Research Article

Computational study of 2,3-disubstituted-4(3H)quinazolinone derivatives as CNS active compounds: QSAR approach

Rakesh Kumar Jain[a], Vaibhav Rajoriya[b], Varsha Kashaw[a]

[a]*SVN Institute of Pharmaceutical Sciences, SVN University, Sagar, Madhya Pradesh, India*

[b]*Department of Pharmaceutical Sciences, Dr. Hari Singh Gour University, Sagar, Madhya Pradesh, India*

Received: 26 June 2018 Revised: 25 July 2018 Accepted: 1 August 2018

Abstract

Objective: Quantitative structure activity relationship (QSAR) model for anticonvulsant activity was developed from a set of twenty seven, 2,3-disubstituted-4(3H)quinazolinone derivatives that exhibited remarkable inhibition by *in-vivo* locomotor activity in Swiss albino mice using phenytoin as model drug. **Material and methods:** The 2D-QSAR studies were carried out using the partial least squares (PLS) method coupled with stepwise variable selection, with r2 = 0.9949 and q2 = 0.9761; the 3D-QSAR studies were performed using stepwise variable selection k-nearest-neighbour molecular field analysis (kNN-MF) approach; with cross-validated correlation coefficient (q2) of 0.7818 and a predicted r2 for the external test (pred_r2) of 0.5904. **Results and conclusion:** Experimental results revealed that the alignment-independent descriptors, electrostatic and steric field descriptors were significantly correlated to anticonvulsant activity of 2,3-disubstituted-4(3H)quinazolinone derivatives. The results helped to understand the nature of substituent around quinazolinone nucleus, thereby providing new guidelines for the design of novel anticonvulsant drugs.

***Keywords*:** 2D-QSAR, 3D QSAR, anticonvulsant activity, 2,3-disubstituted-(3H)quinazolinone, PLS method, kNN-MFA method

Introduction

Convulsion or epilepsy is a common neurological disorder characterize by recurrent spontaneous seizures, is a major health problem that affects 0.5-1% the population and up to 50%. Convulsion is a medical condition where body muscles contract and relax rapidly and repeatedly, resulting in an uncontrolled shaking of the body. Although a convulsion is often a symptom of an epileptic seizure, the term convulsion is sometimes used as a synonym for seizure. Many effective antiepileptic drugs are available on the market and include phenobarbital, phenytoin, carbamazepine and valproic acid (Tripathi, 2013). Despite advances in technology and understanding of biological systems, drug discovery is still a lengthy, expensive, difficult and inefficient process with low rate of new therapeutic discovery (Anson et al., 2009). Currently, the research and development cost of each new molecular entity (NME) is approximately US$1.8 billion (Paul et al., 2010).

Quantitative structure–activity relationship models (QSAR models) are regression or classification models used in the chemical and biological sciences and engineering. Like other regression models, QSAR regression models establish a linear relationship between a set of molecular descriptors of chemicals and the biological activity of the chemical while classification QSAR models shows a non-linear relationship between a set of molecular descriptors of chemicals and the biological activity of the chemical (Pahwa and Papreja, 2014). QSAR studies can reduce the costly failures of drug candidates in clinical trials by In recent year's quantitative structure activity relationship studies (QSAR) have become an integral part of drug discovery processes. 2D and 3D-QSAR have focused on the development of procedure that allows selection of optimal variables from the pool of descriptors of chemical structures i.e. ones that are most meaningful and statistically significant in terms of correlation with biological activity, filtering the combinatorial libraries (Sethi, 2012). In continuation of the research of molecular modelling, here in this article we report the 2D and 3D QSAR analysis of indole/benzoximidazole-5-

Address for Corresponding Author:
Dr. (Mrs.) Varsha Kashaw
Prof. & Head
SVN Institute of Pharmaceutical Sciences,
Swami Vivekananda University, Sagar (M.P.) India
E-mail: varshakashaw@gmail.com

DOI: https://doi.org/10.31024/ajpp.2018.4.5.9

carboximidine derivatives as anti-cancer agents by VlifeSciences MDS molecular modelling package (Dixit et al., 2011; Rathi et al., 2001; Kashaw et al., 2003; Kashaw et al., 2003; Dixit et al., 2004; Pandey et al., 2004). Present work is an effort to develop predictive QSAR models for 2,3-disubstituted-4(3H)-quinazolinone derivatives as anticonvulsant agents.

