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Synthesis and Antifeeding Activities of Tonghaosu Analogues

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Tonghaosu (**1**), a lead for a botanical antifeedant, and its 22 analogues were synthesized according to a previously reported concise and straightforward procedure. The structures of all new compounds were confirmed by NMR, IR, MS, and HREIMS or elemental analysis. Their insect antifeedant activities against the large white butterfly (*Pieris brassicae* L.) were examined, and six analogues (*Z*- and *E*-**6h** and *Z*-isomers of **6i**−**l**), which contain 1,3-diyn or 3,4-methylenedioxyphenyl acetylene group, showed considerable antifeedant activity. Interestingly, *Z*-isomers of **6i**−**k** are much more active than their corresponding *E*-isomers.

KEYWORDS: Tonghaosu; spiroketal; antifeedant; *Pieris brassicae*

INTRODUCTION

Tonghaosu, 2-(2′,4′-hexadiynylidene)-1,6-dioxaspiro[4,4]-non-3-ene (**1**), is an antifeedant component of the Chinese vegetable tonghao (*Chrysanthemum segetum* L. or *Chrysanthemum coronarium* L.) (*1*) and was also found in other plants of tribe *Anthemideae* of the Compositae (*2*−*4*). In our previous studies in the search for new insecticidal compounds against vegetable pests, tonghaosu and a variety of its analogues (**2**) (*5*−*9*) were prepared via a convenient method established by us, and the bioactivities of some analogues were evaluated (*10*−*15*). Preliminary results indicated (*11*−*15*) analogues with 2′-nitrophenyl or a pyridinyl group at C10 (see compound **1** in **Figure 1** for numbering) had appreciable antifeeding activity.

In view of the fact that many other acetylene-containing natural products (*16*−*20*) as well as synthetic compounds (*21*) showed good insect antifeeding activities, we focused on the synthesis of new series of tonghaosu analogues, which would contain an acetylene function and also varied B-rings. Herein, we report recent progress along this line and the antifeeding activities of these newly prepared tonghaosu analogues against the large white butterfly (*Pieris brassicae* L.).

MATERIALS AND METHODS

Chemistry. IR spectra were recorded on Perkin-Elmer 983 or Shimadzu IR-440 spectrometers. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ on an AMX-300, DPX-300, or DRX-400 spectrometer with TMS as the internal standard. Mass spectra were taken on a Mariner, HP5973N, or HP5989A instrument. Flash column chromatography was performed on silica gel H (10−40 μm) with a petroleum ether/ethyl acetate system as eluent.

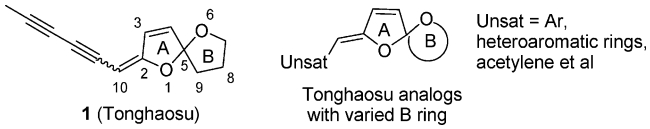

Figure 1. Tonghaosu (**1**) and its analogues.

Insect Rearing. The larvae of the large white butterfly (*P. brassicae* L.) were collected from suburban vegetable fields of Kunming, Yunnan Province, China, and reared with cabbage (*Brassica oleracea* L.) seedling in an environmental chamber held at 25 ± 1 °C under a photoperiod of 14:10 h (light/dark). Larvae of the second generation were reared to third instar for a feeding test.

Evaluation of Test Compounds with Leaf Disk Bioassay. Antifeeding activity was assayed according to the conventional leaf-disk method (*22*). The test compounds were dissolved in acetone at a concentration of 1000 μg/mL. Leaf disks (d = 1.25 cm) of cabbage were dipped into the prepared solutions for 1 s according to the method of Yee et al. (*23*), and control disks were dipped into acetone. These treated disks were allowed to stand on a plate to evaporate the acetone. Three disks and two larvae were placed in a wet filter paper disk in a 9.0 cm diameter Petri dish, with five replicates of each concentration. Remaining uneaten leaf areas were measured using an LI-COR 3000 leaf area meter (LI-COR, Lincoln, NE) 48 h after treatment. Ten randomly chosen leaf disks dipped in acetone and unexposed to larvae were used to determine the leaf areas consumed. The antifeeding percentage was calculated as

$$\text{antifeedancy} = (\text{CK} - T)/\text{CK} \times 100\%$$

where CK and T are control disk areas eaten and treated disk areas eaten, respectively.

The further feeding test of active compounds (azadirachtin as standard control) was carried out at a serial concentrations to obtain antifeeding percentages of 20−90%. The 50% antifeeding concentration (AFC_{50}) was determined by regression analysis (*24*). AFC_{50} values were considered to be significantly different if their 95% confidence limit (CL) did not overlap.

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Preparation of Test Compounds. *1,1-Dibromo-2-(3,4-methylenedioxyphenyl)ethylene (**2d**).* Carbon tetrabromide (33.16 g, 100 mmol) in CH_2Cl_2 (60 mL) was added to a stirred solution of triphenylphosphine (26.2 g, 100 mmol) in CH_2Cl_2 (200 mL) under N_2 at 0 °C. After 10 min, zinc dust (6.5 g, 100 mmol) was added, and the orange suspension was stirred for 2 h at room temperature. To this mixture was added at 0 °C piperonal (7.5 g, 50 mmol) dissolved in CH_2Cl_2 (30 mL), and the reaction mixture was stirred for 16 h at room temperature. The resulting precipitate was filtered off and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel column (petroleum ether/ethyl acetate 10:1) to provide the title compound (13.16 g, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (1H, s), 7.19 (1H, d, J = 1.2 Hz), 6.95 (1H, dd, J = 1.5, 8.1 Hz), 6.80 (1H, d, J = 8.4 Hz), 5.99 (2H, s).

