CoMFA Model and Molecular Design of Anti-excitatory Activity for Benzodiazepinooxazole Derivatives against Mice①

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ABSTRACT A 3*D*-QSAR study was conducted to analyze the anti-excitatory activity (p*E*) of benzodiazepinooxazole derivatives to mice by the comparative molecular field analysis (CoMFA) method. Among the 54 active molecules, a training set of 46 compounds was randomly selected to construct the CoMFA model; the remaining compounds, together with template molecule (No. 54) and two newly designed molecules constitute a test set of 17 compounds to validate the model. The obtained cross-validation coefficient (R_{cv}^2), the non-cross validation coefficient (R^2), and the test value *F* of the CoMFA model for training set are 0.516, 0.899, and 57.57, respectively. The model was used to predict the activities of all compounds in the training and testing sets, and the results indicated that the model had good correlation, strong stability and good predictability. Based on the 3*D* contour maps, eight novel benzodiazepinooxazole derivatives with higher anti-excitatory activity were designed. However, the effectiveness of these novel benzodiazepinooxazole derivatives is still needed to be verified by the experimental results.

Keywords: benzodiazepinooxazole derivative, mice, anti-excitatory activity, 3*D*-QSAR, comparative molecular field analysis; DOI: 10.14102/j.cnki.0254–5861.2011–3164

1 INTRODUCTION

Quantitative Structure-Activity Relationship (QSAR) plays an important role in predicting the biological activity of compounds and has become an important research field in chemistry, medicine, environment and other disciplines[1-8]. Compared with two-dimensional (2*D*) QSAR methods[9, 10], the three-dimensional (3*D*) QSAR methods[10-16] introduce the three-dimensional conformational properties of bioactive molecules. Therefore, they can reflect the real image of the interaction between bioactive molecules and receptors more accurately, and reveal the mechanism of drug-receptor interaction more deeply. Moreover, the fitting results of 3*D*-QSAR are generally better. Owing to these advantages, 3*D*-QSAR methods have been applied extensively in correlating chemical structure features with biological activities, and they can be regarded as the basis for further compound design and synthesis. Especially, the comparative molecular field analysis (CoMFA)[11-14] is a widely used 3*D*-QSAR method that establishes relationships between the biological activity of drug molecules and their steric and electrostatic fields.

3-Ethyl-3-methylglutarimide (bemegride) is a stimulant of central nervous system that can induce epilepsy in rats[17]. Toshiharu et al.[18] studied the effects of oxazolam, cloxazolam, and CS-386, as well as other benzodiazepines, on socially induced suppression and aggression in pairs of monkeys. William[19, 20] studied enantioselective autocatalysis of benzodiazepinooxazole derivatives in detail. Yoshimoto et al.[21] discovered that benzodiazepinooxazole derivatives are excellent, excellent and anti-anxiety sedative, and they further determined the anti-bemegride activity (called anti-excitatory activity) of these compounds to establish the structure-activity relationship.

In this paper, a 3*D*-QSAR model of anti-excitatory activity[21] of benzodiazepinooxazole derivatives was

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established with CoMFA method. According to this model, the key structural features affecting anti-excitatory activity were revealed, and the underlying microscopic mechanism was discussed. Finally, new molecules with better anti-excitatory activity were designed.

2 MATERIALS AND METHODS

2. 1 Studied compounds and their anti-excitatory activity data

Experimental compounds: The basic molecular structure of benzodiazepinooxazole derivatives is shown in Fig. 1, where substituents R_3, R_4, and R_7 to R_{10} are variable parts. The specific molecular structure is shown in Table 1. For toxicity test, benzodiazepinooxazole derivatives[21] were dissolved in 0.85% brine containing 0.5% tragacanth in the form of suspension.

