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Design, Synthesis, and Analysis of the Quantitative Structure–Activity Relationships of 4-Phenyl-acyl-substituted 3-(2,5-Dimethylphenyl)-4-hydroxy-1-azaspiro[4.5]dec-3-ene-2,8-dione Derivatives

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ABSTRACT: A series of 4-phenyl-acyl-substituted 3-(2,5-dimethylphenyl)-4-hydroxy-1-azaspiro[4.5]dec-3-ene-2,8-dione derivatives were designed and synthesized, and their structures were characterized using ^{1}H NMR (or ^{13}C NMR), mass spectrometry, and elemental analysis. The bioactivities of the new compounds were evaluated. These compounds exhibited good inhibition activities against bean aphids (*Aphis fabae*) and carmine spider mite (*Tetranychus cinnabarinus*), and 4-phenyl acyl esters showed stronger bioactivity than 4-arylesterases and alkyl esters. The results showed that compound **8-I-e**, which contains a para-methoxy group on the phenyl acyl, and compound **8-I-m**, which contains a para-trifluoromethyl group on the phenyl acyl, displayed potent insecticidal activity against *A. fabae* and *T. cinnabarinus* respectively. The insecticidal activity showed a clear structure–activity relationship, confirming the importance of the flexible bridge. The DFT/B3LYP/6-31(d) level method was used to calculate molecular geometries and electronic descriptors. These factors included total energy, charge distribution, and the linear orbital level of the title compounds. Quantitative structure–activity relationship studies were performed on these compounds using quantum-chemical and physicochemical parameters as independent variables and insecticidal activity as a dependent variable. Insecticidal activity was most closely correlated ($r > 0.8$) with quantum chemical and physicochemical parameters.

KEYWORDS: *spirocyclic tetronic acids, 3-(2,5-dimethylphenyl)-4-hydroxy-1-azaspiro[4.5]dec-3-ene-2,8-dione, insecticidal activities, QSAR*

INTRODUCTION

Spirocyclic tetronic acid compounds have been attracting the interest of scientists continuously due to their original structures, novel mode of action, and excellent biological activity levels.[1−3] In recent years, some spirocyclic tetronic acid compounds have been developed by Bayer CropScience AG. They include such highly effective acaricides and insecticides as Spirodiclofen, Spiromesifen, and Spirotetramat[4−8] (Figure 1).

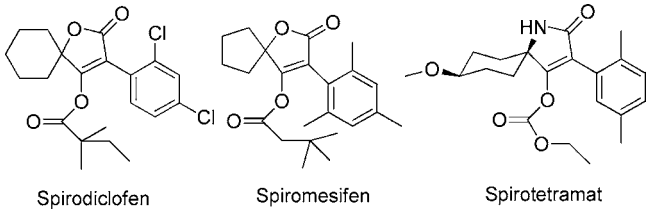

Figure 1. Commercial spirocyclic tetronic acid pesticides.

Spirotetramat has a special mechanism by which it inhibits lipid biosynthesis, and it has no cross-resistance with any other insecticide. Spirotetramat is considered a novel two-way ambimobile systemic insecticide, and it has shown outstanding performance against many species of insects in crops. However, its *cis*-configuration displays the best bioactivity, and it is very costly to prepare.[9−13] To the best of our knowledge, little attention has been paid to structural modification of these compounds, especially arylesterase in their C4 positions. In continuation of our program aimed at the discovery and development of more effective, broad-spectrum, bioactive, low-cost novel compounds, we modified the methoxy group into a keto moiety. Through careful observation of the side chain substituents of the three commercial compounds, we found a flexible bridge and large volume to promote bioactivity (Figure 2). To validate the hypothesis, a series of phenyl-acyl-substituted derivatives were prepared and tested for their insecticidal activity. Some unsubstituted derivatives were also designed. Most of the phenyl-acyl-substituted derivatives exhibited better bioactivity than the unsubstituted derivatives.

At present, quantitative structure–activity relationships (QSAR) are widely used to study the relationships between chemical structures and biological or other functional activities.[14] In this study QSAR models were built using precise density functional theory

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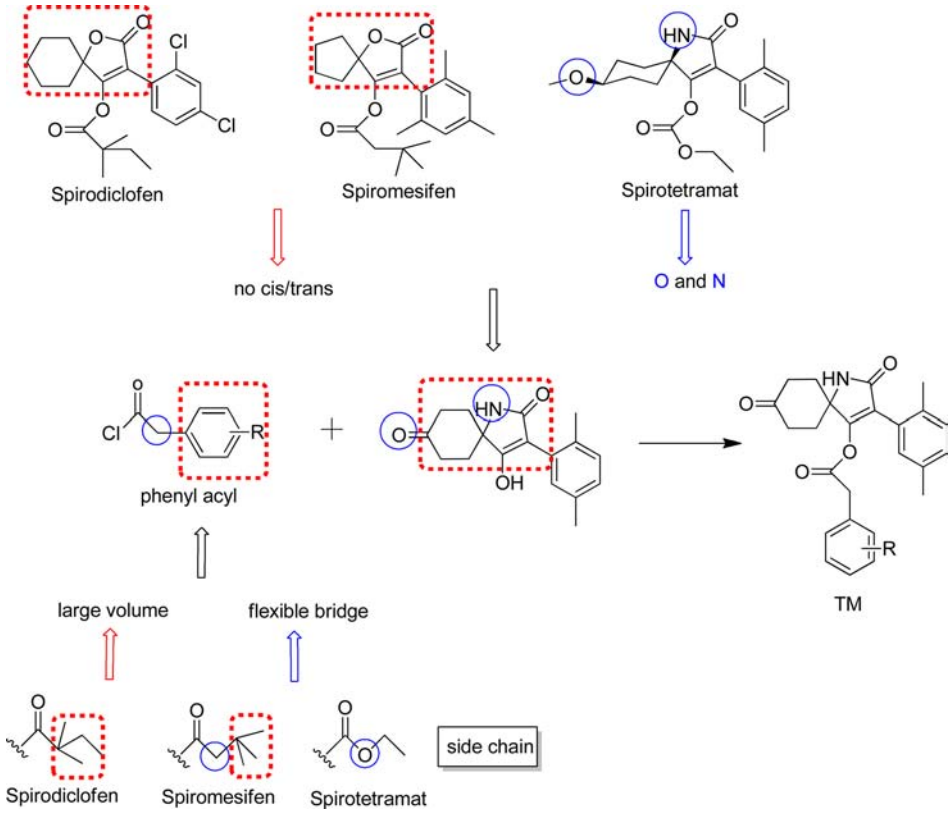

Figure 2. Design of target molecules.

(DFT)-based calculation to determine quantum chemical descriptors, and QSAR studies were performed on **8-I-a−8-II-g** using quantum chemical and physicochemical characteristics as independent parameters and insecticidal activity as the dependent parameter. The derived models showed better performance than the semiempirical models and showed potential predictive capability. This is because DFT is a very precise method, capable of producing compounds in the optimal lowest-energy conformation.[15] The objective of this study was to further understand the QSARs of substituted groups.

MATERIALS AND METHODS

Instruments. ^{1}H NMR and ^{13}C NMR spectra were obtained at 500 MHz using a Bruker AVANCE III spectrometer in $CDCl_3$, D_2O, CD_3OD, or DMSO-d_6 solution with tetramethylsilane as the internal standard. Chemical shift values (δ) were given in parts per million (ppm). MS were recorded with a Finnigan Trace Mass 2000 spectrometer using the electrospray ionization (ESI) method. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected. Yields were not optimized. Column chromatographic purification was carried out using silica gel.

