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Total Synthesis and Biological Activity of (±)-Rocaglamide and Its 2,3-Di-*epi* Analogue

Hongsen Li,[a] B. Fu,[a] M. A. Wang,[a] N. Li,[a] W. J. Liu,[a] Z. Q. Xie,[a] Y. Q. Ma,[a] and Zhaohai Qin*[a]

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By introducing the strategy of intramolecular reductive coupling to construct the cyclopenta[*b*]benzofuran skeleton, the shortest and most efficient synthetic method hitherto was now established to rocaglamide **1** and its 2,3-di-*epi* analogue **3** in racemic form by Michael addition, SmI_2-promoted intramolecular keto–ester coupling, amination of the ester intermediate, and reduction of carbonyl with $Me_4NBH(OAc)_3$. Several steps were highly stereoselective or even stereospecific. The bioassay results indicated that both **1** and **3** were much better repellents against *Plutella xylostella* than azadirachtin; the insecticidal activity of **1** was higher than that of azadirachtin against *Pieris rapae*, *P. xylostella*, *Laphygma exigua*, and *Helicoverpa armigera*, but that of **3** was lower.

Introduction

Rocaglamide **1**, featuring a cyclopenta[*b*]benzofuran ring system, was first isolated from *Aglaia elliptofolia* Merr. by King[1] in 1982, and it showed high cytotoxicity towards a group of human cancer cell lines, such as κB, *p*-388, A-549, etc.[2] Moreover, it has attracted more attention in recent years because of its insecticidal and growth inhibitory activity.[3] Both the structural complexity of rocaglamide and its significant activity make it an attractive synthetic target.

To date, several synthetic routes were developed for **1** and its derivatives.[4] To the best of our knowledge, intramolecular cyclizations, which were established by Taylor and Sy,[4a–4f] and photocycloaddition, which was achieved by Porco,[4h–4j] might be more easily optimized for an agrochemical application than other methods, despite the fact that those methods were also highly academically valuable in terms of synthetic methodology. In the intramolecular cyclization method, the establishment of the tricyclic core (the synthesis of key intermediate **2**) by intramolecular keto–cyano reductive coupling or pinacol coupling followed by oxidation was no doubt a creative strategy. In this method, however, the carboxylation of **2** at the 2-position was unavoidable and troublesome. Although Dobler and his coworkers[4e] considerably and elegantly improved this method by using Stiles carboxylation, a shorter and more convenient synthesis was still attractive to synthetic chemists. Herein we focused on the introduction of a methoxycarbonyl group in a Michael addition acceptor and its subsequent use in SmI_2-promoted intramolecular cyclization strategy (Scheme 1).

In this paper we report the total synthesis of (±)-rocaglamide **1** and its 2,3-di-*epi* analogue **3**, and their repellent and insecticidal activities. The stereochemistry in the process of synthesis is also discussed.

Results and Discussion

We initiated our study with the Michael addition of **4** and **5a**–**5d** under standard experimental condition. Michael acceptor **5a**–**5d** were facilely obtained from Knoevenagel condensation of benzaldehyde and the corresponding carboxylate (3,3-dimethoxy propaneate, cyano acetate, and malonate). Treatment of *trans*-**5a** with **4** in the presence of Triton B (*N*,*N*,*N*-trimethylbenzylammonium hydroxide) at 40 °C afforded a surprising result in that expected product **6a** was not achieved, whereas demethoxy product, both *trans*-isomer **9** and *cis*-isomer **10** were obtained. Their structures were assigned by ^1H NMR spectroscopic analysis.

The addition of methyl α-formylcinnaminate (**5b**) to **4** gave only the enol form of product **6b** as a mixture of two diastereoisomers, which was attributed to the stability gained through the conjugated double bond and intramolecular hydrogen bonding. Disappointedly, when the Dolbler procedure was used to perform the pinacol coupling for **6b**, no desired product was afforded and almost all crude material was recovered. Maybe the enol form was unfavorable for the coupling reaction.

The addition of ethyl α-cyanocinnaminate (**5c**) to **4** afforded two diastereoisomers **6c-1**(β isomer, *cis*-phenyl, 38.8% yield) and **6c-2**(α isomer, *trans*-phenyl, 18.7% yield). Quite surprisingly, intramolecular reductive coupling of **6c-**

[a] College of Science, China Agricultural University, 100094 Beijing, China
Fax: +86-10-950507-710419
E-mail: qinzhaohai@263.net

