JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY
ARTICLE

J. Agric. Food Chem. 2009, 57, 7919–7923 7919
DOI:10.1021/jf9020812

Semisynthesis and Quantitative Structure−Activity Relationship (QSAR) Study of Novel Aromatic Esters of 4′-Demethyl-4-deoxypodophyllotoxin as Insecticidal Agents

Hui Xu,*,† Juanjuan Wang,† Huijun Sun,§ Min Lv,† Xuan Tian,§ Xiaojun Yao,*,§ and Xing Zhang†

†Laboratory of Pharmaceutical Design and Synthesis, College of Life Sciences, Northwest A&F University, 22 Xinong Road, Yangling 712100, Shannxi Province, People's Republic of China, and §Department of Chemistry, Lanzhou University, Gansu Province, People's Republic of China

By using podophyllotoxin as a phytoinsecticidal lead compound, 15 novel aromatic esters of 4′-demethyl-4-deoxypodophyllotoxin were semisynthesized and preliminarily tested for their insecticidal activity against the pre-third-instar larvae of *Mythimna separata* Walker in vivo for the first time. Among all of the tested compounds, especially two compounds, **4m** and **4o**, containing a pyridinyl group, for which final corrected mortality rates against *M. separata* at 1 mg/mL were 62.9 and 59.2%, respectively, showed the most promising and pronounced insecticidal activity as compared with toosendanin, a commercial insecticide derived from *Melia azedarach*. The quantitative structure−activity relationships (QSAR) of compounds **4a**−**4o** showed that the relative number of benzene rings and final heat of formation were very important descriptors to their insecticidal activity.

KEYWORDS: Podophyllotoxin; synthesis; insecticidal activity; structure−activity relationship

INTRODUCTION

In the course of our screening for novel naturally occurring phytoinsecticides from the plants in northwestern China, podophyllotoxin (**1**) (**Figure 1**) was isolated as an insecticidal component by bioassay-guided fractionation from *Juniperus sabina* Linnaeus (*1*). It is well-known that structural modification is an effective method to optimize natural bioactive compounds. Recently, to obtain more potent insecticidal podophyllotoxin analogues, compound **1** has been used as a lead compound for structural modification, and some derivatives exhibited more potent insecticidal activity than **1** against the larvae of *Drosophila melanogaster* Meigen, *Pieris rapae* Linnaeus, or *Mythimna separata* Walker in vivo (*2*−*6*). Obviously, the recent structural modification of **1** as an insecticidal agent has been mainly focused on the C-4 position of **1**. To the best of our knowledge, however, little attention has been paid to structural modification on the C-4′ position of **1**. In continuation of our program aimed at the discovery and development of bioactive molecules (*3*−*7*), we want to investigate the effect of substituents on the C-4′ position of podophyllotoxin analogues to the insecticidal activity. In the meantime, You et al. reported that some alkyl and carboxylalkyl esters of 4′-demethyl-4-deoxypodophyllotoxin exhibited good antitumor activity (*8*). Therefore, in this paper 15 novel aromatic esters of 4′-demethyl-4-deoxypodophyllotoxin (**4a**−**4o**) were semisynthesized from **1** and tested for their insecticidal activity against pre-third-instar larvae of *M. separata* Walker in vivo for the first time. The quantitative structure−activity relationships (QSAR) of these compounds were also studied.

*Author to whom correspondence should be addressed [(H.X.) telephone +86(0)29-87091952; fax +86(0)29-87091952; e-mail orgxuhui@nwsuaf.edu.cn. (X.Y.) e-mail xjyao@lzu.edu.cn].

