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Development of Highly Predictive 2D and 3D QSAR Models Combined with MLR and kNN Technique of Chalcone Derivatives for Inhibition of NO Production and Tumor Cell Proliferation

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ABSTRACT

A series of 23 molecules of 3', 4', 5'-tri-methoxy chalcone derivatives reported in literature Yerra koteswara Rao *et al* (2009) were used for development of 2D and 3D QSAR models. The data set of 23 molecules were divided into training and test set in the ratio of 70:30, The biological activity was converted to the logarithmic scale (pIC_{50}) in a mathematical operation mode of the software. The statistically significant 2D-QSAR models for NO inhibition activity are r^2 =0.8145 and q^2 = 0.5130 and on tumor cell proliferation activity giving r^2 = 0.7207 and q^2 =0.5227. 3D QSAR results for internal (q^2 = 0.6176, q^2=0.7761) and external (predictive r^2 = 0.5055, r^2 = 0.4292) validation criteria. Thus, 3D QSAR models showed that electrostatic effects dominantly determine the binding affinities. 2D QSAR studies revealed that Sds CHE Index descriptors were major contributing descriptor in case of No inhibition activity and DeltaEpsilon B in the case of tumor cell proliferation activity. Methods were performed using the kNN-MFA method. The results derived may be useful in further designing novel more potent agents.

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1. INTRODUCTION:

Chalcones constitute an important group of natural products and serve as precursors for the synthesis of different classes of flavonoids, which are common substances in plants. Chalcones are open-chain flavonoids in which two aromatic rings are joined by a three carbon a, unsaturated carbonyl system (1,3-diphenyl-2-propane-1-ones) [Avila et al 2008]. Chalcone derivatives have received a great deal of attention due to their relatively simple structures, and wide variety of pharmacological activities reported for these compounds include anti-inflammatory [Cheng et al], antibacterial[Rao et al 2009], antifungal [Sortino et al 2007], and antitumor activities [Katsori &Achanta et al 2006]. These activities are largely attributed due to the α,β-unsaturated ketone moiety. The introduction of various substituents into the two aryl rings is also a subject of interest because it leads to useful structure–activity relationship (SAR) conclusions and thus helps to synthesize pharmacologically active chalcones [Kastori et al 2009]. In recent years, noteworthy advancement has been made by computational chemistry, which led new challenges to drug discovery. Quantitative structure activity relationship (QSAR) which has become an reputable tool for establishing quantitative relationship between biological activity and physicochemical properties of the compounds in a series using various statistical methods (linear regression and non-linear regression analysis) and it helps to calculate the biological activities of newly designed analogues contributing to the drug discovery process [Kulkarni et al 2008]. The core idea of the present study is the search for novel 3', 4', 5'-tri methoxy chalcone analogs that would show a promise to become useful as inhibitors of nitric oxide production and tumor cell proliferation. A series of 3', 4', 5'-tri methoxy chalcone analogs which were reported [Rao et al 2009] are chosen for QSAR study in order to establish the quantitative relationship between physiochemical properties and biological activities of the compounds using QSAR pro software (Vlife Science) [VLife software 2017].

The purpose of the present study is to investigate the physicochemical parameters responsible for the inhibition of NO and tumor cell proliferation effect of 3', 4', 5'trimethoxy chalcone derivatives and designing of novel substituted 3', 4', 5'trimethoxy chalcone derivatives with potent protective activity. In the present investigation, three widely used techniques, viz. stepwise forward variable selection method, Genetic algorithm and simulated annealing have been applied for descriptor optimization and multiple linear regression analysis, principal component regression and partial least square has been applied for two and three-dimensional

QSAR models development. The generated models provide insight into the influence of various interactive fields on the activity and, thus, can help in designing and forecasting the protecting effect of the novel of 3', 4', 5'trimethoxy chalcone molecules. The data set was divided into training and test set as in 70:30 ratio.

Traditional QSAR does not directly take into account the three-dimensional nature of molecules. However, three-dimensional QSAR uses steric and electrostatic parameters in an attempt to define the three-dimensional shape and electrostatic fields of a molecule responsible for binding to produce QSAR type equations for predicting the activity of potential drug candidates [Thomas G 2003].

In 3D QSAR the 3D properties of a molecule are considered as a whole rather than by considering individual substituent or moieties. The philosophy of 3D QSAR revolves around the assumptions that the most important features of a molecule are its overall size and shape, and its electronic properties (electronic field). Comparative molecular field analysis (CoMFA) is an important method of 3D QSAR [Cramer et al 1988]. This is based on the assumption that drug – receptor interactions are noncovalent and that changes in the steric and/or electrostatic fields of the drug molecules [Patric 2006].

3D QSAR like traditional QSAR uses a group of compounds, the training set, with either similar structures or having a common pharmacophore and same type of activities but different potencies in an investigation. A 3D QSAR investigation is thus started by selecting one member of the training set as a reference compound and identifying its pharmacophore. The three-dimensional structure of a reference molecule is locked into a rectangular three-dimensional lattice of so-called grid points that are usually set at a finite distance apart, typically 2-angstrom units (0.2 mm), in the x, y, and z directions. A three or four digit number locates each grid point. A suitable molecular mechanical probe, such as a sp^3-hybridized carbon atom with a charge of +1, is placed in turn at each of these grid points. Three probes in common use are a proton (H^+), a methyl carbonium ion ($^+CH_3$) and water (H_2O). H^+ is used for electrostatic, $^+CH_3$ for steric and H_2O for hydrophobic interactions.

