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QSAR Study on Pyridazinone Derivatives

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The 3D structures for 16 kinds of pyridazinone derivatives were confirmed by density functional theory (DFT) method at B3LYP/3-21G level. Then the structure parameters, the electric parameters, the physical property parameters of molecules were obtained. The quantitative structure-activity relationship including bi-parametric, tri-parametric, tetra-parametric models of the title compounds was established by the multiple linear regression method. It is shown in the models that ΔE and log P were the key factors to affect the fungicidal activities against housefly larvae. The higher ΔE and the lower log P, the higher fungicidal activities.

Key Words: Pyridazinone derivatives, Quantum chemistry, B3LYP/3-21G, Multiple linear regression, Fungicidal activities.

INTRODUCTION

Heterocyclic compounds are main compounds for novel pesticides development. Pyridazinone is a kind of heterocyclic compounds with the favourable biological activity[1,2]. In 1949, it was first reported by Schoene and Hofmann that the pyridazinone containing hydroxyl had certain restraining trains for disintegrating of plant cells, which prompted the rapid development of pyridazinone derivatives in agricultural pesticide fields. The use of pyridazinone ring as parent carved out new ways for preparation of novel agricultural pesticides.

Pyridazinone derivatives had the favourable weeding, disinfectant, killing mite and fungicidal capacity[3-5]. At present, some pesticides of pyridazinone derivatives regarded as commodities already appeared, such as plant growing regulators, weedicides, bactericides, insect growing regulators, *etc*. With the rapid development of pyridazinone derivatives research, a great deal of new pesticides with high effect are more and more produced.

The synthesis and biological activity about 16 kinds of pyridazinone derivatives were reported in the document[6]. But the position of substituent R_1 in benzene ring was not confirmed and the quantitative structure-

activity relationship was not discussed. In present study, each kind of isomeric compounds was optimized with DFT at B3LYP/3-21G level to search for the stable configurations. On the basis of stable configurations, QSAR study of pyridazinone derivatives have been developed.

EXPERIMENTAL

The 3D structures of title compounds were built by the Chem3D package. The MM2 force field was applied to search for the lowest 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 Race is 4.18 kJ (atom·ps) and the target temperature is 300 K.

On the basis of lowest energy conformations calculated by MM2 force field, the geometry structures of the pyridazinone derivatives were optimized with DFT at B3LYP/3-21G level and the 16 optimal structures were chosen to further study. The quantum chemistry calculation was performed by Gaussian98 package on Pentium IV PC.

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

RESULTS AND DISCUSSION

Choice of stable configurations: 16 Kinds of pyridazinone derivatives were reported[6] and its 2D structures are shown in Fig. 1 and Table-1. The fungicidal activities (FA) of compounds against housefly larvaes[6] are listed in Table-4. But the position of substituent R_1 in benzene ring was not confirmed. In term of chemical principle, stability of isomeric compounds was discrepant. Organic synthesis reactions could proceed towards a direction what could generate into the most stable production. So in present study, it was the first question required to be selected that searching for the lowest energy configurations, *i.e.*, the stable structures.

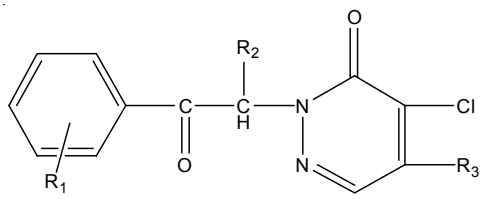

Fig. 1. 2D structures of pyridazinone derivatives

The optimal calculation method had been selected before the stable structures were chosen. To the second class of compounds (**2-a, 2-b, 2-c**), the two methods, HF/3-21G and B3LYP/3-21G, were applied, respectively. The values of total energy are shown in Table-2.

