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Article

Synthesis and Biological Activity of Tonghaosu Analogs Containing Phenoxy-phenyl Moiety†

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A new series of phenoxy-phenyl moieties containing tonghaosu analogs with varied B-ring **9** were synthesized and characterized by spectral studies. Their insect antifeedant activity against *Pieris brassicae* and insecticidal activity against *Culex quinquefasciatus* were investigated. Compound **9e** exhibited excellent antifeeding activity.

Keywords spiroketal, antifeedant, insecticidal activity, *Pieris brassicae*, *Culex quinquefasciatus*

Introduction

2-(2',4'-Hexadiynylidene)-1,6-dioxaspiro[4,4]-non-3-ene (**1**) is a natural product with unique [4,4]-type spiroketal enol ether structure, which was firstly isolated from *Matricaria matricarioides*,[1] and was reported to exhibit antifeedant activity toward silkworm.[2] We isolated the same compound from a Chinese common vegetable tonghao (*Chrysanthemum segetum* L.) and named it as tonghaosu (**1**).[3,4] We also isolated its B-ring homolog **2** from *Chrysanthemum indicum* var. *aromaticum* as main antifeeding principles by bioassay-guided fractionation.[5] The successful achievement in synthesis of tonghaosu and its analogs[4,6-8] prompted us to explore new types of spiroketal compounds in the search for highly effective insecticide against insect pests. Phenoxy-benzyl structure was often found in pyrethroid insecticide, and we wondered if the introduction of phenoxy-benzyl group into tonghaosu would lead to tonghaosu analogs with better biological activities. Herein we would like to report the synthesis and biological activities of phenoxy-phenyl moiety containing tonghaosu analogs **9** (Figure 1).

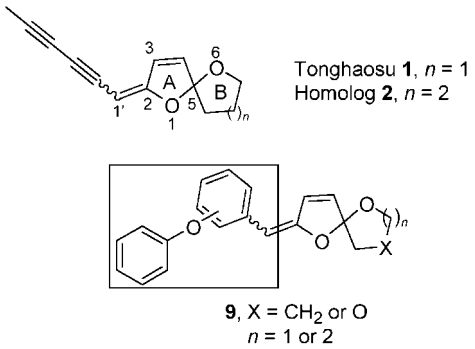

Figure 1 Tonghaosu (**1**), B-ring-homolog (**2**) and their analogs (**9**).

Results and discussion

Chemistry

Scheme 1 outlines the general procedure used to synthesize tonghaosu's analogs. Ullmann reaction[9] between bromobenzene and cresol (**3a—3c**) afforded phenoxytoluene (**4a—4c**). The latter were converted to phenoxybenzaldehyde (**6a—6c**) by bromination with NBS[10] and subsequent Sommelet reaction.[11] Spiroketals **9a—9i** were then successfully synthesized in good yield through the known two-step procedure.[4-8] Thus furan **7**[4-8] was treated with BuLi in dry THF at −78 ℃ and then coupled with aldehyde **6** at room temperature to furnish furandiol **8**. Cyclization of **8** was effected with $CuSO_4$•$5H_2O$ in toluene to yield final products **9**. In the cases of **8a—8c** where the phenoxyl group is adjacent to the other substituent on the benzene ring, compounds **9a—9c** were obtained respectively as a mixture of *Z*- and *E*-isomer with *Z*-isomer as the predominant product, while **8d—8i** afforded **9d—9i**, respectively, as only *Z*-isomer. The stereochemistry of *Z*- and *E*-**9a** was confirmed by NOESY spectra (Figure 2) and that of **9b** and **9c** was assigned by analogy with ^{1}H NMR data of **9a**.

Biological activities

Antifeedant activity: The antifeeding activity of

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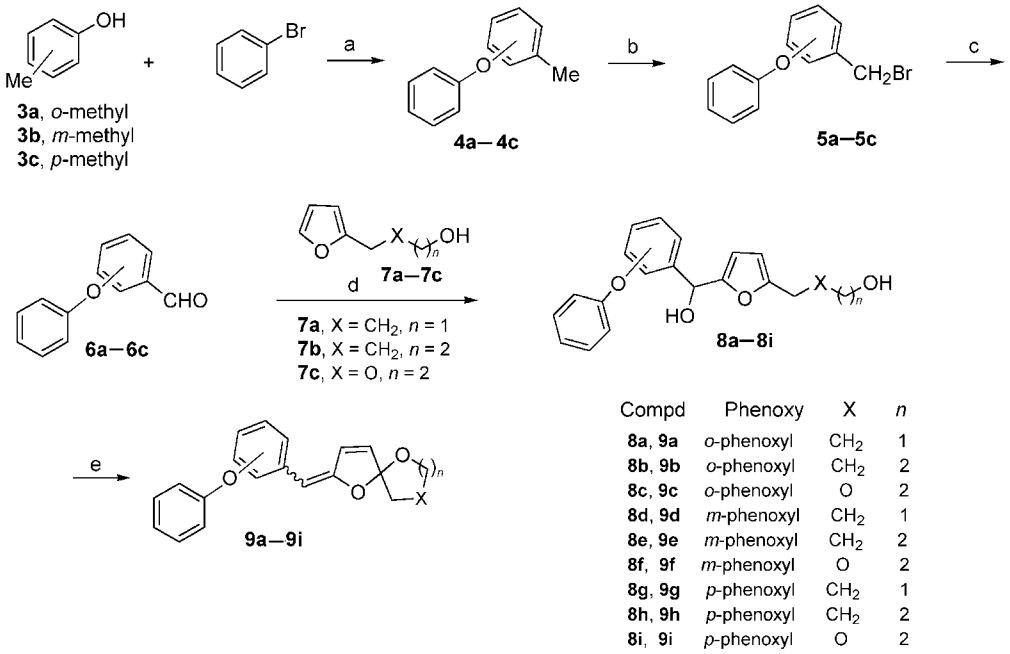
Scheme 1 Synthesis of tonghaosu analogs **9**



