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Der Pharma Chemica, 2015, 7(4):270-277
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Predicting the drug abuse activity of some novel 4-alkoxycarbonyl-1, 5-diaryl-1, 2, 3-triazoles on CB1 cannabinoid receptor using 2D and 3D-QSAR (kNN-MFA) analysis

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ABSTRACT

Two dimensional quantitative structure activity relationship (2D-QSAR) and three dimensional quantitative structure activity relationship (3D-QSAR) studies by means of Multiple Linear Regression (MLR), Partial Least Square (PLS) and Principal Component Regression (PCR) were performed on a series of 4-Alkoxycarbonyl-1, 5-diaryl-1, 2, 3-triazole analogues for the treatment of drug abuse disorder using software MDS 4.2 version (VLife Science). This study was performed with 13 compounds (Data set) using random as well as manual data selection methods for the division of the data into training and test set. MLR methodology with stepwise (SW) forward-backward variable selection method was used for building the QSAR models. Statistically significant QSAR models were generated. Among them most significant model has squared correlation coefficient (r^2) = 0.9895, cross validated correlation coefficient (q^2) = 0.9747 and predictive correlation coefficient (pred_r^2) = 0.9826 for the treatment of drug abuse disorders. The core idea of the present study is the search for novel 4-Alkoxycarbonyl-1, 5-diaryl-1, 2, 3-triazole analogues that would show promise to be useful in the treatment of drug abuse disorders.

Keywords: CB1 cannabinoid receptor, 4-Alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles , 2D QSAR, 3D kNN-MFA, VLife MDS

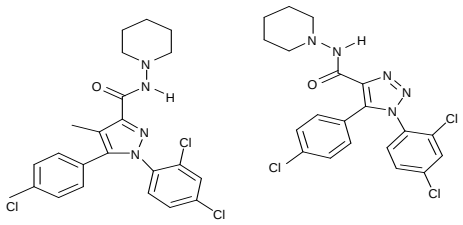
INTRODUCTION

The wide range of pharmacological effects of cannabinoid and endogenous cannabinoid ligands, are mediated by two subtypes of transmembrane G-protein coupled receptors: CB1 and CB2 [1-4]. CB1 receptors are high density in the cerebellum, hippocampus and striatum. [5] CB2 receptors are very low concentration in the CNS.[6] The role of CB1 receptors in these disease states and disorders, the nature of the receptors active sites, and the molecular interactions between the receptors and ligands are not fully understood and are under intensive investigation[7-8].CB1 receptor antagonists or inverse agonists have the ability to attenuate the elevation of dopamine levels that occurs with psycho-stimulant use, suggesting their potential applications in the treatment of drug abuse disorders 10-12 [9-11].The pyrazole derivative SR141716 (**1**) was the first compound reported to be a potent and selective antagonist for the CB1 receptor.[12] Characterization of SR1411716 has shown it to possess an inverse agonist pharmacological profile.[13] This prototypical CB1 receptor antagonist/inverse agonist has been studied as a potential therapeutic for the treatment of obesity, smoking cessation and a variety of other CB1 receptor mediated pathological conditions.[14] Sensitivity, decreased food intake and body weight, disruption of operant behavior and potential nausea in humans.[15–19] Rimonabant (SR141716) strongly disfavors its development as a drug abuse

medication.[20] Based upon the structure of 1,5-diarylpyrazole core template in SR141716 (**1**), bioisosteric replacement has been an important approach to discover new lead compounds of potent CB1 ligands and a variety have been synthesized and identified as potent ligands. [14,21] In reviewing the literature, the absence of 1,2,3-triazole analogues were significant.The purpose of the present study is to investigate the Physico-chemical parameters responsible for the protective effect of 4-alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles derivatives as a drug abuse medication, explore the correlation between them and to obtain more information for designing novel substituted 4-alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles derivatives with potent protective activityA series of 4-alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles analogues which were reported[21] are chosen for QSAR study in order to establish quantitative relationship between physiochemical properties and biological activities of the compounds using MDS software (VlifeScience)[22].