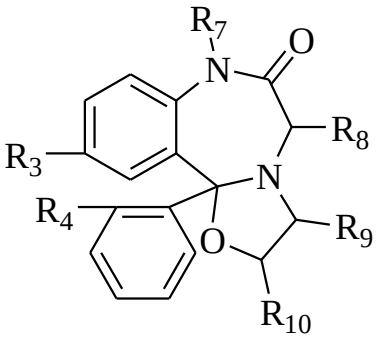


Fig. 1. Basic structure of benzodiazepinooxazole derivative molecules

Table 1. Molecular Structures and Anti-excitatory Activity (p*E*) of Benzodiazepinooxazole Derivatives

No.	Substituents	p*E*exp.[21]	p*E*cal.	*E*rr. (%)
1	3-Cl, 7-CH_3, 10-CH_3	4.80	4.95	–3.13
2*	3-Cl, 7-CH_3	4.86	4.87	–0.21
3	3-Br, 7-CH_3, 10-CH_3	4.92	5.05	–2.64
4	3-Br, 7-CH_3	5.09	5.08	0.20
5	3-Cl, 7-C_2H_5	4.96	4.99	–0.60
6	3-Cl, 10-CH_3	5.16	5.42	–5.04
7	3-NO_2, 7-CH_3, 10-CH_3	5.17	5.20	–0.58
8	3-Cl	5.20	5.26	–1.15
9	3-Br, 10-CH_3	5.34	5.42	–1.50
10	3-Br	5.35	5.43	–1.50
11	3-NO_2, 10-CH_3	5.49	5.55	–1.09
12*	3-NO_2, 7-CH_3	5.53	5.24	5.24
13	3-Br, 4-Cl, 7,10-$(CH_3)_2$	5.55	5.57	–0.36
14	3-NO_2	5.62	5.69	–1.25
15	4-Cl, 10-CH_3	3.96	4.20	–6.06
16	3,4-Cl_2, 7-CH_3	5.84	5.44	6.85
17	3-Cl, 9-CH_3	5.87	5.37	8.52
18*	3-Cl, 4-Cl, 8-CH_3	5.91	5.41	8.46
19	3-Br, 9-CH_3	5.96	5.24	12.08
20	3-Cl, 4-F	5.98	6.16	–3.01
21	3-Cl, 4-Cl, 10-CH_3	6.00	6.23	–3.83
22	3-Br, 4-Cl, 8-CH_3	6.01	6.45	–7.32
23	3-Br, 4-Cl, 7-CH_3	6.11	6.08	0.49
24	3-Cl, 4-Cl	6.18	6.26	–1.29
25	3-Br, 4-Cl, 10-CH_3	6.43	6.45	–0.31
26	3-Br, 4-Cl	6.45	6.39	0.93
27	3-Br, 4-F	6.45	6.48	–0.47
28	3-Cl, 4-F, 9-CH_3	6.50	6.21	4.46

To be continued

29	3,4-Cl_2, 9-CH_3	6.52	6.23	4.45
30	3-Br, 4-Cl, 9-CH_3	6.61	6.45	2.42
31*	4-Cl, 10-CH_3	3.96	4.02	–1.52
32	10-CH_3	4.32	4.41	–2.08
33	3-Cl,7-$CH_2C_6H_4$-2′-Cl	4.33	4.23	2.31
34	3-Cl, 7-C_4H_9, 10-CH_3	4.35	4.21	3.22
35	3-Cl, 10-$(CH_3)_2$	4.68	4.61	1.50
36*	3-Cl, 8-CH_3	4.71	4.76	–1.06
37	3-Cl, 7-$CH_2CH{=}CH_2$, 10-CH_3	4.77	4.88	–2.31
38	3-Cl, 7-$CH_2C_6H_5$, 10-CH_3	4.77	4.77	0.00
39	3-Br, 8-CH_3	4.80	4.96	–3.33
40	3-Cl, 7-CH_2CH_2Cl	4.90	5.05	–3.06
41*	3-Cl, 7-C_2H_5, 10-CH_3	4.93	5.12	–3.85
42	3-Cl, 7-C_2H_5	4.96	4.99	–0.60
43	3,4-Cl_2, 8-CH_3, 10-CH_3	5.13	5.50	–7.21
44	3-NO_2, 7-C_2H_5	5.21	5.44	–4.41
45	3-Br, 7-C_2H_5	5.25	5.18	1.33
46*	3-Cl, 7,9-$(CH_3)_2$	5.60	5.33	4.82
47	3-Cl, 4-F, 7-CH_3	5.81	5.68	2.24
48	3-Cl, 4-Cl, 7-C_2H_5	5.84	5.76	1.37
49	3-Br, 4-Cl, 7-C_2H_5	5.93	5.94	–0.17
50	3-NO_2, 9-CH_3	6.23	6.19	0.64
51*	3,4-Cl_2, 7,9-$(CH_3)_2$	6.23	5.92	4.98
52	3,4-Br_2	6.26	5.93	5.27
53	3,4-Br_2, 9-CH_3	6.48	6.42	0.93
54	3-Br, 4-F, 9-CH_3	6.73	6.66	1.04
55*	3-I, 4-F, 9-CH_3		6.88	
56*	3-I, 4-F, 9-I		7.08	
57*	3-I,4-F,9-Br		6.99	
58*	3-I,4-F,9-Cl		6.99	
59*	3- Br,4-F,9-Cl		6.77	
60*	3- Br,4-F,9-Br		6.76	
61*	3-I, 4-F, 9-I,10-SO_3H		6.68	
62*	3-I, 4-F, 9-Me,10-CO_2H		6.79	