Compd	Phenoxy	X	*n*
8a, **9a**	*o*-phenoxyl	CH_2	1
8b, **9b**	*o*-phenoxyl	CH_2	2
8c, **9c**	*o*-phenoxyl	O	2
8d, **9d**	*m*-phenoxyl	CH_2	1
8e, **9e**	*m*-phenoxyl	CH_2	2
8f, **9f**	*m*-phenoxyl	O	2
8g, **9g**	*p*-phenoxyl	CH_2	1
8h, **9h**	*p*-phenoxyl	CH_2	2
8i, **9i**	*p*-phenoxyl	O	2

Reagents and conditions: (a) Cu, KOH, 210—220 ℃, reflux; (b) NBS, 2,2'-azo-bis-*iso*-butyronitrile, CCl_4, reflux; (c) hexamethylenetetramine, 50% acetic acid glacial, reflux, conc. HCl; (d) *n*-BuLi, TMEDA/THF, −78 ℃; (e) $CuSO_4$•$5H_2O$, toluene, 90 ℃.

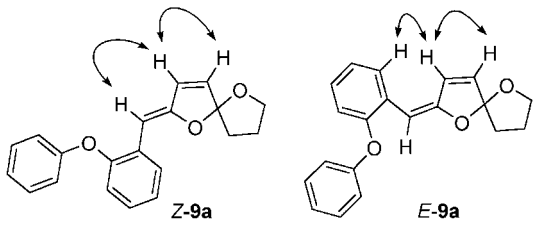


Figure 2 Selected NOESY correlation of compounds *Z*- and *E*-**9a**.

these new tonghaosu analogs **9** was evaluated against 3-rd instar larvae of *P. brassicae* with the no-choice leaf disk method,[5] and *Z*-**1** and azadirachtin were used as controls. As shown in Table 1, most of these compounds showed little activity and there is no much difference between the activity of *Z*-isomer and that of *E*-isomer (*e.g.* *E*-**9a** vs. *Z*-**9a** and *E*-**9b** vs. *Z*-**9b**). However, compound *Z*-**9e** exhibited excellent antifeeding activity, even better than tonghaosu *Z*-**1**. In addition, compound **9h** possessed moderate insect antifeedancy. Although we do not know at present why these two compounds have better activities than others, it seems phenoxy at *ortho* position does not benefit antifeeding activity.

Toxicity to mosquito: The toxicity of compounds **9a**—**9i** against 4-th instar larvae of *C. quinquefasciatus* was also investigated, and results are summarized in Table 2. As can be seen, compounds **9a**—**9i** had weak or no lethal effect on mosquito larvae. In contrast, their parent compounds, *Z*-**1** and *E*-**1** showed very good insecticidal activities comparable to azadirachtin.

Conclusion

In summary, we have synthesized a new type of tonghaosu analogs containing phenoxy phenyl moiety. The introduction of phenoxy phenyl moiety to tonghaosu skeleton substantially increased their stability, however, for most of these analogs their antifeeding and

Table 1 Antifeeding activity of tonghaosu analogs against the third instar larvae of *P. brassicae* (test concentration＝1000 μg/mL)

Comp.	Antifeedancy/%	Comp.	Antifeedancy/%
E-**9a**	19.69	*Z*-**9e**	95.75
Z-**9a**	19.48	*Z*-**9f**	13.65
E-**9b**	10.55	*Z*-**9g**	16.44
Z-**9b**	10.74	*Z*-**9h**	71.30
E-**9c**	28.78	*Z*-**9i**	23.20
Z-**9c**	20.95	*Z*-**1**	88.42
Z-**9d**	41.67	Azadirachtin	92.86

Table 2 Insecticidal activity of tonghaosu analogs on the fourth instar larvae of *C. quinquefasciatus* Say (test concentration＝40 $\times 10^{-6}$)

Comp.	Mortality/% (48 h)	Comp.	Mortality/% (48 h)
E-**9a**	17.86	*E*-**9f**	40.74
Z-**9a**	0	*Z*-**9f**	35.71
E-**9b**	19.23	*Z*-**9g**	0
Z-**9b**	14.29	*Z*-**9h**	0
E-**9c**	3.85	*Z*-**9i**	7.14
Z-**9d**	15.38	*E*-**1**	94.23
Z-**9e**	40.74	*Z*-**1**	96.43
Azadirachtin	**91.07**		

insecticidal activities decreased dramatically. Nevertheless, compound 9e showed excellent antifeeding activity against 3-rd instar larvae of *P. brassicae*, even better than its parent compound, tonghaosu.

Experimental

Melting points were uncorrected. IR spectra were recorded on Perkin-Elmer 983 or Shimadzu IR-440 spectrometers. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ or CD_3COCD_3 on an AMX-300, a DPX-300 or a DRX-400 spectrometer with TMS as the internal standard. Mass spectra were taken on a Mariner, an HP5973N or an HP5989A instrument. Flash column chromatography was performed on silica gel H (10—40 μm) with petroleum ether-ethyl acetate system as eluent.

Biological activity assays: Tonghaosu analogs **9** were tested for antifeeding activity against third-instar larvae of *P. brassicae* by the conventional leaf-disk method described in the previous report.[5]

Mosquito larvicidal bioassay: The mosquito larvicidal effect of tonghaosu analogs was determined in a similar manner as described by Bandara *et al.*[12] and Park *et al.*[13] The test compounds (azadirachtin and tonghaosu as standard controls) were dissolved in acetone at concentration of 4000 μg/mL. Each in acetone was suspended in distilled water with Triton X-100 (5 mL/L) to obtain a concentration of 40×10^{-6}. Batches of 10 laboratory reared fourth instar larvae of *Culex quinquefasciatus* Say were separately put into paper cups (100 mL) containing each test solution (40 mL) using a pipette. Controls received acetone-Triton X-100 solution. All treatments were replicated three times.