The next stage of the analysis is to align the other molecules of the training set in the lattice and measure their steric and electrostatic field. Aligning the pharmacophore of the set molecules with that of reference molecule usually gives good analysis results.

Similarly, an alignment based on matching the positions of the common sections of the structure of the set molecules, such as steroidal ring system, gives good analysis results. The data from all the calculations are converted into a QSAR equation using statistical methods.

A series of 3', 4', 5'trimethoxy chalcone derivatives which were reported [1] are chosen for QSAR study in order to establish a quantitative relationship between physiochemical properties and biological activities of the compounds using MDS software (Vlife Science) [VLife software 2017].

2. MATERIALS AND METHODS:

All molecular modeling studies (2D and 3D) were performed using the Molecular Design Suite (VLife MDS software package, version 4.6; from VLife Sciences, Pune, India), on a Dell computer with a Core I -3processor and a Windows 7 operating system. Structures were sketched using the 2D draw application and converted to 3D structures (Fig.1, Table 1).

2.1 BIOLOGICAL DATA

The inhibitors of nitric oxide production and tumor cell proliferation were taken from the reported work [Rao et al 2009]. The total set of compounds were divided into a training set for generating 2D and 3D QSAR models and a test set for validating the quality of the models. Selection of the training set and test set molecules was done based on structural diversity and a wide range of activity such that the test-set molecules represent a range of biological activity similar to that of the training set; thus, the test set is truly representative of the training set. The biological activity values [IC_{50} (µM)] reported in micro molar units were converted to their negative logarithmic scale and subsequently used as the dependent variable for the QSAR analysis. The values of IC_{50} along with the structure of the compounds in the series are listed in Table 1

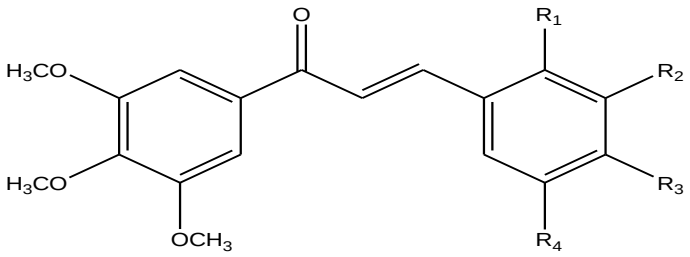


Fig. 1 Parent 3', 4', 5' tri-methoxy chalcone

Table 1-Structures of 3', 4', 5'trimethoxy chalcone derivatives with activity

Compound	R_1	R_2	R_3	R_4	Activity			
					NO*	Log_NO	HEG G2**	Log_HEG G2
1	OMe	OMe	H	H	2.4 ± 0.3	0.3802	11.5 ± 1.4	1.0413
2	H	OMe	OMe	H	4.5 ± 0.5	0.6532	20.3 ± 1.9	1.3074
3	H	OMe	OMe	OMe	2.8 ± 0.2	0.4471	19.6 ± 2.1	1.2922
4	H	H	$N(CH_3)_2$	H	27.0 ± 4.0	1.4313	30.0 ± 3.8	1.4771
5	OMe	H	OMe	OMe	4.6 ± 1.1	0.6627	16.1 ± 2.9	1.2068
6	H	H	OH	H	5.0 ± 0.7	0.6989	16.0 ± 1.8	1.2041
7	H	OMe	OH	H	0.3 ± 0.1	-0.5228	>100	2
8	OMe	H	OMe	H	>50	1.6989	>100	2
9	OH	H	H	OH	>50	1.6989	>100	2
10	OH	OMe	H	H	3.0 ± 0.2	0.4771	13.5 ± 0.8	1.1303
11	H	OH	OH	H	1.5 ± 0.4	0.176	14.9 ± 2.1	1.1731
12	H	OH	H	H	13.5 ± 1.2	1.1303	94.0 ± 4.6	1.9731
13	H	H	OMe	H	7.6 ± 1.9	0.8808	49.5 ± 3.6	1.6946
14	H	OH	OMe	H	1.3 ± 0.3	0.1139	10.6 ± 1.3	1.0253
15	H	OMe	H	H	0.3 ± 0.1	-0.1549	1.8 ± 0.3	0.2552
16	H	H	F	H	17.6 ± 3.6	1.2455	22.0 ± 2.5	1.3424
17	H	H	Br	H	20.0 ± 4.1	1.301	80.0 ± 4.9	1.903
18	H	H	NO_2	H	30.0 ± 4.5	1.4771	>100	2
19	H	H	Me	H	4.5 ± 1.2	0.6532	52.0 ± 4.1	1.7168
20	OH	H	H	NO_2	4.4 ± 0.7	-0.1914	>100	2
21	CHO	H	H	H	27.0 ± 2.5	1.4313	>100	2
22	H	CHO	H	H	>50	1.6989	>100	2
23	H	H	H	CHO	>50	1.6989	>100	2

* Inhibition of Nitric oxide production (Anti-inflammatory activity)

** Human cancer cell lines Hep G2 (human hepatoma cancer cell line), antitumor activity

Regression analysis method for model building. The result of MLR analysis using random data selection and manual data selection methods is shown is shown in Table 2 and 3 respectively for all two activities.