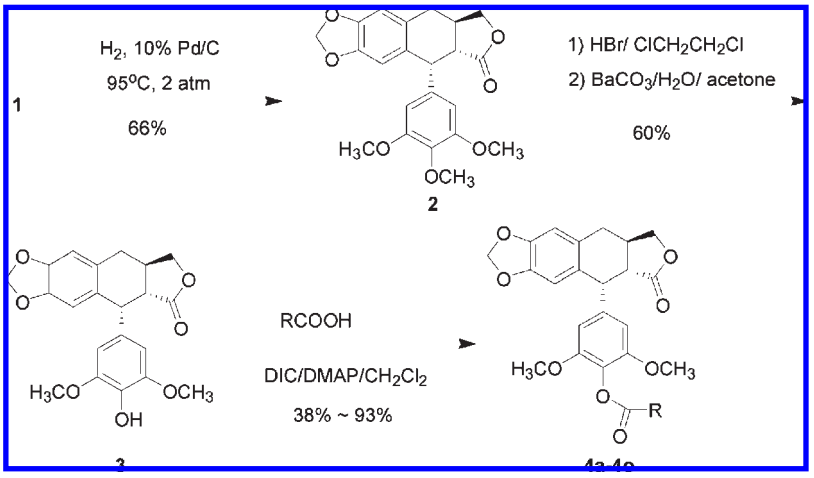
MATERIALS AND METHODS

Synthetic Procedures. Podophyllotoxin was purchased from Gansu Gerui Medicinal Materials Co., Ltd. All reagents and solvents were of reagent grade or purified according to standard methods before use. Analytical thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were performed with silica gel plates using silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co., Ltd.). Melting points were determined on a digital melting-point apparatus and were uncorrected. Infrared spectra (IR) were recorded on a Thermo Nicolet Nexus FTIR-8700 spectrometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker Avance DMX 400 MHz instrument using TMS as internal standard and $CDCl_3$ as solvent. High-resolution mass spectra (HR-MS) and electron ionization mass spectrometry (EI-MS) or electrospray iontrap mass spectrometry (ESI-TRAP-MS) were carried out with APEX II Bruker 4.7T AS and Thermo DSQ GC-MS or Bruker ESI-TRAP Esquire 3000 plus mass spectrometry instruments, respectively.

4-Deoxypodophyllotoxin (2). A mixture of 10% palladium/carbon (12.0 g) and podophyllotoxin (**1**, 16.0 g, 38.6 mmol) in acetic acid solution (150 mL) was stirred at 95 °C under 2 atm of hydrogen for 5 h. After filtration to remove the catalyst and evaporation of the solvent, the residue was purified by silica gel column chromatography (diethyl ether/dichloromethane, 6:1) to give the crude product, which was further purified by recrystallization from methanol to afford 9.8 g (66%) of **2** as a white solid: mp 165−167 °C [lit., 166−168 °C (*9*)]; $[\alpha]^{20}_D = -116°$ (*c* 1 mg/mL, $CHCl_3$); IR cm^{-1} 2892, 2831, 1763, 1587, 1482, 1457, 1223, 1120, 925, 768; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 1H, H-5), 6.52 (s, 1H, H-8), 6.34 (s, 2H, H-2′,6′), 5.93 (d, J = 8.0 Hz, 2H, OCH_2O), 4.60 (s, 1H, H-1), 4.43 (m, 1H,

Published on Web 08/18/2009

Scheme 1



H-11), 3.89 (m, 1H, H-11), 3.79 (s, 3H, 4′-OCH_3), 3.75 (s, 6H, 3′,5′-OCH_3), 3.06 (m, 1H, H-4), 2.71 (m, 3H, H-2,3,4); MS (EI), *m*/*z* (%) 398.1 (M^+, 100).

4′-Demethyl-4-deoxypodophyllotoxin (3). **2** (2 g, 50.2 mmol) was suspended in 1,2-dichloroethane (25 mL) and diethyl ether (2.5 mL) at 0 °C. A flow of dry hydrobromic acid was passed in the above solution. When the reaction was complete according to TLC analysis, water (25 mL), acetone (25 mL), and a little amount of $BaCO_3$ were added to the reaction mixture, which continued to stir for 0.5 h and extracted by EtOAc (30 mL × 4). Subsequently, the combined organic phase was washed by brine (50 mL × 2), dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and purified by silica gel column chromatography (chloroform/ethyl acetate, 5:1) to give 1.16 g (60%) of **3** as a khaki solid: mp 246−248 °C [lit., 244−249 °C (*10*)]; $[\alpha]^{20}_D = -130°$ (*c* 0.4 mg/mL, $CHCl_3$); IR cm^{-1} 2899, 2824, 1757, 1608, 1478, 1458, 1214, 1105, 922, 769; ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (s, 1H, H-5), 6.51 (s, 1H, H-8), 6.35 (s, 2H, H-2′,6′), 5.92 (m, 2H, OCH_2O), 5.39 (s, 1H, 4′-OH), 4.59 (d, J=2.4 Hz, 1H, H-1), 4.42 (m, 1H, H-11), 3.88 (m, 1H, H-11), 3.78 (s, 6H, 3′,5′-OCH_3), 3.05 (m, 1H, H-4), 2.71 (m, 3H, H-2,3,4); MS (EI), *m*/*z* (%) 383.9 (M^+, 100).