General Synthesis. The reagents were all analytically or chemically pure. All anhydrous solvents were dried and purified by standard techniques prior to use. All acyl chlorides were prepared according to the method described in the literature.[16]

*Synthesis of 9,12-Dioxa-1,3-diazadispiro[4.2.4.2]tetradecane-2,4-dione (**2**).*[17] 1,4-Dioxaspiro[4.5]decan-8-one **1** (15.6 g, 100 mmol) was dissolved in 250 mL of 50% aqueous ethanol, and the solution was neutralized by the addition of ammonium solution. Potassium cyanide (8.1 g, 125 mmol) and ammonium carbonate (37.4 g, 390 mmol) were added, and the mixture was maintained at 55−60 °C for 8 h. The product was isolated by acidification of the reaction mixture with hydrochloric acid. Acidification caused the precipitation of a white solid, which was recrystallized from water to afford 15.4 g of 9,12-dioxa-1,3-diazadispiro[4.2.4.2]tetradecane-2,4-dione **2** in 68% yield as a colorless solid. ^{1}H NMR (500 MHz, DMSO-d_6): 10.61 (br s, 1H, (C═O)NH(C═O)), 8.46 (s, 1H, C═ONH−C), 3.87 (s, 4H, $-O(CH_2)_2O-$), 1.89−1.57 (m, 8H, cyclohexane-H_8). ESI-MS (m/z, %): 249 (M + Na^+, 100).

*Synthesis of 8-Amino-1,4-dioxaspiro[4.5]decane-8-carboxylic Acid (**3**).*[18] After **2** (15 g, 66 mmol) was suspended in 3 N sodium hydroxide (154 mL, 462 mmol) under N_2, the resulting mixture was stirred under reflux conditions under N_2 for 4 days and then cooled to 0 °C. The reaction mixture was adjusted to pH 6 by addition of concentrated hydrochloric acid at 0 °C. The solution was filtered and reduced in vacuo to one-third of its original volume. A white crystalline material was precipitated and collected by filtration to give 6.4 g of 8-amino-1,4-dioxaspiro[4.5]decane-8-carboxylic acid **3** in 48% yield as a white powder. ^{1}H NMR (500 MHz, D_2O): 4.03(s, 4H, $-O(CH_2)_2O-$), 2.25−2.20 (m, 2H, cyclohexane-H_2), 1.97−1.87 (m, 4H, cyclohexane-H_4), 1.75−1.73 (m, 2H, cyclohexane-H_2). ESI-MS (m/z, %): 202 (M + H^+, 100).

*Synthesis of Methyl 8-Amino-1,4-dioxaspiro[4.5]decane-8-carboxylate (**4**).*[18] After **3** (6 g, 30 mmol) was dissolved in dry methanol (150 mL) at room temperature, the resulting solution was cooled to 0 °C. Dry hydrogen chloride gas was bubbled into the solution at 0 °C until there was no further increase in weight in the resulting mixture. Then the hydrogen chloride gas-saturated reaction mixture was stirred under reflux conditions for 7 h, cooled to room temperature, and concentrated in vacuo. The residue was partitioned between saturated aqueous sodium bicarbonate (300 mL) and diethyl ether (300 mL) at 0 °C. After the organic layer was separated, the aqueous layer was extracted with diethyl ether (300 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 5.16 g of methyl 8-amino-1,4-dioxaspiro[4.5]-decane-8-carboxylate **4** in 80% yield as a slight yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): 3.89−3.86 (m, 4H, $-O(CH_2)_2O-$), 3.65 (s, 3H, $-OCH_3$), 2.07−2.01 (m, 2H, cyclohexane-H_2), 1.85−1.79 (m, 2H,

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cyclohexane-H_2), 1.58−1.52 (m, 4H, cyclohexane-H_4). ESI-MS (m/z, %): 216 ($M + H^+$, 100).

*Synthesis of Methyl 8-(2-(2,5-Dimethylphenyl)acetamido)-1,4-dioxaspiro[4.5]decane-8-carboxylate (**5**).*[19] Methyl 8-amino-1,4-dioxaspiro[4.5]decane-8-carboxylate **4** (4.5 g, 21 mmol) was initially charged in 60 mL of anhydrous acetonitrile, and ground potassium carbonate (6.9 g, 50 mmol) was added. Then 2,5-dimethylphenylacetyl chloride (5.46 g, 30 mmol) in 30 mL of anhydrous acetonitrile was added dropwise over a period of 20 min. The mixture was stirred at room temperature for 3 h. The reaction solution was poured into 500 mL of ice water, and the precipitate was filtered off with suction. The precipitate was washed with water and taken up in dichloromethane, the mixture was dried, and the solvent was distilled off. The product was purified by column chromatography on silica gel (dichloromethane/ethyl acetate = 3:1) to afford 8-(2-(2,5-dimethylphenyl)acetamido)-1,4-dioxaspiro[4.5]decane-8-carboxylate **5**. Yield: 3.9 g (51% of theory), mp 138−139 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 7.12 (d, 1H, J = 7.6 Hz, Ar−H), 7.05 (d, J = 8 Hz, 1H, Ar−H), 7.03 (s, 1H, Ar−H), 5.46 (s, 1H, NH−C═O), 3.92 (s, 4H, $-O(CH_2)_2O-$), 3.72 (s, 3H, $-OCH_3$), 3.55 (s, 2H, $-CH_2-$Ar), 2.33 (s, 3H, Ar−CH_3), 2.28 (s, 3H, Ar−CH_3), 2.16−1.39 (m, 8H, cyclohexane-H_8). ^{13}C NMR (125 MHz, $CDCl_3$): 173.7, 171.0, 136.2, 134.0, 133.0, 131.1, 130.8, 128.7, 107.4, 64.4, 64.3, 57.8, 52.4, 41.9, 30.4, 30.2, 20.9, 18.9. ESI-MS (m/z, %): 384 ($M + Na^+$, 100).

*Synthesis of 3-(2,5-Dimethylphenyl)-9,12-dioxa-4-hydroxy-1-azadispiro[4.2.4.2]tetradec-3-en-2-one (**6**).*[19] Potassium *tert*-butoxide (1.2 g, 12 mmol) was initially charged in 25 mL of dimethylformamide, cooled on ice, a solution of the compound **5** (2.0 g, 5.5 mmol) in 55 mL of dimethyl formamide was added dropwise at 0 to 10 °C, and the mixture was stirred at 90 °C overnight. Most of the dimethyl formamide was distilled off using a rotary evaporator. The residue was acidified with hydrochloric acid and partitioned between water and ethyl acetate. The ethyl acetate phase was dried and distilled off. The mixture was purified by column chromatography on silica gel (dichloromethane/ethyl acetate = 1:1) to give 3-(2,5-dimethylphenyl)-9,12-dioxa-4-hydroxy-1-azadispiro[4.2.4.2]tetradec-3-en-2-one **6**. Yield: 1.46 g (82% of theoretical yield). ^{1}H NMR (500 MHz, CD_3OD): 7.14 (d, 1H, J = 8 Hz, Ar−H), 7.04 (d, 1H, J = 8 Hz, Ar−H), 6.97 (s, 1H, Ar−H), 3.99 (s, 4H, $-O(CH_2)_2O-$), 2.31 (s, 3H, Ar−CH_3), 2.18 (s, 3H, Ar−CH_3), 2.29−1.58 (m, 8H, cyclohexane-H_8). ESI-MS (m/z, %): 352 ($M + Na^+$, 100).

