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Article

Sinapyl Alcohol Derivatives from the Lipo-soluble Part of *Dichrocephala benthamii* C. B. Clarke

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Abstract: Four new sinapyl alcohol derivatives dichrocephols A–D (compounds **1**–**4**) were isolated from the lipo-soluble part of the whole herb of *Dichrocephala benthamii* C. B. Clarke, together with the known compound syringenin isovalerate (**5**). Their structures were elucidated on the basis of spectroscopic analysis. Their absolute configurations were established by the method of alkaline hydrohysis. Compounds **1**–**3** showed moderate cytotoxity against HeLa cells, with IC_{50} values of 14.8 μM, 51.6 μM and 81.6 μM, respectively. This is the first time that sinapyl alcohol derivatives were isolated from the genus *Dichrocephala*.

Keywords: *Dichrocephala benthamii* C. B. Clarke; Asteraceae; sinapyl alcohol derivatives; absolute configuration determination; cytotoxicity

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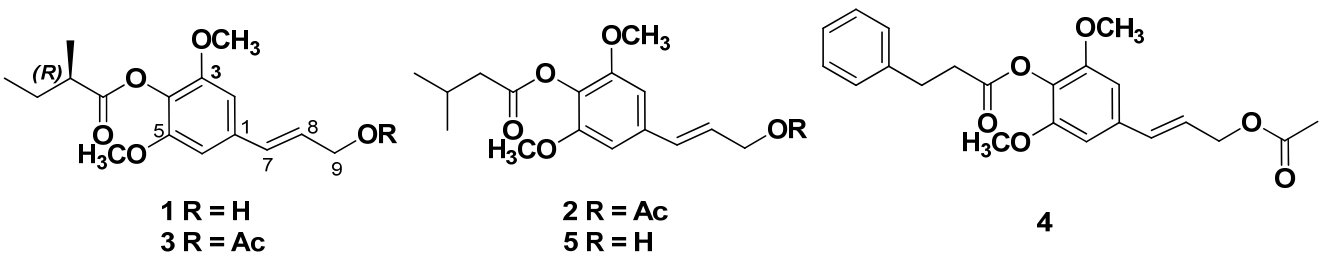
1. Introduction

The Asteraceae plant *Dichrocephala benthamii* C. B. Clarke is an annual herb which is only distributed in China and India [1]. Its whole herb has commonly been used as a fork medicine among the Dai nationality of China for the treatment of indigestion, common cold and fever in children, pneumonia and hepatitis [2,3]. However, to the best of our knowledge, there have been few previous reports on phytochemical investigations of this species [4]. In our search for new bioactive constituents from the medicinal plants used by the Dai nationality in China, we initiated chemical studies of the whole herb of *D. benthamii*.

The air-dried and chopped whole herbs of *D. benthamii* were extracted with 95% EtOH. After removal of solvent, the residue was subject to the diatomaceous silica and bathed successively with petroleum ether, CH_2Cl_2, EtOAc and MeOH. The petroleum ether part led to the isolation of four new sinapyl alcohol derivatives **1**–**4** and the known compound syringenin isovalerate (**5**) (Figure 1) [5].

Figure 1. Structures of compounds **1**–**5**.