2.2 MOLECULAR MODELING FOR 2D QSAR:

In 2D QSAR analysis, significant methods Multiple linear regression, principal component regression and partial least square were applied to generate the 2D-QSAR model. The 2D structures were converted to 3D structures by sending them to MDS software. Each compound was energy minimized and batch optimized by using Merck Molecular Force Field and charges followed by Austin Model-1. The Hamiltonian method was available in MOPAC module with the convergence criterion 0.001 kcal/mol A˚ fixing Root Mean Square Gradients (RMS) to 0.001 kcal/mol A˚. 2D descriptors (physicochemical and alignment independent) were calculated for the optimized compounds on QSAR plus work sheet. The invariable descriptors (the descriptors that are constant for all the molecules) were removed, as they do not contribute to QSAR. Most stable structure for each compound was generated after energy minimization and used for calculating various physicochemical descriptors like thermodynamic, steric and electronic. The energy-minimized geometry was used for the calculation of the various 2D descriptors (Individual, Chi, ChiV, Path count, Chi Chain, ChiV Chain, Chain path count, Cluster, Path cluster, Kappa, Element Count, Estate number, Estate contribution, Semi-empirical, Hydrophilic– hydrophobic, Polar surface area and Alignment independent) and was considered as independent variables in the present study.

QSAR analysis was performed after removal of all the invariable columns, as they do not contribute to the QSAR. The optimal test and training data set were generated using the manual as well as the random data selection method. Sphere exclusion method was also adopted for a division of training and test set. Sphere exclusion method is used for creating training and test set from the data. This is a rational selection method which takes into consideration both biological and chemical space for a division of data set. Dissimilarity value provides handle to vary train/test set size. It needs to be adjusted by trial and error until the desired division of training and test set is achieved. As a rule, the increase in dissimilarity value will lead to increase in a number of molecules in the test set. All 23 molecules were subjected to regression analysis using multiple linear regression analysis, as model building methods coupled with stepwise forward backward variable selection method. Regression analysis was carried out for a treatment of drug abuse disorders and the best model was cross

validated. Best two-dimensional QSAR results obtained by multiple linear regression analysis, Partial Least Squares and Principal Component Regression are obtained shown in Table 2, and 3 respectively.

2.3 MOLECULAR MODELING FOR 3D QSAR

In 3D QSAR All molecules were aligned by using a template based method and aligned molecules were used for 3D QSAR taking consideration on RMS gradient between 0.1 to 0.5. The significant method was used like kNN (nearest neighbor) [Ajmani et al 2006] and neural network methods both methods were combined with the stepwise variable selection forward backward method taking consideration of data in 70:30 ratio of training and test set. The subjected molecules were used for 3D QSAR the Steric and electrostatic parameters used with distance dependent function with the charge of Ga Steiger Marsili of constant 1 and cut offs of electrostatic 10kcal/mole and steric 30kcal/mole was used. Grid selection for those molecules is in table 2

Table 2: Grid Settings for 3', 4', 5' tri-methoxy chalcone derivatives

Axis	From	To	Interval
X	-3.28639	21.0112	2.000
Y	-0.74935	16.4874	2.000
Z	-6.17787	5.7555	2.000

Development and validation of QSAR Models were generated by using significant statistical methods, namely, multiple linear regression (MLR) and kNN-MFA method. The following statistical parameters were considered to compare the generated QSAR models: correlation coefficient (r), squared correlation coefficient (r^2) i.e. q^2, predicted r^2 (pred_r^2), and Fischer's value (F) [Boltan S 2009]

The leave-one-out (LOO) method indicated the value of q^2 (cross-validated explained variance), which is a measure of the internal predictive ability of the model and pred_r^2 which is a measure of the external predictive ability of the model.[Kubinyl H 1994].

3. RESULTS AND DISCUSSION

Table 3: Results of MLR analysis using random data selection method for NO inhibition activity of 3', 4', 5'trimethoxy chalcone derivatives

Sr.no.	r^2	q^2	r^2se	q^2se	F test	Predr^2	Predr^{2}se	n	DOF
1	**0.8145**	**0.5130**	**0.2405**	**0.3897**	**14.63**	**0.3798**	**0.7594**	**14**	**10**
2	0.8214	0.5318	0.2649	0.4289	15.33	0.3225	0.7394	14	10
3	0.8594	0.6749	0.2195	0.3338	20.3821	0.2348	0.8142	14	10

The selection of the best model is based on the values of r^2 (squared correlation coefficient), q^2 (cross-validated correlation coefficient), pred_r^2 (predicted correlation coefficient for the external test set), F (Fisher ratio) value. High values of the F-test indicated that the model was statistically significant. r^2se, q^2se, and pred_r^2se are the standard errors terms for r^2, q^2 and pred_r^2 respectively. The statistically significant 2D-QSAR model is shown as follows.

3.1 Interpretation of the model -1for NO inhibition

Model-(Test set:15, 18, 19, 06, 07, 20 and 22)

***p*IC$_{50}$ (column)** = 1.3490 (SdsCHE-index) +0.7155 (SsFcount)+0.5113 (SsssCount) -3.5528

Statistics:

[n= 14; Degree of freedom= 10; r^2 =0.8145; q^2=0.5130; F test=14.6325; r^2se=0.2405; q^2se= 0.3897; pred_r^2= 0.3798; pred_r^2se = 0.7594]

From the equation, model 1 explains 81.45% (r^2 = 0.8145) of the total variance in the training set as well as it has internal (q^2) and external (pred_r^2) predictive ability of 51.30 % and 37.98 % respectively. The F test shows the statistical significance of 99.99 % of the model which means that probability of failure of the model is 1 in 10000. In addition, the randomization test shows the confidence of 99.9999 (Alpha Rand Pred R^2 = 0.00000) that

the generated model is not random and hence chosen as the QSAR model. The F-test=14.63 which is greater than the tabulated value 1.54 (2). From QSAR model 1 indicated,

1. The positive coefficient value of SdsCHE-index [Electropological state indices for a number of CH group connected with one double and one single bond.] on the biological activity indicated that higher values lead to good inhibitory activity while lower value leads to reduced inhibitory activity.