TABLE-1
SUBSTITUENTS OF PYRIDAZINONE DERIVATIVES

Compound	R_1	R_2	R_3
1-a, b, c	Cl	H	Cl
2-a, b, c	CH_3	H	Cl
3-a, b, c	OCH_3	H	Cl
4-a, b, c	Cl	CH_3	Cl
5-a, b, c	CH_3	CH_3	Cl
6-a, b, c	OCH_3	CH_3	Cl
7-a, b, c	Cl	H	$NHCH_3$
8-a, b, c	CH_3	H	$NHCH_3$
9-a, b, c	OCH_3	H	$NHCH_3$
10-a, b, c	Cl	CH_3	$NHCH_3$
11-a, b, c	CH_3	CH_3	$NHCH_3$
12-a, b, c	OCH_3	CH_3	$NHCH_3$
13	H	H	Cl
14	H	CH_3	Cl
15	H	H	$NHCH_3$
16	H	CH_3	$NHCH_3$

a, b, c: stand for *o*-, *m*- and *p*-positions of substituent R_1, respectively.

TABLE-2
TOTAL ENERGY VALUES OF COMPOUND 2 BY DIFFERENT CALCULATION METHODS

Compounds	Et/A.U. (HF/3-21G)	Et/A.U. (B3LYP /3-21G)
2-a	-1667.0479	-1673.1146
2-b	-1667.0429	-1673.1100
2-c	-1667.0374	-1673.1040

According to Table-2, the calculation results were quite close between HF and B3LYP, but the lowest energy was obtained by the B3LYP method. So B3LYP/3-21G was adopted to calculate the series of pyridazinone derivatives in the succedent research. The values of total energy computed by B3LYP/3-21G are listed in Table-3. In the light of lowest energy principle, 12 stable structures noted by "*" in Table-3 are attained from each class of isomeric compounds (*o*-position, *m*-position, *p*-position). According to Table-3, the positions of substituent R_1 were in *o*- or *p*-commonly, only were compound **7** and **8** in *m*-position.

Molecular descriptors: Certain molecular properties were up to the structure of molecule itself. Once the structure of molecule was confirmed,

TABLE-3
CALCULATED TOTAL ENERGY OF THE TITLE COMPOUNDS BY B3LYP/3-21G METHOD

Compound	Et/A.U.	Compound	Et/A.U.
1-a	-2091.2600	7-a	-1728.1672
1-b	-2091.3994	7-b*	-1728.1732
1-c*	-2091.4008	7-c	-1728.1518
2-a*	-1673.1146	8-a	-1309.8772
2-b	-1673.1100	8-b*	-1309.8788
2-c	-1673.1040	8-c	-1309.8742
3-a*	-1747.9081	9-a*	-1384.6707
3-b	-1747.9012	9-b	-1384.6625
3-c	-1747.9027	9-c	-1384.6517
4-a*	-2130.5063	10-a*	-1767.2678
4-b	-2130.5058	10-b	-1767.2674
4-c	-2130.4997	10-c	-1767.2524
5-a*	-1712.2183	11-a	-1348.9790
5-b	-1712.2177	11-b	-1348.9784
5-c	-1712.2149	11-c*	-1348.9822
6-a	-1787.0112	12-a	-1423.7717
6-b	-1787.0100	12-b	-1423.7707
6-c*	-1787.0175	12-c*	-1423.7737

*Stands for stable configuration among isomeric compounds.

the properties of this molecule were ascertained subsequently. So the purpose that modifying the intrinsic characters to change the properties of molecule could be realized, which was the aim of QSAR research.

Molecular activity might be affected by some physical-chemical properties of molecules, such as frontier molecular orbital. According to the molecular orbital theory of chemical reaction, LUMO, as an electron acceptor, represents the ability to obtain electron, but HOMO, as a donor, displays the capability to donate electron. The transition states are formed during interaction between LUMO (electron acceptor) and HOMO (electron donor) of the reacting compound. So it is significant that the research of frontier molecular orbital to verify the activity position and reaction mechanism.

In addition, skeleton structures, charges in the ring, properties of substituent, physical parameters of compounds all affected to molecular activities to some extent. So these parameters were selected below.

Electronic parameters: Et, E_{HOMO}, E_{LUMO}, ΔE, Q_{ph};
Hydrophobicity parameters: μ, log P, P;
Steric parameters: V, S, M.