Experimental animals: male mice of DDY variety, weighing 20～25 g.

Experimental method: The test compound was orally administered at a standard dose of 30 mg/kg for 1 hour, and the behavior of mice was observed 30 minutes later.

ED_{50} is defined as the dose causing clonic convulsion in 50% of animals. The higher the ED_{50} is, the weaker the anti-excitation ability is; Therefore, ED_{50} can be used as an indicator of anti-excitatory activity. The ED_{50} is calculated by litchfield and Wilkerson method, and the unit is mol/kg description.

All initial anti-excitatory activity (ED_{50}) values are converted into pE(-logED_{50})[21], which is used as a dependent variable in CoMFA[22-24] research. pE values are shown in Table 1. The data set was randomly divided into a training set of 46 compounds for model generation and a test set of 17 compounds (including template molecule No. 54 and eight newly designed molecules, marked with "*" in Table 1) for model validation.

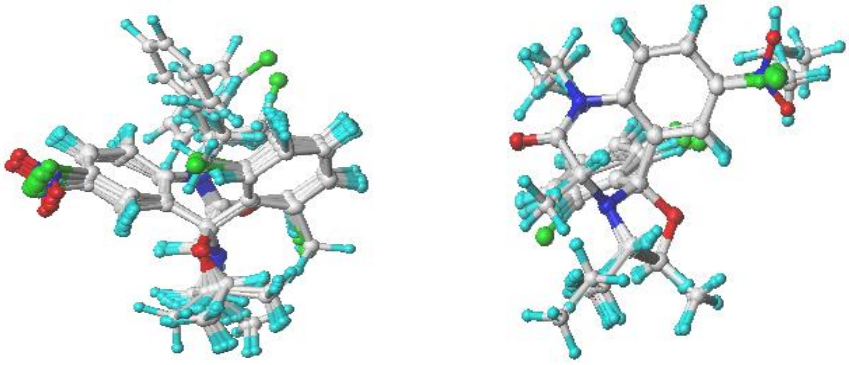
2. 2 Molecular modeling and alignment

In this paper, 3*D*-QSAR analysis and CoMFA model building are completed by using Sybyl-x2.0 molecular simulation software of Tripos company. The modules used include SYBYL, Sketch, Minimize, Database-alignment and CoMFA QSAR method, etc., and default values are adopted unless otherwise specified.

The determination of molecular active conformation is one of the first prerequisites for establishing an effective 3*D*-QSAR model. Usually, the lowest energy conformation of molecules is used instead of the pharmacodynamic active conformation. First, Sketch molecule module in Sybyl-x2.0 software was used to construct the initial three-dimensional molecular structures of 62 benzodiazepinooxazole derivatives (containing two newly designed molecules). Then, minimized module was used to select Tripos force field, add Gasteiger-Huckel charge, and set Max. The number of

iterations was 1000, and Gradient was reduced to 0.005. The convergence gradient of Powell energy gradient method was set to 0.21 kJ·mol^{-1}·nm^{-1}. Finally, the lowest energy conformation of all molecules was obtained through full conformation search, and this lowest energy conformation was taken as the bioactive conformation of molecular superposition.

Bioactive molecules (No. 2, 12, 18, 31, 36, 41, 46, and 51) together with 8 newly designed molecules (No. 55～62) were randomly selected as test set, which are marked with "*" in Table 1, and the remaining 46 molecules was set as the training set. Note that both the test and training sets contain template molecule No. 54. Their common substructure is shown in Fig. 1, with the omission of all substituents (R_3, R_4 and R_7 to R_{10}). No. 54, which has the strongest anti-excitatory activity, is selected as the template molecule, and it is superimposed by the way of common skeleton to ensure the consistency of orientation of all molecules and minimize the root mean square deviation when the molecules overlap with each other. That is, the training and test sets are superimposed by the Align database module using the common skeleton in molecule No. 54. The alignment results from the above strategies are depicted in Fig. 2, and they were subsequently used in calculating the CoMFA probe interaction energy.