*Typical Procedure for the Synthesis of **4a**−**h**. Acetic Acid 3-[5-(1-Hydroxyhept-2-ynyl)furan-2-yl]propyl Ester (**4a**).* To a solution of 1-hexyne (1.64 g, 20 mmol) and TMEDA (2.56 g, 22 mmol) in 20 mL of dry THF at −78 °C under nitrogen was added *n*-butyllithium (1.6 M, 12.5 mL, 20 mmol) via syringe over a period of 10 min. The reaction mixture was stirred for 30 min at −78 °C, warmed to room temperature, and then added dropwise to a solution of 5-(3-acetoxypropyl)-2-furaldehyde (3.92 g, 20 mmol) in 20 mL of dry THF at −78 °C. Stirring was continued at −78 °C for 1 h, after which time the cooling bath was removed and the reaction mixture was stirred for an additional 2 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum ether/ethyl acetate 5:1) yielded acetic ester **4a** (4.89 g, 88%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.33 (1H, d, J = 3.0 Hz), 5.98 (1H, d, J = 3.0 Hz), 5.40 (1H, s), 4.12 (2H, t, J = 6.6 Hz), 2.72 (2H, t, J = 7.5 Hz), 2.61 (1H, br s, −OH), 2.28 (2H, td, J = 2.1, 6.9 Hz), 2.07 (3H, s), 2.00 (2H, m), 1.48 (4H, m), 0.93 (3H, t, J = 7.3 Hz).

*Acetic acid 4-[5-(1-hydroxyhept-2-ynyl)furan-2-yl]butyl ester (**4b**)* was obtained as a brown oil (yield, 95%) according to the typical procedure for **4a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.32 (1H, d, J = 3.3 Hz), 5.95 (1H, d, J = 3.0 Hz), 5.39 (1H, s), 4.07 (2H, t, J = 6.1 Hz), 2.65 (2H, t, J = 6.7 Hz), 2.42 (1H, br s, −OH), 2.27 (2H, td, J = 2.2, 6.6 Hz), 2.05 (3H, s), 1.70 (4H, m), 1.48 (4H, m), 0.92 (3H, t, J = 7.2 Hz).

*Acetic acid 2-[5-(1-hydroxyhept-2-ynyl)furan-2-ylmethoxy]ethyl ester (**4c**)* was obtained as a brown oil (yield, 87%) according to the typical procedure for **4a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.41 (1H, d, J = 3.0 Hz), 6.30 (1H, d, J = 3.3 Hz), 5.44 (1H, s), 4.50 (2H, d, J = 1.8 Hz), 4.22 (2H, t, J = 4.8 Hz), 3.69 (2H, t, J = 4.8 Hz), 2.66 (1H, br s, −OH), 2.27 (2H, td, J = 1.9, 7.2 Hz), 2.09 (3H, s), 1.48 (4H, m), 0.92 (3H, t, J = 7.2 Hz).

4d, **4g**, and **4f** are known compounds reported in ref *6*.

*Acetic acid 4-[5-(1-hydroxy-3-phenylprop-2-ynyl)furan-2-yl]butyl ester (**4e**)* was obtained as a yellow oil (yield, 87%) according to the typical procedure for **4a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (2H, m), 7.34 (3H, m), 6.42 (1H, d, J = 3.0 Hz), 5.98 (1H, d, J = 3.0 Hz), 5.64 (1H, d, J = 6.0 Hz), 4.07 (2H, t, J = 6.4 Hz), 2.68 (2H, t, J = 6.9 Hz), 2.54 (1H, d, J = 7.2 Hz, −OH), 2.04 (3H, s), 1.68−1.75 (4H, m).

*Acetic acid 2-[5-(1-hydroxy-3-phenylprop-2-ynyl)furan-2-ylmethoxy]-ethyl ester (**4f**)* was obtained as a yellow oil (yield, 92%) according to the typical procedure for **4a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (2H, m), 7.31 (3H, m), 6.50 (1H, d, J = 3.0 Hz), 6.33 (1H, d, J = 3.0 Hz), 5.68 (1H, s), 4.52 (2H, d, J = 1.2 Hz), 4.22 (2H, t, J = 4.8 Hz), 3.71 (2H, t, J = 4.8 Hz), 2.08 (3H, s).

*Acetic acid 2-[5-(1-hydroxyhexa-2,4-diynyl)furan-2-ylmethoxy]ethyl ester (**4i**;* general procedure for **4j**−**l**) was obtained as a yellow oil in a manner similar to the synthesis of **4a** except for treatment of 1,1-dibromide **2c** with 2 equiv of *n*-butyllithium instead of 1 equiv of *n*-butyllithium (yield, 60%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.41 (d, J = 3.6 Hz, 1H), 6.30 (d, J = 3.0 Hz, 1H), 5.47 (d, J = 4.5 Hz, 1H), 4.49 (s, 2H), 4.21 (dd, J = 3.9, 5.4 Hz, 2H), 3.69 (dd, J = 4.0, 5.2 Hz, 2H), 2.90 (br s, 1H, −OH), 2.08 (s, 3H), 1.96 (d, J = 1.5 Hz, 3H).

*Acetic acid 3-[5-(3-benzo[1,3]dioxol-5-yl-1-hydroxyprop-2-ynyl)-furan-2-yl]propyl ester (**4j**)* was obtained as a yellow oil (yield, 91%) according to a procedure similar to that used for **4i**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00 (1H, dd, J = 1.8, 7.8 Hz), 6.92 (1H, d, J = 1.2 Hz), 6.76 (1H, d, J = 7.8 Hz), 6.40 (1H, d, J = 3.6 Hz), 6.00 (1H, d, J = 3.3 Hz), 5.98 (2H, s), 5.61 (1H, s), 4.12 (2H, t, J = 6.4 Hz), 2.73 (2H, t, J = 7.5 Hz), 2.62 (1H, br s, −OH), 2.06 (3H, s), 1.95−2.05 (2H, m).