General Synthetic Procedure for Aromatic Esters of 4′-Demethyl-4-deoxypodophyllotoxin (4a−4o). A mixture of the corresponding acid (0.3 mmol), diisopropylcarbodiimide (DIC, 0.3 mmol), 4-dimethylaminopyridine (DMAP, 0.1 mmol), and **3** (0.25 mmol) in dried dichloromethane (10 mL) was stirred at 0 °C. When the reaction was complete according to TLC analysis, the resulting suspension was filtered, and water (25 mL) was added to the solution of the above mixture, which was extracted with dichloromethane (30 mL × 4). Then the organic phase were combined, dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by PTLC to give the pure target products in 38−93% yields. The example data of **4a** and **4b** are shown as follows, whereas data for **4c−4o** can be found in the Supporting Information.

Data for ***4a****:* R_f = 0.52 (petroleum ether/ethyl acetate, 1:1); yield = 93%; white solid, mp 223−225 °C; $[\alpha]^{20}_D = -79°$ (*c* 0.29 mg/mL, $CHCl_3$); IR cm^{-1} 2921, 2849, 1779, 1759, 1597, 1482, 1459, 1224, 1122, 928, 774, 731; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J=7.2 Hz, 2H, H-2″,6″), 7.32 (m, 2H, H-3″,5″), 7.28 (d, J=7.6 Hz, 1H, H-4″), 6.65 (s, 1H, H-5), 6.51 (s, 1H, H-8), 6.35 (s, 2H, H-2′,6′), 5.92 (dd, J=1.2 Hz, J=8.0 Hz, 2H, OCH_2O), 4.61 (d, J=4.4 Hz, 1H, H-1), 4.42 (m, 1H, H-11), 3.88 (m, 3H, H-11 and $\underline{CH_2}C_6H_5$), 3.62 (s, 6H, 3′,5′-OCH_3), 3.03 (m, 1H, H-4), 2.69 (m, 3H, H-2, 3, 4); MS (ESI-TRAP), *m*/*z* (%) 525 ($[M + Na]^+$, 25). HRMS: Anal. Calcd for $C_{29}H_{30}NO_8$ ($[M + NH_4]^+$), 520.1966; found, 520.1960.

Data for ***4b****:* R_f = 0.7 (dichloromethane/acetone, 50:1); yield = 71%; white solid, mp 256−258 °C; $[\alpha]^{20}_D = -80°$ (*c* 0.26 mg/mL, $CHCl_3$); IR cm^{-1} 2921, 2849, 1761, 1738, 1597, 1486, 1454, 1230, 1128, 928, 771, 706; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J=7.6 Hz, 2H, H-2″,6″), 7.59 (t, J= 7.6 Hz, 1H, H-4″), 7.46 (t, J=7.6 Hz, 2H, H-3″,5″), 6.68 (s, 1H, H-5), 6.59 (s, 1H, H-8), 6.43 (s, 2H, H-2′,6′), 5.94 (d, J=7.6 Hz, 2H, OCH_2O), 4.67 (s, 1H, H-1), 4.46 (m, 1H, H-11), 3.89 (m, 1H, H-11), 3.69 (s, 6H, 3′,5′-OCH_3), 3.07 (m, 1H, H-4), 2.76 (m, 3H, H-2,3,4); MS (ESI-TRAP), *m*/*z* (%) 511 ($[M + Na]^+$, 39). HRMS: Anal. Calcd for $C_{28}H_{28}NO_8$ ($[M + NH_4]^+$), 506.1809; found, 506.1802.

