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3D QSAR STUDIES OF FLAVONOID ANALOGUES FOR VASCULAR RELAXANT ACTIVITY IN CORONARY HEART DISEASES

Prajakta Dongare

Shree Babasaheb Gharfalkar College of Pharmacy, Pulgaon, District: Wardha, (M.S.), India

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ABSTRACT

Flavonoids have been reported to potent vascular relaxing agent. In the present study, the three dimensional quantitative structure activity relationship (3D QSAR) study was performed on series of 17 flavonoids analogues using k nearest neighbor Molecular Field Analysis (kNN-MFA) approach for both electrostatic and steric fields. There was Simulated Annealing (SA), 3D QSAR method used for the development of model and tested successfully for internal (q2= 0.6262) and external (predictive r2= 0.4675) validation criteria. Thus 3D QSAR model showed that electrostatic effects dominantly determine the binding affinities for vascular relaxant activity.

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Introduction

Flavonoids are large group of polyphenolic compounds that are widely distributed in nature. Over 6000 flavonoids have been identified, many of which occur in fruits, vegetables and beverages and are dietary antioxidants. The flavonoids have aroused considerable interest recently because of their potential beneficial effects on human health [1,2]. Depending on their structural features, flavonoids can be further subdivided into flavones, flavonols, isoflavones, flavanes and flavanols [3]. They have diverse pharmacological effects such as anticancer, antioxidants, anti-agining and antibacterial properties [4-7]. Many have of them provide protection against cardiovascular mortality [8,9]. Recently many studies have focused on their cardiovascular effects [10, 11]. Epidemiological reports have demonstrated that people have lower incidence of heart diseases if they have high dietary intake of flavonoids 11 and this may help explain the lower mortality of coronary heart diseases in some Asian countries [12]. Furthermore, other studies have demostrated that some flavonoids produce concentration dependent relaxation responses in contracted arterial rings. These relaxations are in part mediated by nitric oxide realease from the endothelium. However, the majority of the relaxation is attributed to direct action of the flavonoids on the vascular smooth muscle [13,14]. Since different flavonoids have different relaxation effects, due to the many benefits flavonoids offer to man, quantification methodologies are an important part of the research and further understanding of flavonoids vasorelaxant activity [15]. In this case, application of computational study was used to study the quantitative structure–activity relationships (QSAR) of flavonoids by using three dimensional molecular interactions and correlates the bioactivity of compounds with structural descriptors and have been proved to be one of the useful approaches for accelerating the drug design and synthesis of new potent vascular relaxant flavonoids derivatives [15,16]. In the present study, a series of 17 flavonoids derivatives were performed by k nearest neighbor by using simulated annealing methods to develop 3D-QSAR. This 3D-QSAR model can be used to identify the structural features essential for enhancing their activities and subsequently can enable the design new potent vascular relaxant compounds.

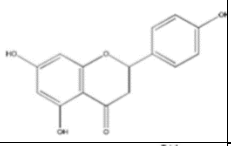
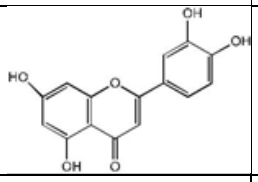
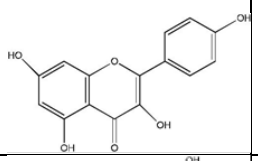
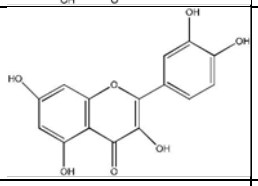
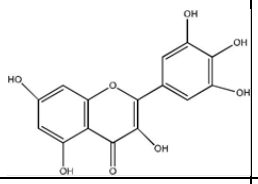
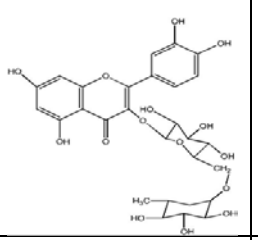
Corresponding Author: Prajakta Dongare