(a) **(b)**

Fig. 2. 3*D* view of all the aligned molecules in the training set (a) and testing set (b)

2. 3 Model generation and validation

CoMFA fields, the interaction energies between a probe atom or a molecule and a set of aligned molecules, are used to build the 3*D*-QSAR model. A sp^3 carbon atom with +1.0 charge served as the probe atom to calculate steric and electrostatic fields.

The Leave-one-out (LOO) method was used for cross-validation to obtain the cross-validation coefficient (R_{cv}^2) and the optimal number of principal components (*N*). First, the prediction ability of the model is measured by R_{cv}^2, and the model with $R_{cv}^2 > 0.5$ is considered to have a reliability of 95%[25, 26], with the randomness less than 5%. Second, the sample ratio (*S*v), that is, the ratio of the number of compounds (*m*) to the number of variables (this is *N*) in the model, should meet the criteria $Sv \geqslant 5$ to ensure that the model has statistical significance, good robustness and low probability[27]. Thirdly, regression analysis is carried out to obtain the non-cross-validation coefficient (R^2) and the statistical variance ratio (*F*). Finally, the contribution of stereo field and static electric field to p*E* of benzodiazepinooxazole derivatives is directly reflected by three-dimensional equipotential diagram using View CoMFA module.

3 RESULTS AND DISCUSSION

3. 1 3*D*-QSAR model of training set

CoMFA model of training set: (1) cross-validation part: $R_{cv}^2 = 0.516 > 0.5$; $N = 6$, $Sv = m/N = 46/6 = 7.67 > 5$, which shows that the model has good prediction ability and robustness. (2) Non-cross-validation part: $R^2 = 0.899 > 0.8$[28], showing that good fitting is obtained; R^2 is also known as reduction error ratio based on R^2 value, and the model contains 89.9% of the factors affecting the anti-excitatory activity of benzodiazepinooxazole derivatives, and only less than 10.1% are unknown factors. (3) At 95% significant level, the critical value of *F* is $F_{0.05}(6,39) = 3.32$[29]. The *F* of the model is 57.571, more than 17 times of its critical value, which indicates that the model is closely related and has statistical stability.

Then, calculated (for the training set) and predicted (for the

test set) p*E* values of benzodiazepinooxazole derivatives (see in Table 1) are obtained using CoMFA model. As shown in Table 1 and Fig. 3, these values are very close to the corresponding experimental data. All the statistical parameters show that the generated model based on CoMFA method is reasonable and has good predictability.

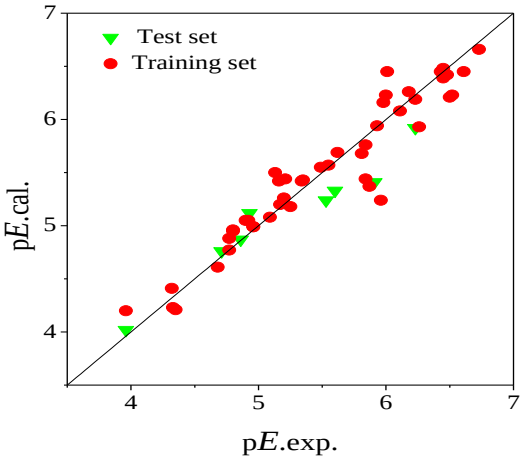


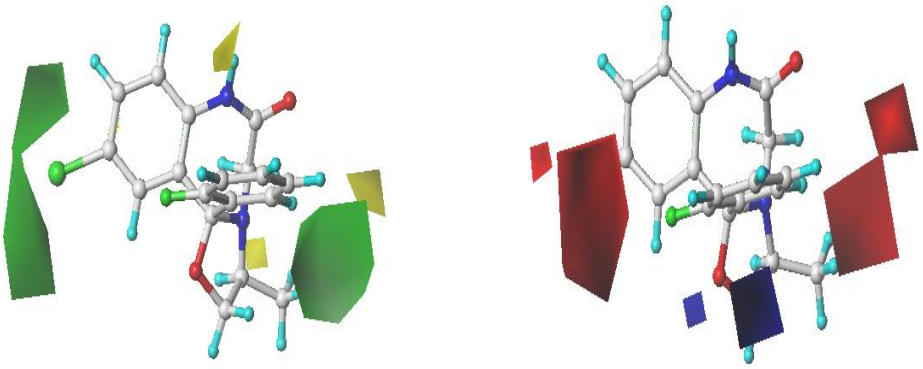
Fig. 3. Scatter plots of the experimental versus the predicted p*E* values