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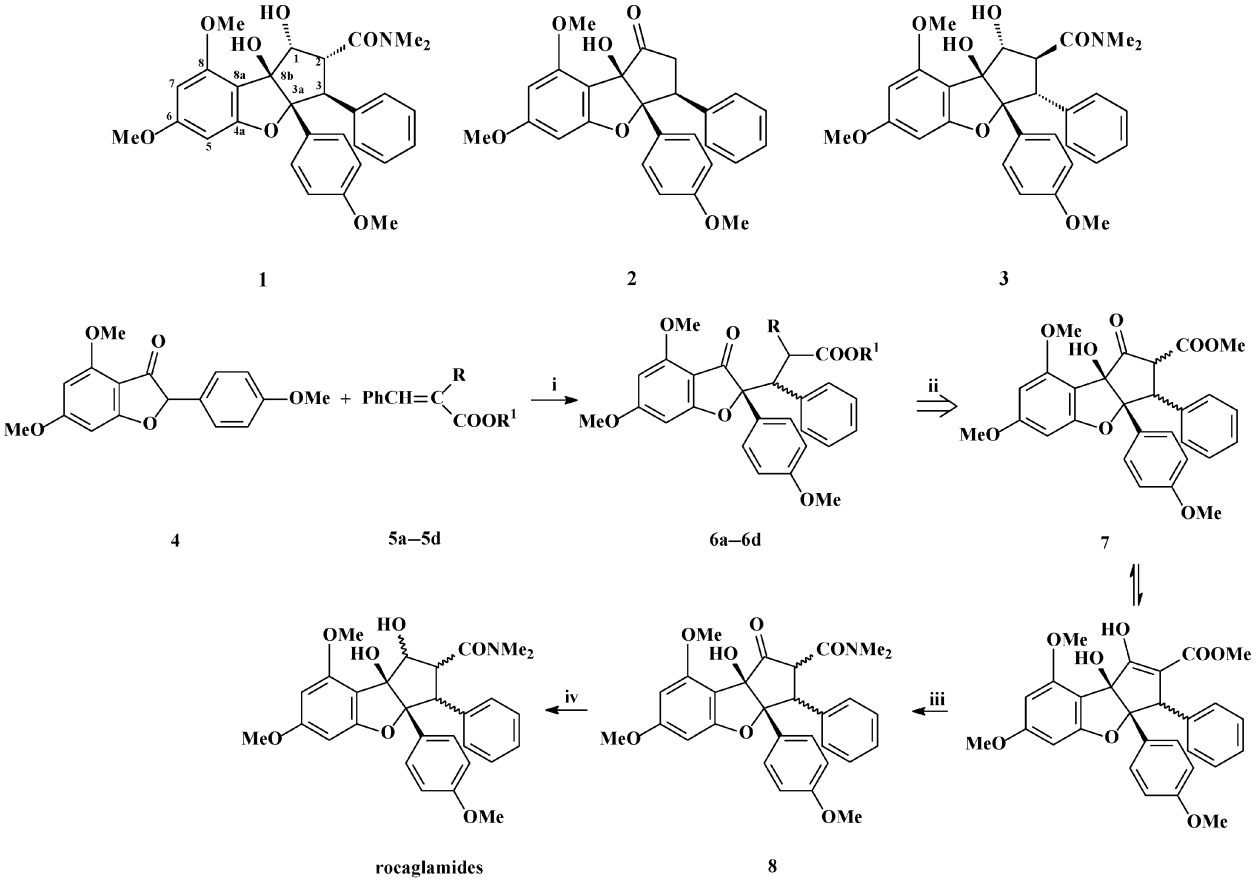
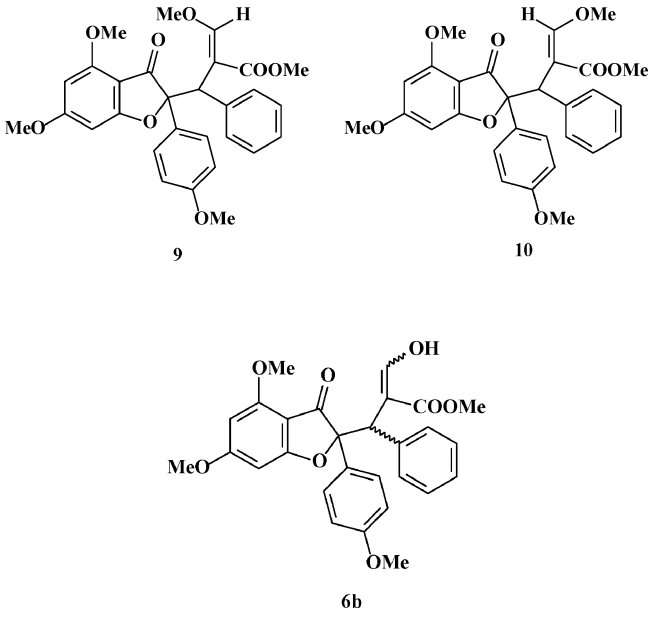


5a: R = CH(OMe)$_2$, R^1 = Me; 5b: R = CHO, R^1 = Me; 5c: R = CN, R^1 = Et;

5d: R = COOMe, R^1 = Me

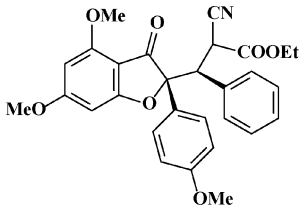
Scheme 1. Reagents and conditions: (i) Triton B, THF or *t*BuOH, N_2, 40 °C; (ii) 1. $SmC_2H_4I_2$, C_6H_6/THF, sonication, N_2, room temp.; 2. Py·SO_3/CH_2Cl_2 for R = CHO; (iii) $LiNMe_2$, THF, –78 °C, N_2; (iv) $Me_4NBH(OAc)_3$, HOAc/MeCN, N_2, room temp.



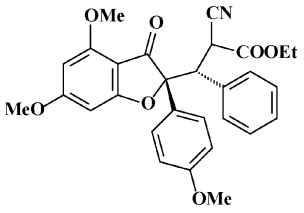
1 promoted by SmI_2 did not give **7**; spectral analysis indicated that keto–ester coupling had taken place, and compound **11** was obtained. Despite the fact that keto–ester and keto–cyano reductive couplings have been disclosed before,[5,6] this is the first report concerning the intramolecular reductive coupling of α-cyano-δ-oxocarboxylates. This result also implied that intramolecular keto–ester coupling was much easier than keto–cyano coupling. An attempt to hydrolyze **11** into 1-oxorocagloic acid **12** failed, but decarboxylic product **2** was isolated.

