Quantitative Structure-Activity Relationship Studies of Bifendate Derivatives

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The quantitative structure-activity relationship ($QSAR$) of bifendate derivatives was investigated by molecular dynamics and quantum chemical *ab initio* method, and E_{HOMO}, E_{LUMO}, Φ and the population of atom charges were calculated. The quantitative relationship between activity of the compounds and E_{HOMO}, log$P$ and Φ was analyzed by using the stepwise multiple regression based on Hansch-Fujita approach. A correlative equation was well established. The multiple correlation coefficient r is 0.6664 and the test-value of F is 3.46085.

Key Words: Bifendate derivatives, QSAR, *Ab initio*, HF/ 3-21G*, Hansh-fujita.

INTRODUCTION

Bifendate is a kind of effective drugs, which enable to decrease the contents of enzyme in the bodies. It can reduce the alanine aminitransferase (ALT) level of blood serum and restrain the cells deteriorating[1], and it has obvious effect on hepatitis caused by chemotheraph medicines[2,3]. Bifendate derivatives based on bifendate have been synthesized by Yue hong-yi *et al*[4,5] in Shenyang Pharmaceutical University. The structure-activity relationship was studied through the comparable molecular force field analysis (CoMFA)[6], but the *QSAR* equation was not given.

In order to further investigate the *QSAR* of the series of compounds, we performed conformation analysis about the title compounds by using molecular mechanics. The geometrical structures of 17 derivatives were optimized by means of the self-consistent *ab initio* method. The *QSAR* of these compounds was discussed based on Hansch-Fujita approach to establish foundation for designing novel bifendate derivatives with higher activity and lower toxicity.

EXPERIMENTAL

The three-dimension structures of the compounds were built by the Chem3D package. The MM2 force field was applied to search for the low energy conformations for each molecule[7], the step interval is 2.0 fs and the

frame interval is 10 fs, the terminative step is 10000, the heating/cooling rate is 4.18 kJ (atom·ps) and the target temperature is 300K.

Based on the lowest energy conformations calculated by MM2 force field, the geometry structures of bifendate derivatives were optimized at the restricted Hartree-Fock(HF) method with the basis set of 3-21G*. The frequency calculations for each molecule were carried out at 298.15K and 1 atmosphere of pressure based on the optimized geometries calculated by HF/3-21G*. All of the quantum chemistry calculations was performed by using the Gaussian98 package on Pentium IV PC.

RESULTS AND DISCUSSION

Structures of the bifendate derivatives: The structures of seventeen compounds were listed in Table-1 and the activities of bifendate derivatives log $(1/c)$[5] were shown in Table-3.

TABLE-1
SKELETON STRUCTURE AND SUBSTITUTING GROUP R_1 OF
BIFENDATE DERIVATIVES

No.	R_1	Skeleton structure
1	CH_3	
2	$CH(CH_3)_2$	
3	$CH_2CH_2CH_3$	
4	$CH_2CH_2CH_2CH_3$	
5	$CH(CH_3)CH_2CH_3$	
6	$CH_2CH(CH_3)_2$	
7	$CH_2(CH_2)_3CH_3$	
8	$(CH_2)_2CH(CH_3)_2$	
9	$CH(((CH_2)_2)_2)CH_2$	
10	$CH_2(CH_2)_6CH_3$	
11	CH_2Ph	
12	$CH(CH_3)Ph$	
13	$CH(CH_2CH_3)Ph$	
14	CH_2CH_2Ph	
15	CH_2CH_2OH	
16	$CH_2CH_2OCH_3$	
17	$CH_2CH_2CH_2OH$	