2. The positive coefficient value of SsFcount[This the total number of Fluorine atom connected with one single bond] on the inhibitory activity indicated that higher value leads to better inhibitory activity whereas lower value leads to decrease inhibitory activity.

3. The positive coefficient value of Sssscount [this is the total number of sulfur atom connected with two single bonds.] on the inhibitory activity indicated that higher value leads to better inhibitory activity whereas lower value leads to decrease inhibitory activity.

Contribution chart Data fitness plot and activity of training and test set for model 1 is represented in Fig. 2, 3, 4, and 5 respectively

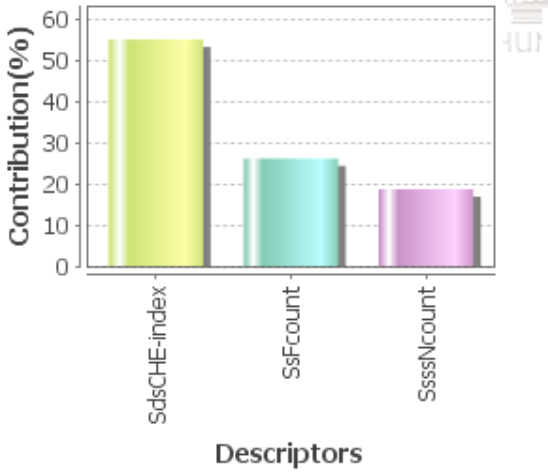


Fig. 2 Contribution Plot

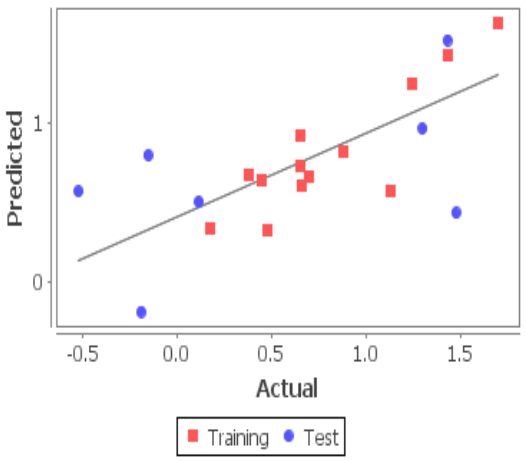


Fig. 3 Fitness plot

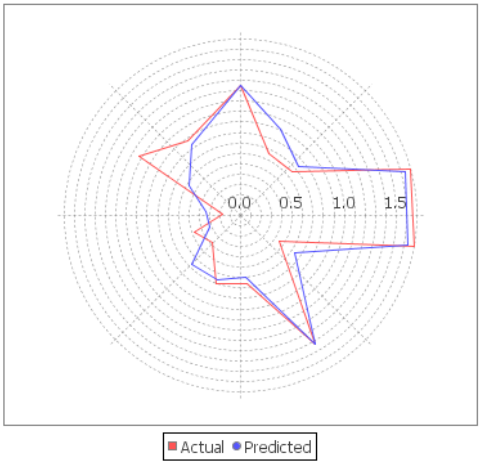


Fig. 4 Training set

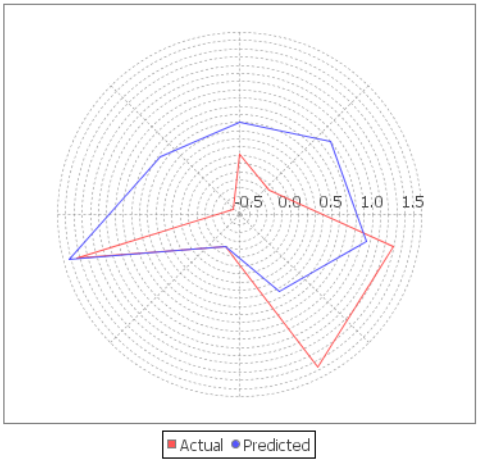


Fig. 5 Test set

Table 4: Results of MLR analysis using random data selection method for HEPG2 cell inhibition activity 3', 4', 5'trimethoxy chalcone derivatives

Sr. no.	r^2	q^2	r^2se	q^2se	F test	$Predr^2$	$Predr^2se$	n	DOF
1	**o.7207**	**0.5227**	**0.3517**	**0.4597**	**1.2903**	**0.7665**	**0.1724**	**16**	**5**
2	0.7628	0.5681	0.3422	0.4617	0.9648	0.22246	0.7485	14	10
3	0.8520	0/5484	0.2079	0.3631	2.8774	0.1624	1.0097	14	10

3.2 Interpretation of the model -1 for HEPG2 Cell Inhibition

(Test set: 3, 6, 8, 13, 14, 15 and 23)

***p*IC$_{50}$ (column)** =) + 0.2682(T_2_C_6) +0.9756 (Psi-1) -0.3302 (T_C_C_7) +1.8202 (DeltaEpsilinB) +0.1223(SaasCE-index)+0.1259(T_T_O_5) – 0.2192(T_O_O_3) - 0.2688(T_T_F_7) – 0.0789 (T_2_T_5) – 0.0709 (Chi4)0.004

Statistics: [n= 16; Degree of freedom=5 r^2 = 0.7207; q^2=0.5227 F test=1.2903; r^2se=0.3517; q^2se = 0.4597; pred_r^2= 0.7665; pred_r^2se = 0.1724

From equation, model 1 explains 72.07% (r^2 = 0.7207) of the total variance in the training set as well as it has internal (q^2) and external (pred_r^2) predictive ability of 52.27 % and 76.65 % respectively. The F test shows the statistical significance of 99.99 % of the model that means that probability of failure of the model is 1 in 10000. In addition, the randomization test

shows confidence of 99.9999 (Alpha Rand Pred R^2 = 0.00000) that the generated model is not random and hence chosen as the QSAR model. The F-test=1.2903 which is greater than the tabulated value 1.12195. From QSAR model 1,

1. Positive value of T_2_C_6 [This is any single or double bond separated from carbon atom by six bond] on the inhibitory activity indicated that higher value leads to better inhibitory activity whereas lower value leads to decrease inhibitory activity.

