Pest Manag Sci **58**:1063–1067 (online: 2002)
DOI: 10.1002/ps.584

Development of novel pesticides based on phytoalexins: Part 2. Quantitative structure–activity relationships of 2-heteroaryl-4-chromanone derivatives†

Guangfu Yang,[1]* Xiaohua Jiang[1] and Huazheng Yang[2]
[1]*Institute of Organic Synthesis, Central China Normal University, Wuhan 430079, People's Republic of China*
[2]*National Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China*

Abstract: Phytoalexins are low-molecular-weight chemicals that immune systems of plants produce and accumulate in response to infections, especially those of fungal origin. Although their content is not high in plants, yet they have shown unique fungicidal activity and played an important role in the defence system of plants. In searching for novel environmentally benign fungicides with high activity, the structures of flavanone derivatives, one of the most important phytoalexins groups, have been modified via bioisosteric substitution and a series of 2-heteroaryl-4-chromanones were designed and synthesized. They showed good fungicidal activities against rice blast disease, *Pyricularia grisea* (Sacc). Their IC_{50} values were tested *in vitro* and the relationship between structure and fungicidal activity was analyzed quantitatively using a Hansch–Fujita approach. The results showed that hydrophobicity was very important for fungicidal activity and there is apparently an optimum hydrophobic property for the molecules at a log P_{ow} value of about 2.7. In addition, the results indicated that electronic effects played an important role in binding with the receptor and that the C=O group was probably a electron-accepting site. The quantitative structure–retention correlative equation of the title compounds was also established.

Keywords: 2-heteroaryl-4-chromanones; phytoalexins; bioisosterism substitution; fungicidal activity; QSAR; molecular design

1 INTRODUCTION

Phytoalexins are compounds involved in the resistance of plants to fungal infection.[1] They exhibit fungistatic, fungicidal and, in some cases, antibacterial activity. However, in comparison with modern synthetic fungicides, phytoalexins are poorly active *in vitro* (ED_{50}: $10^{-4}\sim10^{-5}$ M) and almost inactive in *in vivo* tests.[2] Therefore, suggestions of the possibility of using them as models for the synthesis of new fungicides have been made in the past two decades,[3–6] although so far no commercial fungicide has been obtained.

Flavanones are a group of important phytoalexins inhibiting several biological processes. A drawback to the use of these phytoalexins in fungicide studies is that they are not easily translocated in the plant tissues due to the existence of polyhydroxyl groups in their molecular structure. Many studies have been made on the structural modification and structure–activity relationships of flavanone derivatives in recent decades,[3,4,7–12] but all the modifications have been concerned with the substituents on the aromatic moiety rather than the skeletal structure, and all of structure–activity relationships are of a qualitative nature.[7–11]

Bioisosterism is an important approach used by the medicinal and pesticidal chemist for the rational modification of lead compounds into more effective agents.[13] We have noted the successful use of the classical bioisosteres such as replacement of benzene with thiophene, furane or pyridine, and used the concept of bioisosterism to develop novel environmentally benign fungicidal structures and also to improve the hydrophobicity of flavanone phytoalexins by modifying the skeletal structure of flavanone to give the title compounds, 2-heteroaryl-4-chromanones (**4**), by replacing the benzene ring with thiophene, furane or pyridine. On the basis of systematically determining the fungicidal activity against *Pyricularia grisea* (Sacc),

* Correspondence to: Guangfu Yang, Institute of Organic Synthesis, Central China Normal University, Wuhan 430079, People's Republic of China
E-mail: gfyang@ccnu.edu.cn
† Part 1. Yang G, Jiang X, Ding Y and Yang H, *Chinese J Chem* **19**:423–428 (2001)
Contract/grant sponsor: National Natural Science Foundation of China; contract/grant number: 29802002; contract/grant number: 20172017
Contract/grant sponsor: Foundation for University Key Teacher, Ministry of Education of China; contract/grant number: GG-150-10511-1005
Contract/grant sponsor: Dawn Plan of Science and Technology for Young Scientists of Wuhan City
(*Received 28 March 2002; revised version received 26 April 2002; accepted 27 June 2002*)

a quantitative structure–activity relationship of the title compounds was derived using the Hansch–Fujita approach.[14] To our knowledge, this is the first QSAR study for phytoalexin analogues.