MATERIALS AND METHODS

All molecular modeling studies (2D and 3D) were performed using the Molecular Design Suite (VLife MDS software package, version 3.5; from VLife Sciences, Pune, India), on a HP computer with a Pentium IV processor and a Windows 7 operating system. Structures were sketched using the 2D draw application and converted to 3D structures (Fig.1, Table 1).



(1) **(2)**

Fig. 1: Common Chemical structure of 4-alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles derivative

Table 1: Inhibition of [^{3}H] SR141716A at CB1 receptors

Comp. No.	Code	Activity	
		ClogP[b]	(nM)
1.	HS69	5.33	590 ± 170
2.	HS53-2	4.46	6900 ± 1300
3.	HS57-2	5.11	1420 ± 266
4.	HS53-1	4.68	4400 ± 760
5.	HS57-1	5.32	66 ± 7.0
6.	HS60	4.69	54%[d]
7.	HS57-3	5.68	180 ± 27
8.	HS57-4	6.21	4.6 ± 0.012
9.	HS57-5	6.70	NA[e]
10.	HS57-6	7.62	NA[e]
11.	HS57-8	6.83	11 ± 3.4
12.	HS57-9	6.85	97 ± 55
13.	HS57-7	7.23	240 ± 79

[a] All compounds were tested as the freebase.[b] See Reference 25.
[c] All values are the mean ±SEM of three experiments performed in triplicate.[d] Percent inhibition at 100µM.[e] NA, not available.
The values of IC_{50} along with the structure of the compounds in the series are listed in Table 1.

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. The optimal test and training data set were generated using the manual as well as random data selection method. Sphere exclusion method was also adopted for division of training and test set.

Table 2a: Multiple linear regression analysis (using Random selection method)

Model No. Parameters	I	II	**III**	IV
Test set	1,2,5,13	10,4,7,8	**11,13,3,9**	13,3,4,8
N	9	9	**9**	9
DOF	5	6	**6**	7
r^2	0.9917	0.9995	**0.9871**	0.9670
q^2	0.9696	0.9988	**0.9558**	0.9459
F-test	199.7050	6160.0070	**230.300**	204.86
r^2se	0.1214	0.027	**0.1398**	0.2128
q^2se	0.2328	0.0429	**0.2591**	0.2723
pred_r^2	0.9976	0.9608	**0.9942**	0.9261
pred_r^2se	0.0628	0.2475	**0.1011**	0.3146

THREE DIMENSIONAL (3-D) QSAR STUDIES:

In the kNN-MFA method three models were generated for the selected members of training and test sets, and the corresponding best two models are reported herein.

Molecular alignment:

Molecular alignment was used to visualize the structural diversity in the given set of molecules.

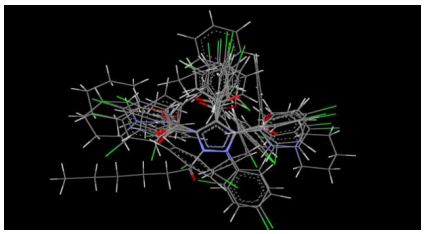


Fig. 2: 3D view of aligned molecules by Atom based type of method of alignment

Table 3: Best results three dimensional (3D) QSAR results obtained by kNN-MFA method

Model No. Parameters	XIII	XIV	XV
kNN-MFA method	**Stepwise Forward Backward (SWFB)**	**Simulated Annealing (SA)**	**Genetic Algorithm (GA)**
Test set	11,13,3,9	13,3,4,8	11,12,6,7
kNN	2	2	3
N	9	9	9
DOF	7	4	5
q^2	0.7063	0.6349	0.1414
q^2se	0.5788	0.6618	1.0508
pred_r^2	-1.4133	-0.9634	-2.6121
pred_r^2se	2.0629	1.6212	2.0034
Descriptors	E_592	E_1100, E_1179, S_1157, E_892	S_910, S_323, E_528

Development and validation of QSAR models: The cross-validation analysis was performed using the leave-one-out method. The following statistical parameters were considered to compare the generated QSAR models: correlation coefficient (r), squared correlation coefficient (r^2), predicted r^2 (pred_r^2), and Fischer's value (F) [24]. To validate the generated QSAR models, the leave-one-out (LOO) method was used, indicated as the value of q2 (cross-validated explained variance), which is a measure of the internal predictive ability of the model. The robustness of the QSAR models for experimental training sets was examined by comparing these models to those derived for random data sets.

