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Quantitative Structure-Activity Relationship Studies of 1,2,4-Triazole Derivatives

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The geometrical structures of the 1,2,4-triazole derivatives were optimized by means of the self-consistent *ab initio* restricted Hartree Fock level with 6-31G basis set. The quantitative structure-activity relationship (QSAR) of the 1,2,4-triazole derivatives was systematically investigated based on Hasch-Fujita approach. A correlative equation between pIC_{50} and *DELH*, E_{LUMO}, log P and MR was well established. The correlation coefficient *r* is 0.7511 and the introduction of electron-withdrawing groups onto the molecule would be favourable to the activity of the compounds. Besides, changing the volume and hydrophobicity of molecule would be useful to design the novel active molecule.

Key Words: 1,2,4-Triazole derivatives, QSAR, *Ab initio*, HF/6-31G , Hansh-fujita.

INTRODUCTION

1,2,4-Triazole derivatives represent an interesting class of heterocycles[1] and have become the most rapidly expanding group of antifungal compounds with the advantage of toxicity, high oral bioavailability and broad-spectrum activity including most yeasts and folanentous fungi[2-4]. The triazole fungicides are agrochemicals used world wide in the agricultural industry due to their wide spectrum of action[5]. Some of the new triazole antifungals with higher activity and lower toxicity can inhibit systemic fungal infections in patients suffered with tumours , immunodeficiency or immunosuppression[6]. Among triazoles efficient stimulators of heart function[7-9], inhibitors of histidine biosynthesis[10] and fungicides of the second generation[11,12] were revealed.

The series of novel 1,2,4-triazole derivatives have been reported[13-15]. In order to investigate the quantitative strucutre activity relationship (QSAR) of this series of compounds, we performed conformation analysis about the title compounds by using molecular mechanics. And the geometry structures of the twelve 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 triazole fungicides with higher activity and lower toxicity.

EXPERIMENTAL

Computational quantum chemistry may be used as an analytical instrument in structure analysis. It has predictive power to assist synthesis and characterization. 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[16], the step interval is 2.0fs and the frame interval is 10fs, the terminative step is 10000, the heating/cooling Race is 4.18 kJ(atom.ps) and the target temperature is 300 K.

Basing on the lowest energy conformations calculated by MM2 force field, the geometrical structures of 1,2,4-triazole derivatives were optimized at the restricted Hartree-Fock(HF) method with the basis set of 6-31G . The frequency calculations for each molecule were carried out at 298.15K and 1 atmosphere of pressure basing on the optimized geometries calculated by HF/6-31G, and there were no imaginary frequencies appeared. Thus the calculation results should be reliable. All of the quantum chemistry calculation was performed by using Gaussian98 package on Pentium IV PC.

In addition, the correlation analysis and regression analysis were computed for the quantum parameters calculated by using Gaussian98 package by the statistics software SPSS.

RESULTS AND DISCUSSION

The structures of 12 derivatives of 1,2,4-triazole are listed in Fig. 1 and Table-1. The characterizations were performed by IR analysis, element analysis and NMR analysis and the activities of title compounds, pIC_{50} (the inhibiting rates towards fungi, such as wheat gibberellin, apple ringspot, tomato early blight)[13], were given in Table-2.

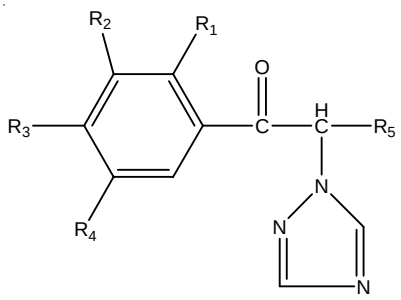


Fig. 1. General structure of the 1,2,4-triazole derivatives

The quantum chemistry and molecular mechanics calculation: The three-dimension structures of the compounds were built by the Chem3D package and the low energy conformations for each molecule were searched by the MM2 force field method.

