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3D QSAR ANALYSIS OF 2,4-DISUBSTITUTED 1,5-BENZODIAZEPINE DERIVATIVES AS CNS DEPRESSANTS

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New 2,4-disubstituted-1,5-benzodiazepine derivatives containing different functional groups have been screened for their CNS depressant activity. The synthesized benzodiazepine derivatives were screened for CNS depressant activity using the actophotometer model for mice. QSAR studies of synthesized derivatives were performed on Vlife MDS 3.5 software. The data set for QSAR studies encompassed activities of 45 molecules and 252 descriptors calculated by Vlife MDS 3.5. The training set comprised of 36 molecules and test set of 9 molecules. QSAR equation revealed that some electronic, steric and liphophillic parameters have correlation with CNS depressant activity. The best equation was selected on basis of correlation coefficient (r^2) and predicitivity of equation.

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Keywords: 1,5-benzodiazepine, 3D QSAR, CNS depressant.

1. Introduction

It is evident from the literature that diazepine derivatives have been found to show various pharmacological activities. Diazepine ring is the backbone of several antibacterial[1-7], antifungal[8] and anti-inflammatory drugs[9]. over the last two decades; benzodiazepines have been widely used therapeutically for their ability to reduce anxiety and act as tranquilizers and for their anticonvulsant effects in epilepsy. Considering the scope for further studies on diazepine derivatives we have synthesized some new 2,4-disubstituted -1, 5-benzodiazepine derivatives and screened for CNS depressant activity.

2. Material and methods

2.1 Synthesis of 2,4 disubstituted 1,5 benzodiazepines (1-45)

Synthesis and characterization of all the derivatives carried out as per reported procedure[10].

2.2 CNS depressant activity

Male or female mice with a bodyweight between 25 and 30 g were used. The animals were starved overnight. The compounds were given in the form of suspension in to 2% acacia. Thirty minutes later, the mice were kept in the actophotometer score is recorded. The same procedure as applied for the control and standard and test compounds. Diazepam was used as standard for the test. The compounds were tested at different dose to determine the minimum effective concentration.

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2.3 QSAR studies

2.3.1. Molecular alignment

The molecules dataset were aligned by using atom-fit technique, using atoms common with the structure of benzodiazepine nucleus. The most active molecule was selected as a template for alignment of the molecules. The alignment of all the molecules on the template is shown in Figure 1.

