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NEW THIOPHENES FROM *ECHINOPS GRIJISII*

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A new thiophene–echinoyne thiophene A (**11**), four new natural products, namely 5,5''-dichloro- α -terthiophene (**1**), 5-chloro- α -terthiophene (**2**), 5-acetyl α -terthiophene (**3**) and 5-carboxyl bithiophene (**12**), together with seven known thiophenes were isolated and purified from ethanol extract of roots of *Echinops grijisii* Hance. Their structures were identified on the basis of spectral data.

Keywords: *Echinops grijisii*; Compositae; Thiophenes; Echinoyne thiophene A

INTRODUCTION

Echinops is a genus in the family of Compositae with about 100 species distributed in South Europe, North Africa and the Far East [1]. Most *Echinops* plants contain thiophenes, a unique type of natural product which possess antitumour, insecticide and antiviral activities [2–4]. Till now, more than 40 thiophenes have been isolated from this genus [5–9].

In China, the roots of *Echinops grijisii* Hance have been used to clear heat, expel miasma and stimulate milk secretion for a long history. It has been recorded in Chinese Pharmacopoeia (2000 Edition) as one of the sources for Yuzhou Loulu [10]. Unfortunately, the chemical constituents of this plant have not been reported in detail yet. This paper describes the extraction, isolation and structural elucidation of 12 thiophenes from ether and *n*-butanol extracts of *E. grijisii* roots. Among the compounds, echinoyne thiophene A (**11**) is a new compound. 5,5''-Dichloro- α -terthiophene (**1**), 5-chloro- α -terthiophene (**2**), 5-acetyl α -terthiophene (**3**) and 5-carboxyl bithiophene (**12**) are four new natural products. Seven known thiophenes were also isolated and their structures were characterized as 5-(3-buten-1-ynyl)-2,2'-bithiophene (**4**), α -terthiophene (**5**), cardopatine (**6**), isocardopatine (**7**), 5-(4-*O*-isopentanoyl-butynyl-1)-2,2'-bithiophene (**8**), 5-(3'',4''-dihydroxy-butynyl-1)-2,2'-dithiophene (**9**), and [2-(3', 4'-dihydroxy-butynyl-1),5-(5''-methy-pentdiyne-1'',3'')] thiophene (**10**), respectively.

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RESULTS AND DISCUSSION

NMR spectra of **1** showed close similarity to those of **5** except for the disappearance of signals corresponding to H-5 and 5'' [11]. EI-MS showed a molecular ion peak at m/z 316(100.0), together with two isotope ions at $320[M + 4]^+$ and $318[M + 2]^+$, suggesting the substitutions of chlorine at C-5 and 5''. Therefore, **1** was identified as the new natural product 5,5''-dichloro- α -terthiophene [12]. NMR spectra showed that **2** and **3** were also terthiophenes, while they lost their structural symmetry due to a single substitution [13]. For **2**, EI-MS spectrum gave a molecular ion at m/z 282 (100.0) and an isotope ion at m/z 284 (45.6)[$M + 2$]⁺, indicating the substitution of a chlorine function at C-5. Compound **3** showed almost the same chemical shifts as **2** except for the additional signals assigned to an acetyl group at C-5. Therefore, **2** and **3** were identified as 5-chloro- α -terthiophene and 5-acetyl α -terthiophene, respectively. They were both new natural thiophenes. Krishnaswamy and co-workers reported these structures in 1993 [13].

EI-MS spectrum of **11** showed a molecular ion at m/z 230, consistent with the formula of C₁₃H₁₀O₂S. The NMR spectra were remarkably similar to those of **10** [14]. In its ¹H-NMR spectrum, the two signals at δ 7.29 and 7.07 (each 1H, d, $J = 3.9$ Hz), corresponding to H-3 and 4, respectively, indicated the existence of a thiophene ring with substitutions at C-2 and C-5. Acetylene functional groups were indicated by ¹³C-NMR (DEPT) spectral signals as singlets between δ 65 and 95. HMBC spectrum showed long-range correlations of C-1'' (δ 72.5, s) with H-4(δ 7.07, d, $J = 3.9$ Hz) and H-3'' (δ 2.07, 3H, s), suggesting the presence of a CH₃-C \equiv C- moiety directly connected to C-5. In addition, long-range correlations of H-3(δ 7.29, d, $J = 3.9$ Hz) with C-1' (δ 70.5, s), and H-5' (δ 4.51, brs) with C-3' (δ 68.9, s) indicated that a but-1,3-diyne group was attached to C-2. On the basis of the above spectral evidence, compound **11** was identified as the new compound echinoyne thiophene A (Fig. 1). All the ¹H- and ¹³C-NMR signals were assigned according to DEPT, HMBC spectra and reference to literature data [15].