*Synthesis of 3-(2,5-Dimethylphenyl)-4-hydroxy-1-azaspiro[4.5]-dec-3-ene-2,8-dione (**7**).*[19] 3-(2,5-Dimethylphenyl)-9,12-dioxa-4-hydroxy-1-azadispiro[4.2.4.2]tetradec-3-en-2-one **6** (1.2 g, 4.2 mmol) was stirred in 4 N hydrochloric acid at 60 °C for two hours. The aqueous layer was extracted with ethyl acetate, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The mixture was purified by column chromatography on silica gel (dichloromethane/ethyl acetate = 1:1) to give 0.78 g of 3-(2,5-dimethylphenyl)-4-hydroxy-1-azaspiro[4.5]dec-3-ene-2,8-dione **7** in 65% yield as a white solid, mp 190−192 °C. ^{1}H NMR (500 MHz, DMSO-d_6): 8.46 (s, 1H, NH-C═O), 7.10 (d, J = 7.5 Hz, 1H, Ar−H), 7.02 (dd, J_1 = 7.5 Hz, J_2 = 1 Hz, 1H, Ar−H), 6.93 (s, 1H, Ar−H), 2.35 (s, 3H, Ar−CH_3), 2.12 (s, 3H, Ar−CH_3), 2.79−1.74 (m, 8H, cyclohexane-H_8). ESI-MS (m/z, %): 286 ($M + H^+$, 100).

*Synthesis of 3-(2,5-Dimethylphenyl)-2,8-dioxo-1-azaspiro[4.5]-dec-3-en-4-yl 2-Phenylacetate (**8-I-a**).* A solution of phenethyl chloride (62 mg, 0.40 mmol) in anhydrous dichloromethane (15 mL) at 0 °C was added dropwise to a solution of compound **7** (100 mg, 0.35 mmol), triethylamine (0.076 g, 0.75 mmol), and *N*,*N*-dimethylpyridin-4-amine (1 mg, 0.01 mmol) in dichloromethane (8 mL). The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with dichloromethane (3 × 10 mL). The organic layer was washed with 5% dilute hydrochloric acid (3 × 10 mL), 5% aqueous sodium bicarbonate (3 × 10 mL), and saturated brine (3 × 10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate (2:1 by volume) as the eluent to afford 107 mg of 3-(2,5-dimethylphenyl)-2,8-dioxo-1-azaspiro[4.5]dec-3-en-4-yl 2-phenylacetate **8-I-a** as a white solid. The spectroscopic data is listed in Table 2.

The target compounds **8-I-b**−**8-II-g** were prepared by following the same procedure as that used for **8-I-a**. The properties and elemental analyses of compounds are listed in Table 1, and their ^{1}H NMR and ^{13}C NMR data are listed in Table 2.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were

Table 1. Physical Properties and Elemental Analyses of the Synthetic Compounds[a]

				elemental anal. (%, calcd)		
compd	R_1/R_2	yield (%)	mp (°C)	C	H	N
8-I-a	H	76	199−200	74.36 (74.42)	6.52 (6.25)	3.48 (3.47)
8-I-b	4-CH_3	84	223−225	74.91 (74.80)	6.42 (6.52)	3.66 (3.35)
8-I-c	2,5-$(CH_3)_2$	54	215−217	75.19 (75.15)	6.92 (6.77)	3.47 (3.25)
8-I-d	2,4,6-$(CH_3)_3$	65	247−249	75.63 (75.48)	7.20 (7.01)	3.11 (3.14)
8-I-e	4-OCH_3	43	196−198	72.12 (72.04)	6.22 (6.28)	3.13 (3.23)
8-I-f	4-F	36	223−225	71.22 (71.24)	5.84 (5.74)	4.72 (4.51)
8-I-g	2-Cl	57	214−216	68.66 (68.57)	5.29 (5.52)	3.24 (3.20)
8-I-h	3-Cl	60	189−191	68.77 (68.57)	5.34 (5.52)	3.21 (3.20)
8-I-i	4-Cl	63	234−236	68.45 (68.57)	5.35 (5.52)	3.33 (3.20)
8-I-j	2,4-$(Cl)_2$	46	234−236	63.47 (63.57)	4.78 (4.91)	2.86 (2.97)
8-I-k	3,4-$(Cl)_2$	42	214−216	63.32 (63.57)	4.96 (4.91)	2.87 (2.97)
8-I-l	4-Br	42	239−241	62.34 (62.25)	5.12 (5.01)	2.89 (2.90)
8-I-m	4-CF_3	27	218−219	66.34 (66.24)	5.12 (5.13)	3.02 (2.97)
8-I-n	4-NO_2	15	207−209	67.02 (66.95)	5.45 (5.39)	6.13 (6.25)
8-II-a	CH_3CH_2O-	55	203−205	67.11 (67.21)	6.48 (6.49)	3.88 (3.92)
8-II-b	$CH_3(CH_2)_2-$	73	192−193	70.88 (70.96)	7.02 (7.09)	3.88 (3.94)
8-II-c	$CH_3C(CH_3)_2CH_2-$	75	230−232	72.02 (72.04)	7.62 (7.62)	3.67 (3.65)
8-II-d	$CH_3CH═CH-$	69	210−212	71.27 (71.37)	6.50 (6.56)	3.87 (3.96)
8-II-e	C_6H_5-	80	198−200	74.11 (74.02)	6.01 (5.95)	3.66 (3.60)
8-II-f	2-$CH_3-C_6H_4-$	82	204−206	74.32 (74.42)	6.25 (6.25)	3.44 (3.47)
8-II-g	4-$Cl-C_6H_4-$	86	229−230	67.91 (68.00)	5.18 (5.23)	3.27 (3.30)

[a]All compounds had the appearance of a white solid.

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Table 2. Spectroscopic Data (^{1}H NMR or ^{13}C NMR) for Synthesized Compounds