The experiment was performed under laboratory conditions at (27±1) ℃ and 40%—60% relative humidity. Brewer's yeast was supplied during the test periods for larval feeding. Larvicidal activity was evaluated 48 h after treatment. The larvae were considered dead if appendage did not move when prodded with a wooden dowel. And the cumulative mortality data were corrected by Abbott's (1925) formula.[14]

***o*-Phenoxytoluene** (**4a**): Bromobenzene (15.7 g, 100 mmol) was added to a well-stirred mixture of *o*-cresol (**3a**, 16.2 g, 150 mmol), copper dust (1.5 g), CuI (1.5 g) and potassium hydroxide (9.8 g, 175 mmol) under nitrogen. The mixture was heated at 220 ℃ for 6 h. The cooled mixture was washed with 10% NaOH and ether, and then filtered. The aqueous phase was extracted with ether, washed with saturated brine, dried over Na_2SO_4, and evaporated. Chromatography of the residue with petroleum ether as eluent yielded 12.35 g of **4a** as a pale oil (64%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.23—7.35 (m, 3H), 6.88—7.19 (m, 6H), 2.24 (s, 3H).

1-Bromomethyl-2-phenoxy-benzene (**5a**): A solution of **4a** (14.7 g, 79.89 mmol), NBS (17.8 g, 100 mmol), 2,2'-azo-bis-iso-butyronitrile (0.4 g) in CCl_4 was heated at reflux for 3 h (internal temperature 81—82 ℃). The cooled solution was filtered, and the filtrate was concentrated *in vacuo* and purified by flash chromatography to give the title compound (14.145 g, matography to give the title compound (14.145 g, 67%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.44 (dt, J=1.2, 7.8 Hz, 1H), 7.35 (m, 2H), 7.24 (m, 1H), 7.01—7.15 (m, 4H), 6.83 (d, J=8.1 Hz, 1H), 4.60 (d, J=0.6 Hz, 2H).

***o*-Phenoxybenzaldehyde** (**6a**): A solution of **5a** (14.115 g, 53.67 mmol), hexamethylenetetramine (15.03 g, 107.36 mmol) in 50% (*V*/*V*) acetic acid/water (60 mL) was heated at reflux for 1 h (internal temperature 104—108 ℃). Concentrated HCl (20 mL) was added to the cooled solution, and the reaction mixture was reheated at reflux for 1 h. The cooled solution was extracted with ether, and the organic phase was washed with water, 5% sodium carbonate aqueous solution and water successively, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate=20/1 *V*/*V*) afforded the title compound (6.129 g, 58%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 10.53 (s, 1H), 7.94 (dd, J=1.8, 7.8 Hz, 1H), 7.51 (m, 1H), 7.40 (m, 2H), 7.19 (m, 2H), 7.07 (m, 2H), 6.90 (d, J=7.8 Hz, 1H).

***m*-Phenoxytoluene** (**4b**): It was obtained from *m*-cresol (**3b**) and bromobenzene as a colorless oil in a manner similar to the synthesis of **4a**, 70% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.35 (m, 2H), 7.23 (t, J=7.8 Hz, 1H), 7.11 (m, 1H), 7.02 (m, 2H), 6.93 (d, J=7.5 Hz, 1H), 6.83 (m, 2H), 2.35 (s, 3H); EIMS *m*/*z* (%): 184 (M^+, 100), 169 (12.6), 155 (17.4), 141 (23.2), 91 (16.9), 77 (12.3).

1-Bromomethyl-3-phenoxy-benzene (**5b**): It was obtained from **4b** as a pale oil in a manner similar to the synthesis of **5a**, 88% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.26—7.38 (m, 3H), 7.13 (m, 2H), 7.03 (m, 3H), 6.92 (dt, J=1.2, 8.1 Hz, 1H), 4.44 (s, 2H); EIMS *m*/*z* (%): 262 (M^+, 25.6), 183 (100), 168 (9.0), 153 (11.9), 89 (19.1), 77 (17.0).

***m*-Phenoxybenzaldehyde** (**6b**): It was obtained from **5b** as a pale yellow oil in a manner similar to the synthesis of **6a**, 91% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.97 (s, 1H), 7.62 (d, J=7.5 Hz, 1H), 7.51 (t, J=7.7 Hz, 1H), 7.47 (m, 1H), 7.39 (t, J = 7.9 Hz, 2H), 7.30 (m, 1H), 7.18 (t, J=7.5 Hz, 2H), 6.90 (dd, J=1.0, 8.1 Hz, 1H); IR ν_{max}: 3382, 3065, 2854, 2833, 2732, 1702, 1584, 1490, 1450, 1389, 1316, 1251, 1211 cm^{-1}.

***p*-Phenoxytoluene** (**4c**): It was obtained from *p*-cresol (**3c**) and bromobenzene as a colorless oil in a manner similar to the synthesis of **4a**, 63% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.27—7.34 (m, 2H), 7.13 (d, J=8.7 Hz, 2H), 7.06 (m, 1H), 6.89—7.03 (m, 4H), 2.33 (s, 3H).

1-Bromomethyl-4-phenoxy-benzene (**5c**): It was obtained from **4c** as a colorless oil in a manner similar to the synthesis of **5a**, 96% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.35 (m, 4H), 7.13 (m, 1H), 7.02 (m, 2H), 6.95 (td, J=1.8, 8.7 Hz, 2H), 4.50 (s, 2H).