*Acetic acid 4-[5-(3-benzo[1,3]dioxol-5-yl-1-hydroxyprop-2-ynyl)-furan-2-yl]butyl ester (**4k**)* was obtained as a brown oil (yield, 72%) according to a procedure similar to that used for **4i**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00 (1H, dd, J = 1.8, 8.1 Hz), 6.91 (1H, t, J = 1.5 Hz), 6.76 (1H, dd, J = 2.1, 8.1 Hz), 6.39 (1H, d, J = 2.4 Hz), 5.98 (1H, s), 5.97 (2H, s), 5.61 (1H, s), 4.07 (2H, t, J = 5.8 Hz), 2.96 (1H, br s, −OH), 2.67 (2H, t, J = 6.6 Hz), 2.04 (3H, d, J = 2.4 Hz), 1.71 (4H, m).

*Acetic acid 2-[5-(3-benzo[1,3]dioxol-5-yl-1-hydroxyprop-2-ynyl)-furan-2-ylmethoxy]ethyl ester (**4l**)* was obtained as a brown oil (yield, 57%) according to a procedure similar to that used for **4i**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01 (1H, dd, J = 1.8, 8.4 Hz), 6.91 (1H, d, J = 1.5 Hz), 6.77 (1H, d, J = 7.8 Hz), 6.47 (1H, d, J = 3.3 Hz), 6.32 (1H, d, J = 3.3 Hz), 5.98 (2H, s), 5.64 (1H, s), 4.51 (2H, d, J = 1.5 Hz), 4.22 (2H, t, J = 4.9 Hz), 3.71 (2H, t, J = 4.6 Hz), 2.96 (1H, br s, −OH), 2.08 (3H, s).

*Typical Procedure for the Synthesis of **5**. 1-[5-(3-Hydroxypropyl)-furan-2-yl]hept-2-yn-1-ol (**5a**).* Potassium carbonate (1.0 g) was added to a solution of furanmethanol (1.455 g, 5.23 mmol) in methanol (20 mL) and H_2O (2 mL) and stirred for 6 h for deacetylation. Methanol was evaporated, and the resultant mixture was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 2:1 + 1% v/v triethylamine) to give the title compound (1.074 g, 87%) as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.33 (1H, d, J = 3.0 Hz), 5.97 (1H, d, J = 3.3 Hz), 5.40 (1H, s), 3.69 (2H, t, J = 6.3 Hz), 2.73 (2H, t, J = 7.2 Hz), 2.67 (1H, br s, −OH), 2.27 (2H, td, J = 2.1, 7.2 Hz), 1.90 (2H, m), 1.77 (1H, br s, −OH), 1.48 (4H, m), 0.92 (3H, t, J = 7.2 Hz); IR υ_{max} 3347, 2958, 2935, 2874, 2231, 1665, 1558, 1432 cm^{-1}; EIMS, *m*/*z* (%) 236 (M^+, 21.4), 219 (26.5), 187 (83.2), 177 (27.9), 147 (16.6), 131 (32.4), 107 (43.8), 91 (100), 77 (51.5), 55 (49.3), 41 (66.1). HREIMS for $C_{14}H_{20}O_3$: calcd 236.1412, found 236.1423.

*1-[5-(4-Hydroxybutyl)furan-2-yl]hept-2-yn-1-ol (**5b**)* was obtained as a brown oil (yield, 98%) according to the procedure for **5a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.29 (1H, d, J = 3.0 Hz), 5.92 (1H, dd, J = 0.7, 3.1 Hz), 5.37 (1H, s), 3.60 (2H, t, J = 6.1 Hz), 2.91 (1H, br s, −OH), 2.65 (2H, t, J = 7.3 Hz), 2.27 (2H, td, J = 1.7, 6.9 Hz), 2.01 (1H, br s, OH), 1.37−1.77 (8H, m), 1.26 (1H, br s, OH), 0.93 (3H, t, J = 7.6 Hz); IR υ_{max} 3352, 2957, 2935, 2873, 2231, 1609, 1558, 1510, 1459, 1432 cm^{-1}; EIMS, *m*/*z* (%) 249 (M^+ − 1, 2.7), 190 (17.5), 177 (8.9), 161 (8.7), 146 (14.7), 131 (15.0), 107 (18.6), 91 (23.2), 81 (21.0), 55 (23.3), 41 (27.8). HREIMS for $C_{15}H_{20}O_2$ (M^+ − H_2O): calcd 232.1463, found 232.1469.

*1-[5-(2-Hydroxyethoxymethyl)furan-2-yl]hept-2-yn-1-ol (**5c**)* was obtained as a brown oil (yield, 93%) according to the procedure for **5a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.38 (1H, d, J = 3.6 Hz), 6.28 (1H, d, J = 3.0 Hz), 5.41 (1H, s), 4.48 (2H, s), 3.70 (2H, t, J = 4.3 Hz), 3.58 (2H, t, J = 4.5 Hz), 2.78 (1H, br s, −OH), 2.34 (1H, br s, −OH), 2.26 (2H, td, J = 2.0, 7.2 Hz), 1.46 (4H, m), 0.91 (3H, t, J = 7.2 Hz); IR υ_{max} 3370, 2959, 2873, 2287, 2231, 1602 cm^{-1}; EIMS, *m*/*z* (%) 252 (M^+, 20.8), 234 (35.0), 190 (60.9), 177 (100.0). HREIMS for $C_{14}H_{20}O_4$: calcd 252.1361, found 252.1355.

*4-[5-(1-Hydroxy-3-phenylprop-2-ynyl)furan-2-yl]butan-1-ol (**5e**)* was obtained as a brown oil (yield, 96%) according to the procedure for **5a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (2H, m), 7.32 (3H, m), 6.40 (1H, d, J = 3.0 Hz), 5.97 (1H, d, J = 3.3 Hz), 5.63 (1H, s), 3.64 (2H, t, J = 6.4 Hz), 3.08 (1H, br s, −OH), 2.66 (2H, t, J = 7.3 Hz), 1.57−1.78 (4H, m), 1.79 (1H, br s, −OH); IR υ_{max} 3341, 2941, 2868, 2229, 1600, 1558, 1491, 1457, 1444 cm^{-1}; EIMS, *m*/*z* (%) 270 (M^+, 3.0), 252 (41.9), 197 (25.4), 165 (20.5), 129 (27.9), 86 (100), 58 (21.1), 43 (22.4). HREIMS for $C_{17}H_{18}O_3$: calcd 270.1256, found 270.1256.