compd	^{1}H or ^{13}C NMR δ (ppm)	ESI-MS (m/z %)
8-I-a	^{1}H NMR (500 MHz, $CDCl_3$) 9.11 (1H, s, −NH−), 7.27−7.25 (3H, m, Ar−H), 7.07−7.01 (4H, m, Ar−H), 6.86 (1H, s, Ar−H), 3.62 (2H, s, $CO-CH_2-$), 2.26, 2.14 (6H, s, Me_2−Ar), 2.72−2.00 (8H, m, cyclohexane-H_8); ^{13}C NMR (125 MHz, $CDCl_3$) 208.8, 171.8, 166.5, 164.3, 134.9, 134.2, 133.8, 132.1, 130.2, 129.8, 128.8, 128.5, 127.8, 123.6, 60.8, 40.8, 37.9, 33.8, 20.8, 19.1	404 (M + H$^+$, 100)
8-I-b	^{1}H NMR (500 MHz, $CDCl_3$) 9.18 (1H, s, −NH−), 7.09−7.05 (4H, m, Ar−H), 6.92 (1H, s, Ar−H), 6.90 (1H, s, Ar−H), 6.85 (1H, s, Ar−H), 3.58 (2H, s, $CO-CH_2-$), 2.34 (3H, s, Me−Ar), 2.26, 2.15 (6H, s, Me_2−Ar), 2.70−1.98 (8H, m, cyclohexane-H_8)	418 (M + H$^+$, 100)
8-I-c	^{1}H NMR (500 MHz, $CDCl_3$) 9.39 (1H, s, −NH−), 7.06−7.05 (2H, m, Ar−H), 6.99 (2H, m, Ar−H), 6.87 (1H, s, Ar−H), 6.82 (1H, s, Ar−H), 3.60 (2H, s, $CO-CH_2-$), 2.26, 2.11 (6H, s, Me_2−Ar), 2.24, 1.92 (6H, s, Me_2−Ar), 2.76−2.00 (8H, m, cyclohexane-H_8)	432 (M + H$^+$, 100)
8-I-d	^{1}H NMR (500 MHz, $CDCl_3$) 9.06 (1H, s, −NH−), 7.05 (2H, s, Ar−H), 6.84 (1H, s, Ar−H), 6.80 (2H, s, Ar−H), 3.64 (2H, s, $CO-CH_2-$), 2.26, 2.12 (6H, s, Me_2−Ar), 2.25, 1.99 (9H, s, Me_3−Ar), 2.74−2.00 (8H, m, cyclohexane-H_8)	446 (M + H$^+$, 100)
8-I-e	^{1}H NMR (500 MHz, $CDCl_3$) 9.39 (1H, s, −NH−), 7.06−7.05 (2H, m, Ar−H), 6.99 (2H, m, Ar−H), 6.87 (1H, s, Ar−H), 6.82 (1H, s, Ar−H), 3.60 (2H, s, $CO-CH_2-$), 2.26, 2.11 (6H, s, Me_2−Ar), 2.24, 1.92 (6H, s, Me_2−Ar), 2.76−2.00 (8H, m, cyclohexane-H_8)	434 (M + H$^+$, 100)
8-I-f	^{1}H NMR (500 MHz, $CDCl_3$) 8.71 (1H, s, −NH−), 7.08−7.02 (2H, m, Ar−H), 6.95−6.93 (4H, m, Ar−H), 6.82 (1H, s, Ar−H), 3.60 (2H, s, $CO-CH_2-$), 2.25, 2.14 (6H, s, Me_2−Ar), 2.68−2.04 (8H, m, cyclohexane-H_8); ^{13}C NMR (125 MHz, $CDCl_3$) 208.7, 171.4, 166.5, 164.3, 163.2, 161.2, 135.0, 134.0, 130.5, 130.4, 130.2, 129.8, 129.6, 127.8, 127.7, 123.9, 115.8, 115.6, 60.7, 39.9, 37.9, 33.9, 20.8, 19.1	422 (M + H$^+$, 100)
8-I-g	^{1}H NMR (500 MHz, $CDCl_3$) 8.91 (1H, s, −NH−), 7.36−7.34 (1H, t, J = 8 Hz, Ar−H), 7.26−7.01 (5H, m, Ar−H), 6.90 (1H, s, Ar−H), 3.77 (2H, s, $CO-CH_2-$), 2.30, 2.19 (6H, s, Me_2−Ar), 2.73−2.02 (8H, m, cyclohexane-H_8); ^{13}C NMR (125 MHz, $CDCl_3$) 208.9, 171.5, 166.6, 164.2, 135.0, 134.4, 134.0, 131.1, 130.6, 130.3, 129.9, 129.6, 127.7, 127.1, 123.9 60.8, 38.6, 37.9, 33.9, 20.9, 19.2	438 (M + H$^+$, 100)
8-I-h	^{1}H NMR (500 MHz, $CDCl_3$) 8.79 (1H, s, −NH−), 7.27−7.05 (4H, m, Ar−H), 7.02 (1H, s, Ar−H), 6.88 (1H, d, J = 8 Hz, Ar−H), 6.84 (1H, s, Ar−H), 3.60 (2H, s, $CO-CH_2-$), 2.26, 2.17 (6H, s, Me_2−Ar), 2.72−2.03 (8H, m, cyclohexane-H_8); ^{13}C NMR (125 MHz, $CDCl_3$) 208.6, 172.1, 168.6, 166.7, 163.5, 137.4, 135.4, 134.1, 133.5, 132.9, 130.1, 129.7, 129.1, 128.9, 127.1, 126.5, 122.7, 59.8, 39.0, 37.3, 32.9, 20.4, 18.7	438 (M + H$^+$, 100)
8-I-i	^{1}H NMR (500 MHz, $CDCl_3$) 8.62 (1H, s, −NH−), 7.22 (2H, dd, J = 1.5 Hz, J = 6.5 Hz, Ar−H), 7.08 (1H, s, Ar−H), 7.07 (1H, d, J = 8 Hz, Ar−H), 6.90 (2H, d, J = 8.5 Hz, Ar−H), 6.80 (1H, s, Ar−H), 3.59 (2H, s, $CO-CH_2-$), 2.25, 2.13 (6H, s, Me_2−Ar), 2.71−2.05 (8H, m, cyclohexane-H_8)	438 (M + H$^+$, 100)
8-I-j	^{1}H NMR (500 MHz, $CDCl_3$) 8.18 (1H, s, −NH−), 7.37 (1H, d, J = 2 Hz, Ar−H), 7.15−7.13 (1H, m, Ar−H), 7.11−7.06 (2H, m, Ar−H), 6.92 (1H, d, J = 8 Hz, Ar−H), 6.88 (1H, s, Ar−H), 3.74 (2H, s, $CO-CH_2-$), 2.29, 2.16 (6H, s, Me_2−Ar), 2.69−2.06 (8H, m, cyclohexane-H_8)	472 (M + H$^+$, 100)
8-I-k	^{1}H NMR (500 MHz, $CDCl_3$) 8.74 (1H, s, −NH−), 7.29 (1H, d, J = 8 Hz, Ar−H), 7.08−7.06 (3H, m, Ar−H), 6.79−6.76 (2H, m, Ar−H), 3.57 (2H, s, $CO-CH_2-$), 2.26, 2.14 (6H, s, Me_2−Ar), 2.74−2.07 (8H, m, cyclohexane-H_8)	472 (M + H$^+$, 100)
8-I-l	^{1}H NMR (500 MHz, $CDCl_3$) 8.45 (1H, s, −NH−), 7.37 (2H, d, J = 8.5 Hz, Ar−H), 7.07 (2H, s, Ar−H), 6.84−6.80 (3H, m, Ar−H), 3.58 (2H, s, $CO-CH_2-$), 2.25, 2.14 (6H, s, Me_2−Ar), 2.70−2.04 (8H, m, cyclohexane-H_8)	482 (M + H$^+$, 100)
8-I-m	^{1}H NMR (500 MHz, $CDCl_3$) 8.95 (1H, s, −NH−), 7.50 (2H, d, J = 8 Hz, Ar−H), 7.07 (2H, s, Ar−H), 7.06 (2H, s, Ar−H), 6.80 (1H, s, Ar−H), 3.69 (2H, s, $CO-CH_2-$), 2.24, 2.13 (6H, s, Me_2−Ar), 2.75−2.06 (8H, m, cyclohexane-H_8)	472 (M + H$^+$, 100)
8-I-n	^{1}H NMR (500 MHz, $CDCl_3$) 8.48 (1H, s, −NH−), 8.28 (2H, d, J = 8.5 Hz, Ar−H), 7.69 (2H, d, J = 8 Hz Ar−H), 7.15 (1H, d, J = 8 Hz, Ar−H), 7.10 (1H, s, Ar−H), 7.07 (1H, d, J = 7.5 Hz, Ar−H), 3.64 (2H, s, $CO-CH_2-$), 2.26, 2.15 (6H, s, Me_2−Ar), 2.73−2.05 (8H, m, cyclohexane-H_8)	449 (M + H$^+$, 100)
8-II-a	^{1}H NMR (500 MHz, $CDCl_3$) 8.97 (1H, s, −NH−), 7.14 (1H, d, J = 8 Hz, Ar−H), 7.08 (1H, m, Ar−H), 6.99 (1H, s, Ar−H), 4.06 (2H, q, J = 7 Hz, CH_3-CH_2-), 2.31, 2.24 (6H, s, Me_2−Ar), 2.78−2.06 (8H, m, cyclohexane-H_8), 1.13 (3H, t, J = 7 Hz, CH_3-CH_2-); ^{13}C NMR (125 MHz, $CDCl_3$) 208.7, 171.5, 164.2, 149.9, 135.0, 134.1, 130.3, 129.9, 129.7, 127.6, 122.1, 65.8, 60.5, 37.9, 33.8, 20.8, 19.2, 13.7	358 (M + H$^+$, 100)
8-II-b	^{1}H NMR (500 MHz, $CDCl_3$) 9.67 (1H, s, −NH−), 7.12 (1H, d, J = 8 Hz, Ar−H), 7.06 (1H, d, J = 8 Hz, Ar−H), 6.92 (1H, s, Ar−H), 2.27,2.22 (6H, s, Me_2−Ar), 2.26−2.25 (2H, m, $CH_3-CH_2-CH_2-$), 2.84−2.05 (8H, m, cyclohexane-H_8), 1.55−1.47 (2H, m, CH_3-CH_2-), 0.77 (3H, t, J = 7 Hz, CH_3-CH_2-); ^{13}C NMR (125 MHz, $CDCl_3$) 209.0, 171.5, 168.5, 164.5, 134.9, 134.0, 130.2, 129.9, 129.5, 128.0, 123.5, 60.7, 38.0, 35.6, 20.8, 19.2, 18.2, 13.1	356 (M + H$^+$, 100)
8-II-c	^{1}H NMR (500 MHz, $CDCl_3$) 9.53 (1H, s, −NH−), 7.11 (1H, d, J = 8 Hz, Ar−H), 7.05 (1H, d, J = 8 Hz, Ar−H), 6.91 (1H, s, Ar−H), 2.28, 2.25 (6H, s, Me_2−Ar), 2.24−2.21 (2H, m, Me_3C-CH_2-), 2.82−2.07 (8H, m, cyclohexane-H_8), 0.84 (9H, s, Me_3C-CH_2-)	384 (M + H$^+$, 100),
8-II-d	^{1}H NMR (500 MHz, $CDCl_3$) 9.29 (1H, s, −NH−), 7.11 (1H, d, J = 8 Hz, Ar−H), 7.09−7.01 (2H, m, Ar−H+ CH_3-CH═$CH-$), 6.97 (1H, s, Ar−H), 5.84 (1H, dd, J = 16.0 Hz, J = 1.5 Hz, CH_3-CH═$CH-$), 2.29, 2.23 (6H, s, Me_2−Ar), 2.81−2.06 (8H, m, cyclohexane-H_8), 1.91 (3H, dd, J = 1.5 Hz, J = 7 Hz, CH_3-CH═)	354 (M + H$^+$, 100)
8-II-e	^{1}H NMR (500 MHz, $CDCl_3$) 9.76 (1H, s, −NH−), 7.98 (2H, d, J = 8 Hz, Ar−H), 7.62 (1H, m, Ar−H), 7.46 (2H, t, J = 6 Hz, Ar−H), 7.07 (1H, d, J = 7.5 Hz, Ar−H), 7.02−6.99 (2H, m, Ar−H), 2.27, 2.23 (6H, s, Me_2−Ar), 2.87−2.16 (8H, m, cyclohexane-H_8)	390 (M + H$^+$, 100)
8-II-f	^{1}H NMR (500 MHz, $CDCl_3$) 9.94 (1H, s, −NH−), 7.86 (1H, d, J = 7.5 Hz, Ar−H), 7.47−7.44 (1H, m, Ar−H), 7.28−7.23 (2H, m, Ar−H), 7.09−7.01 (3H, m, Ar−H), 2.36 (3H, s, Me−Ar), 2.28,2.24 (6H, s, Me_2−Ar), 2.91−2.17 (8H, m, cyclohexane-H_8)	404 (M + H$^+$, 100)
8-II-g	^{1}H NMR (500 MHz, $CDCl_3$) 9.49 (1H, s, −NH−), 7.91 (2H, d, J = 8.5 Hz, Ar−H), 7.45 (2H, d, J = 8.5 Hz, Ar−H), 7.08−7.00 (3H, m, Ar−H), 2.26, 2.23 (6H, s, Me_2−Ar), 2.84−2.15 (8H, m, cyclohexane-H_8)	424 (M + H$^+$, 100)