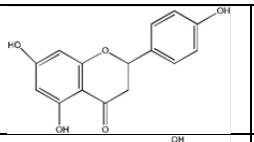
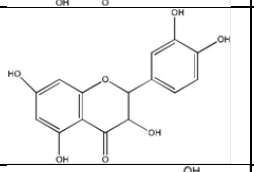
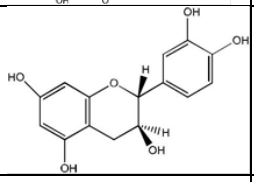
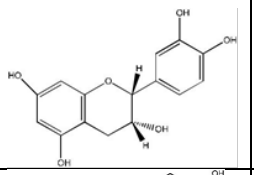
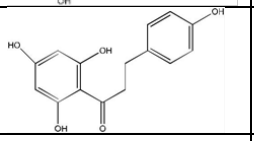
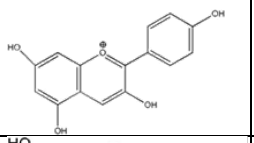
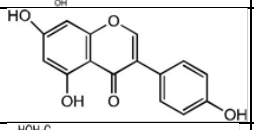
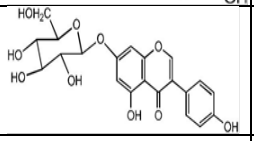
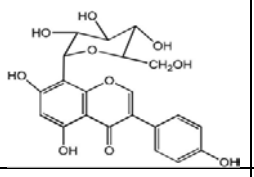
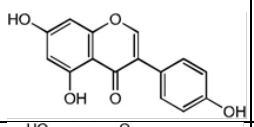
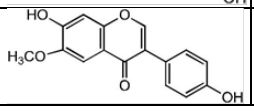
Patients and Methods
3D-QSAR Modeling
Dataset
In this study, all computational work (3D-QSAR) was performed using Vlife MDS QSAR plus software on Lenovo computer with Intel core i3 processor and windows 7 operating system.
Dataset of 17 molecules (table1) taken from the reported work15 consider as independent variable and pEC50 activity field as dependent variable and various 3D descriptors calculated for the compounds as independent variables.

Calculation of field descriptors
Electrostatic and steric field descriptors were calculated with cutoffs of 10.0 kcal/mol for electrostatic and 30.0kcal/mol for steric, and charge type was selected as by Gasteiger-Marsili. The dielectric constant was set to1.0, considering distance-dependent dielectric function. Probe setting was carbon atom with charge 1.0. A total of 2,080 field descriptors (1,040 for each electrostatic and steric) were calculated for all the compounds in separate columns. 3D-QSAR analysis was performed after exclusion of all the invariable columns, as they do not contribute to QSAR.

Biological Activities
Biological Activity data- The vascular relaxant activity data EC50 (µM) were taken from the reported work [15]. The negative logarithm of the measured EC50 (µM) [pEC50 = -log (EC50)] was used as dependent variable for 2D QSAR analysis (table 1).

Table 1: Structure and experimental activity of flavonoid derivatives

Sr. No.	Name of Compound	Structure of flavonoids compound	Activity (pEC50) ug/ml.
1.	Apigenin		3.9262
2.	Luteolin		3.9423
3.	Kaemferol		3.9340
4.	Quercetin		3.9329
5.	Myrecetin		4.2533
6.	Rutin		4.1331
			3.9650

7.	Naringenin		
8.	Taxifolin		4.0936
9.	Catechin		4.2502
10.	Epicatechin		4.1752
11.	Phloretin		3.9755
12.	Pelargonidin		4.0560
13.	Genistein		3.9738
14.	Genistin		4.6003
15.	Puerarin		4.3467
16.	Daidzein		3.9875
17.	Glycetin		4.0310

Bi Selection of training and test set

The data set of 17 flavonoid molecules was divided into training set containing 11 compounds and test set containing 6 compounds by using random selection method.