EXPERIMENTAL SECTION

General Experimental Procedures

Melting points were determined on an XT4A apparatus and the thermometer are uncorrected. UV spectra were obtained on a UV-260 spectrophotometer, using MeOH as the solvent. IR spectra were measured in KBr on a Perkin-Elmer 983 IR spectrometer. ¹H- and ¹³C-NMR were recorded on JOELA-500 and VXR 300 instruments using TMS as internal standard. MS spectra were measured on AEI-MS-500 and JMS-DX303 mass spectrometers. FAB-MS and ESI-MS were performed in the positive mode. For TLC, silica gel G, GF₂₅₄, HF₂₅₄ were used. Thiophenes were visualized by spraying with 10% (v/v) H₂SO₄ to produce a red colour. For CC, silica gel (100–200 mesh, 200–300 mesh, Qingdao Marine Chemistry, China) and

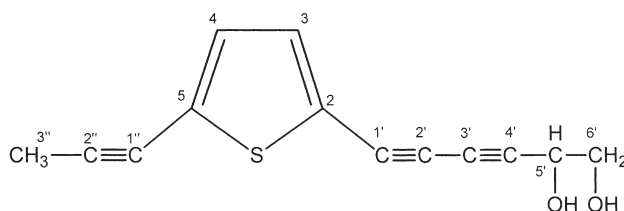


FIGURE 1 Structure of compound **11**.

D101 macroporous resin (Nankai chemical Industry, China) were employed as the packing materials. HPLC was performed with a Waters 600 pump connected to a 486 tunable absorbance detector. The C₁₈ column was from Merck (Lichrosorb 7 μm, 10 mm I. D. × 25 cm).

Plant Material

E. grijisii was collected from Yuzhou, Henan Province, P.R. China (October, 1996) and identified by Prof. De-an Guo (Peking University, China). The voucher specimen was deposited at the herbarium of School of Pharmaceutical Sciences, Peking University, Beijing, China.

Extraction and Isolation

Air-dried root (10 kg) was pulverized and extracted with 95% ethanol (v/v) at 60°C for 8 h. The extract was concentrated *in vacuo* and then dissolved in 5 l water, which was further extracted with ether and *n*-BuOH successively. The organic phase was concentrated to afford ether and *n*-BuOH soluble extracts (306 and 440 g, respectively). The ether extract was subjected to repeated CC and preparative TLC on silica gel with various proportional mixtures of CHCl₃ and MeOH to afford **1** (10 mg), **2** (12 mg), **3** (6 mg), **4** (10 mg), **5** (5 mg), **6** (7 mg), **7** (8 mg) and **8** (20 mg). The *n*-BuOH extract was applied to a macroporous resin column and eluted with EtOH–H₂O. The eluate was concentrated to dryness and chromatographed over silica gel, eluting with CHCl₃–MeOH to give two fractions. Fr. 1 was rechromatographed by HPLC eluting with MeOH–H₂O (60:40) to yield **9** (7 mg), **10** (9 mg) and **11** (10 mg); Fr. 2 was further purified by HPLC (MeOH–H₂O 65:35) to give **12** (9 mg).

5,5''-Dichloro- α -terthiophene (1): yellow crystals (petroleum ether–acetone), m.p. 134–135°C; C₁₂H₆S₃Cl₂; IR (KBr) ν_{\max} : 2914, 1427, 849, 787 cm⁻¹; ¹H-NMR (CDCl₃, 300 MHz) δ 6.83(2 × 1H, d, *J* = 4.2 Hz, H-3, 3''), 6.92(2 × 1H, d, *J* = 4.2 Hz, H-4, 4''), 6.98(2 × 1H, s, H-3', 4'); ¹³C-NMR(CDCl₃, 75 MHz) δ 123.0(C-3, 3''), 124.5(C-3', 4'), 127.0(C-4, 4''), 129.1(C-5, 5''), 135.5(C-2', 5'), 135.7(C-2, 2''); EI-MS: *m/z* 320[M + 4]⁺, 318[M + 2]⁺, 316[M]⁺, 281 [M – Cl]⁺, 246[M – 2Cl]⁺, 237, 201, 158, 145, 119.

5-Chloro- α -terthiophene (2): yellow crystals (petroleum ether–acetone), m.p. 129–130°C; C₁₂H₇S₃Cl; IR (KBr) ν_{\max} : 2914, 1586, 1422, 833, 788, 686 cm⁻¹; ¹H-NMR(CDCl₃, 300 MHz) δ 6.83(1H, d, *J* = 3.9 Hz, H-4), 6.92(1H, d, *J* = 3.9 Hz, H-3), 6.99(1H, d, *J* = 3.9 Hz, H-4'), 7.02(1H, dd, *J* = 3.3, 3.3 Hz, H-4''), 7.07(1H, d, *J* = 3.9 Hz, H-3'), 7.16(1H, dd, *J* = 1.2, 3.3 Hz, H-3''), 7.22(1H, dd, *J* = 1.2, 3.3 Hz, H-5''); ¹³C-NMR(CDCl₃, 75 MHz) δ 122.7(C-3), 123.9(C-3''), 124.3(C-5''), 124.6(C-3' 4'), 126.9(C-4), 127.9(C-4''), 129.3(C-5), 135.2(C-2'), 135.8(C-2), 136.7(C-5'), 136.9(C-2''); EI-MS: *m/z* 284[M + 2]⁺, 282[M]⁺, 247 [M – Cl]⁺, 237, 214, 203, 141, 127, 102, 93.