*1-[5-(2-Hydroxyethoxymethyl)furan-2-yl]-3-phenylprop-2-yn-1-ol (**5f**)* was obtained as a brown oil (yield, 97%) according to the procedure for **5a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (2H, m), 7.31 (3H, m), 6.47 (1H, d, J = 3.0 Hz), 6.30 (1H, d, J = 3.0 Hz), 5.66 (1H, s), 4.49 (2H, s), 3.71 (2H, t, J = 4.8 Hz), 3.60 (2H, m), 3.36 (1H, br s, −OH), 2.45 (1H, br s, −OH); IR υ_{max} 3363, 2933, 2869, 2231, 1733, 1653, 1599, 1558, 1491, 1444 cm^{-1}. HREIMS for $C_{14}H_{20}O_4$: calcd 252.1361, found 252.1355.

*1-[5-(2-Hydroxyethoxymethyl)furan-2-yl]hexa-2,4-diyn-1-ol (**5i**)* was obtained as a brown oil (yield, 96%) according to the procedure for **5a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.41 (1H, d, J = 3.6 Hz), 6.29 (1H, d, J = 3.0 Hz), 5.46 (1H, s), 4.49 (2H, br s), 3.72 (2H, t, J = 4.3 Hz), 3.60 (2H, t, J = 4.5 Hz), 3.26 (1H, br s, OH), 2.45 (1H, br s, OH), 1.96 (s, 3H); IR υ_{max} 3349, 2916, 2730, 2260, 1653, 1105, 1065, 1015 cm^{-1}; EIMS, *m*/*z* (%) 234 (M$^+$, 6.7), 217 (10.9), 189 (10.6), 172 (52.2), 143 (100), 115 (46.7), 91 (62.5), 77 (24.4).

*3-Benzo[1,3]dioxol-5-yl-1-[5-(3-hydroxypropyl)furan-2-yl]propynol (**5j**)* was obtained as a brown oil (yield, 98%) according to the procedure for **5a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00 (1H, dd, J = 1.5, 8.1 Hz), 6.91 (1H, d, J = 1.5 Hz), 6.76 (1H, d, J = 8.1 Hz), 6.39 (1H, d, J = 3.0 Hz), 5.99 (1H, d, J = 3.3 Hz), 5.98 (2H, s), 5.60 (1H, s), 3.70 (2H, t, J = 6.3 Hz), 2.75 (2H, t, J = 7.3 Hz), 1.92 (2H, m); IR υ_{max} 3350, 2942, 2900, 2231, 1734, 1604, 1558, 1504, 1490, 1443, 1249, 1211 cm^{-1}; EIMS, *m*/*z* (%) 300 (M$^+$, 38.7), 283 (13.0), 265 (8.9), 251 (12.0), 238 (9.7), 173 (14.0), 101 (19.3), 86 (100), 58 (28.2), 43 (31.3). HREIMS for $C_{17}H_{16}O_5$: calcd 300.0998, found 300.0999.

*4-[5-(3-Benzo[1,3]dioxol-5-yl-1-hydroxyprop-2-ynyl)furan-2-yl]butan-1-ol (**5k**)* was obtained as a brown oil (yield, 82%) according to the procedure for **5a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.99 (1H, dd, J = 1.6, 8.2 Hz), 6.91 (1H, d, J = 1.5 Hz), 6.75 (1H, d, J = 7.8 Hz), 6.38 (1H, d, J = 3.0 Hz), 5.97 (2H, s), 5.96 (1H, d, J = 4.2 Hz), 5.60 (1H, s), 3.63 (2H, t, J = 6.3 Hz), 2.65 (2H, t, J = 7.4 Hz), 1.68 (4H, m); IR υ_{max} 3387, 3206, 2949, 2901, 2867, 2685, 2228, 2195, 1856, 1604, 1557, 1504, 1490, 1480, 1441, 1412, 1248, 1212, 1194 cm^{-1}; EIMS, *m*/*z* (%) 314 (M$^+$, 21.5), 296 (100), 267 (13.4), 251 (27.0), 238 (34.4), 149 (30.6), 126 (15.6), 74 (14.2), 55 (19.1). HREIMS for $C_{18}H_{16}O_4$ (M$^+$ − H_2O): calcd 296.1049, found 296.1047.

*3-Benzo[1,3]dioxol-5-yl-1-[5-(2-hydroxyethoxymethyl)furan-2-yl]-prop-2-yn-1-ol (**5l**)* was obtained as a brown oil (yield, 91%) according to the procedure for **5a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00 (1H, dd, J = 1.5, 8.1 Hz), 6.91 (1H, d, J = 1.5 Hz), 6.75 (1H, d, J = 7.8 Hz), 6.45 (1H, d, J = 3.3 Hz), 6.31 (1H, d, J = 3.3 Hz), 5.98 (2H, s), 5.64 (1H, s), 4.50 (2H, s), 3.73 (2H, t, J = 4.2 Hz), 3.61 (2H, t, J = 4.6 Hz); IR υ_{max} 3368, 2901, 2230, 1733, 1604, 1555, 1504, 1490, 1443, 1250, 1212 cm^{-1}; EIMS, *m*/*z* (%) 316 (M$^+$, 43.5), 298 (18.2), 241 (44.8), 197 (44.0), 181 (32.2), 173 (33.4), 129 (43.5), 86 (100), 58 (28.1), 43 (35.1). HREIMS for $C_{17}H_{16}O_6$: calcd 316.0947, found 316.0942.