2 MATERIALS AND METHODS

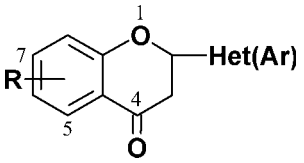
2.1 Synthesis of the title compounds

2-Heteroaryl-4-chromanones (**4**) used in this work are listed in Table 1, and were designed and synthesized according to the synthetic pathway outlined in Fig 1. All the products **4** were purified by chromatography over silica gel and their structures were confirmed by ^{1}H NMR and mass spectroscopy as well as elemental analyses. In order to enrich the electronic effect in the title compounds, we have cited three flavanone derivatives **4x**–**4z** with pI_{50} values from our previous study.[15]

2.2 Biological tests

The fungicidal activity of the title compounds against *P grisea* was tested in *vitro* according to the modified method described previously.[16] A set amount of each sample was dissolved in chloroform to which a drop of a Tween 20 was added. The solution was then diluted with water until it reached the concentration required. Compound-amended agar media were dispersed aseptically into 9-cm-diameter plastic Petri dishes (15 ml). Inocula consisted of plugs (7 mm diameter) taken from the edges of actively growing colonies and inverted on the agar (two per dish) with two replicate plates for each fungus-compound combination. Colony diameters (mm) were measured after 12, 36, and 72 h incubation at 28 °C in the dark. The data reported in Table 1 refer to the 72-h results. The molar concentration of each compound required to inhibit the mycelial growth to half the length of the control (I_{50} value) was evaluated by the probit method.[17] The I_{50} measurements were repeated for at least three runs and the pI_{50} values were averaged over repeats, the standard deviation being ±0.20. The activity pI_{50} values of the compounds are listed in Table 1.

Table 1. Structure, fungicidal activity and physicochemical parameters of 2-heteroaryl-4-chromanones (4)