Biological Assay. The insecticidal activity of **4a−4o** against the pre-third-instar larvae of *M. separata* Walker was assessed by leaf-dipping method as described previously (*5*). For each compound, 30 larvae (10 larvae per group) were used. Acetone solutions of **4a−4o** and toosendanin (used as a positive control) were prepared at the concentration of 1 mg/mL. Fresh corn leaves were dipped into the corresponding solution for 3 s, then taken out, and dried in a room. Leaves treated with acetone alone were used as a control group. Several treated leaves were kept in each dish, where every 10 larvae were raised. If the treated leaves were consumed, corresponding ones were added to the dish. After 48 h, untreated fresh leaves were added to all dishes until the adult emergence. The experiment was carried out at 25 ± 2 °C and relative humidity (RH) 65−80% on a 12 h/12 h (light/dark) photoperiod. The insecticidal activity of the tested compounds against the pre-third-instar larvae of *M. separata* was calculated by the formula

$$\text{corrected mortality rate } (\%) = (T - C) \times 100/(1 - C)$$

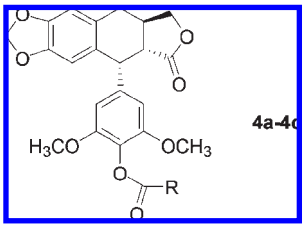
where T is the mortality rate in the treated group expressed as a percentage and C is the mortality rate in the untreated group expressed as a percentage.

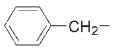
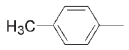
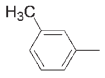
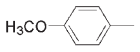
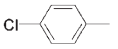
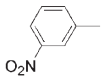
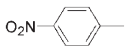
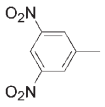
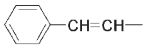
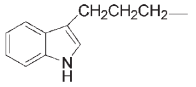
RESULTS AND DISCUSSION

Synthesis. As shown in **Scheme 1**, 4-deoxypodophyllotoxin (**2**) was first obtained in a 66% yield by catalytic hydrogenolysis of **1** in the presence of 10% palladium/carbon (*9*). Then regioselective 4′-demethylation of **2** with dry hydrobromide, followed by the mixed solvent system (water/acetone) and $BaCO_3$, could proceed readily to give the 4′-demethyl-4-deoxypodophyllotoxin (**3**) in a 60% yield (*10*). Finally, 15 esters of 4′-demethyl-4-deoxypodophyllotoxin (**4a−4o**) were obtained by the reaction of **3** with the corresponding acids containing aromatic cycles in the presence of DIC and DMAP. The structures of the target compounds were well characterized by ^1H NMR, HRMS, MS, optical rotation, and IR.

Biological Activity. The insecticidal activity of **4a−4o** against the pre-third-instar larvae of *M. separata* Walker in vivo was investigated by the leaf-dipping method at the concentration of 1 mg/mL. Toosendanin, a commercial insecticide derived from *M. azedarach*, was used as a positive control. As shown in **Table 1**, the corresponding corrected mortality rates caused by these compounds after 36 days were far higher than those after 12 and 24 days. For example, the corrected mortality rate of **4m** against *M. separata* after 12 days was only 3.5%; after 24 days, the corresponding mortality rate was increased to 10.7%, but after 36 days the corresponding mortality rate was sharply

Table 1. Insecticidal Activity of Novel Aromatic Esters of 4′-Demethyl-4-deoxypodophyllotoxin (**4a**−**4o**) against *Mythimna separata* Walker in Vivo



Compounds	R	Corrected Mortality Rate (%)		
		12 d	24 d	36 d
4a		10.7 ± 4.7	25.0 ± 8.2	29.6 ± 4.7
4b		28.5 ± 9.4	42.8 ± 4.7	48.1 ± 4.7
4c		7.1 ± 12.5	17.8 ± 4.7	33.3 ± 8.2
4d		17.8 ± 4.7	25.0 ± 8.2	40.7 ± 4.7
4e		3.5 ± 0	21.4 ± 9.4	25.9 ± 9.4
4f		17.8 ± 9.4	25.0 ± 16.3	37.0 ± 4.7
4g		0 ± 4.7	14.2 ± 8.2	29.6 ± 4.7
4h		7.1 ± 4.7	17.8 ± 9.4	37.0 ± 4.7
4i		3.5 ± 8.2	14.2 ± 8.2	51.8 ± 4.7
4j		7.1 ± 12.5	17.8 ± 12.5	40.7 ± 4.7
4k		14.2 ± 8.2	25.0 ± 8.2	22.2 ± 10
4l		10.7 ± 4.7	17.8 ± 4.7	48.1 ± 4.7
4m		3.5 ± 8.2	10.7 ± 9.4	62.9 ± 4.7
4n		10.7 ± 4.7	14.2 ± 8.2	40.7 ± 9.4
4o		14.2 ± 8.2	21.4 ± 4.7	59.2 ± 4.7
toosendanin	/	21.4 ± 4.7	35.7 ± 14.1	40.7 ± 4.7