Materials and Methods

Selection of molecules and Data set

QSAR studies were carried out on synthesized 2,3-disubstituted-4(3H)quinazolinone derivative. The compounds of the series were reported to be potent inhibitor of locomotor activity. The series contain a total of 27 compounds shown in table 1. The experiment was performed on albino mice and the results were expressed in percent inhibition.

2D QSAR

All the compounds for 2D QSAR were subjected to energy minimization to get 3D structure by MMFF (Molecular mechanics force field method). The QSAR work sheet was generated using biological activity as dependent variable and various 2D descriptors as independent variables (Sharma et al., 2010). Various 2D descriptors like topological, physicochemical, alignment-independent descriptors (Leszczynski, 2010) were calculated after which by invariable column was removed and the training and test set was selected by Manual Selection Method. The model for the 2D- QSAR study was generated using PLS with forward backward as the variable selection method.

3D QSAR

3D-QSAR refers to the application of force field calculations requiring three-dimensional structures, e.g. based on protein crystallography or molecule superimposition (Ibezim et al., 2009).

In 3D QSAR conformers were generated by Monte Carlo conformational search method and the conformers of least

Table 1. Structures of the compounds in the series along with their biological activity

S. No.	Code	R	R_1	log P	Percent decrease/ inhibition in locomotor action
1.	RKJ46	2,4,6-trimethylaniline	4-bromophenyl	6.54	58
2.	RKJ47	2,4,6-trimethylaniline	4-chlorophenyl	6.27	56
3.	RKJ48	2,4,6-trimethylaniline	4-methylphenyl	6.2	54
4.	RKJ30	2,4-dichloroaniline	4-bromophenyl	6.19	55
5.	RKJ38	2,4-dimethylaniline	4-bromophenyl	6.05	53
6.	RKJ31	2,4-dichloroaniline	4-chlorophenyl	5.92	52
7.	RKJ32	2,4-dichloroaniline	4-methylphenyl	5.85	53
8.	RKJ39	2,4-dimethylaniline	4-chlorophenyl	5.78	52
9.	RKJ40	2,4-dimethylaniline	4-methylphenyl	5.71	52
10.	RKJ45	2,4,6-trimethylaniline	Phenyl	5.71	50
11.	RKJ18	4-chloroaniline	4-bromophenyl	5.64	50
12.	RKJ26	4-methylaniline	4-bromophenyl	5.56	49
13.	RKJ42	2,3,4-trifluoroaniline	4-bromophenyl	5.55	55
14.	RKJ34	2,4-difluoroaniline	4-bromophenyl	5.39	51
15.	RKJ19	4-chloroaniline	4-chlorophenyl	5.37	51
16.	RKJ29	2,4-dichloroaniline	Phenyl	5.37	49
17.	RKJ20	4-chloroaniline	4-methylphenyl	5.29	55
18.	RKJ27	4-methylaniline	4-chlorophenyl	5.29	52
19.	RKJ43	2,3,4-trifluoroaniline	4-chlorophenyl	5.28	53
20.	RKJ22	4-fluoroaniline	4-bromophenyl	5.24	48
21.	RKJ28	4-methylaniline	4-methylphenyl	5.22	54
22.	RKJ37	2,4-dimethylaniline	Phenyl	5.22	51
23.	RKJ44	2,3,4-trifluoroaniline	4-methylphenyl	5.21	50
24.	RKJ35	2,4-difluoroaniline	4-chlorophenyl	5.12	48
25.	RKJ36	2,4-difluoroaniline	4-methylphenyl	5.05	54
26.	RKJ8	2,4,6-trimethylphenyl		5.37	54
27.	RKJ4	2,4-dichlorophenyl		5.02	52