*Typical Procedure for the Synthesis of **6**.* 2-Hept-2-ynylidene-1,6-dioxaspiro[4.4]non-3-ene (***6a***). To a solution of furandiol (1.18 g, 5 mmol) in 20 mL of toluene was added 1.5 g of $CuSO_4$·$5H_2O$ (6 mmol). The reaction mixture was stirred at 90 °C over 6 h until the starting material disappeared according to TLC and the copper salts were filtered. The filtrate was concentrated in vacuo, and the residue was carefully chromatographed (silica gel, petroleum ether/ethyl acetate 20:1 + 0.5% triethylamine) to give the title compound (*Z*-isomer, 328 mg; *E*-isomer, 566 mg, 82%) as a yellow oil. *Z*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22 (1H, d, J = 5.7 Hz), 6.04 (1H, dd, J = 0.7, 5.5 Hz), 4.57 (1H, td, J = 0.6, 1.8 Hz), 4.23 (1H, m), 3.97 (1H, m), 2.37 (2H, td, J = 2.4, 6.9 Hz), 2.26 (2H, m), 2.04 (2H, m), 1.52 (4H, m), 0.91 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.40, 127.58, 133.25, 120.39, 95.24, 80.41, 75.79, 69.26, 35.61, 30.89, 24.50, 21.88, 19.66, 13.58; IR υ_{max} 3094, 3047, 2959, 2874, 1645, 1586, 1458, 1345, 1240 cm^{-1}; EIMS, *m*/*z* (%) 218 (M$^+$, 100), 189 (12.1), 176 (51.8), 161 (38.7), 147 (55.0), 133 (50.0), 105 (23.3), 91 (31.2), 77 (20.9), 55 (18.5). HREIMS for $C_{13}H_{12}O_3$: calcd 218.1307, found 218.1322. E-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.68 (1H, d, J = 5.7 Hz), 6.11 (1H, dd, J = 1.9, 4.9 Hz), 4.92 (1H, dd, J = 2.2, 4.3 Hz), 4.18 (1H, m), 3.97 (1H, m), 2.33 (2H, td, J = 2.4, 6.6 Hz), 1.97−2.28 (4H, m), 1.46 (4H, m), 0.92 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.06, 125.95, 133.88, 120.17, 91.82, 81.30, 76.15, 69.26, 35.52, 31.02, 24.47, 21.91, 19.31, 13.57; IR υ_{max} 2959, 2934, 1639, 1581, 1458, 1344, 1224 cm^{-1}; EIMS, *m*/*z* (%) 218 (M$^+$, 100), 189 (13.8), 176 (65.0), 161 (51.2), 147 (61.5), 133 (74.7), 105 (42.5), 91 (56.0), 77 (50.6), 55 (55.9). HREIMS for $C_{13}H_{12}O_3$: calcd 218.1307, found 218.1258.

*2-Hept-2-ynylidene-1,6-dioxa-spiro[4.5]dec-3-ene (**6b**)* was obtained as a yellow oil (yield, 69%) according to the procedure for **6a**. *Z*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.20 (1H, d, J = 5.7 Hz), 6.08 (1H, d, J = 5.7 Hz), 4.57 (1H, t, J = 2.4 Hz), 4.12 (1H, td, J = 1.0, 11.4 Hz), 3.83 (1H, dt, J = 2.3, 11.2 Hz), 2.40 (2H, m), 1.49−1.81 (10H, m), 0.94 (3H, td, J = 2.6, 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.51, 135.93, 126.76, 111.97, 95.01, 80.35, 76.01, 63.95, 32.71, 30.91, 24.58, 21.77, 19.57, 19.21, 13.58; IR υ_{max} 3093, 3049, 2955, 2873, 1773, 1645, 1586, 1467, 1441, 1232 cm^{-1}; EIMS, *m*/*z* (%) 232 (M$^+$, 100), 189 (26.9), 175 (29.6), 161 (33.6), 147 (55.5), 133 (24.8), 105 (15.5), 91 (18.6), 77 (18.1), 55 (19.3). HREIMS for $C_{15}H_{20}O_2$: calcd 232.1463, found 232.1462. *E*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.63 (1H, dd, J = 0.6, 5.7 Hz), 6.13 (1H, dd, J = 2.1, 5.7 Hz), 4.95 (1H, m), 3.99 (1H, td, J = 3.6, 11.4 Hz), 3.82 (1H, m), 2.32 (2H, td, J = 2.4, 6.9 Hz), 1.38−1.81 (10H, m), 0.92 (3H, t, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.98, 125.17, 136.49, 111.88, 91.68, 81.23, 76.30, 63.99, 31.07, 32.65, 24.47, 21.91, 19.33, 19.25, 13.54; IR υ_{max} 2958, 2874, 1639, 1583, 1220 cm^{-1}; EIMS, *m*/*z* (%) 232 (M$^+$, 100), 189 (25.5), 175 (27.8), 161 (31.2), 147 (57.0), 133 (21.8), 105 (13.6), 91 (15.6), 77 (14.9), 55 (14.0). HREIMS for $C_{15}H_{20}O_2$: calcd 232.1463, found 232.1511.

*2-Hept-2-ynylidene-1,6,9-trioxaspiro[4.5]dec-3-ene (**6c**)* was obtained as a yellow oil (yield, 62%) according to the procedure for **6a**. *Z*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.33 (1H, d, J = 5.7 Hz), 6.04 (1H, dd, J = 0.9, 5.7 Hz), 4.67 (1H, t, J = 1.9 Hz), 4.35 (1H, td, J = 3.1, 10.5 Hz), 3.69−3.88 (5H, m), 2.39 (2H, td, J = 2.4, 6.9 Hz), 1.51 (4H, m), 0.93 (3H, t, J = 7.2 Hz); IR υ_{max} 3095, 3048, 2960, 2934, 2874, 2860, 2780, 2210, 1646, 1585, 1455, 1432 cm^{-1}; EIMS, *m*/*z* (%) 234 (M$^+$, 100), 191 (17.4), 177 (35.8), 139 (28.9), 107 (16.3), 91 (19.3), 77 (18.0), 55 (11.6). HREIMS for $C_{14}H_{18}O_3$: calcd 234.1256, found 234.1259. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.68; H 7.86. *E*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.76 (1H, dd, J = 0.7, 5.5 Hz), 6.06 (1H, dd, J = 1.8, 5.7 Hz), 5.08 (1H, m), 4.26 (1H, m), 3.66−3.86 (5H, m), 2.32 (2H, td, J = 2.4, 7.2 Hz), 1.49 (4H, m), 0.91 (3H, t, J = 7.2 Hz); IR υ_{max} 2961, 2934, 2859, 1639, 1581, 1456, 1213 cm^{-1}; EIMS, *m*/*z* (%) 234 (M$^+$, 100), 191 (22.3), 177 (57.2), 139 (53.3), 105 (46.8), 91 (70.9), 77 (80.1), 55 (62.7). HREIMS for $C_{14}H_{18}O_3$: calcd 234.1256, found 234.1256.