2. Results and Discussion

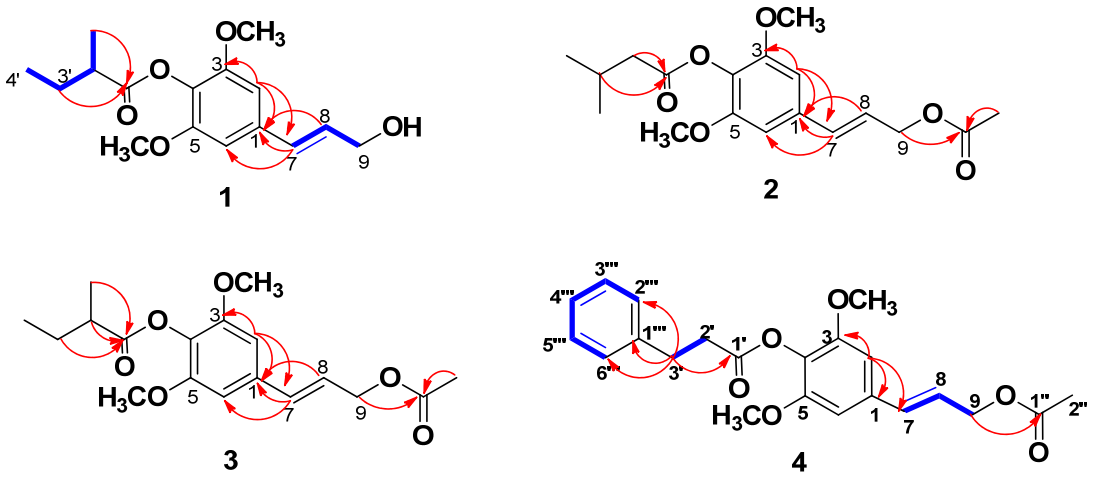
Compound **1**, a colorless oil, had the molecular formula of $C_{16}H_{22}O_5$, as determined by analysis of its HRESIMS (*m/z* 317.1358 $[M+Na]^+$). The IR spectrum of **1** showed absorption bands at 1757 (C=O), 1596, 1507, 1463 (-phenyl) cm^{-1}. Analysis of the ^1H-, ^{13}C-, DEPT, and HSQC NMR data revealed that there was a 1,3,4,5-tetrasubstituted phenyl in **1**. The signals at δ_C 56.6 and δ_H 3.84 (6H, s) indicated that there were two overlapped methoxy groups, which were symmetrically located on the phenyl ring. Interpretation of the ^1H-^1H COSY NMR data of **1** led to the identification of two isolated proton spin-systems corresponding to C-7–C-9, C-2′–C-5′ units. The remaining fragment connections were determined by HMBC data, and established a skeleton similar to that of sinapyl alcohols [5,6]. The HMBC correlations from δ_H 6.79 (H-2) to δ_C 137.2 (C-1), 131.4 (C-7), δ_H 6.61 (H-7) to δ_C 137.2 (C-1), 104.3 (C-2, 6), δ_H 6.39 (H-8) to δ_C 137.2 (C-1) indicated that C-1 was connected to C-7. The HMBC correlations from δ_H 1.64 (1H, m, H-3′a), 1.80 (1H, m, H-3′b), 1.30 (3H, d, J = 7.2 Hz, H-5′) to δ_C 176.5 (C-1′) indicated that there was a 2-methylbutyryl group in **1**. Due to absence of HMBC correlation between δ_H 4.27 (H-9) and δ_C 176.5 (C-1′) together with consideration of the chemical shift values of C-9, and compared with its analogues [5,6], 2-methylbutyryloxy was suggested to be connected with C-4. Thus the planar structure of **1** was established as (*E*)-3,5-dimethoxy-4-(2-methylbutyryloxy) phenylpropanol.

The absolute configuration at C-4 in the 2-methylbutyryl group was established by the alkaline hydrolysis method. According to the α_D values of (−14.3) for (*R*)-2-methylbutyric acid and (+19.3) for

(*S*)-2-methylbutyric acid and compared with the data reported in the literature [7–11], the absolute configuration of the 2-methylbutyryl group in **1** was supposed as *R* by the negative α_D value {$[\alpha]_D^{25}$ −4.6 (c 0.04, MeOH)} of the 2-methylbutyric acid. Therefore the structure of **1** was established as (*E*)-3, 5-dimethoxy-4-(2*R*-methylbutyryloxy)phenylpropanol, which was named dichrocephol A.

Compound **2**, a colorless oil, was assigned the molecular formula $C_{18}H_{24}O_6$ by HRESIMS analysis (*m/z* 359.1510 $[M+Na]^+$). The ^{1}H- and ^{13}C-NMR data of **2** was similar to that of **1** except the substituent at C-4 and C-9. The signals at δ_H 2.04 (3H, s, H-2″) and δ_C 170.9 (C-1″), 20.8 (C-2″) indicated the existence of the acetyl group. In addition, the signals at δ_H 1.06 (6H, d, *J* = 6.6 Hz, H-4′, 5′), 2.24 (1H, m, *J* = 7.2, 6.6 Hz, H-3′), 2.41 (2H, d, *J* = 7.2 Hz, H-2′) together with the HMBC correlations shown in Figure 2 revealed that isopentanoyl had replaced the 2-methylbutyryl group in **1**. The overlapped signals of C-1″and C-1′ in ^{13}C-NMR led to the complexity that the two substituents could not be determined to connect with C-4 or C-9 by HMBC correlations. Detailed analysis of the chemical shift values of **2**, and comparison of its analogues implied that isopentanoyloxy should be anchored at C-4 [5,6]. The EIMS fragment ions of **2** also supported the above-mentioned deduction.

