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CoMFA Study on Novel Substitute Oxazolidine Derivatives

Ying Fu, Haitao Li, Qingshan Zhao and Fei Ye*

College of Science

Northeast Agricultural University

Harbin, Heilongjiang, P.R. China, 150030

yefei@neau.edu.cn. Corresponding author, E-mail: yefei@neau.edu.cn

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Abstract. A series of novel Substitute oxazolidine derivatives with potential herbicide safener activity has been modeled using a 3D quantitative structure-activity relationships approach known comparative molecular field analysis (CoMFA). The cross-validated q2 of CoMFA was 0.612, non-cross-validated R2 was 0.986, and F-test value was 120.1, respectively, with the biological activity of the compounds was expressed by pRC30 (root length). The results are critically discussed using a variety of statistical parameters. The CoMFA model was satisfactory and would be useful for the future design of new N-dichloroacetyl oxazolidine herbicide safener.

Introduction

For the last 30 years, studies on Quantitative Structure Activity Relationships (QSAR) have been unquestionably ranked as among the most important in modern chemistry and biochemistry[1]. QSAR modeling has shown to be very effective for this purpose. The underlying assumption in a QSAR study is that the structural formula contains, in principle, coded within it all of the information which predetermines the chemical, biological and physical properties of the chemical. If we could elucidate in detail how these properties are determined by structure we were able to predict such properties simply from the molecular structure[2].

CoMFA (Comparitive-molecular-field-analysis) is a 3D-QSAR method in which the molecules are placed in a 3D grid and electrostatic and steric field properties are correlated with biological activities. Since its introduction by Crammer et al. it has been extensively used for rational drug designing of ligands acting on various targets. 3D-QSAR methods facilitate the correlation of the three dimensional structures of potential drug molecules with their biological activity and in turn help to predict the activity of new molecules prior to synthesis [3].

Substituted oxazolidines are important synthetic targets due to their biological activity, pharmacological activity and their extensive use as chiral auxiliaries for synthesis of many chiral compounds[4-9]. In addition, the discovery of N-dichloroacetyl oxazolidine acting as herbicide safener has drawn widespread attention in agricultural biochemistry. The literature survey revealed that there were no reports on the 3D-QSAR of these compounds. So it was very significant to investigate the 3D-QSAR of these compounds to help us understand which factors were the key factors affecting the biological activity in order to design some novel N-dichloroacetyl oxazolidine derivatives with higher biological activity.

Computional methods

The Studied Compounds and Biological Activity Data

CoMFA studies were performed using SYBYL 6.5 molecular modeling software, running on an SGI O2 workstation. The common skeleton structure of N-dichloroacetyl oxazolidine was given in Figure 1. All studied compounds structures were list in Table I . We used the literature data for RC30, which is the concentration of drug causing 30% recovery rate of plant height or root length. All original RC30 values were converted to negative logarithm of RC30 (pRC30) in QSAR studies[10].

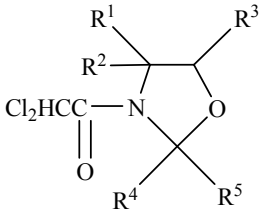

Figure 1 General structure of N-dichloroacetyl oxazolidine derivatives.

Table I Structures of all studied compounds

Entry	R^1	R^2	R^3	R^4	R^5
1	H	H	H	CH_3	C_2H_5
2	H	H	CH_3	CH_3	$CH_2CH_2CH_3$
3	H	H	CH_3	$(CH_2)_4$	
4	H	H	C_2H_5	H	H
5	H	H	C_2H_5	CH_3	CH_3
6	H	H	C_2H_5	CH_3	C_2H_5
7	H	H	C_2H_5	$(CH_2)_5$	
8	CH_3	CH_3	H	H	H
9	H	H	H	CH_3	$CH_2CH_2CH_3$
10	CH_3	CH_3	H	H	$CH_2CH_2CH_3$
11	H	H	$CH_2CH_2CH_3$	$(CH_2)_5$	
12	CH_3	H	$CH_2CH_2CH_3$	$(CH_2)_5$	
13	H	H	H	CH_3	$CH_2CH(CH_3)_2$
14	H	H	CH_3	CH_3	CH_3
15	H	H	CH_3	C_2H_5	C_2H_5
16	H	H	H	$(CH_2)_5$	
17	H	H	H	CH_3	CH_3
18	H	H	CH_3	$(CH_2)_5$	
19	C_2H_5	H	H	$(CH_2)_5$	
20	H	H	C_2H_5	C_2H_5	C_2H_5
21	CH_3	CH_3	H	$(CH_2)_5$	
22	H	H	H	C_2H_5	C_2H_5
23	H	H	CH_3	CH_3	$CH_2CH(CH_3)_2$