Molecular mechanics calculation: The lowest energy conformation of compound 3, which has the higher activity was searched by the MM2 force field method firstly. The different conformations and the relative energy values of the compound 3 were shown in Fig.1 and Table-2, respectively. The difference among the conformations was mainly represented in the space position of the two benzene rings of molecule. The total energy of conformation 1 was lower than that of conformation 2, so conformation 1 was regarded as the lowest energy conformation. This method was used to search the lowest energy conformations of other bifendate derivatives.
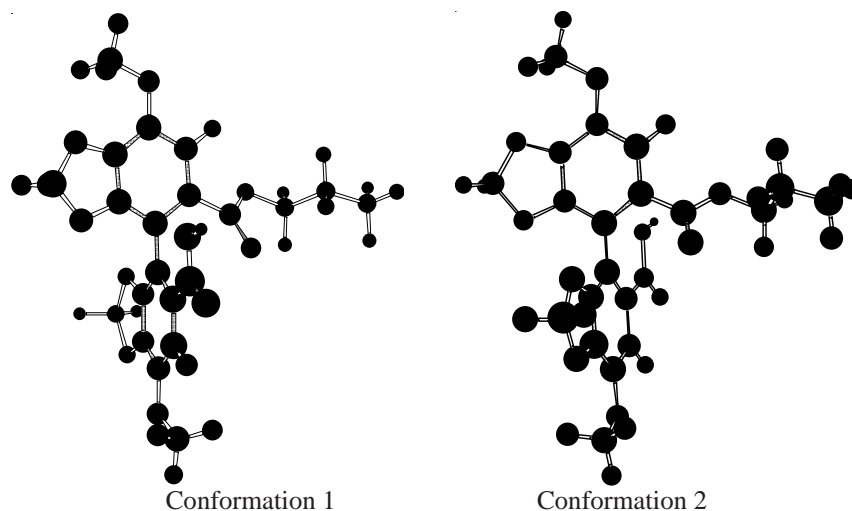
Conformation 1   Conformation 2
Fig. 1. The different conformations of compound 3

TABLE-2
ENERGY OF THE DIFFERENT CONFORMATIONS OF
COMPOUND 3 BASED ON MM2 FORCE FIELD(kJ/mol)

Energy	Conformation 1	Conformation 2
Stretch	2.0005	2.0289
Bend	24.4943	21.3051
Stretch-Bend	0.2579	0.1639
Torsion	-8.5240	-1.5638
Non-1,4 VDW	-5.0884	-7.0943
1,4 VDW	15.5091	16.4550
Dipole	7.2551	7.5121
Total	35.8860	38.8089

Quantum chemistry calculation: Computational quantum chemistry may be used as an analytical instrument in structure analysis. It has power predictive to assist synthesis and characterization. The *ab initio* method was performed to optimize the lowest energy conformations calculated by MM2 force field of the bifendate derivatives at HF/3-21G* level. The frequency calculations for each molecule showed that there were no imaginary frequencies appeared, so the calculation results should be reliable. A great variety of the quantum chemical parameters were taken from the calculation results, such as the highest occupied molecular energy (E_{HOMO}), the lowest unoccupied molecular orbital energy (E_{LUMO}), the total charges of the group except R group (Q_1), the angel between the two benzene rings (Φ) etc.. Besides, the physical property parameters of molecule had important effects on the activity of the compound. The hydrophobic parameter (log P) of title compounds were determined in the documents reported[5]. The selected parameters were listed in Table-3.

TABLE-3
THE VALUE OF THE SELECTED PARAMETERS

No.	E_{HOMO}/ Hartree	E_{LUMO}/ Hartree	Q_1	$\Phi/°$	$\log P$	$\log(1/c)$[5]
1	-0.30128	0.09105	-0.39120	68.2	1.404	0.389
2	-0.30425	0.09409	-0.40076	68.5	1.970	1.540
3	-0.30087	0.09125	-0.39892	68.2	2.067	2.650
4	-0.30364	0.08701	-0.37414	63.3	2.474	1.165
5	-0.30451	0.09356	-0.40781	77.3	2.366	2.217
6	-0.30116	0.09078	-0.39680	67.8	2.453	0.703
7	-0.30327	0.09052	-0.40464	68.9	2.923	0.994
8	-0.30807	0.08629	-0.41720	63.6	2.840	1.241
9	-0.30865	0.08603	-0.41491	63.9	2.850	-0.515
10	-0.30279	0.09083	-0.40120	68.9	3.117	1.239
11	-0.30694	0.09117	-0.37833	69.5	2.378	0.604
12	-0.30891	0.07958	-0.39252	61.1	2.733	0.116
13	-0.30994	0.07973	-0.38801	62.1	3.146	0.302
14	-0.31351	0.08015	-0.40613	67.4	2.806	0.457
15	-0.30646	0.09150	-0.39581	68.6	0.882	-0.243
16	-0.30787	0.08824	-0.41482	64.5	1.421	0.733
17	-0.30497	0.09287	-0.39272	66.4	0.990	-0.671

The stepwise multiple regression (*SMR*) analysis: Linear correlation level was measured by correlation analysis through comparing the correlation coefficient among the parameters[8,9], the value of the correlation coefficient was between -1 and 1. The Pearson correlation coefficient(R) was common coefficient, which measured the degree of the linear correlation between two parameters. The larger the coefficient, the better the correlation. The Pearson correlation coefficient was listed in Table-4, which was obtained through the correlation analysis among the parameters in Table-3.