Compound			Parameters								pI_{50}				
No	*R*	*Het*[a]	*log* k	*clog* P	*CMR*	E_{HOMO}	E_{LUMO}	ΔE	F^E_{O1}	F^N_{C4}	*Obsd*	*Eqn (3)*	Δ[c]	*Eqn (4)*	δ
4a	6-Br	A	0.4579	3.84	7.19	−9.36	−0.68	8.68	1.25	18.28	5.83	5.81	0.02	5.79	0.04
4b	7-CH_3	A	0.2504	3.44	6.88	−9.30	−0.45	8.85	1.52	29.15	5.90	5.92	−0.02	5.91	−0.01
4c	7-CH_3O	A	0.0212	2.96	7.03	−9.20	−0.39	8.81	0.86	31.65	6.29	6.28	0.01	6.27	0.02
4d	H	A	(−0.0044)[b]	2.95	6.41	−9.37	−0.47	8.90	1.61	30.03	5.14	5.55	−0.41	5.56	−0.42
4e	6-Br	B	0.2833	3.37	6.59	−9.45	−0.76	8.69	0.88	16.27	5.40	5.35	0.05	5.30	0.10
4f	H	B	(−0.1505)[b]	2.48	5.82	−9.38	−0.52	8.86	0.32	27.37	4.66	4.83	−0.17	4.86	−0.20
4g	7-CH_3O	B	−0.2366	2.49	6.43	−9.28	−0.44	8.84	0.77	31.59	5.87	5.60	0.27	5.60	0.27
4h	7-CH_3	B	0.0294	2.97	6.28	−9.35	−0.51	8.84	0.74	26.63	5.66	5.33	0.33	5.34	0.32
4i	7-CH_3O	C	−0.6021	1.82	7.01	−9.26	−0.41	8.85	0.77	32.31	6.04	6.02	0.02	5.94	0.10
4j	6-Cl	C	−0.0132	2.55	6.88	−9.37	−0.69	8.68	1.26	17.93	5.84	5.83	0.01	5.84	0.00
4k	6-CH_3	C	−0.1675	2.30	6.86	−9.19	−0.45	8.74	1.34	31.07	5.84	6.03	−0.19	6.08	−0.24
4l	H	C	−0.6021	1.80	6.39	−9.44	−0.48	8.96	1.56	28.97	4.98	5.24	−0.26	5.19	−0.21
4m	6-Br	C	0.0253	2.70	7.17	−9.42	−0.71	8.71	1.20	17.12	5.76	6.15	−0.39	6.13	−0.37
4n	H	D	(−0.5120)[b]	1.80	6.39	−9.50	−0.57	8.93	1.55	25.25	5.09	5.16	−0.07	5.23	−0.14
4o	6-Br	D	−0.0862	2.70	7.17	−9.48	−0.79	8.69	1.17	15.83	6.22	6.13	0.09	6.13	0.09
4p	6-CH_3	D	−0.0862	2.30	6.86	−9.25	−0.53	8.72	1.33	26.85	6.13	5.95	0.18	6.00	0.13
4q	6-Cl	D	−0.1612	2.55	6.88	−9.45	−0.78	8.67	1.22	16.38	5.87	5.80	0.07	5.81	0.06
4r	7-CH_3	D	−0.3768	2.30	6.86	−9.48	−0.45	9.03	1.46	28.27	6.01	5.98	0.03	5.93	0.08
4s	7-CH_3O	D	(−0.4769)[b]	1.82	7.01	−9.32	−0.49	8.83	0.75	27.41	6.24	5.92	0.32	5.99	0.25
4t	6-CH_3	B	(0.0492)[b]	2.97	6.28	−9.22	−0.49	8.73	1.30	29.11	5.44	5.38	0.06	5.38	0.06
4u	6-CH_3	A	(0.2613)[b]	3.44	6.88	−9.14	−0.44	8.70	1.40	32.03	5.89	5.98	−0.09	5.96	−0.07
4v	6-Cl	B	(0.1737)[b]	3.22	6.31	−9.41	−0.74	8.67	1.10	17.08	5.18	5.11	0.07	5.10	0.08
4w	6-Cl	A	(0.3488)[b]	3.69	6.90	−9.45	−0.67	8.78	0.08	16.97	5.73	5.56	0.17	5.59	0.14
4x[d]	H	E	0.2201	3.04	7.21	−9.68	−1.20	8.48	1.46	0.0522	5.85	5.81	0.04	5.73	0.12
4y[d]	7-CH3	E	0.2765	3.54	7.68	−9.60	−1.19	8.41	1.34	0.0490	6.23	6.17	0.06	6.20	0.03
4z[d]	6-Cl	E	0.3927	3.79	7.71	−9.61	−1.26	8.35	1.14	0.0783	5.86	6.05	−0.19	6.10	−0.24

[a] A: 2-thienyl; B: 2-furanyl; C: 2-pyridinyl; D: 3-pyridinyl; E: 3′-nitrophenyl.

[b] Calculated according to eqn (2).

[c] Difference between observed and calculated values.

[d] Cited from Reference 15.

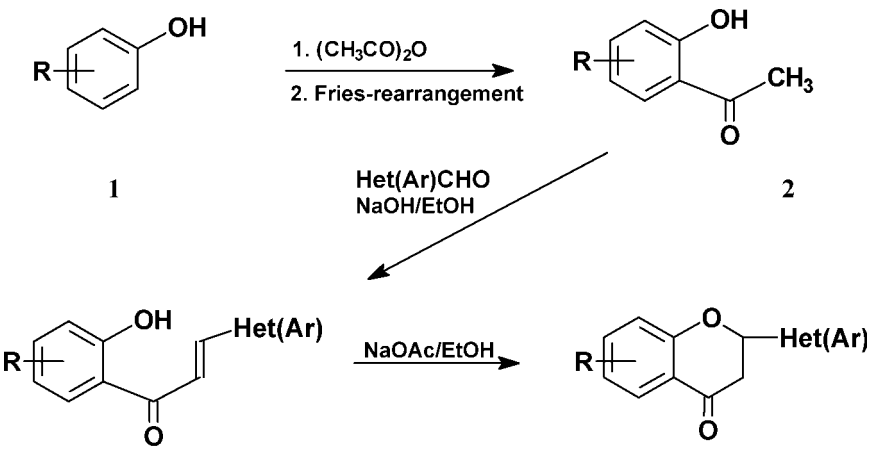


Figure 1. Synthesis route for compounds discussed.