2. The positive coefficient value of Psi1 [Kubinyl H 1994] [This is a measure of hydrogen bonding propensity of the molecule and or polar surface area.] on the inhibitory activity indicated that higher value leads to better inhibitory activity whereas lower value leads to decrease inhibitory activity.

3. The negative coefficient value of T_C_C_7 [This is the count of a number of any single or double bonded carbon separated by other carbon by seven bonds] on the inhibitory activity indicated that lower value leads to better inhibitory activity whereas higher value leads to decrease inhibitory activity.

4. The positive coefficient value of DeltaEpsionB [Roy et al 2011] [A measure of the contribution of unsaturation.]On the biological activity indicated that higher values lead to good inhibitory activity while lower value leads to reduced inhibitory activity.

5. Positive coefficient value of SaasCEindex [Electropological state indices for number of carbon atom connected with one single bond along with two aromatic bonds.]On the biological activity indicated that higher values lead to good inhibitory activity while lower value leads to reduced inhibitory activity

6. The positive coefficient value of T_T_O_5 [count of a number of oxygen atom separated from any double or single bond by five bonds.]On the biological activity indicated that higher values lead to good inhibitory activity while lower value leads to reduced inhibitory activity.

7. The negative coefficient value of T_O_O_3 [This is the count of a number of the oxygen atom (single double or triple)separated from any other oxygen atoms by three bonds] on the inhibitory activity indicated that lower value leads to better inhibitory activity whereas higher value leads to decrease inhibitory activity.

8. The negative coefficient value of T_T_F_7 [This is the count of a number of any single or double or triple bonded fluorine atom separated by seven bonds] on the inhibitory activity indicated that lower value leads to better inhibitory activity whereas higher value leads to decrease inhibitory activity.

9. The negative coefficient value of T_2_T_S [This is the count of a number of any single double or triple bond separated from the sulphur atom by two bonds] on the inhibitory activity indicated that lower value leads to better inhibitory activity whereas higher value leads to decrease inhibitory activity.

10. The negative coefficient value of Chi4 [Hall et al 1991,1995] [This is the retention index (fourth order) derived directly from gradient retention time] on the inhibitory activity indicated that lower value leads to better inhibitory activity whereas higher value leads to decrease inhibitory activity.

Contribution chart Data fitness plot and activity of training and test set for model 4 is represented in Fig. 6, 7, 8, and 9 respectively.