made on a dead/alive basis, and mortality rates were corrected using Abbott's formula.[20] Evaluations were based on a percentage scale of 0−100, in which 0 = no activity and 100 = total mortality. The deviation of values was ±5%. Each test sample was prepared in *N*,*N*-dimethylformamide at a concentration of 0.5 mg L^{-1} and diluted to the required concentration with distilled water containing TW-80 (0.1 mL L^{-1}).

Inhibition Activity against Bean Aphids (Aphis fabae). The inhibition activities of derivative compounds against bean aphids were evaluated according to the reported procedure.[21,22] Bean aphids were dipped according to a slightly modified FAO dip test. Tender soybean shoots with fifty healthy apterous third-instar nymphae were dipped into the diluted solutions of the compounds for 5 s, superfluous fluid was removed, and the nymphae were placed in an air-conditioned room. Mortality was calculated

72 h after treatment. Each treatment was performed three times. Control groups were tested with water only.

Inhibition Activity against Carmine Spider Mite (Tetranychus cinnabarinus). The larvicidal activities of derivative compounds against carmine spider mites were tested according to the reported procedure.[23,24] Fifty third-instar mite larvae were dipped in the diluted solutions of related chemicals for 5 s, the superfluous liquor was removed, and the larvae were kept in an air-conditioned room. Mortality was evaluated 72 h after treatment. Controls were treated under the same conditions. Each test was performed in triplicate. Control groups were treated with water only.

Commercial insecticides Spirodiclofen, Spiromesifen, and Spirotetramat were tested and compared under the same conditions. The insecticidal activity levels are summarized in Table 3.