Here and hereafter, Et, E_{HOMO}, E_{LUMO}, ΔE and Q_{ph} computed with Gaussian represented the total energy of stable configurations. The highest occupied molecular orbital energy, the lowest unoccupied molecular orbital energy, energy difference between the frontier molecular orbitals and total charges of benzene ring, respectively. And μ, log P, P, V, S and M obtained by Hyperchem software were on behalf of dipole moments, logarithm of *n*-octanol/water partition coefficient, polarizability, molecular volume, molecular surface and molecular weight, respectively. The above parameters are shown in Table-4.

Statistical analysis: To investigate the relationships of molecular structure and activity, the relativity between these parameters selected and biological activity required to be further studied. In multiple linear regression analysis, the descriptors in the regression equation must be independent and the correlation of each one of descriptors with each other and with fungicidal activity was calculated and presented by a Pearson correlation matrix in Table-5. To eliminate the inter-correlated parameters and minimize the information overlap in the equation, the variables with lower inter-correlation ($|r| < 0.5$) were considered only[8].

According to Table-5, the parameters which had positive relations with fungicidal activity were Et, E_{HOMO}, E_{LUMO}, ΔE, μ, V, S and R; the others, Q_{ph}, log P, P and M, had negative correlative to fungicidal activity.

In the molecular orbital theory, the reaction between the active molecules and the receptor mainly happened on the frontier molecular orbital and near orbital. If the compound works as an electron donor in the reaction with the receptor, higher E_{HOMO} means easy to donate electrons. If the compound works as an electron acceptor in the reaction with the receptor, lower E_{LUMO} means it is easy to accept electrons.

Due to the positive relationship between fungicidal activity and the frontier molecular orbital (E_{HOMO}, E_{LUMO}), it was illustrated that the aim compounds regarded as donors had reacted with acceptors. In Table-5, the Pearson coefficient between fungicidal activity and log P was best (R = -0.72), which showed that log P had been an important factor affected fungicidal activity.

To further study the correlative factors affected fungicidal activity, bi-, tri- and tetra-parametric models were established, respectively.

Bi-parametric models: 35 Bi-parametric equations were founded by the optional two parameters with the lower inter-correlation each other ($|r| < 0.5$) as the independent parameters and fungicidal activity as the dependent parameter. The best model eqn.1 were picked from the 35 equations ($R > 0.75$, $R_A^2 > 0.6$).

$$FA = -9.947 + 1594.436\Delta E - 35.189 \log P$$
$$R = 0.813;\ R_A^2 = 0.608;\ F = 12.646 \quad (1)$$