Methods used for 3D QSAR Modeling

We have performed 3D QSAR by using KNN-MFA method that adopts a kNN principle for relationship between molecular fields and vasorelaxant activity. The kNN-MFA models were generated using training set of 11 compounds 3D QSAR model were validated using a test set of 6 compounds. The stearic and electrostatic descriptor signify the regions, where variation in the structural features of different compounds in training set leads to increase or decrease in activities.

k-Nearest neighbor molecular field analysis (kNN-MFA)

The kNN methodology relies on a simple distance learning approach whereby an unknown member is classified according to the majority of its kNN in training set. The nearness is measured by an appropriate distance metric. In kNN-MFA method, several models were generated for selected members of training and test sets. Once training and test sets are generated, kNN methodologyis applied to descriptors generated over the grid.16 The steric and electrostatic interaction energies are computed at lattice points of the grid using a methyl probe of charge +1. These interaction energy values are considered for relationship generation and utilized as descriptors to decide nearness between molecules.

kNN-MFA with simulated annealing

SA is the simulation of a physical process, 'annealing', which involves heating the system to a high temperature and then gradually cooling it down to a preset temperature (e.g., room temperature). During this process, the system samples possible configurations distributed according to the Boltzmann distribution so that at equilibrium, low energy states are the most populated by using kNN-MFA we have selected simulated annealing (SA) for generating the best one 3D QSAR model.

Validation of QSAR Model

Validation of QSAR study is important to test the internal stability and predictive ability of the QSAR models & was validated by the following procedure as given below. There are two types of validation,

- Internal Validation
- External Validation

Internal validation

It was carried out using leave-one-out (q2, LOO) method. For calculating q2, each molecule in the training set was eliminated once and the activity of the eliminated molecule was predicted by using the model developed by the remaining molecules. The q2 was calculated using the equation (Eq. 2) which describes the internal stability of a model.

$$q^2 = 1 - \frac{\sum[yi(Act) - yi(Pred)]^2}{\sum[yi - y\,(mean)]^2}$$

Where yi (Act) and yi (Pred) are the actual and predicted activity of the i th molecule in the training set, respectively, and y mean is the average activity of all molecules in the training set.

External Validation

The predictive ability of the selected model was also confirmed by external validation of test set compounds which is also denoted with pred_r2. The pred_r2 value is calculated as follows

$$pred\_r2 = 1 - \frac{\sum[yi(Act) - yi(Pred)]^2}{\sum[yi - y\,(mean)]^2}$$

Where yi and yi are the actual and predicted activity of the I th molecule in the training set, respectively, and y mean is the average activity of all molecules in the training set.

RESULT AND DISCUSSION

Table 2: Uni-column statistics for the training set and test set of 3D QSAR

Uni-column statics	Average	Max	Min	Standard Deviation
Training set	4.1068	4.6003	3.9329	0.2150
Test set	4.0669	4.2502	3.9329	0.1218

Where, Maximum value of training set is greater than or equal to test set. And Minimum value of training set is less than or equal to test set. 3D-QSAR model was generated by dividing dataset of molecules into training set 11 compounds and test set 6 compound by using kNN MFA method in which simulated annealing method gives best model, we have experimental and predicted activity from this method given in table 3.

Table 3: Experimental and predicted activity of flavonoid analogues

Sr. No.	Flavonoid Compound	EC_{50} (μM)	Expt. pEC_{50}	Pred. pEC_{50}
1.	Apigenin	118.5	3.9262	3.9733
2.	Catechin	56.2	4.2502	4.2501
3.	Daidzein	102.9	3.9875	3.9644
4.	Epicatechin	66.8	4.1752	4.1659
5.	Genistein	106.2	3.9738	4.0504
6.	Genistin	25.1	4.6003	4.3463
7.	Glycetin	93.1	4.0310	3.9731
8.	Kaemferol	116.4	3.9340	3.9559
9.	Lueteolin	114.2	3.9423	4.1169
10.	Myrecetin	55.8	4.2533	4.1112
11.	Naringenin	108.4	3.9650	4.0721
12.	Pelargonidine	87.9	4.0560	3.9529
13.	Phloretin	105.8	3.9755	3.9336
14.	Puerarin	45	4.3467	4.5996
15.	Quercetin	116.7	3.9329	3.9582
16.	Rutin	73.6	4.1331	4.1682
17.	Taxifolin	80.6	4.0936	4.0930