Table 3. Inhibitive Activity of the Synthetic Compounds

		% inhibition			
		against *A. fabae*		against *T. cinnabarinus*	
compd	R_1/R_2	100 mg/L	10 mg/L	100 mg/L	10 mg/L
8-I-a	H	95.59	62.76	66.79	38.86
8-I-b	4-CH_3	73.45	48.36	70.82	21.75
8-I-c	2,5-$(CH_3)_2$	76.16	37.29	61.57	24.55
8-I-d	2,4,6-$(CH_3)_3$	69.17	25.22	39.44	12.11
8-I-e	4-OCH_3	92.11	87.34	80.48	24.38
8-I-f	4-F	93.65	69.27	49.05	29.86
8-I-g	2-Cl	96.53	59.22	53.53	28.33
8-I-h	3-Cl	44.60	13.55	24.70	3.23
8-I-i	4-Cl	89.82	47.32	58.03	17.82
8-I-j	2,4-$(Cl)_2$	85.59	26.88	75.91	31.22
8-I-k	3,4-$(Cl)_2$	97.32	49.31	71.67	28.90
8-I-l	4-Br	47.83	9.78	32.47	5.25
8-I-m	4-CF_3	98.56	59.96	85.27	48.97
8-I-n	4-NO_2	92.15	32.29	73.79	16.33
8-II-a	CH_3CH_2O–	93.55	45.89	62.3	30.35
8-II-b	$CH_3(CH_2)_2$–	98.69	37.28	54.72	19.66
8-II-c	$(CH_3)_3CCH_2$–	62.15	21.57	26.15	8.76
8-II-d	CH_3CH=CH–	85.56	34.85	58.22	23.45
8-II-e	C_6H_5–	91.78	29.33	49.80	18.22
8-II-f	2-CH_3–C_6H_4–	25.47	6.27	59.38	17.28
8-II-g	4–Cl–C_6H_4–	68.25	10.85	42.87	9.23
Spirodiclofen		60.27	19.36	70.62	36.70
Spiromesifen		62.45	14.35	80.21	42.10
Spirotetramat		100	96.78	74.96	26.34

Quantum Chemical and Physicochemical Parameters. To determine the structural requirements of phenyl-acyl-substituted 3-(2,5-dimethylphenyl)-4-hydroxy-1-azaspiro[4.5]dec-3-ene-2,8-dione derivatives for bioactivity, activity values were quantitatively analyzed using quantum-chemical and physicochemical parameters.

In the present study, quantum-chemical parameters included highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), HOMO–LUMO energy gap, Mulliken population, dipole moment (DM), total energy (E_T), and rms force. Each molecular structure was first preoptimized with a molecular mechanics force field (MM) procedure, and the resulting geometric conclusions were further refined by means of semiempirical method AM1. All molecules were then subjected to density functional theory (DFT)-based B3LYP/6-31G calculation using Gaussian 03W (version 6.0).[25,26]

Physicochemical parameters were calculated using ChemBio3D Ultra 12.0 software,[27] including ClogP (octanol–water partition coefficient), molar refractivity (MR), van der Waals volume (Vw), parachor (Pc), the index of refraction (η), surface tension (ST), density (D), and polarizability (Pol).

A stepwise regression procedure was used to identify key descriptors. To achieve an accurate model for inhibition activity, descriptors were analyzed for evidence of intercorrelation, using Pearson and Spearman rank correlation procedures. Parameters that were highly correlated were noted. The multiparameter linear regression analysis was carried out using SPSS 16.0.

The key descriptors correlating with the final equations are summarized in Table 4.

RESULTS AND DISCUSSION

Synthesis. Compound **7** was synthesized in a series of steps as shown in Figure 3. First, compound **2** was prepared by Bucherer–Bergs synthesis from **1** using ammonium carbonate and potassium cyanide. It was then hydrolyzed with aqueous sodium hydroxide into the corresponding 8-amino-1,4-dioxaspiro[4.5]decane-8-carboxylic acid **3**, followed by methyl esterification in acidic conditions. The obtained methyl 8-amino-1,4-dioxaspiro[4.5]decane-8-carboxylate **4** was treated with 2,5-dimethylphenylacetyl chloride to produce compound **5**. Compound **5** was treated with potassium *tert*-butoxide via Dieckmann condensation to convert it to **6**, followed by 4 N hydrochloric acid in reflux to generate primary **7**. Phenyl-acyl-substituted and other groups reacted with **7**, generating the corresponding compounds **8-I-a**–**8-II-g**. The derivatives of compounds **8** were prepared with DMAP as catalyst giving the best yield and short reaction time. In comparison to the phenyl-acyl-substituted compounds, some non-phenyl-acyl-substituted group compounds were designed and prepared. It was found that the chemical shift of NH ranged from 8.18 to 9.94 in different compounds (Table 2). In addition, it was observed that the substituted groups on the phenyl acyl had a great effect on the yield of compounds **8**, where electron withdrawing group substituted phenyl acyl gave a low yield, while the electron donating group substituted phenyl acyl afforded the best yield (Table 1).

Bioassay. *Inhibition Activity against Bean Aphids (A. fabae).* The inhibition activities of compounds **8-I-a**–**8-II-g** against *A. fabae* are shown in Table 3. The commercial insecticides Spirodiclofen, Spiromesifen, and Spirotetramat were used as standards. Two levels of concentration inhibition were observed. As expected, the activity levels of compounds substituted with phenyl acyl groups were predominantly higher than those of other compounds, suggesting that the flexible bridge maybe important. Fortunately, when a methoxy group existed at the para-position in the benzene ring, compound **8-I-e** showed the most activity. Moderate activity was observed for compounds **8-I-a**, **8-I-f**, **8-I-g**, and **8-I-m**. It was also observed that introduction of a multisubstituted benzene ring decreased the bioactivity and replacement of the nitro group (**8-I-n**) with a bromine atom (**8-I-l**) caused an obvious decrease in activity. According to the result of **8-II-b** and **8-II-c**, it may be deduced that the side chain must be of suitable volume. The hypothesis that introducing huge volume moieties favors activity may not be accurate.

Inhibition Activity against Carmine Spider Mite (T. cinnabarinus). As shown in Table 3, most of the compounds were found to display promising insecticidal activity against *T. cinnabarinus*. The most promising one was compound **8-I-m** bearing the para-trifluoromethyl group, whose inhibition activity at 10 mg L^{-1} was 48.97%, higher than that of the commercial compounds Spirodiclofen, Spiromesifen, and Spirotetramat. However, compounds **8-I-a**, **8-I-e**, **8-I-f**, **8-I-m**, and **8-II-a** only showed moderate insecticidal activity at the same

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Table 4. Quantum-Chemical and Physicochemical Parameters[a]

	HOMO	LUMO	Q_N	Q_O	ClogP	MR	Vw	DM	E_T
8-I-a	−0.22700	−0.04499	−0.628053	−0.429435	3.139	115.042	321.563	4.4341	−86.74
8-I-b	−0.22624	−0.04377	−0.628054	−0.429793	3.626	120.083	334.275	4.6277	−94.54
8-I-c	−0.22344	−0.05014	−0.677501	−0.444494	4.113	125.124	311.735	4.4189	−98.51
8-I-d	−0.22725	−0.04507	−0.628593	−0.429829	4.600	130.165	371.943	4.1550	−108.42
8-I-e	−0.22626	−0.04420	−0.627780	−0.429695	3.013	121.505	394.280	4.0321	−124.98
8-I-f	−0.22916	−0.04847	−0.628298	−0.428548	3.297	115.258	312.222	3.9249	−131.53
8-I-g	−0.22812	−0.04832	−0.629739	−0.42991	3.697	119.847	294.103	4.1645	−92.27
8-I-h	−0.22882	−0.04875	−0.628729	−0.428903	3.697	119.847	343.995	4.9283	−93.25
8-I-i	−0.23159	−0.05067	−0.631186	−0.429249	3.697	119.847	274.821	3.5041	−93.21
8-I-j	−0.23166	−0.05269	−0.630178	−0.429197	4.256	124.651	353.848	4.1319	−98.51
8-I-k	−0.23009	−0.05305	−0.631545	−0.402639	4.256	124.651	324.508	3.7193	−98.08
8-I-l	−0.22926	−0.04920	−0.628665	−0.428612	3.968	122.665	389.395	3.8303	−81.33
8-I-m	−0.23214	−0.06014	−0.628962	−0.427224	4.060	121.016	337.164	4.2311	−241.85
8-I-n	−0.23392	−0.09926	−0.629124	−0.426360	2.725	121.654	344.650	5.0256	−81.60
8-II-a	−0.22914	−0.04786	−0.680131	−0.440759	2.221	96.642	278.293	3.9901	−159.87
8-II-b	−0.22894	−0.04719	−0.680322	−0.406776	2.368	99.548	281.710	3.8564	−126.90
8-II-c	−0.22743	−0.04841	−0.679789	−0.406419	3.169	108.572	310.630	3.8306	−134.33
8-II-d	−0.22531	−0.07048	−0.680361	−0.407804	2.348	100.641	256.594	5.1295	−98.28
8-II-e	−0.22662	−0.07691	−0.666019	−0.418992	3.195	110.493	266.629	4.0102	−73.80
8-II-f	−0.22639	−0.07021	−0.679893	−0.444377	3.682	115.534	280.323	4.7993	−84.34
8-II-g	−0.22837	−0.08369	−0.649780	−0.443196	3.752	115.297	352.880	2.5413	−85.27