RESULTS AND DISCUSSION

All the calculated descriptors were considered as independent variable and biological activity as dependent variable. In 2D QSAR analysis, significant methods like Multiple linear regression analysis, Partial Least Square (PLS) and Principal Component Regression (PCR) were applied to generate the model having good q^2 and pred_r^2 values, one of which was selected having good internal and external predictivity. This result shows that the test is interpolative i.e., derived from the min-max range of training set. The mean and standard deviation of the training and test set provides insight to the relative difference of mean and point density distribution of the two sets The QSAR models developed by kNN-MFA include both the electrostatic, steric descriptors along with their range to indicate their importance for interaction in molecular field. Models 5, 6 and 7 are with 3D QSAR studies. QSAR investigations of the substituted 4-alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles derivatives series resulted in several QSAR equations. Some statistically significant 2D and 3D QSAR models were chosen for discussion

2D-QSAR model:

Model III:By Random data selection method;

$_{50}$ = 1.1144(±0.0582) XlogP + 0.1834(±0.0541) SsCH$_3$E-Index – 0.5761n = 9, Degree of freedom = 6, r^2 = 0.9871, q^2 = 0.9558, F test = 230.300, r^2 se = 0.1398, q^2 se = 0.2591, pred_r^2 = 0.9942, pred_r^2 se = 0.1011

Among all the significant models the above is the best model generated for anti drug abuse disorders. The equation explains 98.71% (r^2 = 0.9871) of the total variance in the training set and has an internal (q^2) and external (pred_r^2) predictive ability of ~95.58% and ~99.42% respectively.

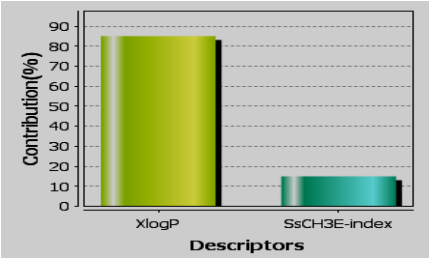


Fig. 3a: Contribution plot of 2D-QSAR Model III

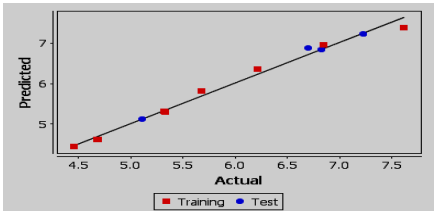


Fig. 3b: Graph of actual activity versus predicted activity Model II

Model VIII:By Manual data selection method;$_{50}$ = 1.1627(±0.0506) XlogP + 0.3031(±0.0908) SsCH$_3$count – 0.8332

n = 9, Degree of freedom = 6, r^2 = 0.9895, q^2 = 0.9747, F test = 281.5701, r^2 se = 0.1345, q^2 se = 0.2082, pred_r^2 = 0.9826, pred_r^2 se = 0.1390

Among all the significant models the above are the best models generated for anti drug abuse disorders. The equation explains 98.95% (r^2 = 0.9895) of the total variance in the training set and has an internal (q^2) and external (pred_r^2) predictive ability of ~97% and ~98% respectively.

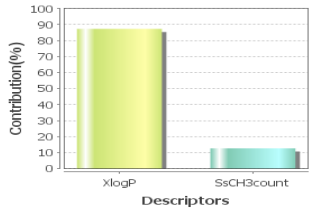


Fig. 4a: Contribution plot of 2D-QSAR Model VIII

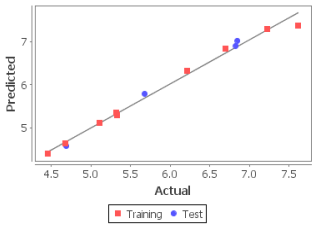


Fig. 4b: Graph of actual activity versus predicted activity Model VIII

Model XI:By partial least square method;

$_{50}$ = 1.1847 XlogP – 0.7883n = 9, Degree of freedom = 7, r^2 = 0.9700, q^2 = 0.9382, F test = 226.0004, r^2 se = 0.2107, q^2 se = 0.3014, pred_r^2 = 0.9388, pred_r^2 se = 0.2607

Among all the significant models the above are the best models generated for anti drug abuse disorders. The equation explains 97% (r^2 = 0.9700) of the total variance in the training set and has an internal (q^2) and external (pred_r^2) predictive ability of ~93.82% and ~93.88% respectively. The F-test = 226.0004 which is far greater than the F-tabulated value = 3.2850.