energy were selected for the alignment. All the compounds were aligned by template based method, where, a template was built by considering common substructures in the series. Usually, the lowest energy conformer of the most active compound is selected as a reference (Xu et al., 2002). For 3D the molecules were converted from 2D to 3D structures, optimized by MMFF (Molecular mechanics force field method) and then were aligned using Template based Alignment method by taking most active molecule (Figure1) as the reference molecule and basic moiety (Figure 2) as the template. The alignment is shown in figure 3. The QSAR model was build by KNN method using forward-backward as variable selection method .It examines the steric fields and the electrostatic fields.

Results and discussion

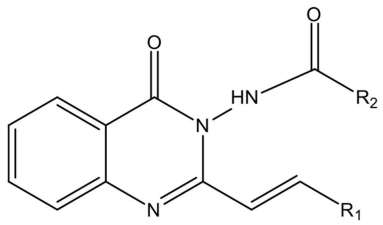

Figure 1. Reference molecule used for alignment by template based alignment

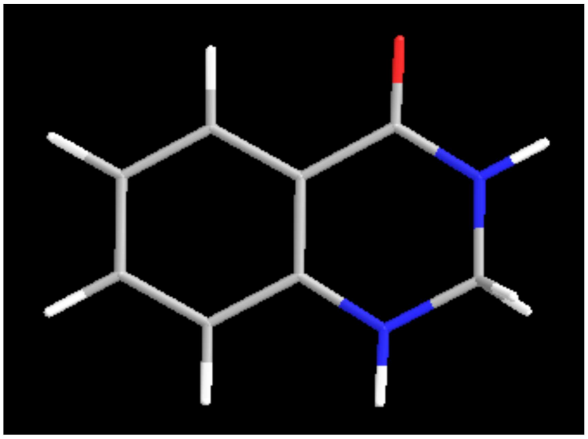

Figure 2. 2,3-disubstituted-4(3H)-quinazolinone used as template

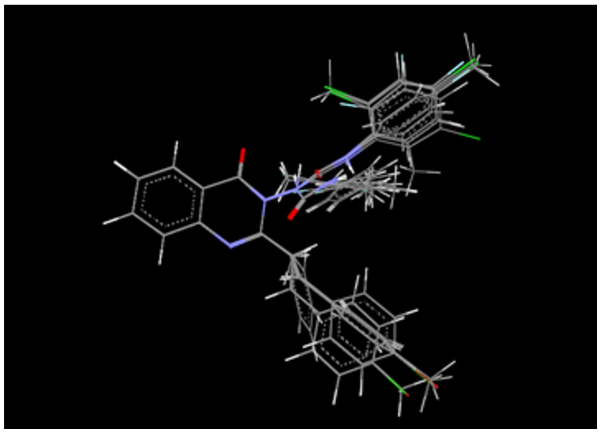

Figure 3. 3D view of aligned molecules

2D QSAR

In the present study, training and test sets were generated by using manual method followed by partial least squares regression coupled with stepwise forward-backward variable selection method. Compounds were divided in training and test set in a way that biological activities of all compounds in test set lie within the maximum and minimum value range of biological activities of training set of compounds. 2D QSAR equations were selected by optimizing the statistical results generated along with variation of the descriptors in these models. The frequency of use of a particular descriptor in the population of equations indicated the relevant contributions of the descriptors. Several 2D QSAR model were constructed and the best one regression equation obtained is represented in Eq. 1:

Percent Inhibition= 2.5529chiV3Cluster + 0.3533Bromines Count -0.1499 T_N_Cl_4 + 0.411 1chi4 +1.7509.

