

## Design, Synthesis, and Quantitative Structure–Activity Relationship Study of Herbicidal Analogues of Pyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)ones

YOU-QUAN ZHU, CHAO WU, HUA-BIN LI, XIAO-MAO ZOU,\* XUE-KAI SI,  
 FANG-ZHONG HU, AND HUA-ZHENG YANG\*

State Key Laboratory of Elemento-organic Chemistry, Research Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China

A series of pyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)one derivatives were designed, synthesized, and evaluated for their herbicidal activities where some of these compounds provided >80% control of *Brassica campestris* at 10  $\mu\text{g/mL}$ . Quantitative structure–activity relationship studies were performed on these compounds using physicochemical parameters (electronic, Verloop, or hydrophobic) as independent parameters and herbicidal activity as a dependent parameter, where herbicidal activity correlated best ( $r > 0.8$ ) with physicochemical parameters in this set of molecules. The herbicidal activity against *B. campestris* was mainly affected by the molar refractivity (MR) for  $R^1$ , Taft ( $E_s$ ) for  $R^2$  or  $R^6$ , Verloop ( $L_m$ ) for  $R^3$  or  $R^5$ , and electronic parameters (Hammett's constants) for  $R^4$ . The optimal MR for herbicidal activity is 0.95. The herbicidal activity against *Echinochloa crus-galli* was mainly related with the substituents' hydrophobic parameter. The optimal  $\pi$  parameters for  $R_1$  and  $R_4$  for herbicidal activity are 0.72 and 0.68, respectively. In general, these compounds showed greater herbicidal activity toward *B. campestris* than *E. crus-galli*.

**KEYWORDS:** Pyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)one; hydrophobic; herbicidal activity; quantitative structure–activity relationship (QSAR)

### INTRODUCTION

Tetrazinone compounds represented an important class of heterocyclic compounds. They displayed a wide range of biological and pharmaceutical activities (1, 2) and have attracted considerable attention. For example, mitozolomide **A** and temozolomide **B** (Figure 1) exhibited outstanding antineoplastic activity and drew attention to azolotetrazine systems. For the sake of finding valuable herbicidal candidates, the imidazotetrazinone moiety was modified into pyrazolotetrazinone in our previous report and some of them provided 50–66% control of *Brassica campestris* at 200  $\mu\text{g/mL}$  (3). It was also noticed that many compounds, containing the moiety of polysubstituted benzene ring, exhibited excellent inhibition activity against protoporphyrinogen-IX oxidase (4) and that the structure unit was crucial for their herbicidal activity. To find potent lead compounds, the compound **C** (Figure 1) was designed and synthesized.

At present, quantitative structure–activity relationships (QSAR), an important area of chemometrics, are widely utilized to study the relationship between chemical structures and biological or other functional activities. QSAR has become increasingly helpful in understanding many aspects of chemical–biological interactions in drug and pesticide research as well as in many

other areas (5). The other objective of this study was to further understand the QSAR for  $R^1$ – $R^6$  through preparing a series of **C** (Figure 1 and Table 1).

### MATERIALS AND METHODS

**Synthetic Procedures.** Proton NMR spectra were obtained at 300 MHz using a Bruker AC-P300 spectrometer in  $\text{CDCl}_3$  solution with tetramethylsilane as an internal standard. Chemical shift values ( $\delta$ ) are given in ppm. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Solvents were dried by standard methods and distilled prior to use. Yields were not optimized.

**General Synthetic Procedures for Diazonium Inner Salt (E) and Aryl Isocyanate (G).** Compound **E** (Scheme 1) was synthesized as the literature described (3, 6). Compound **G** was synthesized as the literature described (7). They were identified by  $^1\text{H}$  NMR spectroscopy.

**General Synthetic Procedure for Compound C (3).** The mixture of 2 mmol of **E** and 2 mmol of aryl isocyanate **G** in 5 mL of dichloromethane was stirred for 40–48 h at room temperature. After the reaction was completed as monitored by thin-layer chromatography, the solvent was removed in vacuo. The crude product was purified by flash column chromatography on silica gel, using ethyl acetate–petroleum ether ( $V/V = 3:1$ ) as the eluant to afford the pure target product. The melting points, yields, and elemental analyses of compounds **C1**–**28** are listed in Tables 1 and 2, and their  $^1\text{H}$  NMR are listed in Table 3.

\* To whom correspondence should be addressed. Tel: +86-22-23503799. Fax: +86-22-23503627. E-mail: nk\_yanghz@126.com.