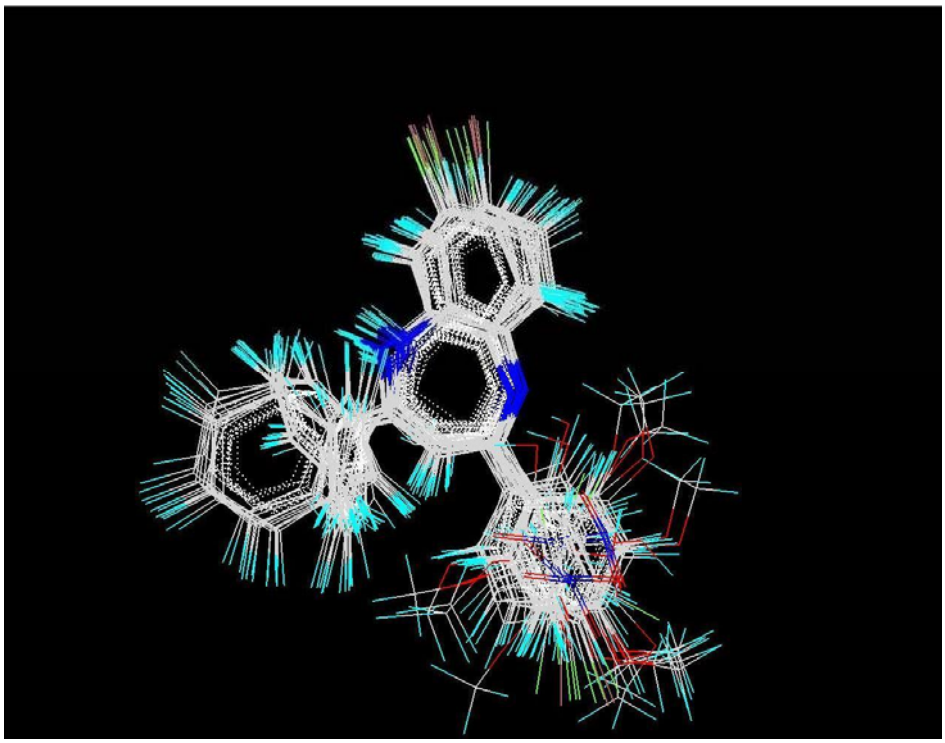


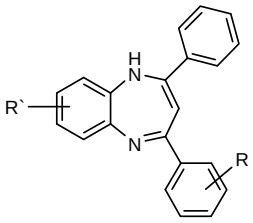
Fig. 1. The alignment of molecules

2.3.2 Descriptor Calculation

The allinement of the molecules is necessary to perform the 3 D QSAR analysis, and which was carried out on Vlife MDS 3.5 Engine, after a rectangular grid was generated around the molecules the energies which are utilized in the QSAR analysis like hydrophillic, steric and electrostatic interaction were calculated at the lattice points of the grid using a methyl probe of charge +1.

2.3.3 Data Set

The builder module of the Vlife 3.5 program was used to generate molecular models of 45, 1,5-benzodiazepine derivatives. They were then energy-minimized using the Merck Molecular Force Field (MMFF). The charge equilibration method was used to assign atomic partial charges to each of the compounds. Activity values for the QSAR equation were obtained using the negative logarithm of Minimum Effective Concentration, which had been determined by actophotometer model for CNS depressant The molecules which are selected for QSAR analysis are shown in table 1.



(1-45)

R` = H, Cl, Br

Table 1. Substitution of the 2,4 disubstituted 1,5 benzodiazepine derivatives.

Comp code	R	R’	Comp code	R	R’
1	H	H	24	3,4-Cl	Cl
2	4-CH_3	H	25	2,4-OCH_3	Cl
3	4-Br	H	26	2,5-OCH_3	Cl
4	4-Cl	H	27	3,4-OCH_3	Cl
5	4-NO_2	H	28	4-OH	Cl
6	3-NO_2	H	29	2-OH	Cl
7	4-OCH_3	H	30	3-OH	Cl
8	2,4-Cl	H	31	H	Br
9	3,4-Cl	H	32	4-CH_3	Br
10	2,4-OCH_3	H	33	4-Br	Br
11	2,5-OCH_3	H	34	4-Cl	Br
12	3,4-CH_3	H	35	4-NO_2	Br
13	4-OH	H	36	3-NO_2	Br
14	2-OH	H	37	4-OCH_3	Br
15	3-OH	H	38	2,4-Cl	Br
16	H	Cl	39	3,4-Cl	Br
17	4-CH_3	Cl	40	2,4-OCH_3	Br
18	4-Br	Cl	41	2,5-OCH_3	Br
19	4-Cl	Cl	42	3,4-OCH_3	Br
20	4-NO_2	Cl	43	4-OH	Br
21	3-NO_2	Cl	44	2-OH	Br
22	4-OCH_3	Cl	45	3-OH	Br
23	2,4-Cl	Cl			

2.4 Full Search Multiple Linear Regression Method

A relationship between independent and dependent variables (physicochemical descriptors and biological activities, respectively) were determined statistically using regression analysis. Linear regression is achieved by fitting a best-fit straight line to the data using the least squares method. Descriptors that are included in a reasonable QSAR equation should exhibit low inter-correlation and thus, behave as independent variables. The inter-correlation between descriptors was used for selecting descriptors for equation and the quality of fit for a regression equation was assessed relative to its correlation coefficient and standard deviation. The F value represents the level of statistical significance of the regression. The predictive quality of a regression model can be evaluated using the leave-one-out cross-validation procedure (XR^2).

For a regression model, R was used to describe the fitness of data and fitness is considered to improve as R approaches 1. Each molecule was eliminated from the training set and cross-validated XR^2 was calculated using the predicted values for the missing molecule. Given that the full search method performs an exhaustive examination all possible descriptor combinations, there is little concern that important descriptors might be missed and this method enables identification of the QSAR equation with the best correlations. The program determines inter-correlation between descriptors and those combinations containing high inter-descriptor inter-correlation were discarded. QSAR equations that have correlation coefficient which equal or exceed a preset value are reported. We specified 0.5 and 0.65 as the inter-correlation and correlation coefficient cutoff values.

2.5 Activity prediction

To systematically assess a QSAR model, a reliable validation is required. Usually, a QSAR model is evaluated by the predictive results for the given dataset. Selected models having r^2 above 0.7 were checked for their external predictivity. The observed and the predicted values for CNS depressant activity are shown in Table 3.