Molecular Modeling and Alignment Active conformation selection was a key step for CoMFA analysis. Since the crystal structure of the complex was not available, we adopted the systematic conformational search method to discover the global energy-minimum conformation for the most active compound by rotating rotatable bonds. The conformational search was performed using systematic search protocol. The rotatable bonds in all molecules were searched from 0 to 360º in 10º increments. The minimum energy conformation was thus obtained. Then the conformation with minimum energy was further optimized by SYBYL 6.5 software using minimizing module. The rest of the molecules were built by changing the required substitution of the most active compound and were minimized similarly. Finally, Gasteiger-Huckel charges were assigned to all the molecules.

Structural alignment was considered as one of the most sensitive parameters in CoMFA analysis. The accuracy of the prediction of CoMFA models and reliability of the contour are directly dependent on the structural alignment rule[11]. The most active compound was used as a template for super imposition; the common fragment was selected for alignment and the rest of the molecules were aligned on it. The aligned compounds are shown in Figure 2.

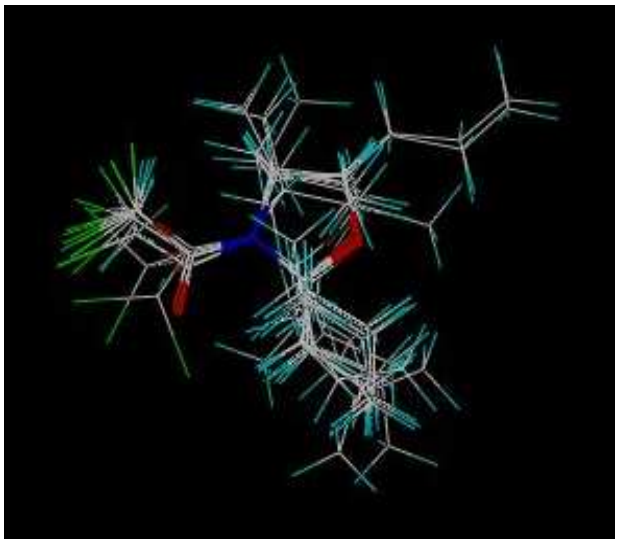

Figure 2 Alignment of the 16 studied molecules (root length)

Generation of CoMFA and Partial Least Squares (PLS) Analysis PLS analysis was used to construct a linear correlation between the CoMFA descriptors (independent variables) and the activity values(dependent variables).

To select the best model, the cross validation analysis was performed using the LOO method, which educed the square of cross validation coefficient (q^2) and the optimum number of components n. The non-cross-validation was performed with a column filter value of 2.0 to speed up the analysis and reduce the noise.

Results and Discussion.

For a reliable predictive model, the square of cross validation coefficient q^2 should be greater than 0.5. The 3D-QSAR model had high R^2 (0.986), F (120.1), and q^2 (0.612), suggesting that the established model was reliable and predictive.

The CoMFA predicted biological activity values (root length) of studied compounds and experimental values were listed in Table II. A good correlation between the predictive values and corresponding experimental values were shown in Figure 3. All data points were close to the line $Y=X$, which further indicated that the model had a good predictive ability.

