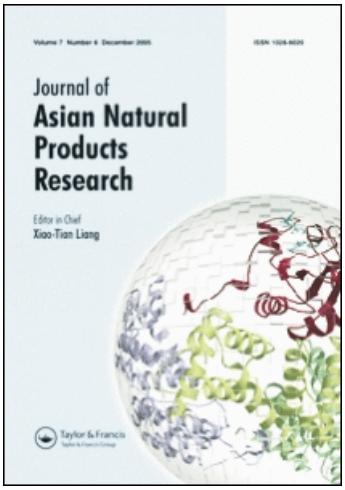

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Thiophenes from *Echinops latifolius*

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Six thiophenes were isolated and purified from ethanol extract of the roots of *Echinops latifolius* Tausch. Their structures were identified on the basis of spectral data. Among them, 5-(3-hydroxmethyl-3-isovaleroyloxyprop-1-ynyl)-2,2′-bithiophene (**6**) is a new compound, and 5-(3-hydroxy-4-isovaleroyl-oxybut-1-ynyl)-2,2′-bithiophene (**5**) was isolated from this plant for the first time.

Keywords: *Echinops latifolius*; Compositae; Thiophenes; 5-(3-Hydroxmethyl-3-isovaleroyloxyprop-1-ynyl)-2,2′-bithiophene

1. Introduction

Echinops latifolius Tausch. (Compositae) is widespread in north China. The roots of this plant have been used to clear heat, expel miasma and stimulate milk secretion for a long history, and it has been recorded in *Chinese Pharmacopoeia* (2000 edition) as one of the sources for Yuzhou Loulu [1]. Previous chemical investigation on this plant demonstrated the presence of thiophenes [2], a unique type of natural product which has phototoxic activities with the irradiation of long wavelength ultraviolet (UVA) [3–6]. We report here the isolation and structural elucidation of six thiophenes from ethanol extract of the roots of *E. latifolius*. The thiophenes isolated from the plant were identified as 5-(but-3-en-1-ynyl)-2,2′-bithiophene (**1**), α-terthienyl (**2**), cardopatine (**3**), 5-(4-isovaleroyloxybut-1-ynyl)-2,2′-bithiophene (**4**), 5-(3-hydroxy-4-isovaleroyloxybut-1-ynyl)-2,2′-bithiophene (**5**) and 5-(3-hydroxmethyl-3-isovaleroyloxyprop-1-ynyl)-2,2′-bithiophene (**6**), respectively. Among them, **6** is a new compound, and **5** was isolated from this plant for the first time.

2. Results and discussion

Compound **6** was obtained as yellow oil, $[\alpha]_D^{20}$ −9.0 (*c* 0.001, $CHCl_3$). In the TLC experiment, **6** was colorized as green spot by isatin/H_2SO_4, indicating that it was a thiophene derivate [7].

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The HRMS showed a molecular ion peak at *m/z* 334.0696, compatible with the molecular formula $C_{17}H_{18}O_3S_2$. The ESI-MS spectrum showed $[M + Na]^+$ at *m/z* 357.0, $[M + 1 + Na]^+$ at *m/z* 358.0, $[M + 2 + Na]^+$ at *m/z* 359.0 and $[M + 3 + Na]^+$ at *m/z* 360.2. And the fragment $[M - 102 + Na]^+$ at *m/z* 254.8 (100.0) implied the loss of 1 mole of 3-methyl-butyric acid from the parent molecular ion. The ^{1}H-NMR spectrum of **6** showed characteristic signals [8] of 5-substituted 2,2′-bithiophene protons at δ 7.25 (1H, dd, $J = 5.2, 0.9$ Hz), 7.18 (1H, dd, $J = 3.1$, 0.9 Hz), 7.14 (1H, d, $J = 3.8$ Hz), 7.03 (1H, d, $J = 3.8$ Hz) and 7.02 (1H, dd, $J = 5.2, 3.1$ Hz). Additionally, the signals of CH_2CH protons appeared at δ 5.71 (1H, t, $J = 5.3$ Hz) and 3.91 (2H, d, $J = 5.3$ Hz). The signals at δ 2.31 (2H, d, $J = 6.4$ Hz), 2.17 (1H, m) and 1.00 (6H, d, $J = 6.5$ Hz) indicated the protons due to the isopentanoyl group. The ^{13}C-NMR spectrum of **6** had 16 carbon signals, of which eight bithiophene carbons appeared at δ 139.7, 136.4,134.0, 128.0, 125.2, 124.5, 123.3 and 120.1, along with the ynyl carbons at δ 88.2 and 79.9. Two oxygen carbons of CH_2CH appeared at δ 65.4 and 64.4. The carbon signals ascribed to the isopentanoyl unit at δ 172.2, 43.2, 25.8 and 22.4 (table 1).