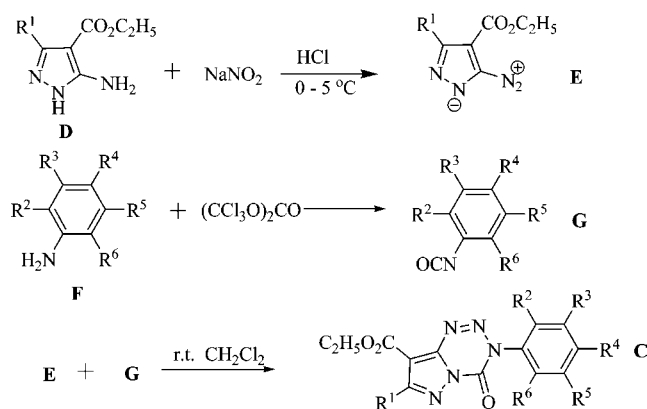

**Figure 1.** Chemical structures of **A**, **B**, and **C**.

**Table 1.** Melting Points and Yields of Compounds **C1–28**

compd	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	appearance	yield (%)	mp (°C)
<b>C1</b>	CH <sub>3</sub> S	F	H	Cl	propynyloxy	H	yellow	34.3	132–134
<b>C2</b>	CF <sub>3</sub>	F	H	Cl	propynyloxy	H	white	33.7	117–119
<b>C3</b>	CH <sub>3</sub>	F	H	Cl	allyloxy	H	yellow	77.2	122–123
<b>C4</b>	CH <sub>3</sub> S	F	H	Cl	allyloxy	H	yellow	60.8	129–130
<b>C5</b>	CF <sub>3</sub>	F	H	Cl	allyloxy	H	white	47.6	105–106
<b>C6</b>	CH <sub>3</sub>	F	H	Cl	<i>n</i> -propoxy	H	white	39.7	103–105
<b>C7</b>	CH <sub>3</sub> S	F	H	Cl	<i>n</i> -propoxy	H	yellow	60.5	130–131
<b>C8</b>	CF <sub>3</sub>	F	H	Cl	<i>n</i> -propoxy	H	white	32.3	110–111
<b>C9</b>	CH <sub>3</sub> S	F	H	Cl	<i>i</i> -propoxy	H	yellow	62.3	126–128
<b>C10</b>	CH <sub>3</sub> S	H	CF <sub>3</sub>	H	H	H	yellow	85.1	145–146
<b>C11</b>	CF <sub>3</sub>	H	CF <sub>3</sub>	H	H	H	white	62.9	124–125
<b>C12</b>	CH <sub>3</sub>	CF <sub>3</sub>	H	H	H	H	white	76.2	107–108
<b>C13</b>	CH <sub>3</sub> S	CF <sub>3</sub>	H	H	H	H	yellow	77.6	144–145
<b>C14</b>	CF <sub>3</sub>	CF <sub>3</sub>	H	H	H	H	yellow liquid	58.3	
<b>C15</b>	CH <sub>3</sub>	H	H	CF <sub>3</sub>	H	H	yellow	73.5	134–136
<b>C16</b>	CH <sub>3</sub> S	H	H	CF <sub>3</sub>	H	H	yellow	70.1	150–151
<b>C17</b>	CF <sub>3</sub>	H	H	CF <sub>3</sub>	H	H	yellow	66.5	133–134
<b>C18</b>	CH <sub>3</sub>	CF <sub>3</sub>	H	Cl	H	H	white	84.6	149–150
<b>C19</b>	CF <sub>3</sub>	CF <sub>3</sub>	H	Cl	H	H	white	32.9	110–111
<b>C20</b>	CH <sub>3</sub>	Cl	H	H	CF <sub>3</sub>	H	white	79.7	127–129
<b>C21</b>	CH <sub>3</sub> S	Cl	H	H	CF <sub>3</sub>	H	white	78.4	134–135
<b>C22</b>	CF <sub>3</sub>	Cl	H	H	CF <sub>3</sub>	H	white	48.3	116–118
<b>C23</b>	CH <sub>3</sub>	H	CF <sub>3</sub>	Cl	H	H	white	84.6	130–132
<b>C24</b>	CH <sub>3</sub> S	H	CF <sub>3</sub>	Cl	H	H	yellow	94.5	139–140
<b>C25</b>	CH <sub>3</sub>	Cl	H	CF <sub>3</sub>	H	Cl	yellow	32.1	90–92
<b>C26</b>	CH <sub>3</sub> S	Cl	H	CF <sub>3</sub>	H	Cl	yellow	49.1	88–90
<b>C27</b>	CF <sub>3</sub>	Cl	H	CF <sub>3</sub>	H	Cl	yellow	32.6	78–80
<b>C28</b>	CF <sub>3</sub>	H	CF <sub>3</sub>	Cl	H	H	yellow	44	108–109

**Table 2.** Elemental Analysis of Compounds **C1–28**

compd	elemental analysis (% calcd)		
	C	H	N
<b>C1</b>	46.44 (46.63)	3.10 (2.99)	15.90 (16.00)
<b>C2</b>	44.37 (44.41)	2.28 (2.19)	15.21 (15.23)
<b>C3</b>	49.95 (50.07)	3.87 (3.71)	17.15 (17.17)
<b>C4</b>	46.30 (46.42)	3.46 (3.44)	15.80 (15.92)
<b>C5</b>	44.11 (44.22)	2.75 (2.62)	14.96 (15.17)
<b>C6</b>	50.05 (49.82)	4.14 (4.18)	16.98 (17.09)
<b>C7</b>	46.16 (46.21)	3.72 (3.88)	16.03 (15.85)
<b>C8</b>	44.09 (44.03)	3.08 (3.04)	15.26 (15.10)
<b>C9</b>	46.27 (46.21)	3.74 (3.88)	15.78 (15.85)
<b>C10</b>	44.90 (45.11)	3.11 (3.03)	17.56 (17.54)
<b>C11</b>	42.60 (42.77)	2.33 (2.15)	16.40 (16.63)
<b>C12</b>	49.12 (49.05)	3.21 (3.29)	19.18 (19.07)
<b>C13</b>	44.95 (45.11)	2.90 (3.03)	17.44 (17.54)
<b>C14</b>	42.54 (42.77)	2.38 (2.15)	16.37 (16.63)
<b>C15</b>	49.02 (49.05)	3.40 (3.29)	19.22 (19.07)
<b>C16</b>	45.34 (45.11)	3.13 (3.03)	17.43 (17.54)
<b>C17</b>	42.50 (42.77)	2.19 (2.15)	16.68 (16.63)
<b>C18</b>	45.01 (44.85)	2.72 (2.76)	17.60 (17.43)
<b>C19</b>	39.28 (39.53)	1.87 (1.77)	15.54 (15.37)
<b>C20</b>	44.74 (44.85)	2.73 (2.76)	17.56 (17.43)
<b>C21</b>	41.68 (41.53)	2.54 (2.56)	16.18 (16.14)
<b>C22</b>	39.40 (39.53)	1.64 (1.77)	15.49 (15.37)
<b>C23</b>	44.72 (44.85)	2.83 (2.76)	17.56 (17.45)
<b>C24</b>	41.48 (41.53)	2.50 (2.56)	16.34 (16.14)
<b>C25</b>	39.59 (39.53)	1.65 (1.77)	15.38 (15.37)
<b>C26</b>	41.38 (41.30)	2.46 (2.31)	16.09 (16.06)
<b>C27</b>	36.90 (36.76)	1.51 (1.44)	14.03 (14.29)
<b>C28</b>	39.59 (39.53)	1.65 (1.77)	15.48 (15.37)

