 group in the 3-position of thiophene ring.

The same activity trend can be seen between compounds 11 ($pIC_{50} = 0.66$) and 15 ($pIC_{50} = 0.60$) and

also between compounds 12 ($pIC_{50} = 0.001$) and 16 ($pIC_{50} = -0.41$). As it can be seen from Fig. 6b, the red electrostatic contours are very small, which indicates that electronegative groups at 3 and 4-position of thiophene ring has a minor effect on the inhibitory activity.

Recognize the effective interactions of the new nicotine analogue on the inhibitory activity individually due to change in the number and position of the effective atom is hard and confusing. With considering such points, applying the best-fitted model by CoMFA approach and draw the steric and electrostatic counter maps help to characterize the effective interactions of new nicotine analogue.

5 Conclusion

The main goal of the present study was to develop 2D and 3D-QSAR models for predicting the inhibitory activities of nicotine derivatives on CYP2A6 enzyme. Therefore, a linear MLR and a nonlinear LS-SVM methods were used to generate 2D-QSAR models. The statistical results of this investigation revealed that LS-SVM method was more reliable and had remarkable superiority over the MLR model and can be successfully employed to predict the biological activities of nicotine derivative compounds. Moreover, 3D-QSAR studies using CoMFA and CoMSIA methods were performed on the same training and test set of 2D-QSAR study. The statistical results of 3D-QSAR analyses indicated that CoMFA model was more acceptable than CoMSIA to predict the inhibitory activities of the test set. Further, the good correlation coefficient ($R^2 = 0.874$) between observed and predicted inhibitory activity values for the test set compounds validated the predictability power of generated CoMFA model. Finally, steric and electrostatic contour maps of the CoMFA model helped to recognize the important structural features responsible for the interaction between the inhibitor molecule and receptor. Overall, the superior statistical results of the CoMFA over the CoMSIA model reveal the importance of steric and electrostatic fields in these compounds. The information extracted from this study can be helpful in the

design of novel CYP2A6 inhibitors with enhanced inhibitory activities which may be used as a potent drug candidate.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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