Table 2.The QSAR model.

Model	Equation	r^2	q^2	*F* value	r^2 perdicted
Model A	pEC_{50} = 0.0026+35.8875(±2.5198) H_517+89.4130(±9.8047) S_526+347.2890(±50.1811) S_347+0.2402(±0.0339) S_380+0.3386(±0.0854) S_567+ 0.2325(±0.0514) E_571- 0.0702(±0.0223) S_525	0.9276	0.8776	51.2687	0.7440

Table 3. Table showing the observed activity and predicted activity (PEC)of compounds.

Comp no	Observed activity	Predicted activity	residuals	Comp no	Observed activity	Predicted activity	residuals
1.	2.10623	2.0907	0.015529	24.	6.97631	6.9121	0.064209
2.	4.77383	4.8643	-0.09047	25.	7.47152	8.9647	-1.49318
3.	4.1914	3.9727	0.218701	26.	5.34191	4.6832	0.658705
4.	4.34739	3.5005	0.846889	27.	8.32679	7.9956	0.331188
5.	3.55698	2.681	0.875981	28.	6.42401	5.0583	1.36571
6.	4.10735	5.571	-1.46365	29.	8.67272	7.296	1.37672
7.	4.64178	4.0109	0.630879	30.	7.48687	6.999	0.487873
8.	6.05048	6.9444	-0.89392	31.	6.7401	6.3574	0.382698
9.	6.38261	6.7512	-0.36859	32.	9.97274	6.6654	3.307339
10.	7.22279	7.1333	0.089486	33.	9.88111	8.3968	1.484313
11.	10.6117	9.6153	0.996414	34.	7.92796	8.6632	-0.73524
12.	6.64158	7.33	-0.68843	35.	7.61278	7.5298	0.082984
13.	4.43287	4.9572	-0.52433	36.	8.91743	8.5765	0.340928
14.	1.80355	4.1987	-2.39515	37.	10.3818	9.7569	0.624863
15.	3.46066	5.2083	-1.74764	38.	10.1875	11.8661	-1.67861
16.	3.50518	3.7552	-0.25002	39.	9.83829	9.9732	-0.13491
17.	5.33155	5.2562	0.075353	40.	10.9528	10.5112	0.441598
18.	4.50035	4.3001	0.20025	41.	20.2922	20.9911	-0.69893
19.	4.59829	4.0213	0.576991	42.	14.3148	14.8989	-0.58415
20.	9.80757	10.65	-0.84244	43.	9.88959	11.2954	-1.40581
21.	7.7217	5.6519	2.069798	44.	20.6656	19.6868	0.978755
22.	6.08035	5.6766	0.403753	45.	17.7542	19.3595	-1.60527
23.	7.2895	7.7953	-0.5058				

3. Results and discussion

In the present study, 36 molecules were used in the training set (Table 1) to derive QSAR models with the number of field grid points being not more than seven per model. To evaluate the predictive ability of generated 3D-QSAR models, a test set of nine molecules with regularly distributed biological activities was used. A prerequisite for QSAR study is a congeneric series of molecules, all having the same mechanistic profiles with similar functional properties. Congenericity is a challenging task to define, though it is well-documented that all molecules in a set should have the same molecular framework with structural variation in one or several positions. On successful runs of MLR, different sets of equations were generated by keeping the chain length of equations to seven, and these equations were further analyzed statistically to select the best model. As shown in one models were selected after screening various combination of different descriptors.

3.1 Interpretation of QSAR Model

The model A describes the structural features optimum for the CNS depressant activity. The steric and electrostatic fields were calculated. A training set of 36 molecules, and a test set of 9 molecules was used as described earlier. The model was selected on basis of r^2, q^2, pred r^2, F and p values. The r^2 value for model A was 0.9032, and the external predictivity of model A is found to be 0.8776. The F test and p significance values were considered for the selection of model. The points that were found optimum for the activity after the QSAR study are shown in figure 2. The contribution of points E_571 which is the electrostatic and S_526, S_347, S_380, S_567 and S_525 which are steric interaction fields (Blue and green points respectively) at lattice points 526,347,380,567 and 525along with points H_517 which are the hydrophilic interaction field

(yellow points) at lattice point 517, imply that these points are indeed significant for the structure-activity relationship. The positive contribution of all the fields point indicates that the addition of groups having higher steric interaction at lattice point 526,347,380,430 (Green points in figure 2) and groups having electrostatic interactions at lattice points 571 (Blue point in figure 2) are required for amplified GABAnergic activity. Along with this the fields S_525 which contribute negatively to the activity also need to be taken into account. The streic interactions at lattice point 294 needs to be reduced.these probe points are need to be taken into consideration the streic parameters are showing the major bulk of contribution because the steric behavior favors the orientation of the molecules in receptors and important for the binding along the hydrophilic parameters which contributes towards the passing the barriers in biological systems.