Furthermore the Michael addition of methyl α-methoxycarbonylcinnaminate (**5d**) to **4** also gave two diastereoisomers, **6d-1** (β isomer, *cis*-phenyl, 36.1% yield) and **6d-2** (α isomer, *trans*-phenyl, 16.5% yield). In the following keto–ester coupling reaction, the stereoselectivity was very interesting: whether it be **6d-1** and **6d-2**, the hydroxy group at C-8b always had a *cis* orientation with respect to the 3a-phenyl group. The enol form of **7** (keto/enol, 0.7:1 according to ^{1}H NMR spectroscopy − this was also described by Taylor and Sy[4b,4d]) led to the disappearance of the chiral center at the 2-position; thus, this was a stereospecific reaction. Actually, we only obtained **7a** (3β isomer) from **6d-1** and **7b** (3α isomer) from **6d-2**.

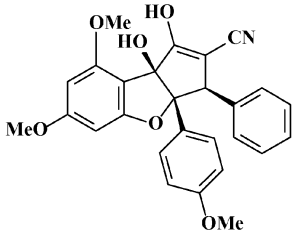
With the key intermediate **7** in hand, the next work was the amination of **7** according to Taylor's method. ^{1}H NMR analysis indicated that the product **8** only existed as a single keto form.



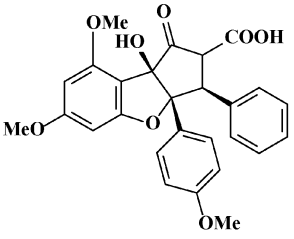
6c–1



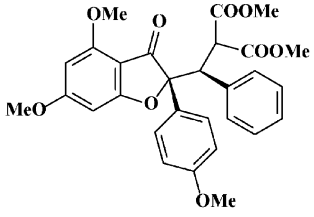
6c–2



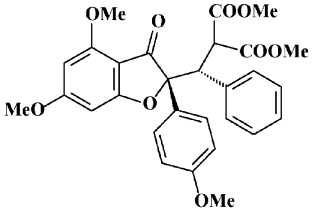
11



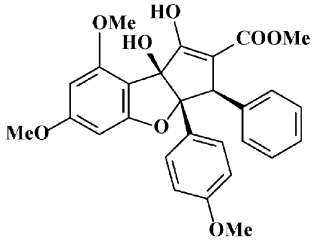
12



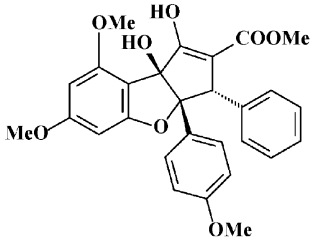
6d–1



6d–2

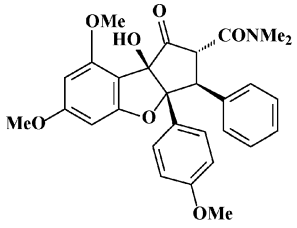


7a

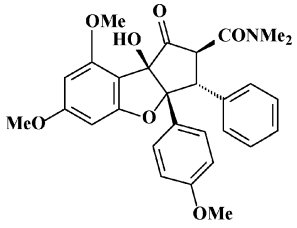


7b

Fortunately in the conversion of enol form to keto form, i.e. the formation of 2-position new chiral center was not only stereospecific, but also as the desired configuration. Thus we obtained **8a** (2α, 3β) from **7a**, and **8b** (2β, 3α) from **7b**.



8a



8b

Finally, the reduction of **8** by $Me_4NBH(OAc)_3$ was highly stereoselective to give target rocaglamides, because reduction could be accomplished only from the β face by templating the reducing agent with the neighboring hydroxy group.[4k] Thus, (±)-rocaglamide **1** was generated from **8a**, whereas the (±)-2,3-di-*epi* analogue of rocaglamide **3** was obtained from **8b**. Their analytical data were identical to the data in the literature.[4b,4d]

We evaluated the repellent and insecticidal activity of both title compounds, and compared them with aza-dirachtin. As shown in Tables 1 and 2, both **1** and **3** demonstrated good repellent activity against *Plutella xylostella*, but the insecticidal activities were quite different. Under the concentration of 200 μg mL^{-1}, the repellent ratio of **1** was 71.9% and that of **3** was 70.9%; at a concentration of 100 μg mL^{-1} the repellent ratios were 63.7 and 60.0%, respectively. Apparently they are much higher than that of azadirachtin (33.3 and 40.0%, respectively, under the same concentrations). The insecticidal activity of **1** was higher than that of azadirachtin, whereas that of **3** was lower. The results implied the difference of configuration had little effect on repellent activity, but it was a very important factor to insecticidal activity.

Table 1. Repellency of (±)-**1** and (±)-**3** against *P. xylostella*.

Compound	Concentration [μg mL^{-1}]	Repellency [%]
(±)-**1**	200	71.9
	100	63.7
(±)-**3**	200	70.9
	100	60.0
Azadirachtin	200	33.3
	100	40.0

Table 2. Insecticidal activities of (±)-**1** and (±)-**3** (% mortality).