Figure 2. ^{1}H–^{1}H COSY, HMBC for compounds **1**–**4**.



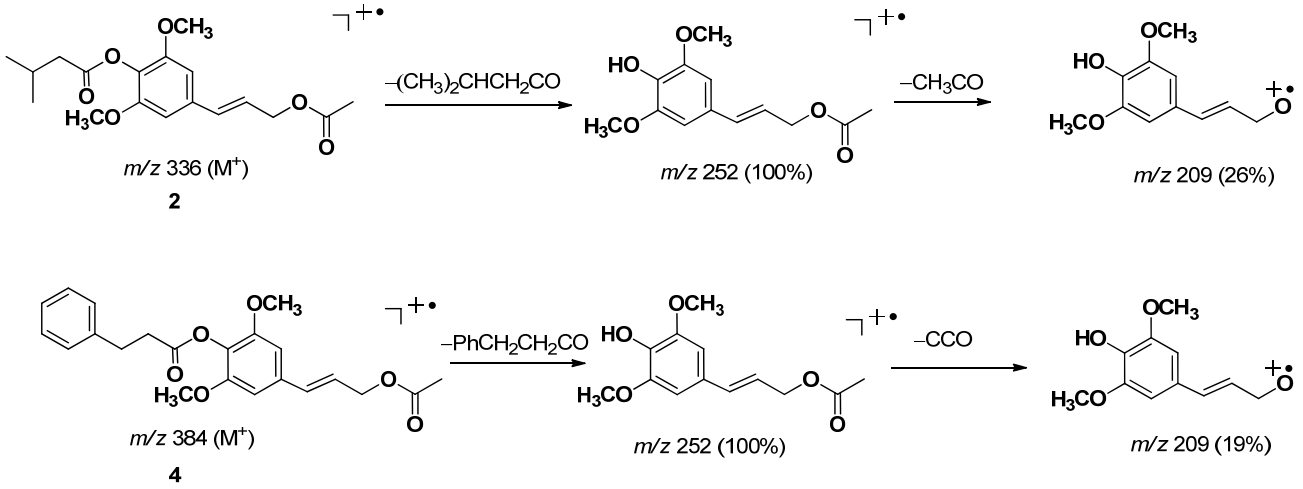
The abundance the peak of *m/z* 252 was 100%, which implied that the isopentanoyl moiety was repelled by the two methoxy units and lost easily (Figure 3). Therefore 2 was established as (*E*)-3,5-dimethoxy-4-isopentanoyloxy phenylpropanol acetate, which was named dichrocephol B.

Compound **3**, a colorless oil, was isolated together with **2**. The mole ratio of **3** to **2** was determined to be 1:0.6 according to their ^{1}H-NMR integration. The ^{1}H and ^{13}C-NMR data of **3** was very similar to that of **2**, except that isopentanoyl in **2** was replaced by the 2-methylbutyl group, which was confirmed by HMBC correlations. The absolute configuration at C-4 in the 2-methylbutyl group was also established by alkaline hydrolysis method, and was suggested as *R* by the negative α_D value {$[\alpha]_D^{25}$ −8.0 (c 0.05, MeOH)} of the 2-methylbutyric acid. Thus the structure of **3** was established as (*E*)-3, 5-dimethoxy-4-(2*R*-methylbutyryloxy)phenylpropanol acelate, which was named dichrocephol C.

Compound **4**, a colorless oil, had the molecular formula $C_{22}H_{24}O_6$, as determined by analysis of its HRESIMS (*m/z* 385.1640 $[M+H]^+$). Analysis of the ^{1}H and ^{13}C-NMR data revealed the same structural of (*E*)-3, 5-dimethoxyphenylpropanol acelate as those in compound **2** and **3**. The ^{1}H-NMR signals at δ_H 2.90 (2H, t, *J* = 6.5 Hz, H-2′), 3.05 (2H, t, *J* = 6.5 Hz, H-3′), 7.23 (1H, m, *J* = 7.0, 1.5 Hz, H-4‴), 7.36

(4H, m, H-2‴, 3‴, 5‴, 6‴), and the HMBC correlations from δ_H 3.05 (H-3′) to δ_C 170.8 (C-1′), 141.7 (C-1‴), 129.3 (C-2‴, 6‴) both indicated the existence of the phenylpropionyl group [12,13]. The HMBC correlations from δ_H 4.71 (H-9) to δ_C 170.8 (C-1″ and C-1′ were overlapped) could not determine that the phenylpropionyloxy and acetyloxy groups was connected with C-4 or C-9, whereas taking account for the chemical shift values and compared with NMR data of compounds **1**–**3**, the phenylpropionyloxy group was supposed to connect to C-4. This hypothesis was also supported by the EIMS spectra the same way as those of **2** (Figure 3). Therefore, compound **4** was characterized as (*E*)-3, 5-dimethoxy-4-phenylpropionyloxyphenylpropanol acetate, which was named dichrocephol D.