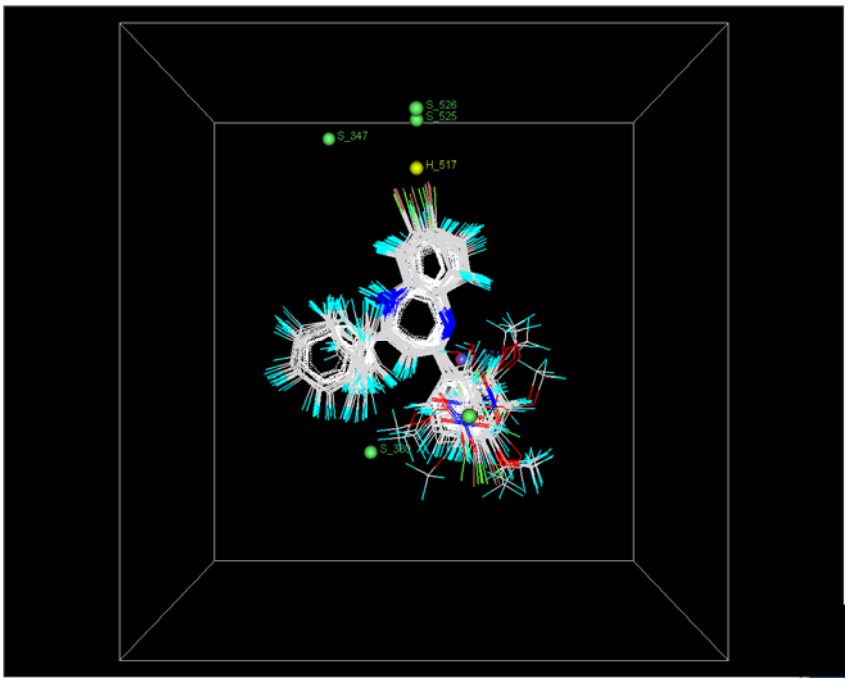


Fig. 2. The QSAR model.

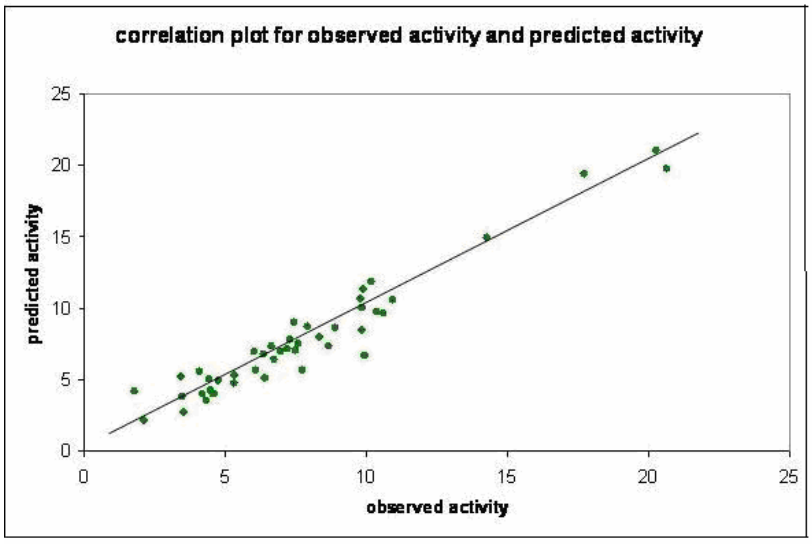


Fig. 3. The correlation plot between observed activity and predicted activity.

4. Conclusions

The 3D QSAR statistical models described in this work show both good internal and external consistency, and represent important contribution to the QSAR field in the area of designing novel CNS depressants drugs. From the 3D QSAR studies steric and electrostatic contour maps we can conclude that electronegative groups surrounding the bezodiazepine moiety are related to improved potency. In addition, the favorable steric contours suggest that aromatic bulky groups at the bezodiazepine moiety may increase ligand potency. The 3D QSAR models should be useful for the design of new structurally related potential CNS depressants improved affinity and potency.

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