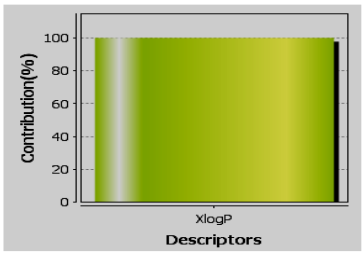


Fig. 5a: Contribution plot of 2D QSAR Model XI

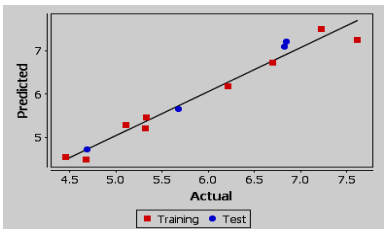


Fig. 5b: Graph of actual activity versus predicted activity Model XI

Model XII:By principal component regression method;

$_{50}$ = 1.1739 SlogP – 0.4720 n = 9, Degree of freedom = 7, r^2 = 0.9670, q^2 = 0.9459, F test = 204.86, r^2 se = 0.2128, q^2 se = 0.27, pred_r^2 = 0.9261, pred_r^2 se = 0.3146

Among all the significant models the above are the best models generated for anti drug abuse disorders. The equation explains 96.70% (r^2 = 0.9670) of the total variance in the training set and has an internal (q^2) and external (pred_r^2) predictive ability of ~94.59% and ~92.61% respectively

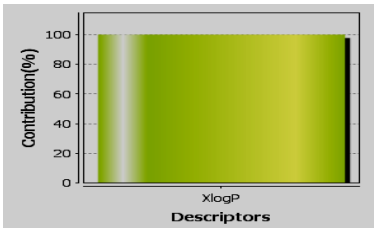


Fig. 6a: Contribution plot of 2D QSAR Model XII

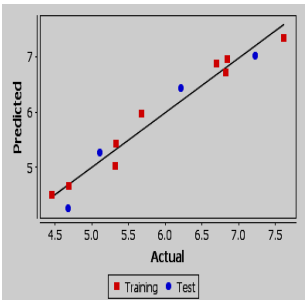


Fig. 6b: Graph of actual activity versus predicted activity Model XII

3D-QSAR model:Model XIII:By stepwise forward backward method;$_{50}$ = E_592 (-0.1075, -0.0342)N= 9, Degree of freedom = 7, q^2 = 0.7063, q ^{2}se = 0.5788, pred_r^2 =-1.4133, and pred_r^2 se = 2.0629 Values of it prove the equation statistically to be significant. It also shows the predictive power of the model as 70.63%. It showed steric and electrostatic field energy of interactions between probe (CH) and compounds at their corresponding spatial grid points of 592. Numbers nearest neighbor's k of 2 were observed with this model i.e. two values are proved statistically significant. It is observed from the Fig6 that the negative coefficient of E_592 suggested that electronegative substituent may be favorable on the position of triazole ring for better activity.