5-Acetyl α -terthiophene (3): yellow crystals (petroleum ether), m.p. 135–137°C; C₁₄H₁₀S₃O; IR (KBr) ν_{\max} : 2919, 2850, 1731, 1636 cm⁻¹; ¹H-NMR(CDCl₃, 300 MHz) δ 2.46(3H, s, CH₃CO), 7.04(1H, dd, *J* = 3.9 Hz, 3.9 Hz, H-4''), 7.12(1H, d, *J* = 3.6 Hz, H-3), 7.16(1H, d, *J* = 3.9, H-3''), 7.22(1H, d, *J* = 3.6 Hz, H-3'), 7.23(1H, d, *J* = 3.6 Hz, H-4'), 7.26(1H, d, *J* = 3.9 Hz, H-5''), 7.59(1H, d, *J* = 3.6 Hz, C-4); ¹³C-NMR (CDCl₃, 75 MHz) δ 29.7 (CH₃CO), 123.9(C-3''), 124.4(C-5''), 124.6(C-3' 4'), 125.2 (C-3), 126.3(C-4), 128.2 (C-4''), 133.4(C-5), 136.2(C-2, 2', 5', 2''), 196.4(CH₃CO); EI-MS: *m/z* 290[M]⁺, 275[M – CH₃]⁺, 247[M – CH₃CO]⁺, 203, 138.

α -terthiophene (5): colourless needles (petroleum ether), m.p. 91–92°C; C₁₂H₈S₃; IR (KBr) ν_{\max} : 3434, 2931, 2862, 1637, 1460, 1378, 1240, 1050, 1021, 969, 958, 837, 800 cm⁻¹; ¹H-NMR(CDCl₃, 300 MHz) δ 7.02 (2 × 1H, dd, *J* = 3.6, 4.8 Hz, H-4, 4''),

7.07(2 × 1H, s, H-3', 4'), 7.17(2 × 1H, d, $J = 3.6$ Hz, H-3, 3''), 7.21(2 × 1H, d, $J = 4.8$ Hz, H-5, 5''); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 123.7(C-3, 3''), 124.4(C-5, 5''), 124.5(C-3', 4'), 127.9(C-4, 4''), 136.3(C-2', 5'), 137.2(C-2, 2''); EI-MS: m/z 248[M]⁺, 216, 203, 190, 171, 140, 127, 95, 82.

[2-(3', 4'-dihydroxy-butynyl-1), 5-(5''-methyl-pentadiyne-1'', 3'')]thiophene (**10**): yellow needles (acetone), m.p. 113–115°C; $\text{C}_{13}\text{H}_{10}\text{O}_2\text{S}$; $^1\text{H-NMR}$ (acetone- d_6 , 500 MHz): δ 7.31(1H, d, $J = 3.9$ Hz, H-4), 7.18(1H, d, $J = 3.9$ Hz, H-3), 4.69(1H, d, $J = 5.6$ Hz, 3''-OH), 4.60(1H, dd, $J = 5.6, 5.6$ Hz, H-3''), 4.11(1H, t, $J = 6.4$ Hz, 4''-OH), 3.69(2H, m, 4''-CH₂), 2.09(3H, s, 5'-CH₃); $^{13}\text{C-NMR}$ (acetone- d_6 , 125 MHz) [15]: δ 135.1(d, C-4), 133.9(d, C-3), 125.9(s, C-5), 123.6(s, C-2), 95.6(s, C-2''), 85.0(s, C-4'), 79.8(s, C-2'), 77.2(s, C-1''), 66.9(t, C-4''), 66.7(s, C-1'), 64.5(d, C-3''), 64.3(s, C-3'), 4.2(q, C-5'); EI-MS: m/z 230[M]⁺, 212[M - H₂O]⁺, 200, 199, 183, 171, 170, 139, 127.

*Echinoyne*thiophene A (**11**): yellow needles (acetone), m.p. 122–123°C; $\text{C}_{13}\text{H}_{10}\text{O}_2\text{S}$; $^1\text{H-NMR}$ (acetone- d_6 , 500 MHz): δ 7.29(1H, d, $J = 3.9$ Hz, H-3), 7.07(1H, d, $J = 3.9$ Hz, H-4), 4.75(1H, brs, 5'-OH), 4.51(1H, brs, H-5'), 4.16(1H, brs, 6'-OH), 3.65(2H, m, 6'-CH₂), 2.07(3H, s, 3''-CH₃); $^{13}\text{C-NMR}$ (acetone- d_6 , 125 MHz): δ 135.0(d, C-3), 131.6(d, C-4), 127.5(s, C-5), 121.6(s, C-2), 92.7(s, C-2''), 86.3(s, C-4'), 84.0(s, C-2'), 72.5(s, C-1''), 70.5(s, C-1'), 68.9(s, C-3'), 66.8(t, C-6'), 64.7(d, C-5'), 4.3(q, C-3''); EI-MS: m/z 230[M]⁺, 212, 199, 183, 170.

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