[a]HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital), Q_N,Q_O (Mulliken charge of N atom on the amide bonds, O atom on cyclohexane respectively), ClogP (octanol−water partition coefficient), MR (molar refractivity), Vw (van der Waals volume), DM (dipole moment), E_T (total energy).

concentrations. Compound **8-I-h**, containing meta-chlorine, and compound **8-I-l**, containing para-bromine, showed much lower levels of activity. Compounds **8-I-a** and **8-I-i** had more insecticidal activity than the corresponding compounds **8-II-e** and **8-II-g**, indicating that the flexible bridge in the substituent group improved activity.

QSAR. To further explore the structural requirements for the activity of the compounds, the data were analyzed using a physicochemical-based QSAR (Hansch) approach involving quantum-chemical and physicochemical factors as independent parameters (Table 4). Insecticide activity data (% I) was converted to $\log\{I/[(100 - I) \times MW]\}$and used as a dependent parameter. MW is molecular weight.[28]

The resulting best models for each concentration are given in Table 5, where N is the number of compounds included in the model, r is the correlation coefficient, SE is the standard deviation of the regression, F is the Fisher ratio, and P is the significance of the model. Variations in the insecticide activities against *A. fabae* and *T. cinnabarinus* were analyzed at concentrations of 100 mg L^{-1} and 10 mg L^{-1}, respectively, using the corresponding eqs 1, 2, 3, and 4.

It is worth noting that all equations were found to be suitable for the prediction of insecticidal activities according to the statistical parameters, especially taking into account that all the models showed an $r > 0.8$ and the $P < 0.05$, and the eq 2 was the best because the $r = 0.937$ with $P = 0.0002$. However, eqs 3 and 4 described the worst statistical significance, especially when predictive capability was higher than the critical value of 0.01 (P value). For eq 3, improvement of the correlation (r value) was achieved by removing compounds **8-I-i**, **8-I-j**, and **8-I-n**. Compounds **8-I-a** and **8-I-j** were excluded from the regression analysis for eq 4 to improve the correlation (r value).

The entire correlation matrix of the regression variables in eq 2 is shown in Table 6. The activities calculated using eq 2 are listed in Table 7. The correlation relationship between observed values and predicted values for eq 2 of the insecticidal activity is shown in Figure 4.

The four equations show that the bioactivity of each compound is highly correlated with HOMO, LUMO, Q_N, Q_O, ClogP, MR, Vw, DM, and E_T.

HOMO and LUMO energies, measures of nucleophilicity and electrophilicity, respectively, are used for description of electron donating and accepting power. In most cases, the HOMO−LUMO energy gap is widely used as a measure of chemical reactivity with bigger gaps implying larger excitation energies and higher stability. The Pearson and Spearman rank correlation demonstrates the high correlation between HOMO and HOMO−LUMO ($R^2 = 0.97$), so the HOMO−LUMO energy gap was not involved in the final equations, similar to the conclusion of Wang et al.[29] This may suggest that a compound with higher E_{HOMO} has higher electron-donating ability in agreement with its higher inhibition activity.

It has been shown that the Mulliken population of the molecule may be important to the inhibition activity.[30] The stepwise regression shows that Mulliken population most related with biological activity was the electric charges at Q_N and Q_O, which reflects the overall effect of the electron withdrawing/donating substituents to the charge distribution. Equations 1 and 2 indicate that an increase in the Mulliken population at the Q_N and Q_O increases the biological activity. Results from these models highlight the importance of electronic properties. It also suggests that electronic properties of the molecule can help explain the relationship between structure and inhibition activity.

ClogP (hydrophobic constant) is used to rationalize interactions of small ligands with various macromolecules in the fields of biochemistry, medicinal chemistry, and environmental sciences. ClogP is also considered to be one of the principal parameters for the evaluation of the lipophilicity of a chemical compound, and it significantly influences the bioactivity in