**Scheme 1**


**Bioassays.** The herbicidal activities of the target compounds (**C1–28**) were determined with *B. campestris* L. and *Echinochloa crus-galli* L. Beauv as samples of annual dicotyledonous and monocotyledonous plants, respectively, using a previously reported procedure (8). For all of the bioassay tests, each treatment was repeated three times.

**Treatment.** The emulsions of purified compounds were prepared by dissolving them in 100  $\mu$ L of *N,N*-dimethylformamide with the addition of 2  $\mu$ L of Tween 20. The mixture of the same amount of water, *N,N*-dimethylformamide, and Tween 20 was used as control.

**Inhibition of the Root-Growth of Rape (*B. campestris* L.).** Rape seeds were soaked in distilled water for 4 h before being placed on a filter paper in a 6 cm Petri plate, to which 2 mL of inhibitor solution had been added in advance. Usually, 15 seeds were used on each plate. The plate was placed in a dark room and allowed to germinate for 65

h at 28 ( $\pm$ 1) °C. The lengths of 10 rape roots selected from each plate were measured, and the means were calculated. The percentage inhibition was used to describe the control efficiency of the compounds. The herbicidal activity was summarized in **Table 4**.

**Inhibition of the Seedling Growth of Barnyard Grass [*E. crus-galli* (L.) Beauv].** Ten *E. crus-galli* seeds were placed into a 50 mL cup covered with a layer of glass beads and a piece of filter paper at the bottom, to which 5 mL of inhibitor solution had been added in advance. The cup was placed in a bright room, and the seeds were allowed to germinate for 65 h at 28 ( $\pm$ 1) °C. The heights of the above-ground parts of the seedlings in each cup were measured, and the means were calculated. The percentage inhibition was used to describe the control efficiency of the compounds. The herbicidal activity is summarized in **Table 4**.

## RESULTS AND DISCUSSION

**Preparations.** The syntheses of **E**, **G**, and **C** have been reported (3, 6, 7) (**Scheme 1**). The diazotization of compound **D** using nitrous acid at 0–5 °C followed by neutralization with saturated aqueous sodium carbonate gave 5-diazo-4-ethoxycarbonyl-1H-pyrazole **E** (3, 6). **G** was synthesized as the literature described (7) by reaction of triphosgene with aromatic amine. The target molecules **C**, described in **Table 1**, were obtained by the cycloaddition of **E** with aryl isocyanate **G** in anhydrous CH<sub>2</sub>Cl<sub>2</sub> at room temperature.

**QSAR Analysis.** Different substituents were introduced into the pyrazole and benzene rings of target products **C**. Their herbicidal activities were given in **Table 4**.

By replacing the methylsulfonyl group (R<sup>1</sup>) of related compounds of ref 3 by methyl, methylthio, or trifluoromethyl