2.3 Physicochemical parameters

It is difficult to take substituent parameters from the literature to represent the physicochemical properties of 2-thienyl, 2-furanyl, 2-pyridinyl and 3-pyridinyl groups. Therefore, we used clog$P$ and CMR values calculated by the ClogP and CMR programs on the SGI workstation. In addition, we carried out quantum chemical calculations for all compounds. Molecular models were constructed using the SKETCH program and optimized based on a Tripos 6.5 force field with Gasteiger–Huekel charges. All energy calculations and optimization were implemented by an AM1 semi-empirical method. Because each molecular structure is rigid, the minimum energy conformation was selected as the bioactive conformation. These conformations were used to calculate electronic parameters such as HOMO and LUMO energies, F^E_{O1} (approximate electrophilic superdelocalizability of the oxygen atom at the 1 position), F^N_{C4} (approximate nucleophilic superdelocalizability of the 4-position carbon atom), etc.[18] Approximate nucleophilic superdelocalizability and approximate electrophilic superdelocalizability are defined as

$$F^N(i) = [f^N(i)/ - E_{\mathrm{LUMO}}] \times 100$$

$$F^E(i) = [f^E(i)/ - E_{\mathrm{HOMO}}] \times 100$$

where $f^N(i)$ is the frontier electron density of LUMO at atom i and E_{LUMO} is the energy of LUMO orbital (measured in ev), $f^E(i)$ is the frontier electron density of HOMO at atom i and E_{HOMO} is the energy of HOMO orbital (also measured in EV). $f(i)$ represents the reactivity of different atoms within a molecule, while $F(i)$ can represent the reactivity and the electronic effect relatively among different compounds.[18] All computations were done on a Silicon Graphic O2 workstation with the molecular modeling software package SYBYL, version 6.5.[19]

2.4 Determination of partition coefficients by HPLC

Direct determination of the partition coefficient (log$P$) of this series of compounds in the 1-octanol/water system by the shaking-flask method is certainly the most direct method but is tedious, requires a large amount of pure sample and is therefore impracticable in most situations. For these reasons, the logarithm of the retention factor (k) in reversed-phase HPLC was employed as an alternative hydrophobicity parameter. The relevancy of log$k$ as a hydrophobicity parameter has been shown in the literature.[20–25] Retention times (t_R) were determined on a HP-1100 HPLC apparatus equipped with an UV absorbance detector (254 nm). The column was a Description-Eclipse XDB-C_8 (5-μm particle size, 150 mm × 4.6 mm), the solvent methanol + water (60 + 40 by volume) and the flow rate 1 ml min^{-1}. Each compound was injected three times and mean log$k$ values were calculated from eqn (1), where t_0 represents the elution time of an unretained peak:

$$\log k = \log[(t_R - t_0)/t_0] \qquad (1)$$

We determined the log$k$ values of 18 title compounds as shown in Table 1 and established their quantitative structure retention relationships as eqn (2) using their physicochemical and electronic parameters. Using eqn (2) we evaluated the log$k$ values of another eight compounds as shown in Table 1.

$$\log k = 1.0652(\pm 0.0202) + 0.4345(\pm 0.0433)\mathrm{clog}P - 0.2642(\pm 0.1517)\Delta E_{\mathrm{LUMO–HOMO}} \qquad (2)$$

$$n = 18,\ r = 0.9651,\ s = 0.0860,\ F = 101.93$$

where clog$P$ is the hydrophobicity parameter calculated from the ClogP program, $\Delta E_{\mathrm{LUMO–HOMO}}$ is the interval between E_{LUMO} and E_{HOMO}, n is the number of compounds, r is the correlation coefficient, and s is the standard derivation. F is the ratio of regression and residual variances.