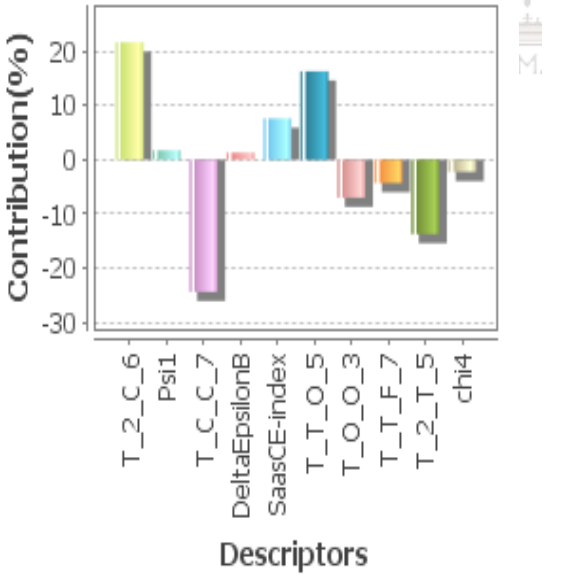


Fig. 6 Contribution Plot

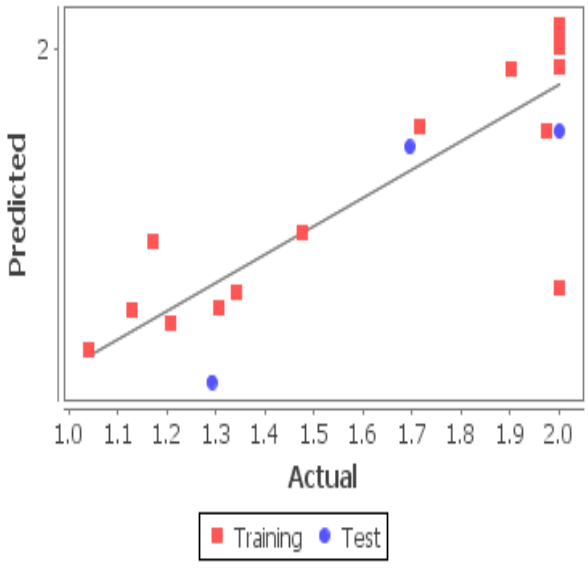


Fig. 7 Fitness plot

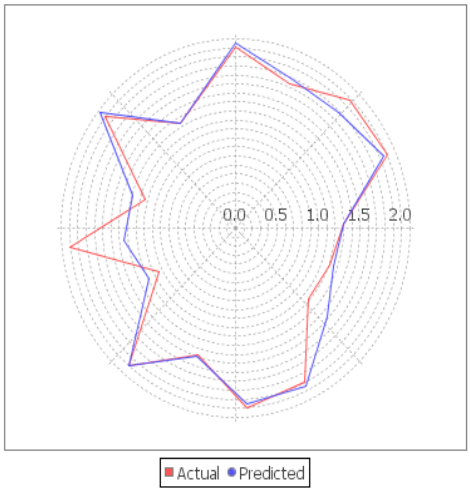


Fig. 8 Training Set

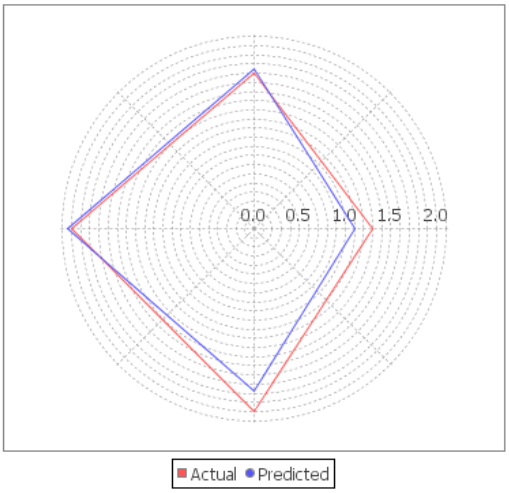


Fig.9 Test Set

3.3 3D QSAR for 3', 4', 5' tri-methoxy chalcone derivatives

kNN-MFA samples the steric and electrostatic fields surrounding a set of ligands and constructs 3D-QSAR models by correlating these 3D fields with the corresponding biological activities. Molecular alignment was used to visualize the structural diversity in the given set of molecules. The template structure i.e. 3', 4', 5'trimethoxy chalcone derivatives were used for alignment by considering the common elements of the series as shown in Fig. 10 and 11.

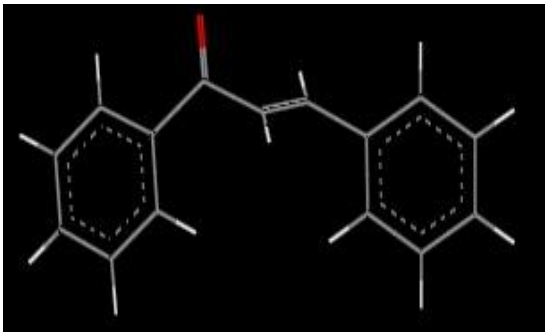


Fig. 10 Template molecule

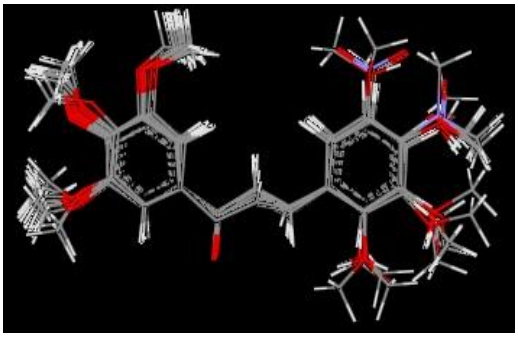


Fig. 11 Stereo view of aligned molecules

3.4 3D QSAR for NO inhibition

Table 5: Statistical evaluation of 3D-QSAR models of 3', 4', 5'trimethoxy chalcone derivatives

Trials	kNN	DOF	q^2	q^2_se	pred_r^2	pred_r^2se
1(Model-1)	**2**	**14**	**0.6176**	**0.4208**	**0.5055**	**0.5521**
2(Model-2)	2	14	0.7389	0.3175	0.3023	0.7122
3(Model-3)	2	14	0.7898	0.2805	0.4457	0.6686

Model-1(Test set:10, 13, 17, 22, 23, 6 and 8)

***p*IC$_{50}$**= E_75 -0.2677-0.2510

Statistics: [kNN= 2; n = 16; DOF= 14; q^2= 0.6176; q^2_se = 0.4208; pred_r^2 = 0.5055; pred_r^2se = 0.5521]

The model 1 explains values of k (2), q^2 (0.6176), pred_r^2 (0.5055), q^2_se (0.4208), and pred_r^2 se (0.5528) prove that QSAR equation so obtained is statistically significant and shows the predictive power of the model is 61.76% (internal validation). **Table 7** represents the predicted inhibitory activity by the model-1 for training and test set.

The data fitness plot for model 1 is shown in Fig.12. The plot of observed vs. predicted activity Fig. 13 provides an idea about how well the model was trained and how well it predicts the activity of the external test set.