Table 3. <sup>1</sup>H NMR of Compounds C1–28

compd	<sup>1</sup> H NMR (CDCl <sub>3</sub> ), δ
C1	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.59 (s, 1H, -C≡H), 2.71 (s, 3H, -SCH <sub>3</sub> ), 4.51 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 4.81 (s, 2H, -CH <sub>2</sub> C≡H), 7.29 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 6.0 Hz, Ar-H), 7.43 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 8.7 Hz, Ar-H)
C2	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.60 (s, 1H, -C≡H), 4.53 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 4.82 (s, 2H, -CH <sub>2</sub> C≡H), 7.30 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 6.3 Hz, Ar-H), 7.46 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 9.0 Hz, Ar-H)
C3	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.76 (s, 3H, -CH <sub>3</sub> ), 4.50 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 4.63 (m, 2H, -CH <sub>2</sub> CH=CH <sub>2</sub> ), 5.37 (m, 2H, -CH <sub>2</sub> CH=CH <sub>2</sub> ), 6.03 (m, 1H, -CH <sub>2</sub> CH=CH <sub>2</sub> ), 7.08 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 6.3 Hz, Ar-H), 7.41 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 9.0 Hz, Ar-H)
C4	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.71 (s, 3H, -SCH <sub>3</sub> ), 4.50 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 4.63 (m, 2H, -CH <sub>2</sub> CH=CH <sub>2</sub> ), 5.41 (m, 2H, -CH <sub>2</sub> CH=CH <sub>2</sub> ), 6.04 (m, 1H, -CH <sub>2</sub> CH=CH <sub>2</sub> ), 7.08 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 6.0 Hz, Ar-H), 7.42 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 9.0 Hz, Ar-H)
C5	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 6.9 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 4.53 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 6.9 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 4.64 (m, 2H, -CH <sub>2</sub> CH=CH <sub>2</sub> ), 5.43 (m, 2H, -CH <sub>2</sub> CH=CH <sub>2</sub> ), 6.05 (m, 1H, -CH <sub>2</sub> CH=CH <sub>2</sub> ), 7.07 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 6.3 Hz, Ar-H), 7.44 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 9.0 Hz, Ar-H)
C6	1.07 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 1.45 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 1.87 (m, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 2.75 (s, 3H, -CH <sub>3</sub> ), 3.98 (t, 2H, <sup>3</sup> J <sub>HH</sub> = 6.8 Hz, -CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 4.49 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 7.04 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, Ar-H), 7.39 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 9.2 Hz, Ar-H)
C7	1.07 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 1.45 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 1.88 (m, 2H, <sup>3</sup> J <sub>HH</sub> = 6.8 Hz, -CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 2.70 (s, 3H, -SCH <sub>3</sub> ), 3.98 (t, 2H, <sup>3</sup> J <sub>HH</sub> = 6.8 Hz, -CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 4.50 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 7.04 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 6.0 Hz, Ar-H), 7.40 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 8.8 Hz, Ar-H)
C8	1.08 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 1.45 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 6.8 Hz, -CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 1.88 (m, 2H, <sup>3</sup> J <sub>HH</sub> = 6.8 Hz, -CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 3.99 (t, 2H, <sup>3</sup> J <sub>HH</sub> = 6.4 Hz, -CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 4.52 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 7.04 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 6.4 Hz, Ar-H), 7.42 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 8.8 Hz, Ar-H)
C9	1.40 (d, 6H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH(CH <sub>3</sub> ) <sub>2</sub> ), 1.45 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 2.70 (s, 3H, -SCH <sub>3</sub> ), 4.50 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> ), 4.53 (m, 1H, -OCH(CH <sub>3</sub> ) <sub>2</sub> ), 7.08 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 6.4 Hz, Ar-H), 7.39 (d, 1H, <sup>3</sup> J <sub>HH</sub> = 8.8 Hz, Ar-H)
C10	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.72 (s, 3H, -SCH <sub>3</sub> ), 4.51 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.84 (m, 4H, Ar-H)
C11	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 4.53 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.85 (m, 4H, Ar-H)
C12	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.76 (s, 3H, -CH <sub>3</sub> ), 4.50 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.75 (m, 4H, Ar-H)
C13	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.71 (s, 3H, -SCH <sub>3</sub> ), 4.50 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.75 (m, 4H, Ar-H)
C14	1.45 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 4.51 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.77 (m, 4H, Ar-H)
C15	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.76 (s, 3H, -CH <sub>3</sub> ), 4.50 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.85 (m, 4H, Ar-H)
C16	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.71 (s, 3H, -SCH <sub>3</sub> ), 4.50 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.85 (m, 4H, Ar-H)
C17	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 4.53 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.87 (m, 4H, Ar-H)
C18	1.45 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.75 (s, 3H, -CH <sub>3</sub> ), 4.50 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.70 (m, 3H, Ar-H)
C19	1.45 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 4.52 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.72 (m, 3H, Ar-H)
C20	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 6.8 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.76 (s, 3H, -CH <sub>3</sub> ), 4.50 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 6.8 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.84 (m, 3H, Ar-H)
C21	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.71 (s, 3H, -SCH <sub>3</sub> ), 4.50 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.82 (m, 3H, Ar-H)
C22	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 4.53 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.83 (m, 3H, Ar-H)
C23	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.75 (s, 3H, -CH <sub>3</sub> ), 4.49 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.88 (m, 3H, Ar-H)
C24	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.71 (s, 3H, -SCH <sub>3</sub> ), 4.50 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.90 (m, 3H, Ar-H)
C25	1.47 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.77 (s, 3H, -CH <sub>3</sub> ), 4.51 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.84 (s, 2H, Ar-H)
C26	1.38 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 6.8 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 2.71 (s, 3H, -CH <sub>3</sub> ), 4.38 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.84 (s, 2H, Ar-H)
C27	1.46 (t, 3H, <sup>3</sup> J <sub>HH</sub> = 6.8 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 4.42 (q, 2H, <sup>3</sup> J <sub>HH</sub> = 6.8 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.87 (s, 2H, Ar-H)
C28	1.45 (t, 3H, J = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 4.53 (q, 2H, J = 7.2 Hz, -CH <sub>2</sub> CH <sub>3</sub> ), 7.90 (m, 3H, Ar-H)

groups, the herbicidal activity was generally improved. When a trifluoromethyl group existed at the meta-position in the benzene ring, most of them (C) showed similar inhibition at 100 and 10 μg/mL (e.g., C10, C20, C23, C24, and C28) for *B. campestris*. When the substituent at the para-position in benzene ring was chloro- or trifluoromethyl groups, most of the corresponding compounds showed lower herbicidal activity (except C15, C18, and C23). The comparison between C18 and C23 implied that the presence of trifluoromethyl group may have some influence on their metabolism process. It was also

observed that introduction of a polysubstituted benzene ring also improved the bioactivity. For example, when R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> were methyl, hydrogen, trifluoromethyl, chloro, hydrogen, and hydrogen, respectively, the corresponding compound C23 provided 89% control of *B. campestris* at 10 μg/mL. In order to gain insight into structure–activity relationships of compounds C, the data were analyzed by a physicochemical-based QSAR (Hansch) approach using physicochemical parameters as independent and herbicidal activity data (% I) at 100 μg/mL being converted to log {I/[(100 - I) × MW]} listed in