3 RESULTS AND DISCUSSION

Variations in the fungicidal activity of 23 title com-

Table 2. Development of QSAR of equation (3)

Intercept	*CMR*	*clog* P	*(clog* P*)*^{2}	F^N_{C4}	r	s	F *test*
0.6736	0.7422				0.7639	0.2802	33.63
0.6104	0.7990	−0.1155			0.7806	0.2772	17.94
−2.0980	0.8868	1.5033	−0.2946		0.8217	0.2583	15.25
−4.6590	1.1250	1.7468	−0.3192	0.0208	0.8966	0.2055	21.53

Table 3. Correlation matrix for variables used to derive equation (3)

	CMR	*clog* P	*(clog*P*)*^{2}	F^N_{C4}
CMR	1.0000			
clog *P*	0.1170	1.0000		
(clog *P*)^2	0.1389	0.9877	1.0000	
F^N_{C4}	0.3605	0.2468	0.2551	1.0000

pounds (Table 1) were analyzed using clog*P*, CMR and F^N_{C4}, giving

$$\begin{aligned} pI_{50} = &-4.6590(\pm 0.0403) + 1.1250(\pm 0.1233)\text{CMR} \\ &+ 1.7468(\pm 0.6163)\text{clog}\,P \\ &- 0.3192(\pm 0.1110)(\text{clog}\,P)^2 \\ &+ 0.0208(\pm 0.0056)F^N_{C4} \qquad (3) \end{aligned}$$

$$n = 26,\ r = 0.8966,\ s = 0.2055,\ F = 21.53$$

with the best correlation. In this and the following equations, n is the number of compounds, r is the correlation coefficient, and s the standard derivation. The figures in parentheses accompanying each coefficient are the 95% confidence intervals of the regression coefficient. The development of this equation and the interrelation of variables are shown in Tables 2 and 3, respectively.

Equation (3) indicates that hydrophobicity is the most important physical property in determining fungicidal activity. The negative coefficient of the $(\text{clog}\,P)^2$ term indicates that variations in the activity are parabolically related to the hydrophobic parameters. The optimum clog*P* value in eqn (3) is about 2.74. The positive coefficient of CMR term indicates that the more polarizable the molecule, the higher the activity. In addition, Table 2 shows that introduction of the F^N_{C4} term led to a significant improvement in the correlation. The positive coefficient of F^N_{C4} term indicates that the higher the approximate nucleophilic superdelocalizability of the carbon 4, the higher the activity, suggesting that the greater the ability of the carbonyl group to accept electrons from an electron-rich plant receptor, the higher the activity.

Replacment of clog*P* with another hydrophobic parameter for the whole molecule, log*k*, yield a similar correlation equation, eqn (4)

$$\begin{aligned} pI_{50} = &-2.1307(\pm 0.0401) + 1.1065(\pm 0.1208)\text{CMR} \\ &- 0.2578(\pm 0.1862)\log k \\ &- 1.3147(\pm 0.4494)(\log k)^2 \\ &+ 0.0197(\pm 0.0057)F^N_{C4} \qquad (4) \end{aligned}$$

$$n = 26,\ r = 0.8977,\ s = 0.2045,\ F = 21.80$$

The development of eqn (4) and the interrelation of variables are shown in Tables 4 and 5, respectively. Equation (4) is similar to eqn (3) in terms of *r, s* and *F* values, as well as in the coefficients of CMR and F^N_{C4}, which indicates that log*k* is a suitable parameter to describe the whole hydrophobicity of molecules. The negative coefficient of the $(\log k)^2$ term indicates that variations in the activity are parabolically related to the hydrophobic parameters. The optimum log*k* value in eqn (4) is about −0.0981. The fungicidal activities calculated by eqns (3) and (4) are listed in Table 1.