Figure 3. EIMS fragment ions of **2** and **4**.



The sinapyl alcohol derivatives exhibited notable cytotoxicity against KB, BEL-7404 cancer cell lines [14] and HIV-1 replication [15]. Therefore, compounds **1**–**5** were tested for their cytotoxicity against HeLa cell lines [16] and inhibitory effect against COX-2 [17] by applying MTT and initial velocity method respectively. The results showed that compounds **1**–**3** showed moderate cytotoxic activities against HeLa cells with IC_{50} values of 14.8 μM, 51.6 μM, and 81.6 μM respectively. All of these compounds had no significant effect against COX-2 enzyme unfortunately.

3. Experimental

3.1. General

Optical rotations were measured on a Perkin-Elmer 241 polarimeter (Waltham, MA, USA), and UV data were recorded on Beckman Coulter DU 800 spectrometer (Tokyo, Japan). IR data were recorded using a Shimadzu FTIR-8400S spectrophotometer (Tokyo, Japan). ^{1}H and ^{13}C-NMR data were acquired with a Bruker 600 (Munich, Germany) and Bruker 500 instruments using the solvent signals (CD_3OD: δ_H 3.30/δ_C 49.0, CD_3COCD_3: δ_H 2.05/δ_C 29.9, 206.7) as references. HRESIMS data were acquired using a LTQ Orbitrap XL mass spectrometer (Santa Clara, CA, USA). EIMS data were recorded on a GCMS-QP 2010 Shimadzu spectrometer (Tokyo, Japan). Sephadex LH-20 (Pharmacia Biotech AB, Uppsala, Sweden), diatomaceous silica, silica gel (80–100, 100–200, 200–300 mesh) and silica gel GF254 sheets (0.20–0.25 mm) (Qingdao Marine Chemical Plant, Qingdao, China) were used for column chromatography and TLC, respectively.

3.2. Plant Material

The whole herb of *D. benthamii* was collected from Xishuangbanna county, Yunnan Province of People's Republic of China in October 2008. The sample was identified by one of the authors C. Z. Peng and the voucher specimen (No. DB2008) has been deposited in the Herbarium of the Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences, Beijing.

3.3. Extraction and Isolation

The air-dried and chopped whole herbs of *D. benthamii* (20 kg) were extracted with 95% EtOH (3 × 80 L) at 70 °C for 1 h/two times. The 95% EtOH extracts were concentrated under reduced pressure at 50 °C. The residue (1.7 kg) was subject to the diatomaceous silica (45 × 18 cm, 1.8 kg) and bathed successively with petroleum ether, CH_2Cl_2, EtOAc and MeOH. The petroleum ether part (275 g) was subject to silica gel column chromatography (CC) (45 × 12 cm, 80–100 mesh, 2.0 kg), using petroleum ether–Me_2CO gradient elution (1:0–0:1) to afford 6 corresponding fractions (A–F). Fraction C (43 g) was fractionated over silica gel CC (50 × 12.5 cm, 100–200 mesh, 1.0 kg) using petroleum ether-Me_2CO elution (30:1) to give seven fractions (C-1–C-7). The mixture of **2** and **3** (290 mg) was isolated from fraction C-4 (4.4 g) by further chromatography over silica gel CC (60 × 4.5 cm, 200–300 mesh, 220 g), using petroleum ether-Me_2CO (30:1) elution. Fraction C-5 (1.6 g) was further fractionated by silica gel CC (50 × 3.5 cm, 200–300 mesh, 80 g) using petroleum ether-Me_2CO (10:1) elution to give five fractions (C-5a–C-5e). Fraction C-5c (50 mg) was purified by semipreparative HPLC (70% aqueous MeOH, 2 mL/min, 210 nm) to afford **2** (t_R 34.4 min; 33.0 mg). Fraction C-5d (100 mg) was purified by semipreparative HPLC (80% aqueous MeOH, 2 mL/min, 210 nm) to afford **4** (t_R 20.0 min; 9.0 mg). Fraction E (26 g) was fractionated by silica gel CC (50 × 3.5 cm, 100–200 mesh, 0.5 kg) using petroleum ether-Me_2CO elution (5:1) to give four fractions (E-1–E-4). Fraction E-4 (3.8 g) was fractionated over silica gel CC (60 × 4.0 cm, 200–300 mesh, 200 g) using petroleum ether-Me_2CO elution (4:1) to give three fractions (E-4a–E-4c). Fraction E-4b (150 mg) was purified by semipreparative HPLC (65% aqueous MeOH, 2 mL/min, 210 nm) to afford **5** (t_R 27.8 min; 4.9 mg) and **1** (t_R 29.2 min; 17.9 mg).