**Table 4.** Herbicidal Activity of Compounds (% I; Concentration,  $\mu\text{g/mL}$ )

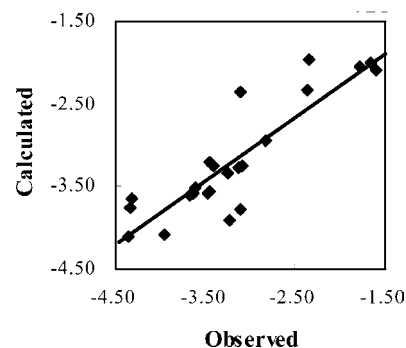
compd	<i>B. campestris</i> root test		<i>E. crus-galli</i> cup test	
	100	10	100	10
C1	0	0	32 ± 1	0
C2	0	0	28 ± 2	0
C3	0	0	24 ± 2	0
C4	25 ± 2	0	22 ± 1	0
C5	2 ± 1	0	16 ± 2	0
C6	0	0	18 ± 1	0
C7	2 ± 1	0	12 ± 1	0
C8	5 ± 1	0	20 ± 1	0
C9	13 ± 2	0	20 ± 1	0
C10	37 ± 2	34 ± 2	0	0
C11	14 ± 2	0	1 ± 1	0
C12	86 ± 2	5 ± 1	6 ± 2	0
C13	23 ± 2	0	0	0
C14	9 ± 1	7 ± 1	9 ± 2	0
C15	90 ± 2	82 ± 2	10 ± 1	0
C16	18 ± 1	4 ± 1	22 ± 1	2 ± 1
C17	2 ± 1	0	18 ± 2	9 ± 1
C18	63 ± 2	0	14 ± 1	6 ± 1
C19	0	0	21 ± 2	0
C20	65 ± 2	61 ± 2	0	0
C21	13 ± 2	0	11 ± 2	2 ± 1
C22	10 ± 1	0	2 ± 1	0
C23	89 ± 2	89 ± 1	4 ± 1	0
C24	24 ± 1	22 ± 1	26 ± 2	0
C25	25 ± 2	4 ± 1	22 ± 1	0
C26	9 ± 1	3 ± 1	28 ± 1	3 ± 2
C27	22 ± 2	2 ± 1	15 ± 1	0
C28	14 ± 1	13 ± 2	0	0

**Table 5.** Topological and Physicochemical Parameters of Compound C

compd	(MR-0.95) <sup>2</sup>	Es <sub>o</sub>	$\sigma_p$	L <sub>m</sub>	X1 <sup>obs</sup>	X1 <sup>calcd</sup>
C1	0.19	-0.46	0.23	6.58		-3.84
C2	0.20	-0.46	0.23	6.58		-4.15
C3	0.15	-0.46	0.23	6.22		-2.55
C4	0.19	-0.46	0.23	6.22	-3.12	-3.79
C5	0.20	-0.46	0.23	6.22	-4.35	-4.10
C6	0.15	-0.46	0.23	6.05		-2.52
C7	0.19	-0.46	0.23	6.05	-4.34	-3.76
C8	0.20	-0.46	0.23	6.05	-3.95	-4.07
C9	0.19	-0.46	0.23	4.80	-3.47	-3.59
C10	0.19	0	0	3.30	-2.83	-2.95
C11	0.20	0	0	3.30	-3.41	-3.26
C12	0.15	-2.40	0	1.00	-1.78	-2.04
C13	0.19	-2.40	0	1.00	-3.13	-3.28
C14	0.20	-2.40	0	1.00	-3.63	-3.59
C15	0.15	0	0.54	1.00	-1.61	-2.09
C16	0.19	0	0.54	1.00	-3.26	-3.33
C17	0.20	0	0.54	1.00	-4.31	-3.65
C18	0.15	-2.40	0.23	1.00	-2.37	-2.34
C19	0.20	-2.40	0.23	1.00		-3.89
C20	0.15	-0.97	0	3.30	-2.34	-1.97
C21	0.19	-0.97	0	3.30	-3.46	-3.21
C22	0.20	-0.97	0	3.30	-3.61	-3.52
C23	0.15	0	0.23	3.30	-1.66	-2.01
C24	0.19	0	0.23	3.30	-3.1	-3.25
C25	0.15	-0.97	0.54	1.00	-3.12	-2.36
C26	0.19	-0.97	0.54	1.00	-3.68	-3.60
C27	0.20	-0.97	0.54	1.00	-3.24	-3.91
C28	0.20	0	0.23	3.30	-3.45	-3.56

**Table 5** as dependent parameters. The values of the physicochemical parameters in the study were taken from the literature (9), and multiparameter linear regression analysis was carried out using SYBYL 6.9 (Tripos Inc.).