***p*-Phenoxybenzaldehyde** (**6c**): It was obtained from **5c** as a colorless oil in a manner similar to the synthesis of **6a**, 90% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.92 (s, 1H), 7.84 (dt, J=2.4, 9.3 Hz, 2H), 7.42 (m, 2H), 7.23 (m,

1H), 7.07 (m, 4H).

Typical procedure for compound 8, **3-{5-[Hydroxy-(2-phenoxy-phenyl)-methyl]-furan-2-yl}-propan-1-ol** (**8a**): It was A solution of *n*-butyllithium (1.6 mol/L, 12.5 mL, 20 mmol) was added slowly to a mixture of 3-(2'-furyl)-propan-1-ol (**7a**, 1.26 g, 10 mmol) and TMEDA (2.56 g, 22 mmol) in 20 mL of dry THF at −78 ℃ under nitrogen. After stirred at room temperature for 2 h, the mixture was cooled again to −78 ℃. To it was added dropwise a solution of *o*-phenoxybenzaldehyde (**6a**, 1.98 g, 10 mmol) in 20 mL of dry THF. After the addition was completed, the reaction mixture was stirred at −78 ℃ for 1 h, and then was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 mL×3). The combined organic layer was 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 = 2/1 containing 0.5% triethylamine (*V*/*V*)] yielded the furandiol (2.426 g, 75 %) as a pale yellow solid. m.p. 75—76 ℃. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.77 (dd, *J*=1.5, 7.2 Hz, 1H), 7.18—7.35 (m, 4H), 7.07 (m, 1H), 6.88 (dd, *J*=0.7, 8.5 Hz, 2H), 6.84 (dd, *J*=1.0, 7.9 Hz, 1H), 6.08 (d, *J*=4.8 Hz, 1H), 5.89 (s, 2H), 4.86 (d, *J*=5.4 Hz, 1H, OH), 3.54 (t, *J*=4.6 Hz, 2H), 3.52 (brs, 1H, OH), 2.60 (t, *J*=7.6 Hz, 2H), 1.74 (m, 2H); IR ν_{max}: 3363, 2950, 2937, 2905, 2854, 1606, 1583, 1560, 1487, 1452, 1423, 1235 cm^{-1}; EIMS *m*/*z* (%): 324 (M^+, 65.0), 306 (20.7), 265 (43.4), 247 (25.2), 197 (100), 181 (72.4), 121 (23.2), 77 (23.7). Anal. calcd for $C_{20}H_{20}O_4$: C 74.06, H 6.21; found C 73.84, H 6.02.

4-{5-[Hydroxy-(2-phenoxy-phenyl)-methyl]-furan-2-yl}-butan-1-ol (**8b**): It was prepared according to the typical procedure for **8a**. Treatment of 4-(2'-furyl)-butan-1-ol (**7b**, 1.40 g, 10 mmol) with *o*-phenoxybenzaldehyde (**6a**, 1.98 g, 10 mmol) provided the title compound (2.473 g, 73%) as pale yellow needles. m.p. 67—68 ℃. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.77 (dd, *J*=1.9, 7.6 Hz, 1H), 7.18—7.35 (m, 4H), 7.07 (t, *J*=7.3 Hz, 1H), 6.88 (dd, *J*=0.6, 8.1 Hz, 2H), 6.84 (dd, *J*=1.3, 8.2 Hz, 1H), 6.08 (d, *J*=4.8 Hz, 1H), 5.89 (d, *J*=6.9 Hz, 1H), 5.89 (s, 1H), 4.87 (m, 1H, OH), 3.54 (t, *J*=5.7 Hz, 2H), 3.44 (m, 1H, OH), 2.53 (t, *J*=7.6 Hz, 2H), 1.56 (m, 4H). IR ν_{max}: 3344, 3185, 2941, 1583, 1522, 1486, 1452, 1234 cm^{-1}. EIMS *m*/*z* (%): 338 (M^+, 21.8), 320 (43.2), 265 (46.0), 247 (27.3), 197 (100), 181 (80.3), 121 (27.5), 77 (24.2). Anal. calcd for $C_{21}H_{22}O_4$: C 74.54, H 6.55, found C 74.35, H 6.43.

2-{5-[Hydroxy-(2-phenoxy-phenyl)-methyl]-furan-2-ylmethoxy}-ethanol (**8c**): It was prepared according to the typical procedure for **8a**. Treatment of 2-(furan-2-ylmethoxy)-ethanol (**7c**, 1.42 g, 10 mmol) with *o*-phenoxybenzaldehyde (**6a**, 1.98 g, 10 mmol) provided the title compound (2.851 g, 84%) as a brown oil. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.77 (dd, *J*=1.5, 7.8 Hz, 1H), 7.31 (m, 3H), 7.21 (td, *J*=1.4, 7.5 Hz, 1H), 7.08 (t, *J*=7.2 Hz, 1H), 6.90 (m, 2H), 6.84 (dd, *J*=1.2, 8.1 Hz, 1H), 6.23 (d, *J*=3.0 Hz, 1H), 6.12 (d, *J*=4.8 Hz, 1H), 6.00 (d, *J*=3.0 Hz, 1H), 5.01 (d, *J*=4.8 Hz, 1H, OH), 4.35 (s, 2H), 3.59 (t, *J*=3.4 Hz, 2H), 3.58 (brs, 1H, OH), 3.46 (t, *J*=4.3 Hz, 2H). IR ν_{max}: 3385, 3067, 3040, 2930, 2869, 1706, 1584, 1485, 1454, 1234 cm^{-1}; EIMS *m*/*z* (%): 340 (M^+, 5.3), 322 (6.2), 278 (88.1), 265 (20.4), 247 (16.2), 197 (100), 181 (40.2), 115 (11.7), 77 (15.5). Anal. calcd for $C_{20}H_{20}O_5$: C 70.57, H 5.92, found C 70.25, H 5.97.