The HMQC experiment gave the C–H direct correlations of **6**. In the HMBC experiment (figure 1, figure 2), the long-range correlations between H-3‴ (δ 2.17), H-3″ (δ 5.71) and C-1‴ (δ 172.2) indicated that C-3″ is substituted by isovaleroyloxyl group. In addition, the long-range correlations between H-3″ (δ 5.71), H-1⁗ (δ 3.91) and C-2″ (δ 88.2), as well as H-1⁗ (δ 3.91), H-4 (δ 7.14) and C-1″ (δ 79.9), indicated that C-1″ connects with bithiophene, and C-2″ with C-3″. From the data above, the structure of **6** was established as 5-(3-hydroxmethyl-3-isovaleroyloxyprop-1-ynyl)-2,2′-bithiophene (**6**).

Compound **5** was also obtained as yellow oil. The ^{1}H-NMR and ^{13}C-NMR data are very similar to those of **6**, except for the ^{1}H-NMR signals of CH_2CH protons. Comparing its spectral data with literature value [8], **5** was identified as 5-(3-hydroxy-4-isovaleroyloxybut-1-ynyl)-2,2′-bithiophene (**5**).

Compounds **1**–**4** were identified as 5-(but-3-en-ynyl)-2,2′-bithiophene (**1**), α-terthienyl (**2**), cardopatine (**3**) and 5-(4-isovaleroyloxybut-1-ynyl)-2,2′-bithiophene (**4**), respectively, by direct comparison of their spectral data with literature values [2].

3. Experimental

3.1 General experimental procedures

The melting point was measured on a Yamaco-hot-stage and is uncorrected. 1D-NMR spectra were recorded on a Bruker ARX-300 spectrometer. 2D-NMR spectra were recorded

Table 1. NMR data of compound **6**.

No.	δ_H	δ_C	*No.*	δ_H	δ_C
2		139.7	2″		88.2
3	7.03 (1H, d, $J = 3.8$ Hz)	123.3	3″	5.71 (1H, t, $J = 5.3$ Hz)	65.4
4	7.14 (1H, d, $J = 3.8$ Hz)	134.0	1‴		172.2
5		120.1	2‴	2.31 (2H, d, $J = 6.4$ Hz)	43.2
2′		136.4	3‴	2.17 (1H, m)	25.8
3′	7.18 (1H, dd, $J = 0.9, 3.1$ Hz)	124.5	4‴	1.00 (6H, d, $J = 6.6$ Hz)	22.4
4′	7.02 (1H, dd, $J = 3.1, 5.2$ Hz)	128.0	5‴		
5′	7.25 (1H, dd, $J = 0.9, 5.2$ Hz)	125.2	1⁗	3.91 (2H, d, $J = 5.3$ Hz)	64.4
1″		79.9			