Variations in the herbicidal activities against *B. campestris* (**Table 5**) were first analyzed. Because the herbicidal activity for C1-3, C6, and C19 was zero, the five target molecules


**Figure 2.** Relationship between observed and calculated activity by eq 1.

**Table 6.** Correlation Matrix of the Parameters Used in QSAR Study

	(MR-0.95) <sup>2</sup>	Es <sub>o</sub>	$\sigma_p$	L <sub>m</sub>
(MR-0.95) <sup>2</sup>	1.000			
Es <sub>o</sub>	0.242	1.000		
$\sigma_p$	-0.072	0.359	1.000	
L <sub>m</sub>	0.325	0.412	-0.295	1.000

were not involved in the following QSAR analysis. Preliminary QSAR analysis showed the molar refractivity [(MR - 0.95)<sup>2</sup>] ( $r = 0.822$ ) for R<sup>1</sup>, and the Verloop parameter (L<sub>m</sub>) parameter for R<sup>5</sup> or R<sup>3</sup> ( $r = 0.381$ ), to a certain extent, showed correlation. In the case of di-ortho or di-meta substituents, only the substituent with higher Es<sub>o</sub> or L<sub>m</sub> values was under consideration. Stepwise regression analysis of different combinations of these parameters were studied, which led to the derivation of eq 1, with the best correlation ( $r = 0.880$ ).

$$X1 = \log\{I/[(100 - I) \times MW]\}$$

where MW is molecular weight and

$$X1 = 3.419 (\pm 0.893) - 31.053 (\pm 4.580) (MR - 0.95)^2 + 0.274 (\pm 0.137) Es_o - 1.320 (\pm 0.519) \sigma_p - 0.141 (\pm 0.060) L_m \quad (1)$$

where  $n = 23$ ,  $r = 0.881$ ,  $s = 0.4135$ , and  $F = 15.615$ .

The analysis indicates that (i) the coefficients of the (MR - 0.95)<sup>2</sup> terms meant that the MR for R<sup>1</sup> had an important impact on the herbicidal activity and the optimum value of MR for herbicidal activity was about 0.95 (such as ethynyl group), the compound that showed the highest herbicidal activity; (ii) the presence of bulkier substituents with positive Es<sub>o</sub> values at the ortho-position of the benzene ring positively contributed for the activity; (iii) the electronic-donating groups for the para-position in the benzene ring helped to elevate their herbicidal activity; and (iv) for the di-meta substituents (R<sup>3</sup> and R<sup>5</sup>), herbicidal activity was mainly affected by the substituent with the higher Verloop parameter (L<sub>m</sub>) value. Because the sums of the values at the substituent pairs performed less well than the maximum, this suggested that a steric clash with the tetrazinone carbonyl was important.

The intercorrelation of variable was given in **Table 6**, and the calculated activities for them by eq 1 were in good agreement with the observed activity (**Table 6** and **Figure 2**).

Variations in the herbicidal activities against *E. crus-galli* were also analyzed (**Table 7**). Because the herbicidal activity for C10, C13, C20, and C28 was zero, the four target molecules were also not involved in the following QSAR analysis. Preliminary QSAR analysis showed the hydrophobic parameter



**Table 7.** Topological and Physicochemical Parameters of Compound C

compd	$\pi R^1$	$(\pi R^1)^2$	$\pi_o$	$\pi_p$	$(\pi_p)^2$	$\sum(\pi R^3 + \pi R^5 + \pi R^6)$	$X2^{obs}$	$X2^{calcd}$
C1	0.61	0.37	0.14	0.71	0.50	0.10	-2.97	-3.03
C2	0.88	0.77	0.14	0.71	0.50	0.10	-3.07	-3.30
C3	0.56	0.31	0.14	0.71	0.50	0.60	-3.11	-3.43
C4	0.61	0.37	0.14	0.71	0.50	0.60	-3.19	-3.14
C5	0.88	0.77	0.14	0.71	0.50	0.60	-3.38	-3.42
C6	0.56	0.31	0.14	0.71	0.50	1.05	-3.27	-3.54
C7	0.61	0.37	0.14	0.71	0.50	1.05	-3.51	-3.25
C8	0.88	0.77	0.14	0.71	0.50	1.05	-3.27	-3.52
C9	0.61	0.37	0.14	0.71	0.50	0.36	-3.25	-3.09
C10	0.61	0.37	0	0	0	0.88		-4.03
C11	0.88	0.77	0	0	0	0.88	-4.62	-4.30
C12	0.56	0.31	0.88	0	0	0	-3.76	-3.86
C13	0.61	0.37	0.88	0	0	0		-3.82
C14	0.88	0.77	0.88	0	0	0	-3.63	-3.84
C15	0.56	0.31	0	0.88	0.77	0	-3.52	-3.40
C16	0.61	0.37	0	0.88	0.77	0	-3.15	-3.11
C17	0.88	0.77	0	0.88	0.77	0	-3.28	-3.39
C18	0.56	0.31	0.88	0.71	0.50	0	-3.39	-3.08
C19	0.88	0.77	0.88	0.71	0.50	0	-3.23	-3.07
C20	0.56	0.31	0.71	0	0	0.88		-4.31
C21	0.61	0.37	0.71	0	0	0.88	-3.55	-3.82
C22	0.88	0.77	0.71	0	0	0.88	-4.35	-4.09
C23	0.56	0.31	0	0.71	0.50	0.88	-3.95	-3.54
C24	0.61	0.37	0	0.71	0.50	0.88	-3.06	-3.25
C25	0.56	0.31	0.71	0.88	0.77	0.71	-3.19	-3.36
C26	0.61	0.37	0.71	0.88	0.77	0.71	-3.08	-3.07
C27	0.88	0.77	0.71	0.88	0.77	0.71	-3.44	-3.34
C28	0.88	0.77	0	0.71	0.5	0.88		-3.52

$\sum[\pi R^1 + (\pi R^1)^2]$  ( $r = 0.391$ ) for  $R^1$ ,  $\sum(\pi_p + (\pi_p)^2)$  ( $r = 0.721$ ) for  $R^4$ , and  $\sum(\pi R^3 + \pi R^5 + \pi R^6)$  for  $R^3$ ,  $R^5$ , and  $R^6$  ( $r = 0.253$ ), to a certain extent, showed correlation. Stepwise regression analysis of different combinations of these parameters was studied, which led to the derivation of eq 2, with a best correlation ( $r = 0.844$ ).