increased to 62.9%, which was nearly 18 times the mortality rate after 12 days. That is, these compounds showed delayed insecticidal activity (*5*), which is different from the conventional neurotoxic insecticides, such as organophosphates, carbamates, and pyrethroids. Meanwhile, the symptoms of the tested *M. separata* were also characterized as the same as our previous reports (*5*). Additionally, the pupation of the larvae and the adult emergence of *M. separata* were inhibited by these compounds; therefore, the stage from the larvae to adulthood of *M. separata* was prolonged as compared to the control group. Moreover, many larvae of the treated groups were unable to reach adulthood and died during the stage of pupation. Among all of the tested

Table 2. BMLR Model and Its Statistical Parameters

descriptor	X^a	DX[b]	t test value[c]
intercept	1.9193×10^2	2.3448×10^1	8.1853
relative number of benzene rings	-1.2144×10^3	2.2330×10^2	−5.4385
final heat of formation	6.4032×10^{-1}	1.1081×10^{-1}	5.7785
RNCS relative negative charged SA (SAMNEG*RNCG) [quantum-chemical PC]	1.1577×10^1	2.5599×10	4.5225

[a] X, regression coefficient of the descriptor. [b] DX, standard errors of the regression coefficient X. [c] t test value, t statistics of the regression coefficient X.

compounds, especially compounds **4m** and **4o** containing a pyridinyl group, for which corrected mortality rates against *M. separata* after 36 days were 62.9 and 59.2%, respectively, exhibited the most promising and best insecticidal activity as compared to toosendanin (40.7%).

Qualitative Structure−Activity Relationships (SAR). As shown in **Table 1**, when the methyl group was introduced at the meta position on the phenyl ring of **4b** to give **4d**, the insecticidal activity of **4d** was more potent than the one having a *p*-methyl group on the phenyl ring of **4b** (**4d** vs **4c**). The same results were also found for compounds **4i** and **4j**; for example, when the nitro group was introduced at the meta position on the phenyl ring of **4b** to give **4i**, the insecticidal activity after 36 days of **4i** was increased as compared with **4b** (48.1% for **4b** and 51.8% for **4i**). However, when the nitro group was introduced at the para position on the phenyl ring of **4b** to give **4j**, the insecticidal activity after 36 days of **4j** was decreased as compared with **4b** (48.1% for **4b** and 40.7% for **4j**). Interestingly, if two nitro groups were stimultaneously introduced at the meta position on the phenyl ring of **4b** to give **4k**, the insecticidal activity after 36 days of **4k** was decreased sharply as compared with **4b** (48.1% for **4b** and 22.2% for **4k**); that is, **4k** exhibited >2-fold less potency than **4b**. Moreover, introducing one electron-withdrawing group (e.g., nitro group) on the phenyl ring of **4b** will usually give more active compounds than the one having an electron-donating group (e.g., methyl, methoxy, and chloro) on the phenyl ring of 4b (**4i** and **4j** vs **4c**−**4g**). It was noteworthy that especially when the pyridinyl ring was substituted for the phenyl ring of **4b**, the corrected mortality rates after 36 days of the corresponding compounds **4m** and **4o** were increased to 62.9 and 59.2%, respectively. Therefore, some aromatic esters of 4′-demethyl-4-deoxypodophyllotoxin containing other heterocyclic rings will be synthesized and studied in our laboratory.

Quantitative Structure−Activity Relationships (QSAR). The structures of 15 molecules **4a**−**4o** were drawn by using Sybyl 6.9 (*11*). All structures were preoptimized by the molecular mechanics force field (MM+) (*12*) and then optimized using the semiempirical method PM3 implemented in Hyperchem and MOPAC (*13*).