*2-(3-Phenyl-2-butynyliden)-1,6-dioxaspiro[4,5]dec-3-ene (**6e**)* was obtained as a pale yellow oil (yield, 94%) according to the procedure for **6a**. *Z*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (2H, m), 7.30 (3H, m), 6.28 (1H, d, J = 5.7 Hz), 6.18 (1H, d, J = 5.7 Hz), 4.82 (1H, s), 4.16 (1H, m), 3.86 (1H, m), 1.62−1.85 (6H, m); IR υ_{max} 3095, 3053, 2948, 2881, 2193, 1639, 1595, 1587, 1489, 1469, 1442, 1227 cm^{-1}; EIMS, *m*/*z* (%) 252 (M$^+$, 100), 223 (23.5), 194 (18.9), 165 (22.5), 139 (19.0), 114 (19.2), 105 (18.6), 55 (15.8). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.78; H, 6.49. *E*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (2H, m), 7.28 (3H, m), 6.76 (1H, d, J = 5.7 Hz), 6.23 (1H, dd, J = 1.8, 5.7 Hz), 5.18 (1H, d, J = 1.8 Hz), 4.02 (1H, m), 3.85 (1H, m), 1.60−1.82 (6H, m); IR υ_{max} 3082, 3052, 2948, 2881, 2852, 2196, 1772, 1635, 1596, 1581, 1490, 1469, 1442 cm^{-1}; EIMS, *m*/*z* (%) 252 (M$^+$, 100), 223 (40.8), 194 (53.7), 165 (43.4), 139 (38.5), 115 (30.3), 105 (44.8), 55 (20.8). HREIMS for $C_{17}H_{16}O_2$: calcd 252.1150, found 252.1171.

*2-(3-Phenylprop-2-ynylidene)-1,6,9-trioxaspiro[4.5]dec-3-ene (**6f**:* yield, 63%) was obtained according to the procedure for **6a**. *Z*-isomer (colorless crystal): mp 100−101 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (2H, m), 7.30 (3H, m), 6.41 (1H, d, J = 6.0 Hz), 6.14 (1H, d, J = 5.7 Hz), 4.92 (1H, s), 4.39 (1H, m), 3.87 (1H, m), 3.77 (4H, m); IR υ_{max} 3102, 3050, 2964, 2914, 2863, 2195, 1636, 1594, 1583, 1488, 1451, 1440 cm^{-1}; EIMS, *m*/*z* (%) 254 (M$^+$, 42.3), 225 (8.3), 197 (100), 181 (12.4), 168 (25.5), 139 (44.4), 115 (31.4), 105 (17.1), 88 (11.7), 63 (12.4), 55 (11.9). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.66; H, 5.59. *E*-isomer (yellow oil): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (2H, m), 7.32 (3H, m), 6.90 (1H, d, J = 5.7 Hz), 6.18 (1H, dd, J = 1.3, 5.5 Hz), 5.34 (1H, d, J = 0.9 Hz), 4.31 (1H, m),

3.86 (1H, m), 3.78 (4H, m); IR υ_{max} 3096, 3053, 2972, 2935, 2881, 2855, 2196, 1635, 1596, 1579, 1490, 1452, 1443 cm^{-1}; EIMS, *m/z* (%) 254 (M^+, 46.4), 225 (5.4), 197 (100), 181 (8.4), 165 (17.4), 139 (35.0), 115 (20.3), 105 (12.1), 82 (10.2), 43 (19.3). HREIMS for $C_{16}H_{14}O_3$: calcd 254.0943, found 254.0935.

*2-Hexa-2,4-diynylidene-1,6,9-trioxaspiro[4.5]dec-3-ene (**6i**)* was obtained as a yellow oil (yield, 45%). *Z*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.36 (1H, d, J = 5.7 Hz), 6.14 (1H, d, J = 5.7 Hz), 4.71 (1H, s), 4.38 (1H, m), 3.87 (1H, m), 3.75 (4H, m), 2.01 (3H, d, J = 1.2 Hz); IR υ_{max} 3096, 3049, 2972, 2912, 2882, 2855, 2230, 2139, 1635, 1584, 1453, 1437, 1267, 1238, 1213, 1164 cm^{-1}; EIMS, *m/z* (%) 216 (M^+, 94.2), 187 (9.4), 171 (8.6), 159 (100), 131 (38.8), 115 (55.2), 102 (62.0), 83 (57.5), 77 (64.2), 50 (70.5). HREIMS for $C_{13}H_{12}O_3$: calcd 216.0781, found 216.0784. *E*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.79 (1H, d, J = 6.0 Hz), 6.22 (1H, dd, J = 1.8, 6.0 Hz), 5.11 (1H, s), 4.26 (1H, m), 3.84 (1H, m), 3.75 (4H, m), 1.99 (3H, d, J = 1.5 Hz); IR υ_{max} 3095, 3046, 2972, 2937, 2912, 2883, 2855, 2231, 2141, 1629, 1579, 1452, 1438, 1283, 1265, 1238, 1199 cm^{-1}; EIMS, *m/z* (%) 216 (M^+, 100), 187 (9.4), 171 (8.4), 159 (96.3), 131 (34.6), 115 (47.6), 102 (50.3), 82 (28.2), 77 (56.3), 50 (54.4). HREIMS for $C_{13}H_{12}O_3$: calcd 216.0781, found 216.0792.