Table II CoMFA results of the studied compounds of pRC_{30}

Compound	pRC_{30}(experimental	pRC_{30}(predicted)	Residuals
	Training set		
1	5.54	5.56	-0.02
2	5.54	5.55	-0.01
4	5.54	5.53	0.01
8	4.86	4.86	0.00
10	4.97	4.97	0.00
11	5.18	5.19	-0.01
12	5.17	5.17	0.00
13	5.93	5.92	0.01
14	5.54	5.53	0.01
15	5.47	5.48	-0.01
16	5.15	5.13	0.02
18	5.38	5.42	-0.04
19	5.49	5.48	0.01
21	5.09	5.08	0.01
22	5.21	5.21	0.00
Testing set			
5	5.34	5.33	0.01
17	4.91	5.09	-0.18
20	4.99	5.12	-0.13
23	5.22	5.33	-0.11

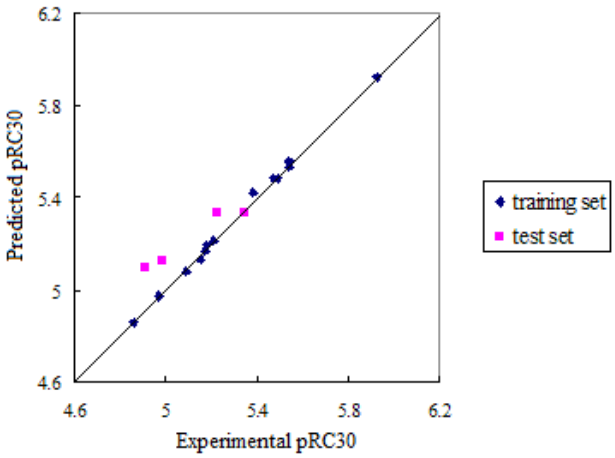

Figure 3 Plot of experimental activities versus predicted ones for CoMFA

The CoMFA steric interactions were represented by green and yellow contours while electrostatic interactions were represented by blue and red contours. The contributions of the steric and electrostatic fields to the biological activity in the CoMFA model were 57.2 and 42.8%, respectively. It indicates that both the steric and electrostatic fields had significant contribution to biological activity, but the steric field was slightly more predominant than electrostatic field. The steric and electrostatic contour map of CoMFA was displayed in Figure 4.

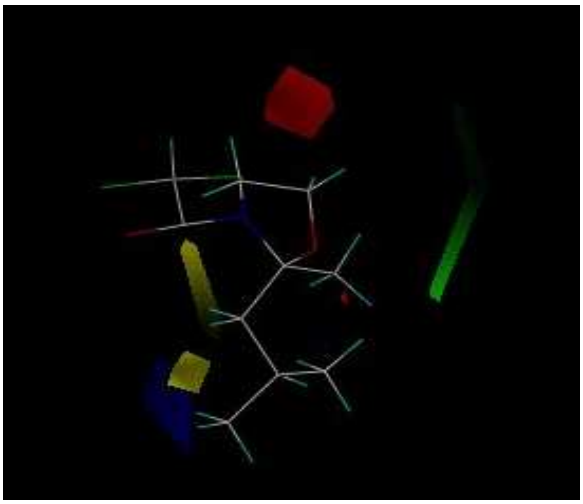

Figure 4. CoMFA steric and electrostatic contour map

The green contours characterize the regions where bulky substituents would increase the biological activity, whereas yellow contours indicate regions where bulky substituents were detrimental to the biological activity. The red contours indicate regions where negative charge increases the activity, whereas the blue contours indicate regions where negative charge reduces the activity. Figure 4 was shown, if we want to get novel N-dichloroacetyl oxazolidine compounds with higher biological activity, we need to join bulky substituents in the green region and add negative charge in the red region.

Conclusion

The study of 3D QSAR was a useful tool for the identification of chemical and structural features responsible for safey potency of this family of N-dichloroacetyl oxazolidine derivatives. In this article a general CoMFA model for N-dichloroacetyl oxazolidine derivatives based herbicides safeners for the prediction of molar pRC30 was reported. The best model developed was found to be statistically significant and could be used for predicting activity for newer scaffolds. The idea model that safety was driven by several interactions (steric, electrostatic, and H bonding) which occur simultaneously and synergically. The model also provided an understanding of the importance of certain structural features, which were necessary for these compounds to exhibit good safty activity, and should be used for the designing of new potentially active compounds to develop novel N-dichloroacetyl oxazolidine herbicide safeners.

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