TABLE-4
REGRESSION PARAMETERS OF TITLE COMPOUNDS

No.	Et (Hartree)	E_{HOMO} (Hartree)	E_{LUMO} (Hartree)	ΔE (Hartree)	μ	Q_{ph}	V	S	log P	R	P	M	FA (%)
1-c	-2091.4008	-0.2573	-0.0889	0.1684	5.2335	-0.9759	778.66	486.31	7.02	31.68	28.72	317.56	6.7
2-a	-1673.1146	-0.2514	-0.0943	0.1570	1.7384	-0.8176	776.05	481.10	6.70	31.79	28.63	297.14	6.7
3-c	-1747.9081	-0.2321	-0.0937	0.1383	2.3057	-0.5556	800.19	490.46	6.15	33.60	29.26	313.14	3.3
4-a	-2130.5063	-0.2530	-0.0871	0.1659	3.2116	-0.9784	822.28	501.89	7.43	36.09	30.55	331.59	3.3
5-a	-1712.2180	-0.2447	-0.0810	0.1637	4.7891	-0.7730	828.02	502.95	7.12	36.21	30.46	311.17	6.7
6-c	-1787.0175	-0.2368	-0.0846	0.1521	3.1995	-0.4988	824.37	485.61	6.56	38.02	31.10	327.17	6.7
7-b	-1728.1732	-0.2317	-0.0674	0.1642	6.6426	-1.0318	808.39	493.55	5.93	35.28	29.98	312.16	96.7
8-b	-1309.8788	-0.2240	-0.0607	0.1633	8.6226	-0.7954	813.16	488.35	5.61	35.40	29.88	291.74	53.3
9-a	-1384.6707	-0.2216	-0.0546	0.1670	6.2985	-0.5678	838.33	512.05	5.06	37.21	30.52	307.74	100.0
10-a	-1767.2678	-0.2200	-0.0677	0.1522	5.7611	-0.9807	860.88	523.61	6.34	39.70	31.81	326.18	3.3
11-c	-1348.9756	-0.2153	-0.0536	0.1617	4.1413	-0.7752	856.70	514.45	6.03	39.82	31.72	305.76	6.7
12-c	-1423.7619	-0.2168	-0.0498	0.1670	5.3868	-0.4975	879.21	525.80	5.47	41.63	32.36	321.76	26.7
13	-1634.0096	-0.2552	-0.0958	0.1593	1.3716	-1.0128	722.95	451.85	6.39	27.18	26.79	283.11	6.7
14	-1673.1132	-0.2469	-0.0825	0.1644	4.3154	-0.9680	775.31	474.05	6.80	31.60	28.63	297.14	3.3
15	-1270.7725	-0.2282	-0.0566	0.1715	6.1646	-1.0222	761.08	469.17	5.30	30.79	28.05	277.71	86.7
16	-1309.8741	-0.2159	-0.0560	0.1598	3.8492	-0.9729	814.90	492.18	5.71	35.21	29.88	291.74	26.7

FA stands for the fungicidal activities (200mg/kg) of compounds for inhibition of housefly larvaes.

TABLE-5
PEARSON CORRELATION MATRIX OF THE PARAMETERS USED IN THIS STUDY

	FA	Et	E_{HOMO}	E_{LUMO}	ΔE	μ	Q_{ph}	V	S	log P	R	P	M
FA	1.000												
Et	0.486	1.000											
E_{HOMO}	0.395	0.726	1.000										
E_{LUMO}	0.579	0.747	0.874	1.000									
ΔE	0.455	0.184	-0.060	0.430	1.000								
μ	0.650	0.353	0.485	0.678	0.492	1.000							
Q_{ph}	-0.040	0.182	0.329	0.125	-0.350	-0.060	1.000						
V	0.006	0.134	0.666	0.581	-0.040	0.362	0.505	1.000					
S	0.016	0.046	0.591	0.534	-0.030	0.352	0.406	0.963	1.000				
log P	-0.720	-0.840	-0.780	-0.770	-0.130	-0.490	-0.270	-0.210	-0.160	1.000			
R	0.010	0.142	0.670	0.580	-0.050	0.347	0.522	0.990	0.926	-0.210	1.000		
P	-0.040	0.068	0.656	0.528	-0.060	0.317	0.492	0.987	0.927	-0.130	0.996	1.000	
M	-0.310	-0.640	0.486	-0.130	-0.230	-0.020	0.364	0.646	0.659	0.402	0.650	0.696	1.000

The statistical quality[9] of the regression equations were gauged by parameters like correlation coefficient (r), explained variance (R_A^2, *i.e.*, adjusted R^2), variance ratio (F)[10,11]. The better regression models were selected on the basis of the higher r, F value (a statistic of assessing the overall significance) and R_A^2. This bivariate combination of DE and log P showed good statistics (r = 0.813) and explained to 60.8 % of the variance in fungicidal activity data.

Tri-parametric models: 60 Tri-parametric equations were set up by the optional three parameters with the lower inter-correlation each other as the independent parameters and fungicidal activity as the dependent parameter. Three better models 2, 3, 4 were chosen from the 60 equations.

$$FA = 216.949 + 830.488DE + 6.627\mu - 0.027V - 29.790 \log P$$
$$R = 0.859;\ R_A^2 = 0.643;\ F = 7.758 \quad (2)$$
$$FA = 206.830 + 927.835DE + 6.206\mu - 0.352S - 29.385 \log P$$
$$R = 0.852;\ R_A^2 = 0.627;\ F = 7.292 \quad (3)$$
$$FA = 331.323 + 8.339\mu - 8.109Q - 28.537 \log P - 5.709 P$$
$$R = 0.842;\ R_A^2 = 0.604;\ F = 6.717 \quad (4)$$

According to eqn. 2-4, it was also shown that DE and log P had been the key factors affected fungicidal activity. Fungicidal activity had the positive relationships with μ and the negative correlative to V and S, but S, V had the smaller Pearson correlation coefficient (0.016, 0.006) to fungicidal activity, respectively.