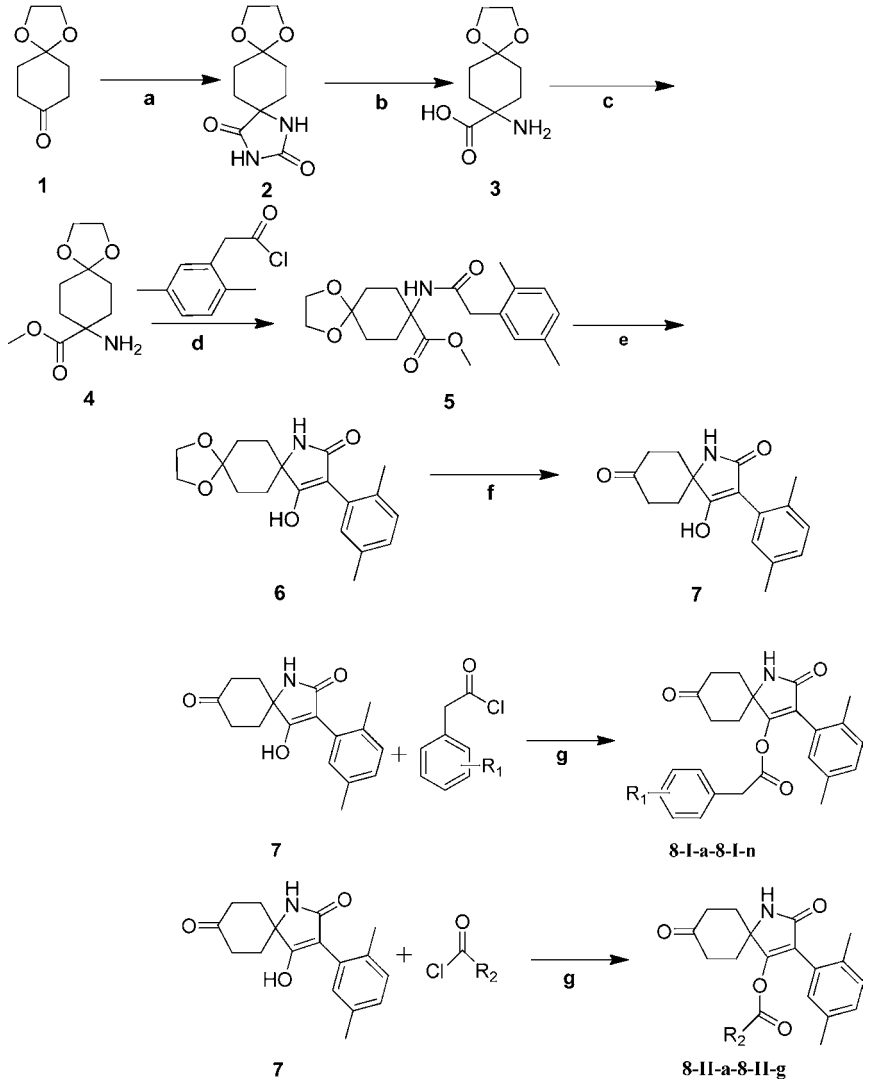

Figure 3. Synthetic route for compounds **8-I-a**−**8-I-n** and **8-II-a**−**8-II-g**. Reagents and conditions: (a) $(NH_4)_2CO_3$, KCN, EtOH/H_2O, 60 °C; then concentrated HCl, 0 °C; (b) 3 N NaOH, reflux; adjusted to pH 6, 0 °C; (c) dry HCl (gas)/MeOH, 0 °C to reflux; (d) CH_3CN, K_2CO_3, rt; (e) DMF, *t*-BuOK; (f) 4 N HCl, reflux; (g) DCM, TEA, 4-DMAP, rt.

Table 5. Comparisons of Different Regression Equations and Statistical Parameters

regression eq	removing compds	*N*	*r*	SE	*F*	*P*
$X1 = 11.438 + 10.371Q_N + 15.194Q_O - 0.869$ ClogP $+ 0.061$ MR $- 0.011$ Vw $- 0.421$DM $- 0.009E_T$ (1)		21	0.829	0.444	4.087	0.014
$X2 = 23.619 + 89.081$ HOMO $+ 8.125$ LUMO $+ 12.218Q_N - 1.136$ ClogP $+ 0.081$ MR $- 0.009$ Vw $- 0.326$ DM $- 0.008E_T$ (2)		21	0.937	0.218	10.734	0.0002
$X3 = -1.779 + 26.824$ HOMO $- 9.587$ LUMO $- 0.888$ ClogP $+ 0.072$ MR $- 0.004$ Vw $- 0.006E_T$ (3)	**8-I-i**, **8-I-j**, **8-I-n**	18	0.805	0.243	3.385	0.038
$X4 = 2.129 + 32.666$ HOMO $- 0.386$ ClogP $+ 0.041$ MR $- 0.007$ Vw $- 0.007E_T$ (4)	**8-I-a**, **8-I-j**	19	0.807	0.243	4.861	0.010

heterogeneous systems.[31] The four equation models indicate that ClogP is negatively correlated with insecticidal inhibition; a decrease in value may increase the bioactivity.

These equations indicate that inhibition activity of the derivatives may be increased with the increase in MR (molar refractivity), which is a very important physicochemical parameter to the understanding of bonding electrons in organic molecules.[32]

The prediction models in each of these descriptors differ in terms of either one or two parameters, but all maintain a negative relationship between inhibition activity and Vw (van der Waals volume). It has been reported that molecular size is an

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Table 6. Correlation Matrix of the Parameters Used in Equation 2

	E_T	Vw	DM	LUMO	HOMO	ClogP	Q_N	MR
E_T	1.000							
Vw	0.245	1.000						
DM	0.157	0.339	1.000					
LUMO	0.340	−0.017	0.002	1.000				
HOMO	−0.430	−0.159	−0.181	−0.523	1.000			
ClogP	0.183	0.331	0.504	−0.259	0.002	1.000		
Q_N	−0.156	−0.193	0.058	−0.451	0.577	0.325	1.000	
MR	−0.229	−0.460	−0.474	0.272	−0.083	−0.881	−0.506	1.000

Table 7. Values of Percentage of Inhibition (I%) Observed and Predicted by Equation 2 and the Standard Residuals for Each Compound

compd	obsd	predicted	residual	std residual
8-I-a	−2.38	−2.44	0.07	0.30
8-I-b	−2.65	−2.62	−0.02	−0.11
8-I-c	−2.86	−2.89	0.03	0.12
8-I-d	−3.12	−3.08	−0.04	−0.17
8-I-e	−1.80	−1.89	0.10	0.44
8-I-f	−2.27	−2.23	−0.04	−0.17
8-I-g	−2.48	−2.47	−0.01	−0.02
8-I-h	−3.45	−3.19	−0.25	−1.16
8-I-i	−2.69	−2.43	−0.25	−1.17
8-I-j	−3.11	−3.53	0.42	1.92
8-I-k	−2.69	−3.03	0.34	1.56
8-I-l	−3.65	−3.44	−0.21	−0.95
8-I-m	−2.50	−2.45	−0.04	−0.21
8-I-n	−2.97	−2.94	−0.03	−0.15
8-II-a	−2.62	−2.65	0.02	0.10
8-II-b	−2.78	−2.80	0.03	0.12
8-II-c	−3.14	−3.04	−0.11	−0.50
8-II-d	−2.82	−2.98	0.16	0.75
8-II-e	−2.97	−3.06	0.09	0.40
8-II-f	−3.78	−3.59	−0.19	−0.86
8-II-g	−3.54	−3.48	−0.06	−0.26

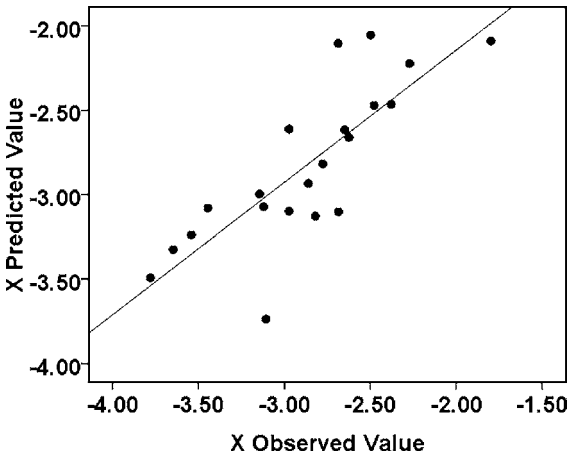

Figure 4. Relationship between observed and predicted activity by eq 2.

important factor how to reach active sites and affect biological activities.[33] As explained by the lock−key model and induced-fit model hypothesis, molecular recognition of chemical compounds by receptors determines the biological activity. In this study, Vw is one of the statistically significant descriptors in all models. The Vw can reflect both the steric influence and the recognition effects.

The DM (dipole moment) gives a measure of bond polarity and charge separation throughout the molecule.[34] In the present study, all models show that the magnitude of DM inversely correlates to the inhibition activity.

E_T, total energy, has been interpreted in other QSAR studies to measure stability.[35] The significance of total energy might relate to the difference in stability of the derivatives. All models highlight the importance of total energy, as it relates to inhibition activity, might include further examination of steric energy, rotational energy barriers, as well as other structural and physicochemical parameters.[36]

In summary, a series of novel 3-(2,5-dimethylphenyl)-4-hydroxy-1-azaspiro[4.5]dec-3-ene-2,8-dione derivatives were designed and synthesized. Their insecticidal activities against *A. fabae* and *T. cinnabarinus* were evaluated. The results showed that most of the derivatives containing phenyl-acyl-substituted groups maintained more powerful insecticidal activity than others, potentially at lower cost. QSAR demonstrated that ClogP, HOMO, LUMO, Vw, MR, DM, and E_T were the critical parameters for the inhibition of target compounds. Although only a small set of derivatives was used to develop these QSAR models, the models still provided insight useful for the design of derivatives and improvement of insecticidal activity.

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