TABLE-1
THE SUBSTITUTING GROUP OF THE TITLE COMPOUNDS

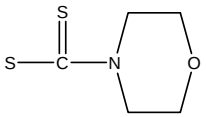
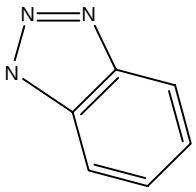
No.	Substituting group				
	R_1	R_2	R_3	R_4	R_5
1			Ph		
2					
3	F			Me	
4			Cl		
1			Me		
2	Cl			Cl	
3					
4	Cl		Cl		
5		Cl	Cl		
6			Cl		
7			Br-Ph		
8			F		

TABLE-2
THE DATA OF THE QUANTUM CHEMICAL PARAMETERS

No.	E_{HOMO}	E_{LUMO}	*DELH*	logP	μ	V	MR	pIC_{50}
1	-0.31952	0.04764	0.36716	4.96	3.8891	1127.62	57.92	120
2	-0.33454	0.02859	0.36313	4.88	4.5586	988.68	63.34	35
3	-0.32017	0.03679	0.35696	4.18	8.7170	969.83	58.86	15
4	-0.33979	0.04091	0.3807	4.25	3.6614	959.44	58.84	35
1	-0.32933	0.05352	0.38285	4.41	4.8883	881.91	24.44	70
2	-0.34035	0.05340	0.39375	5.35	4.2157	911.29	28.82	100
3	-0.33081	0.04980	0.38061	4.10	4.3254	830.33	19.83	125
4	-0.34068	0.05221	0.39289	5.35	1.9405	911.81	28.82	255
5	-0.33973	0.02873	0.36846	5.35	1.9265	917.43	28.82	85
6	-0.33599	0.03830	0.37429	4.73	2.9036	875.53	24.33	155
7	-0.33072	0.03849	0.36921	6.34	3.1759	1107.26	30.72	160
8	-0.33017	0.05506	0.38523	4.35	1.8516	840.95	19.74	100

The *ab initio* method was performed to optimize the lowest energy conformations calculated by MM2 force field of the 1,2,4-triazole derivatives at HF/6-31G level. 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}), E_{LUMO}-E_{HOMO} (*DELH*), the molecular dipole moment (μ) etc.

Besides, the physical properties parameters of molecule had important effects on the activity of the compound. The molecular molar volume (V), the *n*-octanol/water partition coefficient (log *P*) and the molar refractivity (MR) were calculated by using Hyperchem software. The selected parameters were listed in Table-2.

Correlation analysis and regression analysis: Linear correlation level was measured by correlation analysis through comparing the correlation coefficient among the parameters[17,18], the value of the correlation coefficient(R) was between -1 and 1. The Pearson correlation coefficient was common coefficient, which measured the degree of the linear correlation between the two parameters. The larger the coefficient, the better the correlation. The Pearson correlation coefficient was listed in Table-3, which was obtained through the correlation analysis among the parameters in Table-2.

TABLE-3
PEARSON CORRELATION COEFFICIENT AMONG THE QUANTUM CHEMICAL PARAMETERS

R	pIC_{50}	E_{HOMO}	E_{LUMO}	·E	log P	μ	V	MR
pIC_{50}	1.000	-0.275	0.376	0.484	0.505	-0.607	-0.028	-0.548
E_{HOMO}	-0.275	1.000	0.074	-0.570	-0.279	0.588	0.408	0.320
E_{LUMO}	0.376	0.074	1.000	0.777	-0.198	-0.145	-0.334	-0.485
·E	0.484	-0.570	0.777	1.000	0.013	-0.491	-0.532	-0.601
log P	0.505	-0.279	-0.198	0.013	1.000	-0.409	0.531	-0.142
μ	-0.607	0.588	-0.145	-0.491	-0.409	1.000	0.157	0.510
V	-0.028	0.408	-0.334	-0.532	0.531	0.157	1.000	0.618
CMR	-0.548	0.320	-0.485	-0.601	-0.142	0.510	0.618	1.000