Generation of 3D-QSAR Model

3D-QSAR modeling was performed using kNN-MFA method that adopts a kNN principle for generating relationships between molecular fields and vascular relaxant activity. The kNN-MFA model generated using training set of 11 compounds and 3DQSAR models were validated using a test set of 6 compounds. The steric (S) and electrostatic (E) descriptors specify the regions, where variation in the structural features of different compounds in training set leads to increase or decrease in activities. The number accompanied by descriptors represents its position in 3D MFA grid. The simulated annealing method resulted in several statistically significant model, is considered as the best model. The model selection criterion is the value of q2, internal predictive ability of model, and that of pred_r2, ability of the model to predict activity of external test set. Model-SA

pEC50 = E_790 (2.8021 10.0000) E_814 (-0.1734 0.1338).

Model-SA was considerd as 3D-QSAR model for the dataset. Internal predictivity of model by LOO cross validation squared correlation coefficient q2= 0.6262 and external predictive squared correlation coefficient pred_r2= 0.4675 suggested goodness of the prediction of developed model. Model statistics given in table 4. The predicted versus the experimental value for training and test sets are depicted in Figure1. 3D-QSAR models obtained showed that electrostatic and steric interactions play major role in determination of vascular activity. E_790 (2.8021 10.0000) E_814 (-0.1734 0.1338) are electrostatic field descriptors, Negative value in electrostatic field descriptors indicates that negative electronic potential is required to increase activity and more electronegative groups are preferred in that position, positive range indicates that group that imparting positive electrostatic potential is favorable for vascular relaxant activity so less electronegative group is preferred in that region.

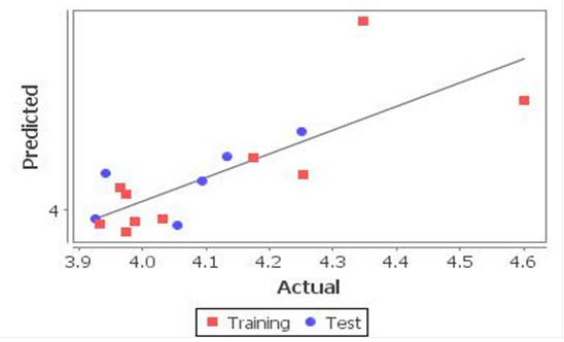


Figure 1: Graphs of experimental versus predicted activitypEC50 using SA (3D-QSAR)

Table 4: Statistical results for 3D QSAR model by using kNN-SA method

S.No.	Statistical parameters	Model- SA
1.	N	11
2.	K	2
3.	Degree of freedom	8
4.	q2	0.6262
5.	q2_se	0.1315
6.	pred_r2	0.4675
7.	pred_r2 se	0.0944
8.	Descriptors	E_790, E_814

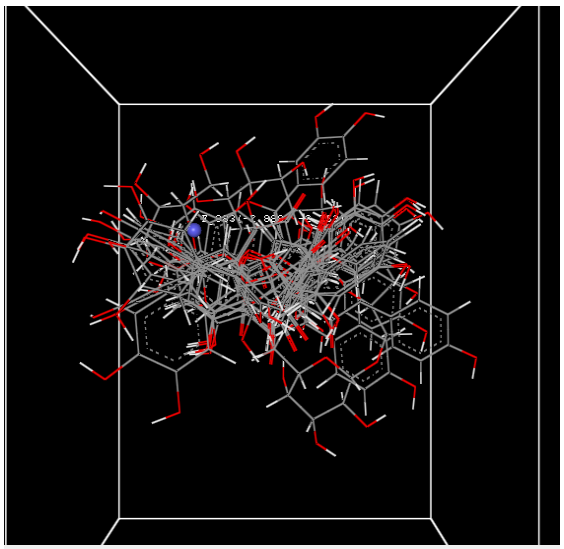


Figure 2: Contour plot of 3D-QSAR model with important electrostatic points contributing to the model with range of values.

CONCLUSION

The master grid obtained for the various kNN-MFA models showed positive value in electrostatic field descriptors, which indicates that positive electronic potential is required to increase vascular relaxant activity [17].. 3D-QSAR suggested the importance of some molecular characteristics, which should significantly affect the binding affinities of compounds. These result provide clues for designing novel vascular relaxant derivatives of flavonoids.

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