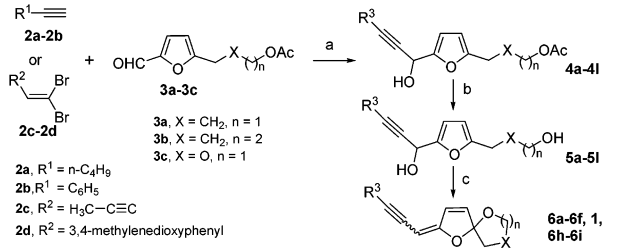
*5-[3-(1,6-Dioxaspiro[4.4]non-3-en-2-ylidene)prop-1-ynyl]benzo[1,3]-dioxole (**6j**)* was obtained as a pale yellow solid (yield, 92%). *Z*-isomer: mp 60−61 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.99 (1H, dd, J = 1.7, 8.3 Hz), 6.92 (1H, d, J = 1.5 Hz), 6.74 (1H, d, J = 8.1 Hz), 6.29 (1H, d, J = 5.4 Hz), 6.13 (1H, dd, J = 0.8, 5.6 Hz), 5.97 (2H, s), 4.79 (1H, s), 4.27 (1H, m), 4.01 (1H, m), 2.31 (2H, m), 2.08 (2H, m); IR υ_{max} 3095, 3047, 2986, 2958, 2895, 1712, 1641, 1602, 1586, 1503, 1488, 1443, 1348 cm^{-1}; HREIMS for $C_{17}H_{14}O_4$: calcd 282.0829, found 282.0908. *E*-isomer: mp 92−93 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93 (1H, dd, J = 1.6, 7.9 Hz), 6.87 (1H, d, J = 1.2 Hz), 6.76 (2H, t, J = 6.9 Hz), 6.22 (1H, dd, J = 1.6, 5.8 Hz), 5.97 (2H, s), 5.13 (1H, d, J = 1.5 Hz), 4.21 (1H, m), 4.01 (1H, m), 2.02−2.34 (4H, m); IR υ_{max} 3088, 2981, 2893, 1639, 1598, 1584, 1504, 1490, 1474, 1444, 1222 cm^{-1}; EIMS, *m/z* (%) 282 (M^+, 100), 251 (25.0), 225 (13.9), 197 (17.8), 149 (37.1), 126 (15.5), 74 (17.3). Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.35; H, 4.86.

*5-[3-(1,6-Dioxaspiro[4.5]dec-3-en-2-ylidene)prop-1-ynyl]benzo[1,3]-dioxole (**6k**:* yield, 84%). *Z*-isomer (yellow oil): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.99 (1H, dd, J = 1.8, 8.1 Hz), 6.92 (1H, d, J = 1.5 Hz), 6.76 (1H, d, J = 8.1 Hz), 6.27 (1H, d, J = 6.0 Hz), 6.17 (1H, d, J = 6.3 Hz), 5.98 (2H, s), 4.80 (1H, s), 4.15 (1H, m), 3.87 (1H, m), 1.64−1.85 (6H, m); EIMS, *m/z* (%) 296 (M^+, 43.5), 268 (16.8), 238 (26.2), 149 (26.3), 126 (13.1), 74 (16.7), 55 (16.1); IR υ_{max} 3058, 3022, 2967, 2943, 2885, 1642, 1601, 1586, 1503, 1484, 1438 cm^{-1}. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 73.07; H, 5.72. *E*-isomer (pale yellow solid): mp 63−94 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.90 (1H, dd, J = 1.5, 8.1 Hz), 6.83 (1H, d, J = 1.5 Hz), 6.72 (1H, d, J = 8.4 Hz), 6.70 (1H, dd, J = 0.8, 5.9 Hz), 6.19 (1H, dd, J = 2.0, 5.9 Hz), 5.94 (2H, s), 5.12 (1H, d, J = 1.8 Hz), 3.99 (1H, td, J = 3.0, 11.4 Hz), 3.86 (1H, m), 1.56−1.79 (6H, m); IR υ_{max} 2948, 2886, 1710, 1637, 1603, 1575, 1501, 1488, 1473, 1447, 1221 cm^{-1}. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 73.15; H, 5.57.

*2-(3-Benzo[1,3]dioxol-5-ylprop-2-ynylidene)-1,6,9-trioxaspiro[4.5]-dec-3-ene (**6l**)* was obtained as a yellow syrup (yield, 69%). *Z*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01 (1H, dd, J = 1.5, 8.1 Hz), 6.93 (1H, d, J = 1.5 Hz), 6.75 (1H, d, J = 8.1 Hz), 6.40 (1H, d, J = 5.4 Hz), 6.12 (1H, dd, J = 0.4, 5.8 Hz), 5.97 (2H, s), 4.88 (1H, s), 4.39 (1H, m), 3.72−3.91 (5H, m); IR υ_{max} 3096, 2975, 2903, 2856, 1735, 1643, 1504, 1488, 1444, 1249, 1224, 1211 cm^{-1}; EIMS, *m/z* (%) 298 (M^+, 100), 269 (6.3), 241 (88.5), 185 (11.7), 139 (17.1), 74 (12.7). Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.79; H, 5.07. HREIMS for $C_{17}H_{14}O_5$: calcd 298.0841, found 298.0821. *E*-isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01 (1H, dd, J = 1.5, 8.1 Hz), 6.93 (1H, d, J = 1.5 Hz), 6.75 (1H, d, J = 8.1 Hz), 6.39 (1H, d, J = 5.4 Hz), 6.12 (1H, dd, J = 0.4, 5.8 Hz), 5.97 (2H, s), 4.88 (1H, s), 4.38 (1H, m), 3.72−3.87 (6H, m); IR υ_{max} 3096, 3047, 2972, 2933, 2887, 2856, 1712, 1636, 1602, 1579, 1503, 1488, 1444 cm^{-1}. HREIMS for $C_{17}H_{14}O_5$: calcd 298.0841, found 298.0821.

For the syntheses of **5d**, **5g**, **5h**, **6d**, **1**, and **6h** and their physical data see previous papers (*6*, *10*).