The statistical result of 2D QSAR model along with the contribution of the descriptors is given in table 2. In 2D QSAR model r2 > 0.9 suggests significant percentage of the total variance in biological activity is accounted by the model. Low value of standard error of estimate (r2_se< 0.0326) indicates the accuracy of the statistical fit. The

Table 2. Statistical results of 2D QSAR model generated by PLS method and 3D QSAR model generated by SW kNN MFA method

Statistical Parameter	Result	
	2D QSAR	3D QSAR
N	18	18
Degree of Freedom	14	14
r^2	0.9949	-
r^2se	0.0326	-
q^2	0.9761	0.7818
q^2se	0.0704	0.1802
pred_r^2	0.9933	0.5904
pred_r2se	0.0356	0.3095
F-test	908.07	-
k-nearest Neighbour	-	2
Contributing descriptor	chiV4 chiV3Cluster Bromines Count T_N_Cl_4	S_664 (-0.6866 - 0.0931) S_1158 (-0.2742 - 0.2311) S_1434 (-0.0084 - 0.0069)

stability of model judged by leave-one-out procedure is fairly good (q2> 0.9) suggesting that the model can be utilized for predictions.

Furthermore, the predictive potential of model is good as observed by the pred_r2 = 0.9933. Low values of q2_se (standard error of q2) = 0.0704 and pred_r2_se (standard error of predicted squared regression) = 0.0356 also suggest significance of the model. The correlation matrix given in table 3 indicated the absence multi co-linearity in the model. Figure 4 gives a pictorial representation of different 2D parameters and their contribution towards percent inhibition.

chiV4: The first contributing descriptor is chiV4 (approx 19%). This signifies atomic valence connectivity index (order 4). Its positive contribution indicating that atom substituted by 4th order i.e. is tetra substituted well for activity.

chiV3 Cluster: This descriptor signifies valence molecular connectivity index of 3rd order cluster. The positive value signifies that increase in 3rd order cluster i.e. is tri substituted groups will favors the activity. chiV3 Cluster was found to be most influencing descriptor (approx 45%) in determining the activity.

Bromines Count: Bromines Count (approx 30%) which is again positively contributing to the activity. Bromines Count signifies number of bromine atoms in a compound i.e substitution of bromine like atoms enhance the activity.

T_N_Cl_4: The fourth contributing descriptor is T_N_Cl_4 which is negatively contributing (approx -10%). This is Alignment Independent descriptor signifies the count of number of Nitrogen atoms (single double or triple bonded) separated from any other chlorine atom by 4 bond distance in a molecule. It is indicating that the substitution of chlorine like atom should not be above said bond distance.

Uni-column statistics (Table 4) for training and test set were generated to check correctness of selection criteria for training and test set molecules. It is clear that the test set was interpolative i.e. derived within the min-max range of the training set. The mean of the test set were higher than the training set indicated the presence of relatively more active molecules as compared to the inactive ones. Figure 5 shows the plot between the observed and predicted activity. From the plot it is clear that the model is able to predict the activity of the training set quite well (all points are close to regression line) as well as external test set (all points of test set are close to regression line and well covered by training points), providing confidence in predictive ability of the model also the residual values were obtained near to zero. Therefore it was concluded that the resulting QSAR model has good predictive ability.

The predicted activity values for the compounds in the

Table 3. Correlation matrix for the descriptors contributing to 2D QSAR model

Contributing descriptor	chiV4	chiV3Cluster	Bromines Count	T_N_Cl_4
chiV4	1			
chiV3Cluster	0.825	1		
Bromines Count	0.129	0.173	1	
T_N_Cl_4	-0.091	-0.162	-0.171	1

Table 4. Uni-Column statistics for training set and test set

Set	Column Name	Average	Max	Min	Std. Dev.	Sum
Training	% inhibition	5.6372	6.5400	5.0200	0.4132	99.6700
Test	% inhibition	5.5378	6.2700	5.0000	5.1200	50.7400