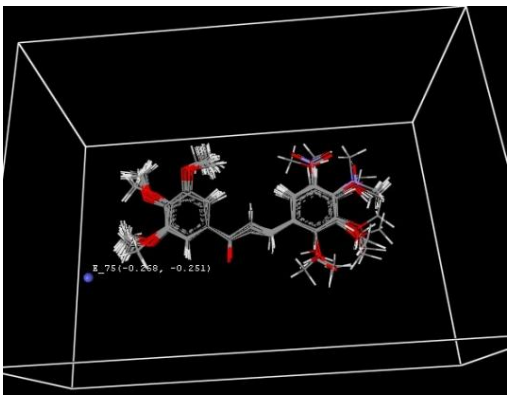


Fig. 12 Plot of contribution chart

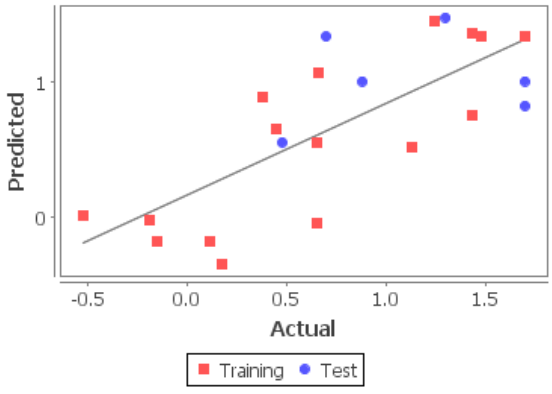
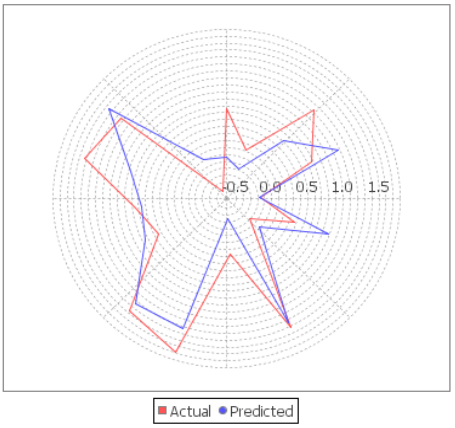


Fig. 13 Data fitness plot



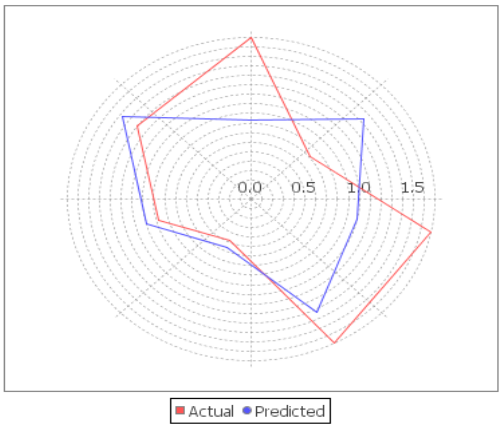


Fig. 14 Training Set

Fig. 15 Test Set

Electrostatic field, E_75 (-0.2677-0.2510) negative Electrostatic potential is favorable for increase in the activity and hence less bulky substituent group is preferred in that region.

3.5 3D QSAR for HEPG2 cell line

Table 6: Statistical evaluation of 3D-QSAR models of 3', 4', 5'trimethoxy chalcone derivatives

Trials	kNN	DOF	q^2	q^2_se	pred_r^2	pred_r^2se
1(Model-4)	**2**	**13**	**0.7761**	**0.1895**	**0.4292**	**0.4899**
2(Model-5)	2	12	0.9266	0.0999	0.3381	0.6031
3(Model-6)	2	13	0.8510	0.1416	0.2279	0.6118

Interpretation of Model-4 (Test set: 13, 15, 18, 3, 6, 8 and 9)

***p*IC$_{50}$**= E_276 (-0.5054-0.4937) S_153 (-0.3058-0.3009)

Statistics: [kNN= 2; n = 16; DOF= 13; q^2= 0.7761; q^2_se = 0.1895; pred_r^2 = 0.4292; pred_r^2se = 04899]

The model 4 explains values of k (2), q^2 (0.7761), pred_r^2 (0.4292), q^2_se (0.1895), and pred_r^2 se (0.4899) prove that QSAR equation so obtained is statistically significant and shows the predictive power of the model is 77.61% (internal validation). **Table 7** represents the predicted inhibitory activity by the model-1 for training and test set.

The data fitness plot for model 4 is shown in Fig.16. The plot of observed vs. predicted activity Fig.17 provides an idea about how well the model was trained and how well it predicts the activity of the external test set.