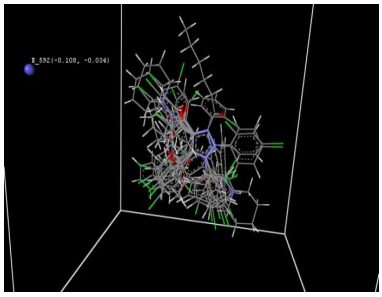


Fig. 7a: Contribution plot of 3D-QSAR Model XIII

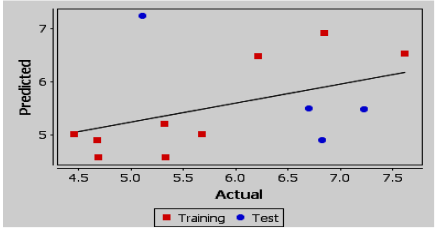


Fig. 7b: Graph of actual activity versus predicted activity Model XIII

Model XIV:By simulated annealing method;$_{50}$ = E_1100 (0.0243, 0.1525) + E_1179 (0.3555, 0.8597) + S_1157 (30.0000, 30.0000) – E_892 (-0.0378, 0.0799) N= 9, Degree of freedom = 4, q^2 = 0.6349, q ^{2}se = 0.6618, pred_r^2 =-0.9634, and pred_r^2 se = 1.6212 Values of it prove the equation statistically to be significant. It also shows the predictive power of the model as 63.49%. It showed steric and electrostatic field energy of interactions between

probe (CH) and compounds at their corresponding spatial grid points of 1100, 1179, 1157, and 892. Numbers nearest neighbor's k of 2 were observed with this model i.e. two values are proved statistically significant. It is observed from the Fig.6 that the positive coefficient of E_1100 and E_1179 suggested that electropositive substituent may be favorable on the position of triazole ring for better activity. Even the steric factor S_1157 is positive which indicates the favorability of bulky groups on the triazole ring to increase the activity. The negative coefficient of E_892 indicates the addition of electronegative atom also at the position is responsible for the increase in biological activity.

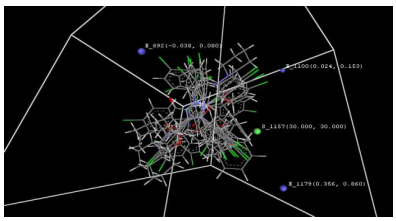


Fig. 8a: Contribution plot of 3D-QSAR Model XIV

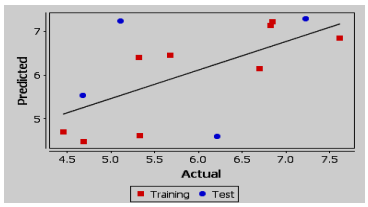


Fig. 8b: Graph of actual activity versus predicted activity Model XIV

Model XV:By genetic algorithm method;

$_{50}$ = - S_910 (-0.1861, -0.0416) – S_323 (-0.0298, -0.0027) + E_528 (0.1386, 2.0222) N= 9, Degree of freedom = 5, q^2 = 0.1414, q^2se = 1.0508, pred_r^2 =-2.6121 and pred_r^2 se = 2.003

Values of it prove the equation statistically to be significant. It also shows the predictive power of the model as 14.14%. It showed steric and electrostatic field energy of interactions between probe (CH) and compounds at their corresponding spatial grid points of 910, 323 and 528. While the positive coefficient of E_528 indicates the electropositive substitution is necessary for better biological activity.

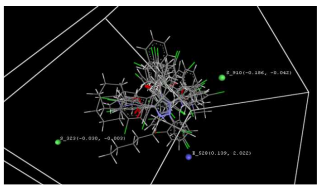


Fig. 9a: Contribution plot of 3D-QSAR Model XV

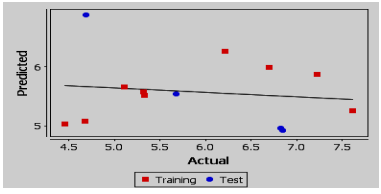


Fig. 9b: Graph of actual activity versus predicted activity Model XV

CONCLUSION

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 4-Alkoxycarbonyl-1, 5-diaryl-

1, 2, 3-triazoles derivatives are mainly involved in 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 descriptor values obtained in this study helped in quantification of the structural features of 4-alkoxycarbonyl-1, 5-diaryl-1, 2, 3-triazole derivative. I have designed 47 compounds among which 11 compounds are showing higher activity than the reported analogues.

Acknowledgment
The author wishes to express gratitude to V-life Science Technologies Pvt. Ltd. for providing the software for the study. Also the authors are thankful to the trustee Bhujbal Knowledge City for providing the necessary facilities to carry out the research work.

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