Compound	Conc. [μg mL^{-1}]	*Pieris rapae*	*Plutella xylostella*	*Laphygma exigua*	*Helicoverpa armigera*
(±)-**1**	200	86.7	90.0	100	88.1
	100	60.0	46.7	100	74.1
(±)-**3**	200	66.7	80.0	50.1	69.3
	100	13.3	33.3	11.5	14.8
Azadirachtin	200	60.0	83.3	96.2	48.1
	100	46.6	66.7	96.2	37.0
CK[a]		0	0	13.3	10.0

[a] Treated only with distilled water.

Conclusions

The shortest and most efficient route to racemic rocaglamide and its 2,3-di-*epi* analogue has been described. In our research, SmI_2-promoted intramolecular keto–ester reductive coupling, amination of the ester group, and reduction of the carbonyl functionality with $Me_4NBH(OAc)_3$ are highly stereoselective, and in some instances even stereospecific. Apparently, if a highly diastereoselective and enantioselective Michael addition method is established, we will conveniently synthesize natural rocaglamides by this method, as this is quite important to both rocaglamides and their derivatives. Further studies are in progress in our laboratory.

Our research also indicates that the configurations of rocaglamides are significantly correlated to their insecticidal activities, but it seems to have little effect on repellency activity.

Experimental Section

Melting points were measured with a XT-4 melting point apparatus and are uncorrected. NMR spectra were recorded with a Bruker Avance DPX300 spectrometer with tetramethylsilane as the internal standard. Mass spectra were obtained with a VG-ZAB-HS mass spectrometer. Solvents used were purified and dried by standard procedures. Compounds **4**, **5c**, and **5d** were synthesized according to literature procedures.[4c,7,8]

Methyl α-Dimethoxymethyl Cinnamate (5a) and Methyl α-Formyl Cinnamate (5b):[9,10] To a solution of methyl 3,3-dimethoxypropionate (3.05 g, 20.6 mmol) and benzaldehyde (2.24 g, 21 mmol) in dry THF (20 mL) was added NaH (70% in mineral oil, 0.8 g, 23 mmol) in portions, and the mixture was stirred for 5 h at room temperature. H_2O (20 mL) was then slowly added, and the aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic phase was washed with brine (2 × 10 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (petroleum ether/EtOAc, 9:1) to give two isomers of **5a**. *trans* Isomer: pale-yellow oil. Yield: 0.91 g, 19.3%. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.39 (s, 6 H, CH_3O), 3.84 (s, 3 H, CH_3O), 5.14 (s, 1 H, 1′-H), 7.37–7.55 (m, 5 H, C_6H_5), 7.80 (s, 1 H, 3-H) ppm. *cis* Isomer: pale-yellow oil. Yield: 1.02 g, 21.6%. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.41 (s, 6 H, CH_3O), 3.84 (s, 3 H, CH_3O), 5.22 (s, 1 H, 1′-H), 7.13–7.35 (m, 6 H, C_6H_5, 3-H) ppm.

The mixture of *trans*-**5a** (0.50 g, 2.11 mmol) and sulfuric acid (15%, 5 mL) was stirred at 80 °C for 5 h and then cooled. The reaction mixture was extracted with diethyl ether (3 × 30 mL), and the combined organic phase was washed to neutral pH with brine and dried with anhydrous Na_2SO_4. The crude product was purified by silica-gel column chromatography (petroleum ether/EtOAc, 9:1) to give *trans*-**5b**. Pale-yellow oil. Yield: 0.26 g, 65.0%. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.84 (s, 3 H, CH_3O), 7.14 (s, 1 H, 3-H), 7.30–7.53 (m, 5 H, C_6H_5), 9.61 (s, 1 H, CHO) ppm.

Methyl 2-Methoxymethylen-3-[4,6-dimethoxy-2-(4-methoxyphenyl)-3-oxo-2,3-dihydrobenzofuran-2-yl]-3-phenylpropionate (6a): Under a N_2 atmosphere, to a solution of **4** (2.0 g, 6.67 mmol) in *tert*-butyl alcohol (100 mL) was added a solution of Triton B (40% in CH_3OH, 0.23 mL) and a solution of *trans*-**5a** (1.91 g, 8.10 mmol) in *tert*-butyl alcohol (40 mL) by syringe. After stirring at 60 °C for 3 h, the solvent was removed in vacuo. To the residue was added a solution of HCl (1 M, 25 mL), and this solution was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phase was washed with brine (2 × 20 mL), dried with Na_2SO_4, and concentrated. The crude product was separated by silica-gel column chromatography (petroleum ether/EtOAc, 1:1) to afford **9** (0.63 g, 18.5%) and **10** (0.44 g, 13.2%). Compound **9**: white solid, m.p. 167–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.60 (s, 3 H, CH_3O), 3.73 (s, 3 H, CH_3O), 3.74 (s, 3 H, CH_3O), 3.75 (s, 3 H, CH_3O), 3.82 (s, 3 H, CH_3O), 5.27 (s, 1 H, 3-H), 5.80 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.21 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.77 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2), 7.04–7.12 (m, 3 H, C_6H_2, C_6H_1), 7.16 (s, 1 H, CH=), 7.33–7.38 (m, 2 H, C_6H_2), 7.47 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2) ppm. Compound **10**: white solid, m.p. 182–184 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.59 (s, 3 H, CH_3O), 3.71 (s, 3 H, CH_3O), 3.75 (s, 3 H, CH_3O), 3.77 (s, 3 H, CH_3O), 3.85 (s, 3 H, CH_3O), 5.20 (s, 1 H, 3-H), 5.80 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.20 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.83 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2), 7.04–7.13 (m, 4 H, C_6H_3, CH=), 7.34–7.36 (m, 2 H, C_6H_2), 7.47 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2) ppm.