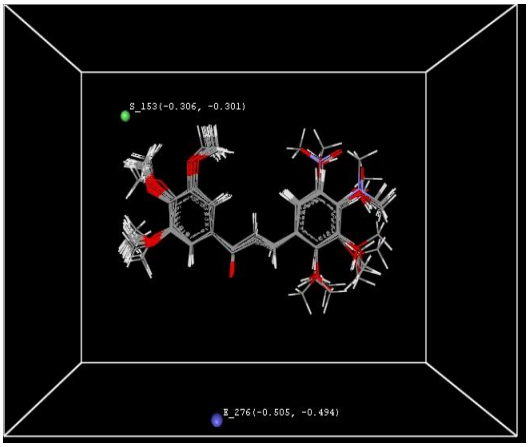


Fig. 16 The plot of contribution chart

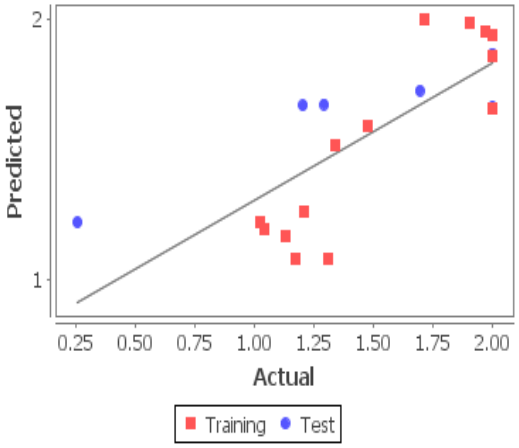


Fig. 17 Data fitness plot

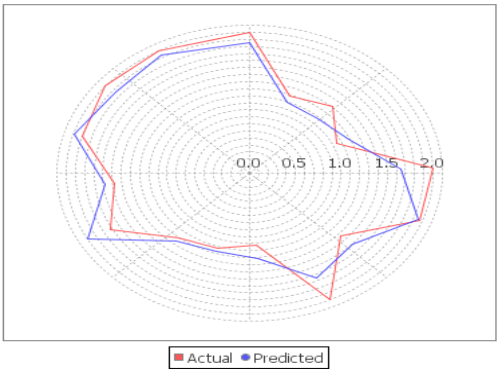


Fig. 18 Training Set

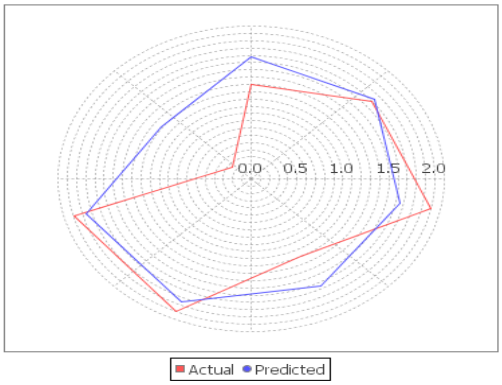


Fig. 19 Test Set

Electrostatic field, E_276 (-0.5054-0.4937) negative electrostatic potential is favorable for the increase in the activity and hence less bulky substituent group is preferred in that region.

Steric field, S_153 (-0.3058-0.3009) negative Steric potential is favorable for the increase in the activity and hence less bulky substituent group is preferred in that region.

Table 7: Actual vs. predicted activity of 3', 4', 5'trimethoxy chalcone derivatives

Molecule	Actual NO-activity	Actual HEP G2 activity	2D NO pre_Activity	2D HEPG pre_Activity	3D NO pre_Activity	3D HEP G2 pre_Activity
1	0.3802	1.0413	0.669165	1.185497	0.754674	1.102264
2	0.6532	1.3074	0.731477	1.303158	0.550215	1.219445
3	0.4471	1.2922	0.640423	1.101029	0.550085	1.671925
4	1.4313	1.4771	1.431311	1.505248	1.008078	1.377529
5	0.6627	1.2068	0.60214	1.25944	1.157399	1.306371
6	0.6989	1.2041	0.66003	1.815417	1.337899	1.667547
7	-0.5228	2	0.568976	1.353669	-0.173674	1.865887
8	1.6989	2	0.693194	1.779079	1.008078	1.864158
9	1.6989	2	0.094924	1.955393	1.479763	1.861189
10	0.4771	1.1303	0.323496	1.294317	0.557315	1.218255
11	0.176	1.1731	0.340404	1.4793	-0.173126	1.152719
12	1.1303	1.9731	0.569929	1.783143	0.755826	1.93906
13	0.8808	1.6946	0.822531	1.736962	1.008078	1.724202
14	0.1139	1.0253	0.502905	1.417216	-0.03778	1.163724
15	-0.1549	0.2552	0.798501	1.641283	-0.338231	1.218574
16	1.2455	1.3424	1.245509	1.341263	1.337899	1.654165
17	1.301	1.903	0.968782	1.946477	1.478634	1.950212
18	1.4771	2	0.433963	2.068976	1.454673	1.661663
19	0.6532	1.7168	0.920032	1.794678	0.391964	1.850914
20	-0.1914	2	-0.189365	2.005639	-0.03972	1.952788
21	1.4313	2	1.526989	1.951949	1.338901	2
22	1.6989	2	1.638899	2.044364	1.338563	1.866658
23	1.6989	2	1.638899	2.044364	0.827454	2

3.6 Design and activity prediction of newer derivatives

From the best models obtained, some newer compounds were designed which had the better activity than the reported one. The structures were not reported earlier anywhere is confirmed by ChemSpider.

4. CONCLUSIONS:

In the present investigation, all proposed QSAR models were statistically significant, thus, from above QSAR investigations, it could be concluded that 2D/3D descriptors properties of substituted 3', 4', 5'trimethoxy chalcone derivatives are mainly involved in the treatment of drug abuse disorders. The good correlation between experimental and predicted biological activity for compounds in the test set further highlights the reliability of the constructed QSAR model. The requirements for the more potent biological activity are explored with 2D, 3D, and group based QSAR studies. The 2D technique indicates the importance of SdsCHE-index, SsFcount, Sssscount for inhibition of Nitric oxide production and T_2_C_6, Psi-1, T_C_C_7, DeltaEpsilinB, SaasCE-index, T_T_O_5, T_O_O_3, T_T_F_7, T_2_T_5, Chi4 for Tumor cell proliferation activity of the compounds. The 3D QSAR analysis makes it possible to relate chemical structures of ligands and their binding affinity with respect to different bio targets by using the kNN-MFA techniques. Thus it provides a direct view of factors expressed in terms of molecular fields (electrostatic, steric) affecting the binding affinity. This, in turn, could give the reasonably good prediction of binding affinity. The location and range of function values at the field points selected by the models provide clues for the design of new molecules. Hence, this method is expected to provide a good alternative for the drug design.

The 3D-QSAR model showed that electrostatic effects dominantly determine the binding affinities for inhibition of Nitric oxide production, Steric and Electrostatic effect dominantly determined the binding affinities for Tumor cell proliferation these QSAR models developed in this study would be useful for the development of new drugs as a medicament for the NO inhibition and tumor cell proliferation The 2D-QSAR studies revealed that SdsCHE index and Psi-1 were the major contributing descriptors for both the activities respectively. The descriptor values obtained in this study helped in the quantification of the structural features of 3', 4', 5'trimethoxy chalcone derivatives.

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