By comparing to the Pearson correlation coefficient of the title compounds, the parameters which had great correlation with the activity, E_{LUMO}, *DELH*, log P, μ, MR, were selected. Basing on the correlation analysis, the four equations were established through the multiple linear regression respectively as below:

pIC_{50} = -65.50293 + 701.1752 *DELH* -14.59534μ-1.01865 MR
n = 12, *r* = 0.67, *F* = 2.2159 (1)

pIC_{50} = -703.06928 +1671.99399 *DELH* +45.79806 log P-1.18196 MR
n = 12, *r* = 0.7354, *F* = 3.14078 (2)

pIC_{50} = -65.50293 +1435.67542 E_{LUMO} -16.69828μ-0.79882 MR
n = 12, *r* = 0.6908, *F* = 2.43421 (3)

pIC_{50} = -204.59123 + 2267.23139 E_{LUMO} + 52.56834 log P-1.21214 MR
n = 12, *r* = 0.7488, *F* = 3.40294 (4)

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

Eq.2 and Eq.4 had the better correlation by comparing to **r** among the four equations, so *DELH*, E_{LUMO}, log P, MR were the main factors affected the activity of the serial compounds. The new equation (5) was established by the regression analysis with *DELH*, E_{LUMO}, log P, MR as the independents and pIC_{50} as the dependent.

pIC_{50} = -404.10002 + 590.64 *DELH* + 1784.56057 E_{LUMO} + 51.4312 log P -1.10839 MR
n = 12 *r* = 0.7511 *F* = 2.2646 (5)

Hansch-Fujita approach showed that if the organics metabolism process in the body are ignored, the activities of compounds are the linearity function of the electronic effect, the volume effect and the hydrophobic effect[19,20]. The parameters described the three kinds of effect were listed in Table-2. E_{HOMO}, E_{LUMO}, *DELH* reflected the electronic effect; log P, μ reflected the hydrophobic effect; V, MR reflected the volume effect.

The electronic parameters selected through correlation analysis were *DELH*, E_{LUMO}, which have very important effect on the activity of 1,2,4-triazole derivatives. *DELH* was indicative of the stability of the compounds. The larger *DELH* , the better the stability of the compounds. The reaction between the active molecules and the receptor mainly happened on the frontier molecular orbital and near orbital. If the compound works as a electron donor in the reaction with the receptor, higher E_{HOMO} means it is easy to donate electrons. So the compound has higher activity accordingly. If the compound works as a electron acceptor in the reaction with the receptor, lower E_{LUMO} means it is easy to accept electrons and its activity should be higher.

log P reflecting hydrophobic effect was taken for important molecular property parameters in Hansch-Fujita approach, which was also the macroscopic hydrophobic parameter. It reported the molecular fat-soluble extent, MR reflecting the volume effect was either steric factor or disporsion force factor. When the coefficient of MR was negative value in the relative equation, MR was caused by steric factor generally. Othewise, it was the measure of polarization factor of molecule or group[21].

According to Table-3, the correlation coefficient of *DELH*, E_{LUMO}, MR, pIC_{50} was 0.484, 0.376, -0.607 and -0.548, respectively, which showed that pIC_{50} had negative correlation with MR and positive correlation with *DELH*, E_{LUMO}. These were in agreement with eq. 5. The multiple correlation *r* of eq. 5 was 0.7511 and F-test value was 2.2646 , which manifested pIC_{50} had better linear correlation with *DELH*, E_{LUMO}, MR. So the QSAR model had good predictability. In the light of Eq.5, E_{LUMO} had maximum effect to the activity of the 1,2,4-triazole derivatives (*r* = 1784.56057), so it is predicted that this series of derivatives react with the receptor as a electron donor. The greater E_{LUMO}, the better activity of corresponding compounds lead to nucleophilic reaction easily. *DELH* had the positive correlation with pIC_{50}, which showed that the smaller *DELH* had lower activity. According to Table-2, *DELH* of I3 was minimum (0.35696) corresponding to the lowest pIC_{50} (15) ; the pIC_{50} of II_4 was highest (255) and its *DELH* was larger (0.39289). Basing on Table-3, the Pearson correlation coefficient of *DELH* and E_{LUMO} was 0.7777, which illustrated the better linear correlation between *DELH* and E_{LUMO}. E_{LUMO} of II_1, II_2, II_4, II_8 were larger corresponding to the higher *DELH*, and the activity of II_4 was highest (0.05221). By the

way, the larger molecular weight of substituting group R_3 followed with the higher activity according to $II_7 > II_6 > II_8 > II_1$.