There is a growing consensus that, in most systems, flavonoid phytoalexins exert their toxicity by some membrane-associated phenomenon, again indicating the possible importance of lipophilicity for their activity.[3–11] The relative lipophilicities of flavonoid phytoalexins have been qualitatively compared and the

Table 5. Correlation matrix for variables used to derive equation (4)

	CMR	*log* k	*(log* k*)*^{2}	F^N_{C4}
CMR	1.0000			
log *k*	0.1209	1.0000		
(log *k*)^2	0.0090	0.2324	1.0000	
F^N_{C4}	0.3605	0.2878	0.0110	1.0000

Table 4. Development of QSAR of equation (4)

Intercept	*CMR*	*log* k	*(log* k*)*^{2}	F^N_{C4}	s	r	F *test*
0.6736	0.7422				0.7639	0.2802	33.63
0.3005	0.7962	−0.2219			0.7785	0.2784	17.69
−0.2906	0.9004	−0.5145	−1.3937		0.8337	0.2504	16.72
−2.1307	1.1065	−0.2578	−1.3147	0.0197	0.8977	0.2045	21.80

relationships between the lipophilicity and fungicidal activity also been discussed qualitatively.[3,4,8,11] Arnoldi *et al*[4] studied the relationships between the lipophilicity and fungicidal activity of 3-(4,5-disubstituted)phenylcoumarins, analogues of the isoflavonoids, and pointed out that an increase in lipophilicity induces a decrease in biological activity both *in vitro* and in hypocotyl tests. They also studied the relationship between the lipophilicity and antifungal activity on *Aphanomyces euteiches* C Drechsler and *Fusarium solani* (Martius) Sacc fsp *cucurbitae* Snyder & Hansen of 18 isoflavonoid phytoalexins whose values of log*P* ranged from 1.5 to 4.2 as measured by reversed-phase HPLC and/or calculated by the use of Hansch hydrophobic parameters.[8] The results indicated that, within groups of compounds of similar structure, an increase in lipophilicity correlates positively with increased antifungal activity. Laks and Pruner[11] studied the relationship between the lipophilicity and antifungal activity of two sets of semi-synthetic flavonoid phytoalexin analogues, epicatechin-4-alkylsulphides and catechin dialkyl ketals, and found that the plots of the activity against *A euteiches* and *F solani* against the lipophilic parameters (R_M) were parabolical and the most active members of the two sets of flavonoid derivatives had very similar R_M values, $c -0.1$. However, all the above results are qualitative, and no clear quantitative results have been reported so far. The results we have obtained have shown that the variations in the fungicidal activity of 2-heteroaryl-4-chromanone derivatives are parabolically related to the hydrophobic parameters and that the optimum clog*P* or log*k* values are about 2.74 or −0.0981, respectively. To our knowledge, this is the first quantitative report on the hydrophobic requirement for phytoalexin analogues.

ACKNOWLEDGEMENTS

This project is supported by the National Natural Science Foundation of China (29802002, 20172017), Foundation for University Key Teacher by the Ministry of Education of China (GG-150-10511-1005) and the Dawn Plan of Science and Technology for Young Scientists of Wuhan City.