Comprehensive Descriptors for Structural and Statistical Analysis (CODESSA) is a comprehensive program for developing quantitative structure−activity/property relationships (QSAR/QSPR) by integrating all necessary mathematical and computational tools. The output files from MOPAC were used by the CODESSA program to calculate molecular descriptors (*14*). The Best Multilinear Regression method (BMLR) was used to select the significant descriptors and develop the QSAR model. Four hundred and seventy-three descriptors were calculated for each molecule. After using the BMLR method, three descriptors correlated with the final corrected mortality rate (%) were selected for the 15 4′-demethyl-4-deoxypodophyllotoxin derivatives **4a**−**4o**. The BMLR model and its statistical parameters are shown in **Table 2**. This model gave a squared correlation coefficient (R^2) of 0.868, a squared standard deviation (s^2) of 23.543, and a cross-validated squared correlation coefficient (R^2_{cv}) of 0.749. Detailed information about the predicted corrected mortality rate, the experimental corrected mortality rate, the errors, and the values of the selected descriptors are given in **Table 3**.

Table 3. Information of Predicted Corrected Mortality Rate, Experimental Corrected Mortality Rate, Errors, and Detail Information of the Selected Descriptors

				selected descriptors		
no.	exptl (%)	pred (%)	error (%)	D1[a]	D2[b]	D3[c]
4a	29.6	31.1	1.5	0.0476	−217.089	3.1080
4b	48.1	44.7	−3.4	0.0500	−208.910	4.0793
4c	33.3	39.6	6.3	0.0476	−218.458	3.9182
4d	40.7	41.4	0.7	0.0476	−218.454	4.0721
4e	25.9	27.4	1.5	0.0469	−247.513	4.3925
4f	37.0	33.2	−3.8	0.0500	−213.294	3.3296
4g	29.6	28.9	−0.7	0.0500	−215.347	3.0755
4h	37.0	36.1	−0.9	0.0580	−199.103	3.6353
4i	51.8	45.7	−6.1	0.0484	−217.155	4.4526
4j	40.7	35.6	−5.1	0.0484	−218.012	3.6289
4k	22.2	26.7	4.5	0.0469	−220.094	2.8180
4l	48.1	56.9	8.8	0.0469	−197.082	4.1559
4m	62.9	58.0	−4.9	0.0339	−201.476	3.1336
4n	40.7	41.4	0.7	0.0411	−209.582	2.8962
4o	59.2	60.3	1.1	0.0339	−201.747	3.3438

[a] D1, relative number of benzene rings. [b] D2, final heat of formation. [c] D3, RNCS relative negative charged SA (SAMNEG*RNCG) [quantum-chemical PC].

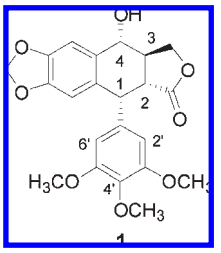


Figure 1. Structure of podophyllotoxin (**1**).

The three selected descriptors belonged to constitutional and quantum-chemical descriptors. They were relative number of benzene rings, final heat of formation, and RNCS relative negative charged SA (SAMNEG*RNCG) [quantum-chemical PC]. According to the t test value, the relative number of benzene rings and final heat of formation were very important descriptors. A negative coefficient before the relative number of benzene rings in this model indicated that an increase of this value led to a decrease in the mortality rate of the compounds due to the reduction in the solubility of the compound. The final heat of formation was proportionally interrelated with the Gibbs free energy. The plot of the predicted corrected mortality rate of the compounds versus their experimental values is shown in **Figure 2**.

In conclusion, 15 novel aromatic esters of 4′-demethyl-4-deoxypodophyllotoxin **4a**−**4o** were semisynthesized and tested for their insecticidal activity against pre-third-instar larvae of *M. separata* in vivo at the concentration of 1 mg/mL. Among all of the tested compounds, especially compounds **4m** and **4o** showed the most promising and best insecticidal activity as compared to toosendanin.

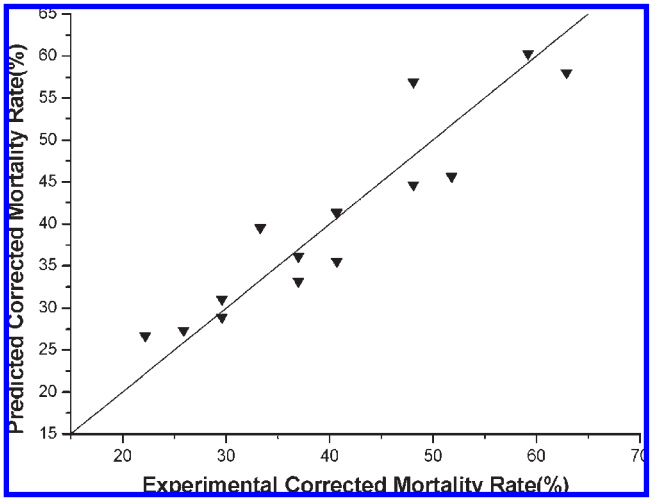


Figure 2. Plot of the predicted versus the experimental corrected mortality rate (%) for the BMLR model.