$$X2 = \log\{I/[(100 - I) \times MW]\}$$

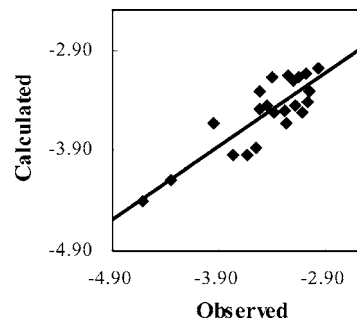
where MW is molecular weight and

$$X2 = 34.520 (\pm 15.107) \pi R^1 - 23.985 (\pm 10.389) (\pi R^1)^2 + 0.289 (\pm 0.171) \pi_o + 2.264 (\pm 0.809) \pi_p - 1.663 (\pm 0.958) (\pi_p)^2 - 0.230 (\pm 0.135) \sum(\pi R^3 + \pi R^5 + \pi R^6) - 16.006 (\pm 5.317) \quad (2)$$

where  $n = 24$ ,  $r = 0.844$ ,  $s = 0.2524$ , and  $F = 6.994$ .

Equation 2 indicated that the substituent  $R^2$  positively contributed for the activity while  $R^3$ ,  $R^5$ , and  $R^6$  at the benzene ring negatively contributed. The coefficients of the  $(\pi R^1)^2$  and  $\pi R^1$  terms meant that the hydrophobic parameter ( $\pi R^1$ ) for  $R^1$  had an optimum value for C and was about 0.72 (such as chloro atom, 0.71). The coefficients of the  $(\pi_p)^2$  and  $\pi_p$  terms also meant that the hydrophobic parameter ( $\pi_p$ ) for  $R^4$  had an optimum value for C and was about 0.68 [such as  $\text{CH}_2\text{CH}_2$ (1-pyrrolidyl), 0.69]. This result showed that when the other conditions were the same and  $\pi R^1$  and  $\pi_p$  were 0.72 and 0.68, respectively, the corresponding compounds had the highest herbicidal activity. The intercorrelation of variable was given in Table 8, and the calculated activities for them by eq 2 were in good agreement with the observed activity (Table 8 and Figure 3).

In addition, the selectivity between *E. crus-galli* and *B. campestris* for this kind compounds was studied and led to the derivation of eq 3, with best correlation ( $r = 0.798$ ) (Table 9).

**Figure 3.** Relationship between observed and calculated activity by eq 2.**Table 8.** Correlation Matrix of the Parameters Used in QSAR Study

	$\pi R^1$	$(\pi R^1)^2$	$\pi_o$	$\pi_p$	$(\pi_p)^2$	$\sum(\pi R^3 + \pi R^5 + \pi R^6)$
$\pi R^1$	1.000					
$(\pi R^1)^2$	1.000	1.000				
$\pi_o$	0.094	0.098	1.000			
$\pi_p$	-0.224	-0.225	-0.383	1.000		
$(\pi_p)^2$	-0.205	-0.205	-0.324	0.977	1.000	
$\sum(\pi R^3 + \pi R^5 + \pi R^6)$	-0.048	-0.051	-0.192	-0.079	-0.120	1.000

**Table 9.** Topological and Physicochemical Parameters of Compound C

	$X1^{obs}$	$\pi_p$	$(\pi_p)^2$	$\pi_m$	$X2^{obs}$	$X2^{calcd}$
C4	-3.12	0.71	0.50	0.60	-3.19	-3.37
C5	-4.35	0.71	0.50	0.60	-3.38	-3.21
C7	-4.34	0.71	0.50	1.05	-3.51	-3.40
C8	-3.95	0.71	0.50	1.05	-3.27	-3.45
C9	-3.47	0.71	0.50	0.36	-3.25	-3.22
C11	-3.41	0	0	0.88	-4.62	-4.10
C12	-1.78	0	0	0.00	-3.76	-3.93
C14	-3.63	0	0	0.00	-3.63	-3.69
C15	-1.61	0.88	0.77	0.00	-3.52	-3.48
C16	-3.26	0.88	0.77	0.00	-3.15	-3.27
C17	-4.31	0.88	0.77	0.00	-3.28	-3.13
C18	-2.37	0.71	0.50	0.00	-3.39	-3.20
C19	-2.34	0.71	0.50	0.00	-3.23	-3.21
C21	-3.46	0	0	0.88	-3.55	-4.10
C22	-3.61	0	0	0.88	-4.35	-4.08
C23	-1.66	0.71	0.50	0.88	-3.95	-3.68
C24	-3.10	0.71	0.50	0.88	-3.06	-3.49
C25	-3.12	0.88	0.77	0.00	-3.19	-3.29
C26	-3.68	0.88	0.77	0.00	-3.08	-3.21
C27	-3.24	0.88	0.77	0.00	-3.44	-3.27

When the herbicidal activity against whether *E. crus-galli* or *B. campestris* was zero, the corresponding compound was not included. In the case of di-meta substituents, only the substituent with the larger hydrophobic parameter ( $\pi_m$ ) was under consideration.

$$X2 = -4.166 (\pm 0.272) - 0.130 (\pm 0.082) X1 + 2.499 (\pm 1.098) \pi_p - 2.241 (\pm 1.378) (\pi_p)^2 - 0.433 (\pm 0.202) \pi_m \quad (3)$$

where  $n = 20$ ,  $r = 0.798$ ,  $s = 0.2793$ , and  $F = 6.561$ .