3-{5-[Hydroxy-(3-phenoxy-phenyl)-methyl]-furan-2-yl}-propan-1-ol (**8d**): It was prepared according to the typical procedure for **8a**. Treatment of 3-(2'-furyl)-propan-1-ol (**7a**, 1.26 g, 10 mmol) with *m*-phenoxybenzaldehyde (1.98 g, 10 mmol) provided the title compound (2.227 g, 69%) as a yellow oil. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.32—7.40 (m, 3H), 7.09—7.21 (m, 3H), 7.01 (m, 2H), 6.91 (qd, *J*=1.2, 7.8 Hz, 1H), 6.00 (d, *J*=3.0 Hz, 1H), 5.95 (dd, *J*=0.9, 2.4 Hz, 1H), 5.74 (d, *J*=4.2 Hz, 1H), 4.97 (brs, 1H, OH), 3.56 (t, *J*=6.1 Hz, 2H), 3.54 (brs, 1H, OH), 2.63 (t, *J*=7.5 Hz, 2H), 1.77 (m, 2H); IR ν_{max}: 3358, 2945, 1656, 1585, 1514, 1489, 1445, 1246, 1213 cm^{-1}; EIMS *m*/*z* (%): 324 (M^+, 21.0), 306 (80.0), 289 (21.9), 275 (100), 265 (29.3), 197 (44.6), 137 (21.3), 115 (25.2), 77 (23.5). HRMS calcd for $C_{20}H_{20}O_4$ 324.1362; found 324.1333.

4-{5-[Hydroxy-(3-phenoxy-phenyl)-methyl]-furan-2-yl}-butan-1-ol (**8e**): It was prepared according to the typical procedure for **8a**. Treatment of 4-(2'-furyl)-butan-1-ol (**7b**, 1.40 g, 10 mmol) with *m*-phenoxybenzaldehyde (1.98 g, 10 mmol) provided the title compound (2.68 g, 79%) as a yellow oil. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.31—7.40 (m, 3H), 7.20 (m, 2H), 7.12 (m, 1H), 7.01 (m, 2H), 6.91 (qd, *J*=1.2, 8.1 Hz, 1H), 6.02 (d, *J*=3.3 Hz, 1H), 5.95 (d, *J*=2.7 Hz, 1H), 5.76 (s, 1H), 5.07 (brs, 1H, OH), 3.64 (brs, 1H, OH), 3.55 (t, *J*=6.3 Hz, 2H), 2.58 (t, *J*=7.5 Hz, 2H), 1.60 (m, 4H); IR ν_{max}: 3365, 2941, 2868, 1658, 1585, 1514, 1489, 1444, 1246, 1212 cm^{-1}; EIMS *m*/*z* (%): 320 (100), 302 (7.6), 275 (40.3), 265 (28.4), 249 (31.4), 197 (39.8), 141 (16.9), 115 (18.1), 77 (16.9). HRMS calcd for $C_{21}H_{22}O_4$ 338.1519, found 338.1479. Anal. calcd for $C_{21}H_{22}O_4$: C 74.54, H 6.55; found C 74.16, H 6.50.

2-{5-[Hydroxy-(3-phenoxy-phenyl)-methyl]-furan-2-ylmethoxy}-ethanol (**8f**): It was prepared according to the typical procedure for **8a**. Treatment of 2-(furan-2-ylmethoxy)-ethanol (**7c**, 1.42 g, 10 mmol) with *m*-phenoxybenzaldehyde (1.98 g, 10 mmol) provided the title compound (2.131 g, 63%) as a pale brown oil. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.33—7.41 (m, 3H), 7.10—7.23 (m, 3H), 7.01 (m, 2H), 6.92 (ddd, *J*=1.2, 2.7, 8.1 Hz, 1H), 6.28 (d, *J*=3.0 Hz, 1H), 6.10 (d, *J*=3.3 Hz, 1H), 5.78 (d, *J*=3.9 Hz, 1H), 5.10 (d, *J*=4.8 Hz, 1H, OH), 4.39 (s, 2H), 3.61 (t, *J*=3.9 Hz, 2H), 3.60 (brs, 1H, OH), 3.49 (t, *J*=4.5 Hz, 2H); IR ν_{max}: 3387, 2929, 2868, 1705, 1585, 1489, 1445, 1247, 1213 cm^{-1}. EIMS *m*/*z* (%): 340 (M^+, 7.23), 322 (100), 278 (44.5), 265 (60.6), 197 (100), 141 (36.6), 115 (35.3), 77 (32.4). HRMS calcd for $C_{20}H_{20}O_5$ 340.1311, found 340.1310.

Anal. calcd for $C_{20}H_{20}O_5$: C 70.57, H 5.92, found C 70.21, H 5.90.

3-{5-[Hydroxy-(4-phenoxy-phenyl)-methyl]-furan-2-yl}-propan-1-ol (8g): It was prepared according to the typical procedure for **8a**. Treatment of 3-(2'-furyl)-propan-1-ol (**7a**, 1.26 g, 10 mmol) with *p*-phenoxybenzaldehyde (1.98 g, 10 mmol) provided the title compound (1.927 g, 59%) as a yellow oil. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.46 (m, 2H), 7.37 (m, 2H), 7.12 (m, 1H), 6.99 (m, 4H), 6.00 (d, J=3.0 Hz, 1H), 5.95 (d, J=3.0 Hz, 1H), 5.74 (d, J=4.2 Hz, 1H), 4.93 (d, J=4.8 Hz, 1H, OH), 3.60 (m, 2H), 3.56 (m, 1H, OH), 2.65 (t, J=7.5 Hz, 2H), 1.79 (m, 2H); IR ν_{max}: 3334, 3242, 3069, 2957, 2936, 2918, 2894, 1611, 1596, 1586, 1558, 1509, 1489, 1472, 1454, 1426, 1250 cm^{-1}. HRMS calcd for $C_{20}H_{20}O_4$ 324.1362; found 324.1379. EIMS *m*/*z* (%): 324 (M^+, 27.6), 306 (100), 275 (36.6), 265 (16.2), 197 (36.3), 129 (26.5), 115 (29.0), 77 (39.1). Anal. calcd for $C_{20}H_{20}O_4$: C 74.06, H 6.21, found C 73.60, H 6.15.