Methyl 2-Formyl-3-[4,6-dimethoxy-2-(4-methoxyphenyl)-3-oxo-2,3-dihydrobenzofuran-2-yl]-3-phenylpropionate (6b): Prepared from **5b** by a similar procedure to that used for **6a** except THF was used to afford **6b** (1.20 g, 36.7%) as a white crystalline solid. M.p. 124–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.65 (s, 3 H, CH_3O), 3.70 (s, 3 H, CH_3O), 3.76 (s, 3 H, CH_3O), 3.86 (s, 3 H, CH_3O), 4.99 (s, 1 H, 3-H), 5.81 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.20 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.83 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2), 7.05–7.15 (m, 3 H, C_6H_3), 7.29–7.34 (m, 2 H, C_6H_2), 7.45 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2), 7.81 (d, $^3J_{H,H}$ = 12.6 Hz, 1 H, CH=), 11.80 (d, $^3J_{H,H}$ = 12.6 Hz, 1 H, OH, disappeared after D_2O exchange) ppm.

Ethyl 2-Cyano-3-[4,6-dimethoxy-2-(4-methoxyphenyl)-3-oxo-2,3-dihydrobenzofuran-2-yl]-3-phenylpropionate (6c): Prepared from **5c** by a similar procedure to that used for **6a** except THF was used to afford **6c-1** (1.27 g, 38.8%) and **6c-2** (0.61 g, 18.7%) as white solids. Data for **6c-1**: M.p. 193–194 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.98 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 3.69 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, 3-H), 3.70 (s, 3 H, CH_3O), 3.81 (s, 3 H, CH_3O), 3.88 (s, 3 H, CH_3O), 3.95 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2O), 4.30 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, 2-H), 5.83 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.38 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.95 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2), 7.16–7.18 (m, 3 H, C_6H_3), 7.55–7.57 (m, 2 H, C_6H_2), 7.82 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 194.0, 174.5, 170.1, 164.9, 160.1, 159.0, 132.8, 130.2, 128.4, 127.4, 126.4, 116.0, 114.5, 103.4, 93.4, 92.4, 88.7, 62.8, 56.1, 55.9, 55.3, 52.1, 39.5 ppm. Data for **6c-2**: M.p. 254–255 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.09 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 3.66 (s, 3 H, CH_3O), 3.88 (s, 3 H, CH_3O), 3.90 (d, $^3J_{H,H}$ = 3.7 Hz, 1 H, 3-H), 3.94 (s, 3 H, CH_3O), 4.06 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2O), 4.34 (d, 1 H, $^3J_{H,H}$ = 3.7 Hz, 2-H), 6.05 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.50 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.65 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2), 7.16–7.19 (m, 3 H, C_6H_3), 7.37 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2), 7.42–7.46 (m, 2 H, C_6H_2) ppm.

Methyl 2-Methoxycarbonyl-3-[4,6-dimethoxy-2-(4-methoxyphenyl)-3-oxo-2,3-dihydrobenzofuran-2-yl]-3-phenylpropionate (6d): Prepared from **5d** by a similar procedure to that used for **6a** except THF was used to afford **6d-1** (1.25 g, 36.1%) and **6d-2** (0.57 g, 16.5%) as white crystalline solids. Data for **6d-1**: M.p. 173–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.17 (s, 3 H, CH_3O), 3.27 (s, 3 H, CH_3O), 3.65 (s, 3 H, CH_3O), 3.77 (s, 3 H, CH_3O), 3.86 (s, 3 H, CH_3O), 4.33 (d, $^3J_{H,H}$ = 10.8 Hz, 1 H, 3-H), 4.53 (d, $^3J_{H,H}$ = 10.8 Hz, 1 H, 2-H), 5.78 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.27(d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.82–6.85 (m, 2 H, C_6H_2), 7.05–7.13 (m, 3 H, C_6H_3), 7.31–7.34 (m, 2 H, C_6H_2), 7.69–7.76 (m, 2 H, C_6H_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 194.4, 174.1, 169.6, 167.7, 167.6, 159.7, 159.2, 135.5, 130.0, 127.8, 127.6, 127.4, 127.0, 113.4, 103.8, 92.9, 92.4, 88.5, 55.9, 55.8, 55.3, 54.2, 52.3, 52.2, 51.5 ppm. MS (EI): *m*/*z* (%) = 520 (3.3) $[M]^+$, 300 (25.0), 299 (100), 191 (3.3), 163 (3.3), 135 (13.0), 121 (3.0). HRMS: calcd. for $C_{29}H_{28}O_9$ $[M]^+$ 520.1739; found 520.1739. Data for **6d-2**: M.p. 169–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.29 (s, 3 H, CH_3O), 3.54 (s, 3 H, CH_3O), 3.67 (s, 3 H, CH_3O), 3.84 (s, 3 H, CH_3O), 3.88 (s, 3 H, CH_3O), 4.21 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, 3-H), 4.47 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, 2-H), 5.97 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.27 (d, 1 H, $^4J_{H,H}$ = 1.8 Hz, C_6H_1), 6.63–6.67 (m, 2 H, C_6H_2), 7.04–7.11 (m, 3 H, C_6H_3), 7.17–7.21 (m, 2 H, C_6H_2), 7.36–7.42 (m, 2 H, C_6H_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 194.6, 174.0, 169.8, 167.8, 167.6, 159.2, 159.1, 136.2, 130.2, 128.4, 127.4, 127.0, 126.9, 113.2, 104.3, 93.2, 92.7, 88.8, 55.9, 55.1, 53.4, 52.5, 52.1, 52.0 ppm. MS (EI): *m*/*z* (%) = 520 (3.3) $[M]^+$, 300 (33.3), 299 (100), 271 (3.3), 241 (2.0), 192 (4.0), 163 (4.0), 135 (13.3), 121 (3.3), 106 (3.0), 77 (2.0). HRMS: calcd. for $C_{29}H_{28}O_9$ $[M]^+$ 520.1739; found 520.1739.