By comparing to the Pearson correlation coefficient of the bifendate derivative, the parameters of E_{HOMO}, E_{LUMO}, Φ, $\log P$ had great correlation with the activity.

The reaction between the active molecules and the receptor mainly happened on the frontier molecular orbital and near orbital. E_{HOMO} can be regarded as the measurement of the capability that the compound offers electrons to receptor, higher E_{HOMO} means the electrons of the compound are transferred to receptor more easily. On the contrary, E_{LUMO} can be regarded as the measurement of the capability that the compound accepts electrons, lower E_{LUMO} means the compound accepts electrons more easily. According to Table-4, the correlation coefficient R between $\log (1/c)$ and E_{HOMO} was 0.440, which showed that $\log (1/c)$ had positive correlation with E_{HOMO}. In a word, the higher E_{HOMO} of the compound, the higher its activity,

and higher E_{HOMO} means the compound donates electrons easily. Simultaneously, E_{LUMO} also had positive correlation with log (1/c), higher E_{LUMO} means the compound accepts electrons difficultly. So the bifendate derivatives work as electron donor in the reaction with the receptor, and E_{HOMO} as electronic parameter was considered.

TABLE-4
PEARSON CORRELATION COEFFICIENT R AMONG THE
SELECTED PARAMETERS

R	log (1/c)	E_{HOMO}	E_{LUMO}	Q_1	Φ	log P
log (1/c)	1.000	0.440	0.320	-0.116	0.467	0.232
E_{HOMO}	0.440	1.000	0.749	0.225	0.407	-0.258
E_{LUMO}	0.320	0.749	1.000	-0.002	0.695	-0.525
Q_1	-0.116	0.225	-0.002	1.000	-0.110	--0.107
Φ	0.467	0.407	0.695	-0.110	1.000	-0.186
log P	0.232	-0.258	-0.525	-0.107	-0.186	1.000

Hansch-Fujita approach showed that if the organics' metabolism process in the bodies were ignored, the activities of compounds were the linear function of the electronic effect, the volume effect and the hydrophobic effect[10,11]. E_{HOMO} reflected the electronic effect, log P reflected the hydrophobic effect, Φ reflected the volume effect. Based on the correlation analysis with E_{HOMO}, Φ, log P as the independents and log (1/c) as the dependent, the regression equation was established through the stepwise multiple regression as eq. 1.

$$\log (1/c) = 23.59228 + 98.09509 E_{HOMO} + 0.08999\Phi + 0.49558 \log P$$
$$n = 17, \quad r = 0.6664, \quad F = 3.46085 \qquad (1)$$

n: The compound numbers, r: The multiple correlation coefficient, F: F-test value.

The multiple correlation r of eq. 1 was 0.6664 and F-test value was 3.46085, which manifested log (1/c) had better linear correlation with E_{HOMO}, Φ, log P. So the QSAR model had good predictability.

In the light of eq. 1, E_{HOMO} had maximum effect to the activity of the bifendate derivatives (The partial coefficient was 98.09509), so it further showed the series of derivatives reacted with the receptor as a electron donor. The greater E_{HOMO}, the better activity of corresponding molecule. Which lead to nucleophilic reaction easily. In Table-3, compared to others, the compound 3 had the best activities (2.650) corresponding to the highest E_{HOMO} (-0.30087).

The hydrophobic parameter (log P) is another important factor that affected the activities log (1/c) of the compounds. The hydrophobic effect was positive to the proportion of the hydrophobic groups in the molecule. The coefficient of log P was positive in eq. 1, which showed that the larger

hydrophobic effect of the compounds linked to the higher $\log(1/c)$ and the compound reacted with acceptor easily.

In addition, the difference of Φ between two benzene rings leads to the variation of the molecular activity. According to Table-3, the bifendate derivatives had the better activities when Φ was between 77.3° and 68.9°.

The above studied results showed that E_{HOMO} was the main factor influencing the activities of bifendate derivative, so we can introduce the donor groups onto the molecular to enhance the activity of the bifendate derivatives. Besides, changing F and hydrophobicity of molecule considered in synthesis would enhance activities of the compounds. The multiple correlation $r = 0.6664$ of eq. 1 illuminated that the activities of bifendate derivative were also affected by other factors,which need to be further studied.

ACKNOWLEDGEMENTS

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