The hydrophobic parameter (log P) is another important factor that would affect the activities (pIC_{50}) 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. 5, which showed that the larger hydrophobic effect of the compounds linked to the higher pIC_{50}, and the compound reacted with acceptor easily. The size of log P was dependent upon V (Pearson correlation coefficient was 0.531) and μ (Pearson correlation coefficient was -0.409). To the highest activity compound II_4, there were the larger log P = 5.35, the larger V = 911.81 and the smaller μ=1.9405.

In addition, the coefficient of log P was negative in eq. 5, which manifested MR had been the symbol of the molecular volume effect. The larger V, the higher pIC_{50}.

All the parameters selected in the regression equation were the general parameters calculated by the quantum chemistry and molecular mechanics method. The parameters weren't dependent upon the synthesis of the compounds, so according to the general parameters which had better predictability, we can adjust the parameters through choosing the different substituting group and get the required compounds corresponding to the best parameters, next to selecting the high activity compound, which was useful for the synthesis and activity study. Thus in this study, we can introduce the electron-withdrawing groups onto the molecular to enhance the activity of the title compounds. Besides, we can also change the volume and hydrophobicity of molecule to design the active molecule.

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REFERENCES

1. M.B. Bushuev, A.V. Virovets, Y. Garcia, C. Gieck, L.A. Sheludyakova, V.N. Ikorskii, W. Tremel, P. Gütlich and L.G. Lavrenova, *Polyhedron*, **21**, 797 (2002).
2. C.A. Kauffman and P. L. Camer, *Adv. Pharmacol.*, **39**, 143 (1997).
3. C.A. Kauffman, *Clin. Infect. Dis.*, **22**, 148 (1996).
4. R. Fromting, *Clin. Microbiol. Rev.*, **1**, 187 (1988).
5. I.S. Kim, L.A. Beaudette, J.H. Shim, J.T. Trevors and Y.T. Suh, *Plant Soil*, **239**, 321 (2002).
6. Y. Chu, M.-X. Xu and L.U. Ding, *Chin. Chem. Lett.*, **15**, 1011 (2004).
7. I.V. Mashevskyaya, L.V. Aniskina, Y.B. Vikharev, V.A. Safin, S.V. Kol'tsova and A.N. Maslivets, *Khim.-Farm. Zh.*, 897 (2001).

8. M. Butters, J. Ebbs, S. Green, J. Morland, C. Matthew, C. Murtiashaw and A. Pettman, *Org. Proc. Res. Dev.*, **5**, 28 (2001).
9. M. Geslin, D. Gully and J.P. Maffrand, French Patent 2802530 (1999); Ref. Zh. Khim., 10133P, (2002).
10. L. Ventura, J.P. Gonzales and D. Ramon, *Microbiol. Lett.*, **149**, 207 (1997).
11. K. Tomoyuki, I. Takashi, Y. Akihiro, H. Hiroshi, M. Yoshihiro, H. Ryogo, O. Kenji and I. Katsumi, *Chem. Pharm. Bull.*, **48**, 1935 (2000).
12. J. Stetter and F. Lied, *Angew. Chem., Int. Ed.*, **39**, 1725 (2000).
13. J. Wan, C.-L. Li, X.-M. Li and S.S. Zhang, *Chem. Res. Chin. Univ.*, **22**, 465 (2006).
14. J. Wan, C.-L. Li, X.-M. Li, S.S. Zhang and P. Kai, *Acta Cryst.*, **E61**, 3232 (2005).
15. J. Wan, C.-L. Li, X.-M. Li, L.-Z, Xu and S.S. Zhang, *Acta Cryst.*, **E61**, 3903 (2005).
16. L.S. Xu, Y.P. He and Z.H. Li, *Acta Chim. Sin.*, **60**, 1784 (2002).
17. L. Xun, Stoichiometry Methods, Peking, Science Press (1997).
18. Z.-Q. He, New Statistics Analysis Methods and Application, Peking: Peking University Press (1998).
19. C. Hansch, Structure-Activity Relationships, New York, Dergmon Elmsford (1973).
20. C. Hansch and A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology, New York (1979).
21. G.F. Yang, Y. Ding and H.Z. Yang, *Chem. J. Chinese Univer.*, **25**, 71 (2004).

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