8b-Hydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8a-tetrahydrocyclopenta[*b*]benzofuran-2-nitrile (11): To the reactant of metal Sm (1.50 g, 10 mmol) in a flame-dried, 100-mL, three-necked round-bottom flask equipped with a stir bar, septum, and nitrogen inlet was added a solution of $C_2H_4I_2$ (1.41 g, 5.0 mmol) in THF (7 mL). After stirring for 1 h, the solution changed to blue, and the reaction was continued for 3 h under ultrasound irradiation. Anhydrous benzene (20 mL) was then added, and the reaction was continued for an additional 2 h. A solution of **6c-1** (1.30 g, 2.6 mmol) in benzene (100 mL) was added, and the reaction was allowed to proceed for 10 h under ultrasound irradiation. The reaction was quenched with the addition of HCl (1 M, 20 mL), and the solution was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phase was washed with brine (2 × 20 mL), dried with anhydrous Na_2SO_4, and concentrated. The crude product was purified by silica-gel column chromatography (petroleum ether/EtOAc, 2:3) to afford **11** (0.28 g, 23.6%) as a white crystalline solid. M.p. 190–191 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 3.60 (s, 3 H, CH_3O), 3.74 (s, 3 H, CH_3O), 3.77 (s, 3 H, CH_3O), 4.50 (s, 1 H, 3-H), 5.64 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 5.88 (s, 1 H, 8b-OH, disappeared after D_2O exchange), 6.06 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.73–6.76 (m, 2 H, C_6H_2), 6.93–6.96 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2), 7.12–7.15 (m, 3 H, C_6H_3), 7.36 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2), 11.33 (s, 1 H, 1-OH, disappeared after D_2O exchange) ppm.

Methyl 8b-Hydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-1-oxo-3-phenyl-2,3,3a,8a-tetrahydrocyclopenta[*b*]benzofuran-2-carboxylate (7): Prepared from **6d-1** by a similar procedure to that used for **11** to afford **7a** (0.68 g, 53.7%) as a white crystalline solid. M.p. 163–164 °C (keto form) (ref.[4d] 87.5–89.5 °C as keto/enol, 65:35). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.04 (s, 1 H, 8b-OH, disappeared after D_2O exchange), 3.66 (s, 3 H, CH_3O), 3.71 (s, 3 H, CH_3O), 3.81 (s, 3 H, CH_3O), 3.85 (s, 3 H, CH_3O), 4.06 (d, $^3J_{H,H}$ = 13.2 Hz, 1 H, 3-H), 4.24 (d, $^3J_{H,H}$ = 13.2 Hz, 1 H, 2-H), 6.10 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.35 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.66–6.70 (m, 2 H, C_6H_2), 6.89–6.97 (m, 4 H, C_6H_4), 7.08–7.12 (m, 3 H, C_6H_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + D_2O, 25 °C): δ = 203.3, 167.2, 164.9, 161.0, 158.9, 158.6, 135.4, 129.1, 128.0, 127.9, 127.7, 127.1, 125.4, 113.2, 112.2, 106.1, 99.3, 92.9, 89.9, 88.5, 56.4, 55.7, 55.6, 55.1, 55.0, 52.9, 52.0, 51.5 ppm. MS (EI): *m*/*z* (%) = 472 (6.0), 414 (4.6), 300 (100), 285 (26.6), 269 (3.0), 242 (3.0), 135 (10.0), 104 (3.0), 77 (3.0), 44 (7.3).

Following the same procedure, **7b** (0.64 g, 50.2%) was obtained from **6d-2**. M.p. 95–96 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.52 (br. s, 1 H, 8b-OH), 3.62 (d, $^3J_{H,H}$ = 6.3 Hz, 1 H, 3-H), 3.70 (s, 3 H, CH_3O), 3.75 (s, 3 H, CH_3O), 3.78 (s, 3 H, CH_3O), 3.80 (s, 3 H, CH_3O), 4.40 (d, $^3J_{H,H}$ = 6.3 Hz, 1 H, 2-H), 6.01 (d, $^4J_{H,H}$ = 2.1 Hz, 1 H, C_6H_1), 6.14 (d, $^4J_{H,H}$ = 2.1 Hz, 1 H, C_6H_1), 6.89 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, C_6H_2), 7.03–7.06 (m, 2 H, C_6H_2), 7.19–7.23 (m, 3 H, C_6H_3), 7.34 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, C_6H_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 203.2, 168.3, 164.7, 163.8, 161.9, 159.4, 159.3, 158.2, 134.0, 130.4, 128.9, 128.7, 128.3, 128.2, 128.1, 127.7, 127.6, 127.4, 127.3, 126.6, 113.5, 113.4, 104.1, 97.2, 92.5, 92.3, 88.4, 88.2, 88.1, 86.8, 55.7, 55.2, 54.8, 54.3, 52.6 ppm. MS (EI): *m*/*z* (%) = 472 (13.3), 458 (2.0), 414 (12.7), 399 (2.0), 300 (100), 285 (27.3), 269 (4.0), 242 (3.0), 181 (2.0), 135 (10.0), 121 (3.0), 103 (4.0), 77 (4.0).