4-{5-[Hydroxy-(4-phenoxy-phenyl)-methyl]-furan-2-yl}-butan-1-ol (8h): It was prepared according to the typical procedure for **8a**. Treatment of 4-(2'-furyl)-butan-1-ol (**7b**, 1.40 g, 10 mmol) and *p*-phenoxybenzaldehyde (1.98 g, 10 mmol) provided the title compound (1.992 g, 59%) as white crystal needles. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.46 (m, 2H), 7.39 (m, 2H), 7.13 (m, 1H), 7.00 (m, 4H), 6.01 (d, J=3.3 Hz, 1H), 5.96 (d, J=3.3 Hz, 1H), 5.75 (d, J=4.5 Hz, 1H), 4.92 (d, J=4.5 Hz, 1H, OH), 3.54 (m, 2H), 3.50 (m, 1H, OH), 2.59 (t, J=7.3 Hz, 2H), 1.49—1.72 (m, 4H). IR ν_{max}: 3358, 3267, 2943, 2862, 1588, 1558, 1508, 1489, 1457, 1237 cm^{-1}. EIMS *m*/*z* (%): 338 (M^+, 2.0), 320 (100), 275 (17.2), 262 (33.3), 197 (17.8), 115 (27.6), 77 (31.9). Anal. calcd for $C_{21}H_{22}O_4$: C 74.54, H 6.55; found C 74.39, H 6.25.

2-{5-[Hydroxy-(4-phenoxy-phenyl)-methyl]-furan-2-ylmethoxy}-ethanol (8i): It was prepared according to the typical procedure for **8a**. Treatment of 2-(furan-2-ylmethoxy)-ethanol (**7c**, 1.42 g, 10 mmol) and *p*-phenoxybenzaldehyde (1.98 g, 10 mmol) provided the title compound (2.667 g, 78%) as a yellow oil. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ: 7.47 (m, 2H), 7.35—7.42 (m, 2H), 7.12 (m, 1H), 6.99 (m, 4H), 6.29 (d, J=3.3 Hz, 1H), 6.11 (d, J=2.7 Hz, 1H), 5.79 (d, J=3.3 Hz, 1H), 5.05 (d, J=4.5 Hz, 1H, OH), 4.40 (s, 2H), 3.61 (t, J=4.6 Hz, 2H), 3.60 (brs, 1H, OH), 3.49 (t, J=4.6 Hz, 2H); IR ν_{max}: 3379, 2931, 2868, 1611, 1590, 1507, 1490, 1457, 1419, 1238 cm^{-1}. EIMS *m*/*z* (%): 340 (M^+, 34.9), 323 (32.1), 278 (30.8), 265 (59.6), 197 (100), 141 (20.5), 115 (24.8), 77 (33.5). HRMS calcd for $C_{20}H_{20}O_5$ 340.1311, found 340.1294.

Typical procedure for compound 9. **2-(2-phenoxy-benzylidene)-1,6-dioxa-spiro[4,4]non-3-ene (9a)**: To a solution of furandiol **8a** (1.793 g, 5.53 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 ℃ over 6 h, and the starting material was consumed as indicated by TLC, the copper salt was then filtrated. The filtrate was concentrated *in vacuo*, the residue was carefully chromatographed (silica gel, petroleum ether/ethyl acetate (20/1) + 0.5% triethylamine) to give the title compound (*Z*-isomer, white solid, 1.051 g; *E*-isomer, white solid, 227 mg, 76%). *Z*-isomer, m.p. 123—124 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.23 (d, J=4.5 Hz, 1H), 7.29 (m, 2H), 7.07 (m, 3H), 6.89 (m, 3H), 6.32 (dd, J=2.1, 5.4 Hz, 1H), 6.03 (d, J=5.4 Hz, 1H), 5.74 (s, 1H), 4.26 (m, 1H), 4.02 (m, 1H), 2.03—2.40 (m, 4H); IR ν_{max}: 3073, 2888, 1654, 1596, 1585, 1564, 1492, 1475, 1450, 1228 cm^{-1}; EIMS *m*/*z* (%): 306 (M^+, 100), 278 (14.2), 219 (17.0), 181 (89.9), 115 (19.4), 77 (15.7). HRMS calcd for $C_{20}H_{18}O_3$ 306.1256, found 306.1258. *E*-isomer, m.p. 90—91 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.36 (dd, J=2.1, 7.8 Hz, 1H), 7.28 (m, 2H), 7.01—7.18 (m, 3H), 6.90 (m, 3H), 6.78 (dd, J=0.9, 5.7 Hz, 1H), 6.17 (dd, J=1.8, 5.7 Hz, 1H), 6.11 (s, 1H), 4.18 (m, 1H), 3.97 (m, 1H), 2.22 (m, 2H), 2.05 (m, 2H); IR ν_{max}: 3067, 2995, 2883, 1644, 1585, 1567, 1492, 1478, 1449, 1234 cm^{-1}; EIMS *m*/*z* (%): 306 (M^+, 100), 278 (14.7), 219 (17.8), 181 (95.1), 115 (20.6), 77 (17.5). HRMS calcd for $C_{20}H_{18}O_3$ 306.1256, found 306.1257.