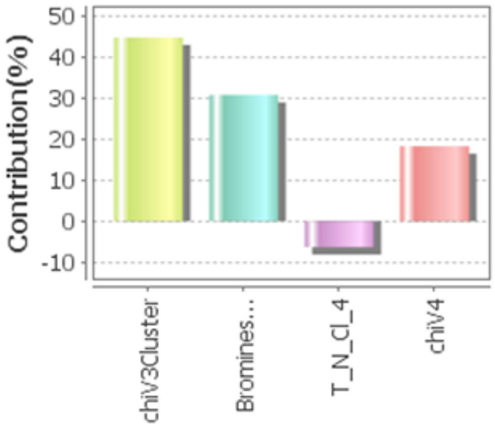

Figure 4. Contribution chart of selected 2D descriptors for CNS activity

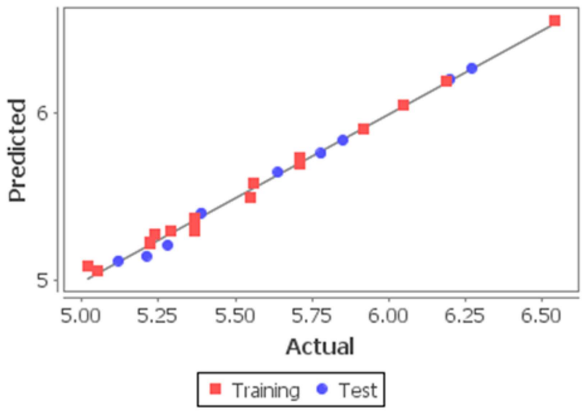

Figure 5. Fitness plot between observed and predicted activities of the training (blue spot) and test (red spot) molecules of 2D QSAR model

training set and test set, along with their corresponding observed activity values are given in table 4.

3D QSAR

3D QSAR models were generated using kNN MFA coupled with stepwise forward-backward variable selection method (SW kNN MFA). This is followed by generation of a common rectangular grid around the molecules. The steric and electrostatic interaction energies are computed at the lattice points of the grid using a methyl probe of charge +1. After the selection of the test and training sets, kNN MFA methodology was applied to the descriptors generated over the grid as shown in the 'Show Point' (Figure 6) and the best SW kNN-MFA 3D QSAR model have a q2 of 0.7818 and pred_ r2 of 0.5904 (Table 2) was considered.

The predicted activity values for the compounds in the training set and test set, along with their corresponding observed activity values, are given in table 4 and the fitness plot shown in figure 7. The range of property values in the generated data points helped for the design of NMEs. These ranges were based on the variation of the field values at the chosen points using the most active molecule and its nearest neighbor set.

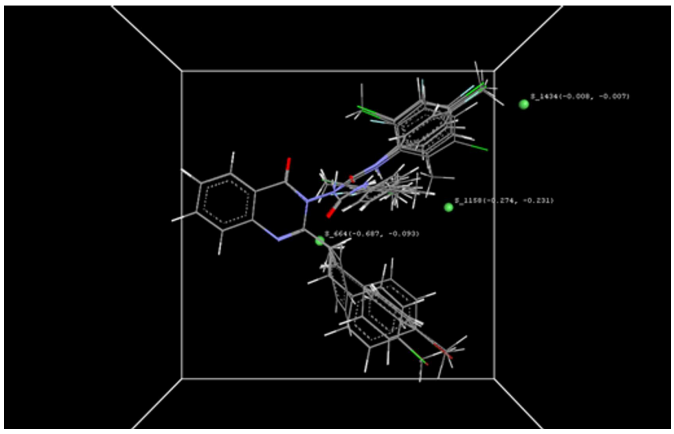

Figure 6. Relative positions of the local fields (steric and electrostatic) around aligned molecules

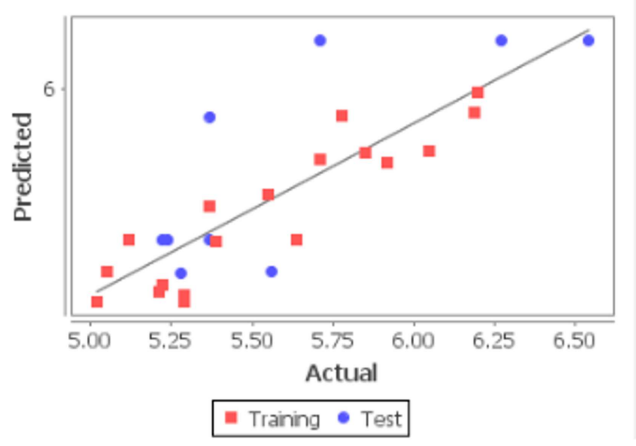

Figure 7. Fitness plot between observed and predicted activities of the training (blue spot) and test (red spot) molecules of 3D QSAR model