8b-Hydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-1-oxo-3-phenyl-2,3,3a,8a-tetrahydrocyclopenta[*b*]benzofuran-2-carboxamide (8): THF (8 mL) in a flame-dried, 50-mL, three-neck, round-bottomed flask equipped with a stir bar, thermometer, septum, and nitrogen inlet was cooled to –78 °C in a dry ice/acetone bath, and to this solution was added $NHMe_2$ (1.07 g, 23.8 mmol) and *n*-butyllithium (1.2 mL, 3 mmol)by syringe. After stirring for 20 min, a solution of **7a** (0.15 g, 0.31 mmol) in THF (6 mL) was added by syringe, and the reaction was continued at –78 °C for 30 min. The cold bath was then removed, and the reaction mixture was allowed to stir at room temperature for an additional 1 h. The reaction was quenched by the addition of CH_3OH (2 mL), and aqueous HCl (1 M, 15 mL) was then added dropwise slowly. The mixture was extracted with CH_2Cl_2 (4 × 15 mL), and the combined organic phase was washed with brine (3 × 10 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by silica-gel column chromatography (petroleum ether/EtOAc, 2:3) to afford **8a** (0.13 g, 84.4%) as a white crystalline solid. M.p. 143–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.90 (s, 3 H, CH_3N), 3.01 (br. s, 1 H, 8b-OH), 3.25 (s, 3 H, CH_3N), 3.73 (s, 3 H, CH_3O), 3.80 (s, 3 H, CH_3O), 3.84 (s, 3 H, CH_3O), 4.33 (d, $^3J_{H,H}$ = 13.2 Hz, 1 H, 3-H), 4.51 (d, $^3J_{H,H}$ = 13.2 Hz, 1 H, 2-H), 6.08(d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.32 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.70–6.73 (m, 2 H, C_6H_2), 6.82–6.85 (m, 2 H, C_6H_2), 6.98–7.01 (m, 2 H, C_6H_2), 7.07–7.09 (m, 3 H, C_6H_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 205.7, 165.3, 164.8, 161.1, 158.9, 158.5, 136.2, 128.0, 127.9, 126.9, 126.1, 113.2, 106.2, 99.3, 93.0, 89.9, 88.6, 55.6, 55.1, 53.9, 52.0, 37.7, 36.2 ppm. MS (EI): *m*/*z* (%) = 485 (25.3) [M]$^+$, 458 (2), 414 (8), 300 (100), 285 (19.3), 176 (3.3), 131 (7.3), 103 (3.3), 72 (5.0).

Following the same procedure, **8b** (0.13 g, 81.8%) was prepared from **7b** (0.15 g, 0.31 mmol). M.p. 209–210 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.96 (s, 6 H, Me_2N), 3.47 (s, 1 H, 8b-OH), 3.77 (s, 3 H, CH_3O), 3.78 (s, 3 H, CH_3O), 3.80 (m, 3 H, CH_3O), 4.54 (d, $^3J_{H,H}$ = 13.2 Hz, 1 H, 3-H), 4.75 (d, $^3J_{H,H}$ = 13.2 Hz, 1 H, 2-H), 6.03 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.16 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.87 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2), 7.03–7.06 (m, 2 H, C_6H_2), 7.17–7.20 (m, 3 H, C_6H_3), 7.37 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, C_6H_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 204.8, 166.3, 164.5, 162.0, 159.2, 158.1, 135.2, 128.9, 128.8, 128.2, 128.0, 127.3, 113.3, 104.8, 97.5, 92.5, 88.6, 87.0, 55.7, 55.6, 55.2, 54.0, 52.3, 37.0, 35.9 ppm. MS (EI): *m*/*z* (%) = 485 (3.3) [M]$^+$, 300 (100), 285 (20.0), 242 (2.3), 176 (5.3), 131 (12.0), 103 (8.0), 72 (12.0), 44 (6.0).

1,8b-Dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydrocyclopenta[*b*]benzofuran-2(1*H*)-carboxamide (±)-1 and (±)-3: Under a N_2 atmosphere, a mixture of $Me_4NBH(OAc)_3$ (0.45 g, 1.71 mmol), CH_3CN (1 mL), and HOAc (1 mL) was stirred at room temperature for 0.5 h, and then a solution of **8a** (0.12 g, 0.24 mmol) in CH_3CN (2.5 mL) was added by syringe. The reaction mixture was stirred at room temperature for an additional 24 h. The reaction was quenched with a saturated solution of $NaHCO_3$ (50 mL), and the solution was then extracted with CH_2Cl_2 (4 × 5 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, and concentrated. The crude product was purified by silica-gel column chromatography (petroleum ether/EtOAc, 1:4) to afford (±)-**1** (0.105 g, 87.2%) as a white crystalline solid. M.p. 120–122 °C (ref.[4d] 119–120 °C). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.94 (s, 3 H, CH_3N), 3.31 (s, 3 H, CH_3N), 3.70 (s, 3 H, CH_3O), 3.83 (s, 3 H, CH_3O), 3.85 (s, 3 H, CH_3O), 4.05 (dd, $^3J_{H,H}$ = 13.5 Hz, $^3J_{H,H}$ = 6.5 Hz, 1 H, 2-H), 4.55 (d, $^3J_{H,H}$ = 13.5 Hz, 1 H, 3-H), 4.93 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H, 1-H), 6.10 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.27 (d, $^4J_{H,H}$ = 1.8 Hz, 1 H, C_6H_1), 6.65–6.70 (m, 2 H, C_6H_2), 6.84–6.87 (m, 2 H, C_6H_2), 7.01–7.13 (m, 5 H, C_6H_5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 169.6, 163.9, 161.1, 158.6, 157.3, 137.6, 128.9, 127.8, 127.7, 127.1, 126.3, 112.7, 107.6, 101.7, 94.1, 92.5, 89.3, 78.6, 56.0,55.7, 55.1, 47.6, 37.0, 35.8 ppm. MS (EI): *m*/*z* (%) = 505 (12.0) [M]$^+$, 487 (10.0), 442 (5.3), 416 (19.3), 390 (60.7), 368 (4.7), 325 (4.0), 313