3. 2 Main factors affecting the activity from a combined CoMFA analysis

The results of CoMFA can be displayed as vivid 3*D* contour maps of steric and electrostatic fields, providing an opportunity to explain the observed variance in the anti-excitatory activity (p*E*).

Fig. 4a shows the steric contour map for the CoMFA model of p*E*, with the most active molecule 54 as a reference. It can be seen from the spatial distribution of three-dimensional field that the introduction of large groups at R_3 (green area, where bulky groups would be favorable for anti-excitatory activity.) and R_9 (green area) position, and the presence of a small group at R_7 (yellow area, where bulky groups would decrease the activity.) position is beneficial to improve the anti-excitatory activity of benzodiazepinooxazole derivatives. For example, when the groups on R_3 and R_9 are -Br/-CH_3 and R_7 is H, p*E* is generally above 6.0 (see Table 1).

Fig. 4b shows the electrostatic contour map for the CoMFA model of p*E*, with the most active compound 54 as a reference. It can be seen from the spatial distribution of electrostatic field that introducing negative charge groups in R_3 and R_9 (red area, where electron-donating groups would be favorable for anti-excitatory activity.) and positive charge groups in R_{10} (blue area, where electron-withdrawing groups would be favorable for anti-excitatory activity.) is helpful to improve the anti-excitatory activity of benzodiazepinooxazole derivatives. For example, the p*E* of No. 17 molecule is 5.87, which is obviously higher than 4.71 of No. 36 molecule, because the substituent of the former is 3-Cl, 9-CH_3 and the latter is 3-Cl, 8-CH_3.



(a) **(b)**

Fig. 4. CoMFA (a) Steric and (b) Electrostatic field contour maps of compound 54

The steric field descriptors account for 75.9% of the total variance, while the electrostatic descriptors account for the remaining 24.1%. Therefore, the effect of electrostatic field is obviously smaller than that of space field, which indicates that hydrophobicity and space fit between substituent and target may be important factors affecting the anti-excitatory activity.

3. 3 Theoretical design of new benzodiazepinooxazole derivatives with higher anti-excitatory activity

One of the purposes of QSAR research is to design molecules from the structural information implied in the established model, and to predict the biological activity of the designed molecules through the model. According to discussions in section 3.2, the introduction of larger and negatively charged groups at R_3 and R_9 is beneficial to enhance the anti-excitatory activity of benzodiazepinooxazole derivatives. Based on this rule, eight compounds *i.e.*, compounds 55 to 62 in Table 1, were designed. According to the 3*D*-QSAR model predictions, these compounds had large p*E* values. Despite they have even better anti-excitatory activity than the most effective drug reported previously in the literature, these theoretically excellent novel benzodiazepinooxazole derivatives need to be further confirmed by biomedical experiments.

4 CONCLUSION

(1) Based on comparative molecular field analysis, a three-dimensional QSAR model was established between the anti-excitability of benzodiazepine derivatives and their structural characteristics. The R_{cv}^2 and R^2 values are 0.516 and 0.899, respectively, showing that the model has good fitting, stability and predictive ability.

(2) The following main conclusions are reached by the CoMFA model: ① electrostatic effect is obviously weaker than steric effect; ② When the substituents R_3 and R_9 are large in volume and strong in electronegativity, the anti-excitatory activity of benzodiazepine derivatives will be greatly enhanced.

(3) According to the established 3*D*-QSAR model, eight novel benzodiazepinooxazole derivatives with excellent anti-excitatory activity are designed, which still need to be verified by biomedical experiments.

The information obtained in this study provides a useful theoretical reference for designing new benzodiazepine derivatives and predicting their anti-excitatory activity, and is also a new attempt in anti-doping research.

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