QSAR of compounds **4a**−**4o** found that the relative number of benzene rings and final heat of formation were very important descriptors for their insecticidal activity.

Supporting Information Available: ^{1}H NMR, HRMS, MS, optical rotation, melting point, and IR data for the target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

LITERATURE CITED

(1) Wang, J. D.; Tian, X.; Zhang, X. The isolation and identification of podophyllotoxin from *Sabina vulgaris* Ant. *Acta Univ. Agric. Boreali-Occidentalis* **2000**, *28*, 25–29.

(2) Miyazawa, M.; Fukuyama, M.; Yoshio, K.; Kato, T.; Ishikawa, Y. Biologically active components against *Drosophila melanogaster* from *Podophyllum hexandrum*. *J. Agric. Food Chem.* **1999**, *47*, 5108–5110.

(3) Di, X. D.; Liu, Y. Q.; Liu, Y. Q.; Yu, X. Y.; Xiao, H.; Tian, X.; Gao, R. Synthesis and insecticidal activities of pyridine ring derivatives of podophyllotoxin. *Pestic. Biochem. Physiol.* **2007**, *89*, 81–87.

(4) Liu, Y. Q.; Yang, L.; Liu, Y. Q.; Di, X. D.; Xiao, H.; Tian, X.; Gao, R. Synthesis and insecticidal activities of novel derivatives of podophyllotoxin. *Nat. Prod. Res.* **2007**, *21*, 967–974.

(5) Xu, H.; Zhang, X.; Tian, X.; Lu, M.; Wang, Y. G. Synthesis and insecticidal activity of novel 4β-halogenated benzoylamino podophyllotoxins against *Pieris rapae* Linnaeus. *Chem. Pharm. Bull.* **2002**, *50*, 399–402.

(6) Xu, H.; Zhang, L.; Su, B. F.; Zhang, X.; Tian, X. Natural products-based insecticidal agents 1. Semisynthesis and insecticidal activity of 4β-benzenesulfonamide derivatives of podophyllotoxin against *Mythimna separata* Walker. *Heterocycles* **2009**, *77*, 293–300.

(7) Xu, H.; Lv, M.; Tian, X. A review on hemisynthesis, biosynthesis, biological activities, mode of action, and structure−activity relationship of podophyllotoxins: 2003−2007. *Curr. Med. Chem.* **2009**, *16*, 327–349.

(8) You, Y.; Kim, Y.; Nam, N.; Bang, S.; Ahn, B. Alkyl and carboxylalkyl esters of 4′-demethyl-4-deoxypodophyllotoxin: synthesis, cytotoxic, and antitumor activity. *Eur. J. Med. Chem.* **2004**, *39*, 189–193.

(9) Gensler, W. J.; Judge, J. F. X.; Leeding, M. V. 2-Carboxydeoxypicropodophyllin. *J. Org. Chem.* **1972**, *37*, 1062–1064.

(10) Kuhn, M.; Keller-Juslen, G.; von Wartburg, A. Partialsynthese von 4′-demethylepipodophyllotoxin. *Helv. Chim. Acta* **1969**, *52*, 944–947.

(11) *Sybyl 6.9*; Tripos Associates: St. Louis, MO, 1999.

(12) *HyperChem 7.0*; Hypercube: Gainesville, FL, 2002.

(13) Stewart, J. P. P. *MOPAC 6.0*; Quantum Chemistry Program Exchange, QCPE;Indiana University: Bloomington, IN, 1989; Vol. *455*.

(14) Katritzky, A. R.; Lobanov, V. S.; Karelson, M. *CODESSA Version 2.0 Reference Manual*; Semichem: Shawnee, KS, 1995−1997.

Received June 19, 2009. Revised manuscript received July 29, 2009. Accepted July 30, 2009. This work was supported by the program for New Century Excellent University Talents, State Education Ministry of China (NCET-06-0868), the Key Project of Chinese Ministry of Education (No. 107105), and the Research Fund for the Doctoral Program of Higher Education of China (No. 20070712025).