(61.3), 285 (22.0), 269 (6.0), 243 (7.3), 223 (4.7), 205 (26.7), 181 (41.3), 176 (100), 148 (5.3), 131 (16.7), 116 (18.0), 91 (3.7), 72 (27.3), 46 (6.7). HRMS: calcd. for $C_{29}H_{29}NO_7$ $[M]^+$ 505.2101; found 505.2104.

Following the same procedure, (±)-**3** (0.10 g, 83.3%) was prepared from **8b**. M.p. 108–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.85 (s, 3 H, CH_3N), 2.99 (s, 3 H, CH_3N), 3.58 (dd, $^3J_{H,H}$ = 10.0 Hz, $^3J_{H,H}$ = 12.2 Hz, 1 H, 2-H), 3.78 (s, 3 H, CH_3O), 3.82 (s, 3 H, CH_3O), 3.83 (s, 3 H, CH_3O), 4.24 (d, $^3J_{H,H}$ = 12.2 Hz, 1 H, 3-H), 4.81 (d, $^3J_{H,H}$ = 10.0 Hz, 1 H, 1-H), 6.10 (d, $^4J_{H,H}$ = 2.0 Hz, 1 H, C_6H_1), 6.20 (d, $^4J_{H,H}$ = 2.0 Hz, 1 H, C_6H_1), 6.84–6.89 (m, 2 H, C_6H_2), 6.99–7.02 (m, 2 H, C_6H_2), 7.13–7.17 (m, 3 H, C_6H_3), 7.37–7.42 (m, 2 H, C_6H_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 171.4, 163.7, 161.9, 159.2, 157.9, 135.8, 129.3, 129.2, 128.3, 127.8, 126.9, 113.4, 105.7, 99.9, 92.4, 91.7, 88.6, 84.7, 55.7, 55.6, 55.2, 54.8, 47.3, 37.4, 36.0 ppm. MS (EI): *m*/*z* (%) = 505 (10.0), 487 (9.3), 469 (2.0), 442 (4.0), 415 (6.7), 390 (95.3), 313 (100), 285 (23.3), 271 (2.7), 243 (10.0), 222 (2.7), 205 (20.0), 181 (46.0), 176 (74.0), 148 (7.3), 135 (18.7), 116 (47.3), 91 (5.0), 72 (30.0), 46 (12.0). HRMS: calcd. for $C_{29}H_{29}NO_7$ $[M]^+$ 505.2101; found 505.2105.

Bioassay: Compounds **1**, **3**, and azadirachtin were dissolved in chloroform (1% M/V), respectively, and then diluted with water containing 0.02% emulsifier and 0.05% Triton X-100 to the tested concentrations.

Insect Repellency: The leaf of *Brassica chinensis* Linn. was washed, dried by airing, and cut as a Ø70 mm round disc, which was then divided into two halves. One half of the disc was daubed with 0.2 mL tested agent prepared above on both sides. The other half of the disc was a control, which was only daubed with water containing emulsifier and Triton X-100. After being dried by airing, the discs were put in a Ø85 mm culture dish and 10 third instar larvae of *Plutella xylostella* (Linnaeus) were put on the half leaf disc containing insecticide, covered with cling film, and kept at (27 ± 1) °C for 24 h. Experiments were replicated three times at every concentration. The contents of worm at each treated or control diet was counted and the repellency (%) was calculated by the following formula:

$$\text{Repellency (\%)} = (C - E)/T \times 100\%$$

where C is the insect numbers in the negative control half of the leaf disc, E is the insect numbers in the treated half of disc, and T is the number of total insects. C, E, and T were the mean data of the three replicates.

Insecticidal Activity: The third instar larvae of *Pieris rapae* Linnaeus, *Brassica napus* Linn., and second instar larvae of *Laphygma exigua* (Hubner) were treated with Potter's method under 200 and 100 $\mu g\,mL^{-1}$.

The leaf of *Brassica chinensis* Linn. was cut to Ø15 mm round discs. These leaf discs were immersed in sample solution for 10 s, dried by airing, and then put in a testing box with ten holes, which in every hole a piece of leaf disc was needed. The third instar larva of *Helicoverpa armigera* was placed in the hole and covered with cling film.

Ten insects were used at every concentration; all experiments were kept at (27 ± 1) °C and were replicated six times. The mortality of insects was determined after 3 d, and Abbotts formula was used to correct the mortality relative to that of negative control. The data was presented in the form of mean mortality (%).

Supporting Information (see footnote on the first page of this article): Spectral data for the synthesized compounds.

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