2-(2-Phenoxy-benzylidene)-1,6-dioxa-spiro[4,5]-dec-3-ene (9b): Following the typical procedure for **9a**, treatment of furandiol **8b** (1.873 g, 5.54 mmol) with $CuSO_4$•$5H_2O$ afforded the title compound (*Z*-isomer, white crystals, 1.105 g; *E*-isomer, yellow oil, 124 mg, 69%). *Z*-isomer, m.p. 109—110 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.30 (dd, J=1.8, 8.1 Hz, 1H), 7.30 (m, 2H), 7.01—7.21 (m, 3H), 6.91 (m, 3H), 6.29 (d, J=6.0 Hz, 1H), 6.07 (dd, J=0.9, 5.7 Hz, 1H), 5.78 (s, 1H), 4.16 (m, 1H), 3.90 (m, 1H), 1.69—2.13 (m, 6H); IR ν_{max}: 3070, 2981, 2943, 2863, 1646, 1598, 1588, 1565, 1491, 1478, 1450, 1227 cm^{-1}; EIMS *m*/*z* (%): 320 (M^+, 100), 262 (12.6), 219 (13.1), 181 (82.3), 137 (10.7), 115 (19.6), 77 (14.7). Anal. calcd for $C_{21}H_{20}O_3$: C 78.73, H 6.29; found C 78.63, H 6.07. *E*-isomer, ^{1}H NMR (CD- Cl_3, 300 MHz) δ: 7.37 (d, J=4.5 Hz, 1H), 7.30 (m, 2H), 7.05—7.15 (m, 3H), 6.91 (m, 3H), 6.76 (d, J=6.0 Hz, 1H), 6.20 (dd, J=1.6, 5.8 Hz, 1H), 6.15 (s, 1H), 4.03 (m, 1H), 3.84 (m, 1H), 1.62—1.81 (m, 6H); IR ν_{max}: 3067, 3037, 2947, 2878, 1649, 1589, 1572, 1490, 1482, 1449, 1240, 1224 cm^{-1}. EIMS *m*/*z* (%): 320 (M^+, 56.0), 262 (7.1), 196 (43.0), 181 (48.5), 131 (37.1), 115 (11.1), 78 (100). HRMS calcd for $C_{21}H_{20}O_3$ 320.1412, found 320.1401.

2-(2-Phenoxy-benzylidene)-1,6,9-trioxa-spiro-[4,5]dec-3-ene (9c): Following the typical procedure for **9a**, treatment of furandiol **8c** (1.515 g, 4.46 mmol) with $CuSO_4$•$5H_2O$ afforded the title compound (*Z*-isomer, pale yellow solid, 880 mg; *E*-isomer, pale yellow oil, 240 mg, 78%). *Z*-isomer, m.p. 102—103 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.35 (dd, J=1.6, 4.6 Hz, 1H), 7.30 (m, 2H), 7.16 (m, 2H), 7.05 (t, J=7.5 Hz, 1H), 6.91 (m, 3H), 6.42 (d, J=5.4 Hz, 1H), 6.00 (d, J=5.4 Hz, 1H), 5.86 (s, 1H), 4.41 (m, 1H), 3.91 (m, 1H), 3.74—3.85 (m, 4H); IR ν_{max}: 2968, 2857, 1647, 1596, 1586, 1565, 1492, 1477, 1450, 1235, 1219 cm^{-1}; EIMS *m*/*z* (%): 322 (M^+, 100), 278 (9.2), 219 (42.1), 181 (81.2), 139 (52.8), 115 (18.8), 77 (11.1). Anal. calcd for $C_{20}H_{18}O_4$: C 74.52, H 5.63; found C 74.35, H 5.52.

E-isomer, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.35 (dd, J= 1.8, 7.5 Hz, 1H), 7.29 (m, 2H), 7.02—7.21 (m, 3H), 6.91 (m, 3H), 6.87 (d, J=6.0 Hz, 1H), 6.26 (d, J=1.2 Hz, 1H), 6.14 (dd, J=2.1, 5.7 Hz, 1H), 4.30 (m, 1H), 3.83 (m, 1H), 3.69—3.79 (m, 4H); IR ν_{max}: 3063, 3014, 2970, 2933, 2880, 2854, 1651, 1588, 1573, 1490, 1482, 1450, 1240, 1220 cm^{-1}. HRMS calcd for $C_{20}H_{18}O_4$ 322.1205, found 322.1220.

2-(3-Phenoxy-benzylidene)-1,6-dioxa-spiro[4,4]-non-3-ene (**9d**): Following the typical procedure for **9a**, treatment of furandiol **8d** (1.434 g, 4.69 mmol) with $CuSO_4$•$5H_2O$ afforded the title compound (1.229 g, 86%) as colorless solid. *Z*-isomer, m.p. 109—110 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.34 (m, 3H), 7.23 (m, 2H), 7.03—7.12 (m, 3H), 6.82 (m, 1H), 6.32 (d, J=5.1 Hz, 1H), 6.04 (d, J=5.4 Hz, 1H), 5.37 (s, 1H), 4.09 (m, 1H), 3.96 (m, 1H), 1.98—2.18 (m, 4H); IR ν_{max}: 2985, 2961, 2901, 1654, 1606, 1591, 1567, 1491, 1481, 1456, 1435, 1368, 1354, 1259, 1234, 1215 cm^{-1}. EIMS *m*/*z* (%): 306 (M^+, 100), 278 (34.1), 129 (16.4), 115 (29.8), 77 (16.9). Anal. calcd for $C_{20}H_{18}O_3$: C 78.41, H 5.92; found C 78.12, H 5.71.