3.4. Spectral Data

Dichrocephol A (**1**): colorless oil; $[\alpha]_D^{25}$ −2.55 (c 0.19, MeOH); UV (MeOH) λ_{max} (log ε) 219 (2.4); IR (KBr) ν_{max} 2967, 1757, 1596, 1507, 1463, 1244, 1147, 845 cm^{-1}; EIMS *m/z* (%): 294 $[M]^+$ (3), 210 (88), 182 (28), 167 (23), 77 (13), 57 (100); HRESIMS *m/z*: 317.1358 $[M+Na]^+$ (calcd for $C_{16}H_{22}O_5Na$, 317.1365); ^{1}H-NMR (600 MHz, CD_3OD) and ^{13}C-NMR (150 MHz, CD_3OD) data see Table 1.

Dichrocephol B (**2**): colorless oil; UV (MeOH) λ_{max} (log ε) 220 (2.6); IR (KBr) ν_{max} 2959, 1738, 1597, 1507, 1456, 1245, 1132 cm^{-1}; EIMS *m/z* (%): 336 $[M]^+$ (3), 252 (100), 209 (26), 149 (8), 57 (41); HRESIMS *m/z* 359.1510 $[M+Na]^+$ (calcd for $C_{18}H_{24}O_6Na$, 359.1471); ^{1}H-NMR (600 MHz, CD_3COCD_3) and ^{13}C-NMR (150 MHz, CD_3COCD_3) see Table 1.

Dichrocephol C (**3**): colorless oil; $[\alpha]_D^{25}$ −4.80 (c 0.06, acetone); UV (acetone) λ_{max} (log ε) 230 (3.7); IR (KBr) ν_{max} 2964, 1732, 1597, 1244, 1130, 848 cm^{-1}; EIMS *m/z* (%): 336 $[M]^+$ (3), 252 (100), 209 (26),

149 (8), 105 (5), 77 (5), 57 (41); HRESIMS *m/z* 359.1510 $[M + Na]^+$ (calcd for $C_{18}H_{24}O_6Na$, 359.1471); ^{1}H-NMR (600 MHz, CD_3COCD_3) and ^{13}C-NMR (150 MHz, CD_3COCD_3) data see Table 1.

Dichrocephol D (**4**): colorless oil; UV (MeOH) λ_{max} (log ε) 218 (2.4); IR (KBr) ν_{max} 2936, 1738, 1597, 1506, 1455, 1245, 1131, 965, 847 cm^{-1}; EIMS *m/z* (%): 384 $[M]^+$ (4), 327 (8), 267 (13), 252 (100), 209 (19), 134 (41), 105 (61), 91 (85), 77 (35), 55 (100); HRESIMS *m/z*: 385.1640 $[M+H]^+$ (calcd for $C_{22}H_{25}O_6$, 385.1651); ^{1}H-NMR (500 MHz, CD_3COCD_3) and ^{13}C-NMR (125 MHz, CD_3COCD_3) see Table 1.

Table 1. ^{1}H and ^{13}C-NMR Spectroscopic Data for dichrocephols A–D (**1**–**4**).