The points generated in SW kNN MFA 3D QSAR model are S_664 (-0.6866 -0.0931), S_1158 (-0.2742 -0.2311) and S_1434 (-0.0084 -0.0069). These points suggested the significance and requirement of electrostatic and steric properties as mentioned in the ranges in parenthesis for structure–activity relationship and maximum biological activity of 2,3-disubstituted-4(3H)quinazolinone analogues. Negative and positive values in steric field descriptors indicated the requirement of negative and positive steric potential, respectively for enhancing the biological activity of 2,3-disubstituted-4(3H)quinazoli-none analogues.

Therefore less steric and more steric substituent were preferred at the position of generated data points S_457 (-0.6725, -0.6305) and S_649 (9.0580, 9.2042), respectively around 2,3-disubstituted-4(3H)quinazolinone pharmacophore. Similarly the positive values of electrostatic descriptors suggested the requirement of electropositive or less electronegative groups at the position of generated data point E_756 (3.9104, 4.5117), around 2,3-disubstituted-4(3H)quinazolinone pharmacophore for maximum activity. Results obtained and points generated around 2,3-disubstituted-4(3H)quinazolinone pharmacophore using the 3D QSAR studies was used for correlation chemical nature of substituents around 2,3-disubstituted-4(3H)quinazolinone rings with their observed activity.

***Substitution at R2*:** Three data points generated at the position of R2 around 2,3-disubstituted-4(3H)-quinazolinone were steric points S_664 (-0.6866 -0.0931); S_1158 (-0.2742 -0.2311) and S_1434 (-0.0084 -0.0069). These points showed that less steric substituent required around 2,3-disubstituted-4(3H)quinazolinone ring, when 2,4,6-trimethylaniline; 2,4-dichloroaniline; 2,4-dimethylaniline; 2,4,6-trimethylaniline, 4-methylaniline; 2,3,4-trifluoroaniline; 2,4-difluoroaniline, 2,4-dichloroaniline; 4-chloroaniline; 4-methylaniline, 2,3,4-trifluoroaniline; 4-fluoroaniline; 2,4-difluoroaniline was added. Simultaneously the steric point S_1158 (-0.2742 -0.2311) and S_1434 (-0.0084 -0.0069) indicated that no steric changes required at lattice 664.

Substitution at R1: 3D QSAR studies showed requirement of more steric group at R1 position. The steric data point generated was S_664 (-0.6866 -0.0931) indicates sterically bulky group like 4-bromophenyl, 4-chlorophenyl, 4-methyl phenyl were required at R1 position.

The overall findings of 2D & 3D QSAR suggested presence of positive steric potential at R2 position in 2,3-disubstituted-4(3H)quinazolinone nucleus i.e. R2 position in 2,3-disubstituted-4(3H)quinazolinone nucleus should acquire

more bulk as well as according to 3D QSAR results substitution on R1 position should be changed sterically with 4-bromophenyl, 4-chlorophenyl, 4-methylphenyl, results indicated to decrease the steric bulk. Results of 2D and 3D QSAR were validated by substituting the groups and atoms on 2,3-disubstituted-4(3H)quinazolinone nucleus. Designed compounds showed potent anticonvulsant activity by the generated QSAR models.

Conclusion

QSAR study was performed on 2,3-disubstituted-4(3H)-quinazolinone derivatives for their CNS activity. In addition, phenyl ring attached should be substituted with less electronegative group and bulkier groups should be placed on R2 position. There proposed changes may produce such physico-chemical changes in the compounds which will help them to bind efficiently with the target receptor.

Acknowledgement

Firstly I am thankful to Dr. Sushil Kumar Kashaw for precious guidance during this work.

Conflicts of interest: None

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