2-(3-Phenoxy-benzylidene)-1,6-dioxa-spiro[4,5]-dec-3-ene (**9e**): Following the typical procedure for **9a**, treatment of furandiol **8e** (1.087 g, 3.22 mmol) with $CuSO_4$•$5H_2O$ afforded the title compound (pale yellow solid, 683 mg, 66%). m.p. 68—69 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.45 (s, 1H), 7.32 (m, 3H), 7.18 (d, J=8.1 Hz, 1H), 7.09 (m, 3H), 6.88 (dd, J=1.5, 7.8 Hz, 1H), 6.28 (d, J=5.7 Hz, 1H), 6.05 (d, J=5.4 Hz, 1H), 5.39 (s, 1H), 5.74 (m, 2H), 1.52—1.76 (m, 6H); IR ν_{max}: 3092, 2946, 2884, 2868, 2846, 1649, 1579, 1572, 1488, 1471, 1456, 1439, 1257, 1212 cm^{-1}. EIMS *m*/*z* (%): 320 (M^+, 100), 292 (9.8), 262 (21.1), 124 (21.0), 115 (25.8), 77 (12.9). HRMS calcd for $C_{21}H_{20}O_3$ 320.1412, found 320.1394.

2-(3-Phenoxy-benzylidene)-1,6,9-trioxa-spiro-[4,5]dec-3-ene (**9f**): Following the typical procedure for **9a**, treatment of furandiol **8f** (1.649 g, 4.85 mmol) with $CuSO_4$•$5H_2O$ afforded the title compound (pale yellow oil, 754 mg, 48%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.29—7.39 (m, 5H), 7.08 (m, 3H), 6.86 (qd, J=1.2, 7.8 Hz, 1H), 6.42 (d, J=5.7 Hz, 1H), 6.00 (d, J=5.7 Hz, 1H), 5.46 (s, 1H), 4.11 (td, J=3.3, 11.4 Hz, 1H), 3.73—3.83 (m, 4H), 3.66 (m, 1H); IR ν_{max}: 2971, 2932, 2879, 2853, 1654, 1593, 1571, 1489, 1456, 1438, 1256, 1219 cm^{-1}. EIMS *m*/*z* (%): 322 (M^+, 100), 277 (13.7), 264 (35.8), 250 (9.3), 236 (9.7), 207 (5.3), 171 (8.6), 139 (23.1), 128 (9.6), 115 (35.6), 77 (12.8). HRMS calcd for $C_{20}H_{18}O_4$ 322.1205, found 322.1216.

2-(4-Phenoxy-benzylidene)-1,6-dioxa-spiro[4,4]-non-3-ene (**9g**): Following the typical procedure for **9a**, treatment of furandiol **8g** (1.277 g, 3.94 mmol) with $CuSO_4$•$5H_2O$ afforded the title compound (943 mg, 78%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.34 (dt, J=2.4, 9.3 Hz, 2H), 7.32 (m, 2H), 7.07 (td, J=1.3, 6.7 Hz, 1H), 6.93—7.02 (m, 4H), 6.34 (d, J= 6.0 Hz, 1H), 6.02 (d, J=6.6 Hz, 1H), 5.39 (s, 1H), 4.25 (m, 1H), 4.03 (m, 1H), 2.02—2.41 (m, 4H); IR ν_{max}: 3041, 2945, 2875, 1654, 1588, 1504, 1490, 1457, 1440, 1243 cm^{-1}. EIMS *m*/*z* (%): 306 (M^+, 100), 278 (42.7), 222 (12.4), 129 (50.4), 115 (35.8), 77 (52.1). HRMS calcd for $C_{20}H_{18}O_3$ 306.1256, found 306.1213.

2-(4-Phenoxy-benzylidene)-1,6-dioxa-spiro[4,5]-dec-3-ene (**9h**): Following the typical procedure for **9a**, treatment of furandiol **8h** (1.728 g, 5.11 mmol) with $CuSO_4$•$5H_2O$ afforded the title compound (1.40 g, 86%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.34 (dt, J=2.4, 9.3 Hz, 2H), 7.33 (m, 2H), 7.09 (t, J= 7.8 Hz, 1H), 6.96—7.04 (m, 4H), 6.33 (d, J=5.4 Hz, 1H), 6.07 (d, J=5.9 Hz, 1H), 5.42 (s, 1H), 4.25 (td, J= 3.8, 11.4 Hz, 1H), 4.03 (dt, J=2.1, 11.4 Hz, 1H), 1.58-2.10 (m, 6H); IR ν_{max}: 2981, 2958, 2895, 1655, 1590, 1581, 1504, 1489, 1455, 1418, 1228 cm^{-1}. EIMS *m*/*z* (%): 320 (M^+, 100), 292 (14.2), 262 (44.4), 183 (21.3), 141 (17.9), 123 (34.8), 115 (53.8), 77 (66.6). HRMS calcd for $C_{21}H_{20}O_3$ 320.1412, found 320.1423.

2-(4-Phenoxy-benzylidene)-1,6,9-trioxa-spiro-[4,5]dec-3-ene (**9i**): Following the typical procedure for **9a**, treatment of furandiol **8i** (2.492 g, 7.33 mmol) with $CuSO_4$•$5H_2O$ afforded the title compound (1.993 g, 84%) as a white solid. m.p. 158—159 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.34 (d, J=9.3 Hz, 2H), 7.33 (m, 2H), 7.09 (m, 1H), 6.96—7.04 (m, 4H), 6.45 (d, J=5.4 Hz, 1H), 6.00 (d, J=6.6 Hz, 1H), 5.49 (s, 1H), 4.39 (td, J=2.7, 11.2 Hz, 1H), 3.74—3.91 (m, 5H); IR ν_{max}: 3092, 3035, 2970, 2856, 1653, 1586, 1504, 1491, 1456, 1239, 1226 cm^{-1}. EIMS *m*/*z* (%): 322 (M^+, 100), 264 (58.8), 236 (8.2), 197 (10.8), 183 (9.6), 139 (22.8), 115 (54.2), 77 (44.1). HRMS calcd for $C_{20}H_{18}O_4$ 322.1205, found 322.1205.

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