Pos	**1** [a] (*J* in Hz)		**2** [b] (*J* in Hz)		**3** [b] (*J* in Hz)		**4** [b] (*J* in Hz)	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	137.2 C		135.6 C		134.6 C		135.8 C	
2	104.3 CH	6.79 s	104.2 CH	6.85 s	103.5 CH	6.62 s	104.3 CH	6.87 s
3	153.7 C		153.4 C		152.4 C		153.5 C	
4	130.7 C		135.6 C		134.6 C		135.8 C	
5	153.8 C		153.4 C		152.4 C		153.5 C	
6	104.3 CH	6.79 s	104.2 CH	6.85 s	103.5 CH	6.62 s	104.3 CH	6.87 s
7	131.4 CH	6.61 d (16.2)	134.1 CH	6.65 d (16.2)	134.2 CH	6.57 d (15.6)	134.2 CH	6.68 d (16.0)
8	130.7 CH	6.39 dt (16.2, 5.4)	125.0 CH	6.36 dt (16.2, 6.6)	123.6 CH	6.20 dt (15.6, 6.6)	125.1 CH	6.39 dt (16.0, 6.5)
9	63.6 CH_2	4.27 dd (5.4, 1.8)	65.2 CH_2	4.70 dd (6.0, 0.6)	65.0 CH_2	4.71 dd (6.6, 0.6)	65.2 CH_2	4.71 dd (6.5, 1.5)
OCH_3	56.6 CH_3	3.84 s	56.4 CH_3	3.83 s	56.2 CH_3	3.81 s	56.6 CH_3	3.83 s
1′	176.5 C		170.9 C		174.5 C		170.8 C	
2′	42.4 CH	2.66 m	43.4 CH_2	2.41 d (7.2)	41.1 CH	2.68 m	35.8 CH_2	2.90 t (6.5)
3′	28.1 CH_2	1.64 m, 1.80 m	26.7 CH	2.24 m	27.1 CH_2	1.61 m, 1.83 m	31.6 CH_2	3.05 t (6.5)
4′	11.9 CH_3	1.07 t (7.2)	22.5 CH_3	1.06 d (6.6)	11.6 CH_3	1.03 t (7.8, 7.2)		
5′	17.4 CH_3	1.30 d (7.2)	22.5 CH_3	1.06 d (6.6)	16.9 CH_3	1.29 d (6.6)		
1″			170.9 C		170.9 C		170.8 C	
2″			20.8 CH_3	2.04 s	21.1 CH_3	2.10 s	20.9 CH_3	2.04 s
1‴							141.7 C	
2‴-6‴							129.3 C	7.36 m
4‴							127.1 C	7.23 tt (7.0, 1.5)

[a] recorded in CD_3OD; [b] recorded in CD_3COCD_3.

3.5. Absolute Configurations at C-4 in the 2-Methylbutyryl Group of Compounds **1** *and* **3**

A mixture of **2** and **3** (20.0 mg) was dissolved in EtOH (2.0 mL) and treated with 5% KOH in H_2O (4.0 mL). After stirring at room temperature for 24 h, the reaction mixture was concentrated and then partitioned between EtOAc and H_2O. After extraction with EtOAc three times, the aqueous layer was acidified with HCl to pH = 3.0 and then extracted with CH_2Cl_2 three times. The CH_2Cl_2 layer was combined and subjected to Sephadex LH-20 CC (CH_2Cl_2–MeOH, 1:1) to yield a mixture of 2-methybutyric acid and isopentoic acid (1.5 mg). Since isopentoic acid is optically inactive, the absolute configuration at C-4 of 2-methybutyric acid was identified as *R* by the α_D value of $\{[\alpha]_D^{25}$ −8.0 (c 0.05, MeOH)$\}$. In the same way, the absolute configuration of C-4 in the 2-methylbutyryl group of **1** was also established as *R* by its α_D value of $\{[\alpha]_D^{25}$ −4.6 (c 0.04, MeOH)$\}$.

3.6. Bioassays

The cytotoxic activities of the isolated compounds were evaluated against HeLa cell line by MTT colorimetric method with 5-fluorouracil as positive control (IC_{50} value 5.9 μM). The inhibitory effect of compounds **1**–**5** on COX-2 (sheep) enzyme (Gayman 760111) were tested by initial velocity method.

4. Conclusions

Four new sinapyl alcohol derivatives dichrocephols A–D **1**–**4** were isolated from the lipo-soluble part of the whole herb of *Dichrocephala benthamii* C. B. Clarke, together with the known syringenin isovalerate (**5**). Compounds **1**–**3** showed moderate cytotoxities against HeLa cells with IC_{50} values of 14.8 μM, 51.6 μM and 81.6 μM respectively. This is the first time that sinapyl alcohol derivatives were isolated from the genus *Dichrocephala*.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/18/2/1720/s1.

Acknowledgements

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Sample Availability: Samples of dichrocephols **A**–**D** are available from the authors.

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