The coefficients of  $X1$  term meant that, for the same compound, its herbicidal activity against *B. campestris* was about 1.3 times that against *E. crus-galli*. The coefficients of the  $(\pi_p)^2$  and  $\pi_p$  terms also meant that when the hydrophobic parameter ( $\pi_p$ ) for  $R^4$  was about 0.56, the selectivity for inhibiting the seedling growth of *E. crus-galli* was the highest. The intercorrelation of variable was given in Table 10, and the

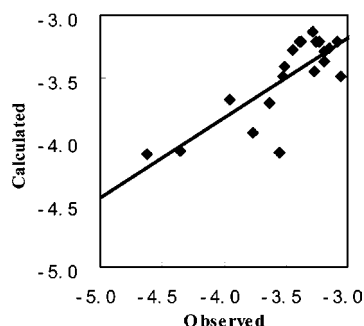


Figure 4. Relationship between observed and calculated activity by eq 3.

Table 10. Correlation Matrix of the Parameters Used in QSAR Study

	$\chi_1^{\text{obs}}$	$\pi_p$	$(\pi_p)^2$	$\pi_m$
$\chi_1^{\text{obs}}$	1.000			
$\pi_p$	-0.010	1.000		
$(\pi_p)^2$	-0.011	0.980	1.000	
$\pi_m$	-0.302	-0.289	-0.392	1.000

calculated activities for them by eq 3 were in good agreement with the observed activity (Table 10 and Figure 4).

In summary, we further extended the study of SAR of pyrazolo[5,1-d][1,2,3,5]tetrazin-4(3H)ones and gained insight about the pharmacophore through physicochemical-based QSAR study. The herbicidal activity in the rape root test for compound C was mainly affected by the MR for R<sup>1</sup>, Taft ( $E_s$ ) for R<sup>2</sup> or R<sup>6</sup>, Verloop's sterimol ( $L_m$ ) for R<sup>3</sup> or R<sup>5</sup>, and electronic parameters (Hammett's constants,  $\sigma_p$ ) for R<sup>4</sup>. When MR was about 0.95, the compound showed the highest herbicidal activity and for the di-meta substituents (R<sup>3</sup> and R<sup>5</sup>) at the benzene ring, their herbicidal activity was mainly affected by the substituent with higher Verloop's sterimol ( $L_m$ ) parameter value.

The herbicidal activity in the barnyard grass cup test for compound C was mainly related with the substituents' hydrophobic parameter. When the other conditions were the same and the hydrophobic parameters ( $\pi$ ) for R<sup>1</sup> and R<sup>4</sup> were 0.72 and 0.68, respectively (eq 2), the corresponding compounds had the highest herbicidal activity. In general, these compounds

showed greater herbicidal activity toward *B. campestris* than *E. crus-galli*.

#### LITERATURE CITED

- (1) Barraja, P.; Diana, P.; Lauria, A.; Montalbano, A.; Almerico, A. M.; Dattolo, G.; Cirrincione, G. Synthesis and antiproliferative activity of [1,2,3,5]tetrazino[5,4-a]indoles, a new class of azolo-tetrazinones. *Biol. Med. Chem.* **2004**, *13* (2), 295–300.
- (2) Diana, P.; Barraja, P.; Lauria, A.; Almerico, A. M.; Dattolo, G.; Cirrincione, G. Pyrrolo[2,1-d][1,2,3,5]tetrazines, a new class of azolo-tetrazines related to the antitumor drug temozolomide. *Synthesis* **1999**, *12*, 2082–2086.
- (3) Wu, Y.-C.; Zou, X.-M.; Hu, F.-Z.; Yang, H.-Z. Design and synthesis of novel sulfone-containing pyrazolo[1,5-a]pyrimidines and pyrazolo[5,1-d][1,2,3,5]tetrazine-4(3H)-ones. *J. Heterocycl. Chem.* **2005**, *42* (4), 609–613.
- (4) Hirai, K.; Uchida, A.; Ohno, R. *Herbicide Classes in Development*; Böger, P., Wakabayashi, K., Hirai, K., Eds.; Springer-Verlag: Berlin, Heidelberg, 2002; pp 255–274.
- (5) van de Waterbeemd, H. Introduction. In *Chemometric Methods in Molecular Design*; van de Waterbeemd, H., Ed.; VCH Publishers: New York, 1995; pp 1–13.
- (6) Zou, X.-M.; Cheng, Y.-H.; Ren, X.-L.; Hu, F.-Z.; Yang, H.-Z. Synthesis of some new hydrazone compounds containing pyrazolyl nucleus. *Chin. J. Org. Chem.* **2005**, *25* (5), 554–557 (in Chinese).
- (7) Du, X.-H.; Xu, X.-S.; Xu, Z.-Y. A safe and effective method for preparation of aromatic isocyanates using bis(trichloromethyl)carbonate. *Chin. J. Pestic. Sci.* **2002**, *4*, 83–85 (in Chinese).
- (8) Zhu, Y.-Q.; Zou, X.-M.; Hu, F.-Z.; Yao, C.-S.; Liu, B.; Li, Y.-H.; Yang, H.-Z. Synthesis and herbicidal evaluation of novel 3-( $\alpha$ -hydroxy-substitutedbenzylidene) pyrrolidine-2,4-diones. *J. Agric. Food Chem.* **2005**, *53*, 9566–9570.
- (9) Hansch, C.; Leo, A.; Hoekman, D. *Exploring QSAR*; ACS Professional Reference Book; American Chemical Society: Washington, DC, 1995.

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