REFERENCES

1 Bailey JA and Mansfield JW, *Phytoalexins*, Blackie, Glasgow and London, Chapter 2 (1986).
2 Rathmell WG and Smith DA, Lack of activity of selected isoflavonoid phytoalexins as protectant fungicides. *Pestic Sci* **11**:568–572 (1980).
3 Arnoldi A, Carughi M, Farina G, Merlini L and Parrino MG, Synthetic analogues of phytoalexins. Synthesis and antifungal activity of potential free-radical scavengers. *J Agric Food Chem* **37**:508–512 (1989).
4 Arnoldi A, Farina G, Galli R, Merlini L and Parrino MG, Analogues of phytoalexins. Synthesis of some 3-phenylcoumarins and their fungicidal activity. *J Agric Food Chem* **34**:185–188 (1986).
5 Weidenborner M and Jha HC, Antifungal activity of flavonoids and their mixtures against different fungi occurring on grain. *Pestic Sci* **38**:347–351 (1993).
6 Weidenborner M and Jha HC, Antifungal spectrum of flavone and flavanone tested against 34 different fungi. *Mycol Res* **101**:733–736 (1997).
7 Aida Y, Tamogami S, Kodama O and Tsukiboshi T, Synthesis of 7-methoxyapigeninidin and its fungicidal activity against *Gloeocercospora sorghi*. *Biosci Biotech Biochem* **60**:1495–1496 (1996).
8 Arnoldi A and Merlini L, Lipophilicity-antifungal activity relationships for some isoflavonoid phytoalexins. *J Agric Food Chem* **38**:834–838 (1990).
9 Carter GA, Chamberlain K and Wain RL, Investigations on fungicides. XX. The fungitoxicity of analogues of the phytoalexin 2-(2′-methoxy-4′-hydroxyphenyl)-6-methoxybenzofuran (Vignafuran). *Ann Appl Biol* **19**:107–124 (1978).
10 Adesanya SA, O'Neill MJ and Roberts MF, Structure-related fungitoxicity of isoflavonoids. *Physiol Mol Plant Pathol* **29**:95–103 (1986).
11 Laks PE and Pruner MS, Flavonoid biocides: structure–activity relations of flavonoid phytoalexin analogues. *Phytochemistry* **28**:87–91 (1989).
12 Kodama O, Miyakawa J, Tadami T and Kiyosawa S, Sakuranetin, a flavanone phytoalexin from ultraviolet-irradiated rice leaves. *Phytochemistry* **31**:3807–3809 (1992).
13 George AP and Edmond JL, Bioisosterism: a rational approach in drug design. *Chem Rev* **96**:3147–3176 (1996).
14 Hansch C and Fujita T, ρ–σ–π Analysis. A method for the correlation of biological activity and chemical structure. *J Am Chem Soc* **86**:1616–1626 (1964).
15 Ding Y and Yang G, Syntheses and fungicidal activity of B-cycle substituted flavanone derivatives. *Chinese J Appl Chem* **18**:785–788 (2001).
16 Yang G, Jiang X, Ding Y and Yang H, Development of pesticides based on phytoalexins. Part 1: Design and synthesis of flavanone analogues *via* bioisosterism substitution. *Chinese J Chem* **19**:423–428 (2001).
17 Finney DJ, *Probit analysis*, Cambridge Univ Press, London, p 183 (1952).
18 Karelson M and Lobanov VS, Quantum-chemical descriptors in QSAR/QSPR studies. *Chem Rev* **96**:1027–1043 (1996).
19 SYBYL Molecular Modeling Software, Tripos Associates, Inc, St Louis, Missouri, USA.
20 Kim KH, Description of the reversed-phase high-performance liquid chromatography (RP-HPLC) capacity factors and octanol–water partition coefficients of 2-pyrazine and 2-pyridine analogues directly from the three-dimensional structures using comparative molecular field analysis (CoMFA) approach. *Quant Struct Act Relat* **14**:8–18 (1995).
21 Terada H, Determination of logP_{oct} by high-performance liquid chromatography, and its application in the study of quantitative structure-activity relationships. *Quant Struct Act Relat* **5**:81–88 (1986).
22 Krikorian SE and Chorn TA, Determination of octanol/water partition coefficients of certain organophosphorus compounds using high-performance liquid chromatography. *Quant Struct Act Relat* **6**:65–69 (1987).
23 Dorsey JG and Khaledi MG, Hydrophobicity estimations by reversed-phase liquid chromatography: Implications for biological partitioning processes. *J Chromatogr A* **656**:485–499 (1993).
24 Yamagami C, Yokota M and Takao N, Hydrophobicity parameters determined by reversed-phase liquid chromatography. IX. Relationship between capacity factor and water-octanol partition coefficient of monosubstituted pyrimidines. *Chem Pharm Bull* **42**:907–912 (1994).
25 Baj S and Dawid M, Correlation between the chemical structures of dialkyl peroxides and their retention in reversed-phses high-performance liquid chromatography. *J Liq Chromatogr* **17**:3933–3949 (1994).