Tetra-parametric models: 31 Tetra-parametric equations were established by the random four parameters with the lower inter-correlation each other as the independent parameters and FA as the dependent parameter. Four better models 5, 6, 7, 8 were selected from the 31 equations.

$$FA = 216.949 + 830.488DE + 6.627\mu - 0.027V - 29.790\log P$$
$$R = 0.859;\ R_A^2 = 0.643;\ F = 7.758 \quad (5)$$
$$FA = 122.468 + 844.468DE + 6.429\mu - 30.005\log P - 2.089R$$
$$R = 0.857;\ R_A^2 = 0.639;\ F = 7.626 \quad (6)$$
$$FA = 197.838 + 851.443DE + 6.443\mu - 29.027\log P - 5.213P$$
$$R = 0.856;\ R_A^2 = 0.638;\ F = 7.595 \quad (7)$$
$$FA = 206.830 + 927.835DE + 6.206\mu - 0.352S - 29.385\log P$$
$$R = 0.852;\ R_A^2 = 0.627;\ F = 7.292 \quad (8)$$

Compared with these four models, eqn. 5 had the best regression effect (R = 0.859, R_A^2 = 0.643, F = 7.758). According to eqn. 5-8, it was shown that fungicidal activity had the positive relations with DE, μ and the negative correlative to log P, V, S, P, R. Through tetra-parametric equations, it was further illustrated that DE and log P had been the important factors effected fungicidal activity.

Conclusions

Through optimizing the geometry structures of 40 compounds at B3LYP/3-21G level, the 16 optimal structures were confirmed, then the structure parameters, the electric parameters, the physical property parameters of pyridazone derivatives were obtained. Accordingly, the bi-parametric, tri-parametric, tetra-parametric models (1~8) were established between biological activities and the parameters obtained by the multiple linear regression. It is shown in the models that ΔE and log P were the key factors to affect fungicidal activity. It's necessary that increasing the polarity of molecules or decreasing the volume and surface of molecules enhance the biological activities of pyridazone derivatives.

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REFERENCES

1. X.J. Zou and G.Y. Jin, *Chin. J. Org. Chem.*, **23**, 62 (2003).
2. T.L. Liu and C.B. Zhou, *Chin. J. Org. Chem.*, **20**, 758 (2000).
3. N. Mochizuki, S. Uchida and H. Miyata, *J. Cardiovasc. Pharmacol.*, **21**, 983 (1993).
4. Q.S. Jiang and D.Y. Hu, *Foreign Med. Sci. Sec. Pharm.*, **27**, 143 (2000).
5. B. Ma, Q.M. Kan, J. Wang and S.J. Wang, *J. Shenyang Pharmaceut. Univ.*, **17**, 441 (2000).
6. H.S. Li, Y. Ling and Y.L. Guo, *J. Org. Chem.*, **21**, 204 (2005).
7. L.S. Xu, Y.P. He and Z.H. Li, *Acta Chim. Sinica*, **60**, 1784 (2002).
8. K. De, C. Sengupta and K. Roy, *Bioorg. Med. Chem.*, **12**, 3323 (2004).
9. G.W. Snedecor and W.G. Cochran, Statistical Methods, Oxford and IBH: New Delhi, pp. 381-418 (1967).
10. S. Chatterjee, A.S. Hadi and B. Price, Regression Analysis by Examples, Wiley VCH: New York, edn. 3 (2000).
11. M.V. Diudea, QSPR/QSAR Studies for Molecular Descriptors, Nova Science, Huntingdon, New York (2000).

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