Scheme 1. Synthesis of Tonghaosu (**1**) and Its Analogues (**6b**–**6l**)[a]



Compound	R^3	X	n
4a, 5a, 6a	$CH_3(CH_2)_3$-	CH_2	1
4b, 5b, 6b	$CH_3(CH_2)_3$-	CH_2	2
4c, 5c, 6c	$CH_3(CH_2)_3$-	O	2
4d, 5d, 6d	C_6H_5-	CH_2	1
4e, 5e, 6e	C_6H_5-	CH_2	2
4f, 5f, 6f	C_6H_5-	O	2
4g, 5g, 1	$CH_3C{\equiv}C$-	CH_2	1
4h, 5h, 6h	$CH_3C{\equiv}C$-	CH_2	2
4i, 5i, 6i	$CH_3C{\equiv}C$-	O	2
4j, 5j, 6j	3,4-methylenedioxyphenyl	CH_2	1
4k, 5k, 6k	3,4-methylenedioxyphenyl	CH_2	2
4l, 5l, 6l	3,4-methylenedioxyphenyl	O	2

[a] Reagents and conditions: (a) *n*-BuLi, TMEDA/THF, −78 °C; (b) K_2CO_3, MeOH/H_2O; (c) $CuSO_4{\cdot}5H_2O$, toluene, 90–110 °C.

Table 1. Antifeeding Activity of Tonghaosu and Its Analogues against the Third-Instar Larvae of *P. brassicae* (Test Concentration = 1000 μg/mL)

compd	antifeedancy (%)	compd	antifeedancy (%)
E-**6a**	59.60	*Z*-**1**	**88.42**
Z-**6a**	47.59	*E*-**6h**	**85.30**
E-**6b**	67.00	*Z*-**6h**	**89.93**
Z-**6b**	39.39	*E*-**6i**	46.64
E-**6c**	45.23	*Z*-**6i**	**92.26**
Z-**6c**	12.79	*E*-**6j**	51.50
E-**6d**	0	*Z*-**6j**	**93.39**
Z-**6d**	9.82	*E*-**6k**	50.10
E-**6e**	10.62	*Z*-**6k**	**96.15**
Z-**6e**	0	*E*-**6l**	77.49
E-**6f**	0	*Z*-**6l**	**93.72**
Z-**6f**	0	azadirachtin	**92.86**
E-**1**	28.22		

RESULTS AND DISCUSSION

Scheme 1 outlines the general procedure used to synthesize tonghaosu and its analogues. 1-Hexyne (**2a**) and phenylacetylene (**2b**) are commercially available, whereas **2c** and **2d** were prepared from corresponding aldehydes (but-2-ynal and piperonal) according to the general method of Corey and Fuchs (*25*). Tonghaosu and its analogues **6** were prepared in good overall yield via a three-step procedure developed by us. Thus, acetylenic lithium salt derived from compound **2** reacted with known furan-2-yl aldehyde **3** (*6*, *7*, *10*) to give alcohol **4**, which was subjected to potassium carbonate to afford precursor diol **5**. On treatment with $CuSO_4{\cdot}5H_2O$ in toluene at 90−110 °C, diol **5** was smoothly converted to spiroketal enol ether **6** as a mixture of *Z*- and *E*-isomers, favoring the *Z*-isomer. The two isomers could be separated by flash chromatography on silica gel with petroleum ether/ethyl acetate/triethylamine (20:1:0.005 v/v/v) as the eluent.

With the above prepared tonghaosu and its 22 analogues in hand, we next examined their antifeeding activities by using the conventional no-choice leaf-disk method (*22*). The results are summarized in **Tables 1** and **2**; azadirachtin was used in the control experiment. As can be seen from **Table 1**, compounds with the 1,3-diyn function group (**1**, **6h**, *Z*-**6i**) demonstrated considerable antifeeding activities, whereas com-

Table 2. Antifeedant Activity (AFC_{50}) of Active Compounds against the Third-Instar Larvae of *P. brassicae*

compd	slope (±SE)	AFC_{50}[a] (μg/mL)	95% CL
Z-**1**	2.2255 (±0.05443)	654.78 a	226.12–556.63
Z-**6h**	1.8601 (±0.08987)	204.77 a	126.77–330.79
Z-**6i**	1.9517 (±0.08854)	376.47 a	224.59–631.06
Z-**6j**	2.2026 (±0.1839)	323.79 a	207.44–505.38
Z-**6k**	2.0004 (±0.1861)	186.61 a	116.77–298.23
Z-**6l**	1.9622 (±0.1272)	413.46 a	242.03–706.31
azadirachtin	0.7008 (±0.05908)	7.15 b	1.35–37.77

[a] Values within a column followed by the same letter were not significantly different.

pounds **6a**−**f**, which contain only one triple bond, have very low or no activity at all. However, in contrast to the lack of activity of compounds **6d**−**f**, *Z*-isomers of **6j**−**l**, which have a 3,4-methylenedioxy substituent on the benzene ring, showed good antifeeding activities comparable to those of compounds **1**, **6h**, and *Z*-**6i**. More interestingly, the *Z*-isomers of **6i**−**k** showed much higher activities than their corresponding *E*-isomers, which deserves further investigation. In addition, the modification of the B ring of tonghaosu had little effect on the activity. All of these results suggest that besides the important spiroketal enol ether system, the side chain of tonghaosu analogues may also play a role in their biological activities. However, the results listed in **Table 2** indicate there were no significant differences among these prepared active compounds, which were all less effective than azadirachtin.

In conclusion, >20 tonghaosu analogues were prepared and characterized. Their antifeeding activity was investigated, and compounds containing a diyn or 3,4-methylenedioxyphenyl acetylene function group demonstrated appreciable antifeeding activities against the third-instar larvae of *P. brassicae*. A further study on the insecticidal activities of these synthetic compounds against common cutworm (*Spodoptera litura*), housefly (*Musca domestica*), and mosquito (*Culex quinquefasciatus*) is currently underway.

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