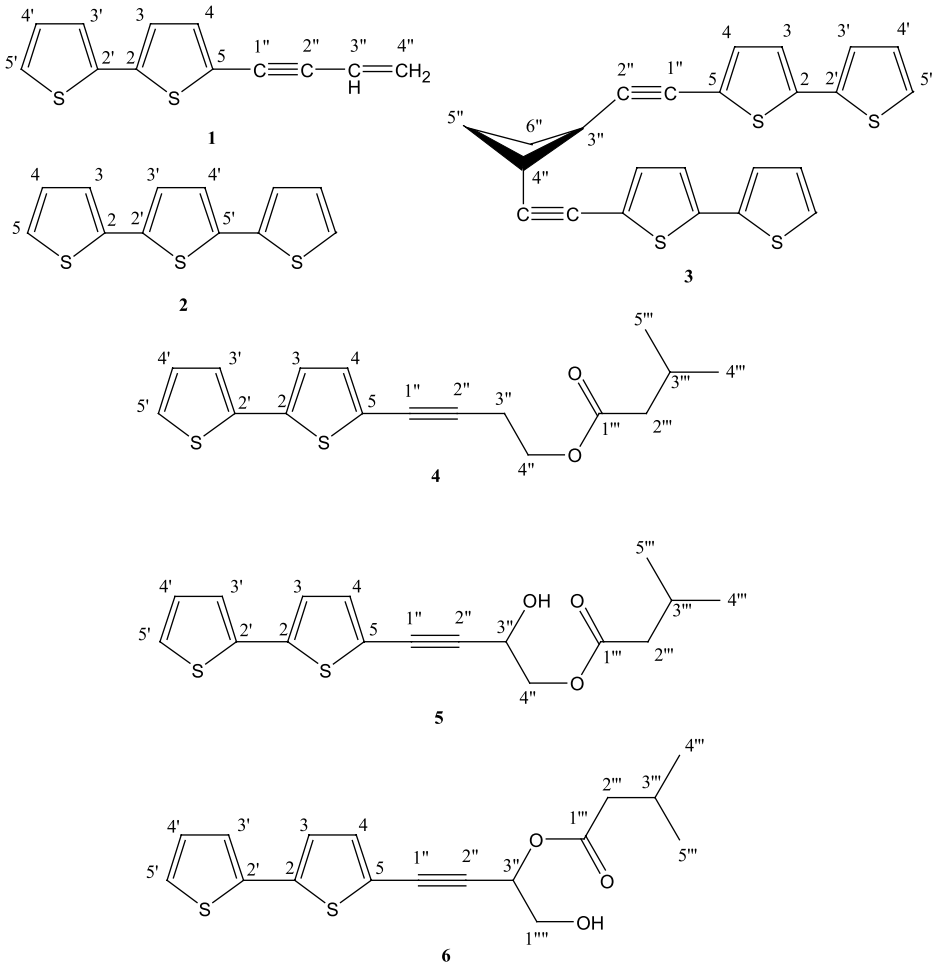

Figure 1. Structures of compounds **1**–**6**.

on a Bruker AV-600 spectrometer, using TMS as an internal standard. HRMS was performed on a QSTAR LCQ mass spectrometer. ESI-MS was performed on a Finnigan LCQ mass spectrometer. The optical rotation was measured on a Perkin-Elmer 241 polarimeter. Silica gel for chromatography was produced by the Qingdao Ocean Chemical Group Co. of China.

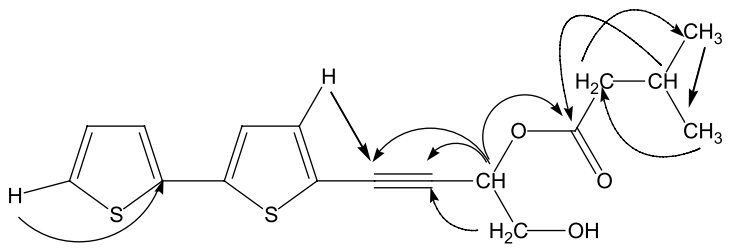

Figure 2. Key HMBC correlations of compound **6**.

3.2 Plant material

The plant material of *Echinops latifolius* was collected in Chifeng city, Inner Mongolia Municipality, China, in September 2003, and identified by Prof. Qishi Sun (Shenyang Pharmaceutical University). A voucher specimen (No. 20030928) is deposited in the Research Department of Natural Medicine, Shenyang Pharmaceutical University.

3.3 Extraction and isolation

Dried roots (8.0 kg) of *Echinops latifolius* were extracted with 95% ethanol. The extract was concentrated *in vacuo*, and then the extract (580.0 g) was partitioned with petroleum ether, chloroform, EtOAc, and n-BuOH successively. The petroleum ether part (135.0 g) was subjected to column chromatography on silica gel eluted with petroleum ether/EtOAc. Fraction 3 (eluted with petroleum ether, 14.0 g) was rechromatographed on a silica gel column eluted with petroleum ether to give **1** (1.5 g) and **2** (8.2 g); fraction 4 [eluted with petroleum ether/EtOAc (100:1), 6.5 g] was rechromatographed on a silica gel column eluted with a 1–5% EtOAc/petroleum ether to give **3** (645.0 mg) and **4** (735.0 mg); fraction 10 [eluted with petroleum ether/EtOAc (100:2), 3.1 g] was rechromatographed on a silica gel column eluted with a 2–10% EtOAc/petroleum ether to give **5** (12.1 mg) and **6** (7.5 mg).

3.3.1 5-(3-Hydroxmethyl-3-isovaleroyloxyprop-1-ynyl)-2,2′-bithiophene (6). Compound **6**: yellow oil. $[\alpha]_D^{20}$ −9.0 (*c* 0.001, $CHCl_3$). HRMS: *m/z* 334.0696 (calcd for $C_{17}H_{18}O_3S_2$, 334.0671). ESI-MS: *m/z* (%) 357.0 ($[M + Na]^+$, 9.0), 358.0 ($[M + 1 + Na]^+$, 1.7), 359.0 ($[M + 2 + Na]^+$, 1.1), 360.2 ($[M + 3 + Na]^+$, 0.3), 254.8 ($[M + Na - 102]^+$, 100.0). ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$) data (see table 1).

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