TẠP CHÍ KHOA HỌC
TRƯỜNG ĐẠI HỌC QUY NHƠN

Thành phần hóa học từ cành cây Máu chó đá (*Knema saxatilis)*

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TÓM TẮT

Nghiên cứu thành phần hóa học của cành cây Máu chó đá *Knema saxatilis* đã phân lập được 6 hợp chất. Cấu trúc hóa học của chúng được xác định dựa trên các phổ MS và NMR, đó là 8-hydroxy eriodictyol (**1**), (2S)-7-hydroxy-3′,4′-methylenedioxideflavan (**2**), sitostenone (**3**), protocatechuic acid **(4)**, 4-hydroxybenzoic acid **(5)** và vanillin **(6).** Trong 6 hợp chất phân lập có **1** và **3-6** là các hợp chất lần đầu tiên được báo cáo cho chi *Knema.*

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Chemical constituents of stems of *Knema saxatilis*

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ABSTRACT

Phytochemical study of *Knema saxatilis* stems led to the isolation of six known compounds. Their chemical structures were determined as 8-hydroxy eriodictyol (**1**), (2*S*)-7-hydroxy-3′,4′-methylenedioxideflavan (**2**), sitostenone (**3**), protocatechuic acid **(4)**, 4-hydroxybenzoic acid **(5)** and vanillin **(6)** using NMR and MS spectral data. Among the isolated compounds, compounds **1** and **3-6** were reported for the first time from the genus *Knema.*

Keywords: *Knema saxatilis*, *flavonoid, phenolic acid, flavan, sterol*.

1. INTRODUCTION

Knema saxatilis, locally called "Mau cho da", is a native plant in Vietnam with red resins in the bark, referred to the word "mau cho" in its local name. *Knema* species have been used in the traditional medicine for the treatment of skin diseases, sore throat pains and cancers.[1] Previous chemical studies of *Knema* species led to the isolation of phenol lipid derivatives, flavonoids, lignans, terpenes and sterols.[2-7] Plants in this genus exhibited possessed a wide range of pharmacological effects such as anticancer, antidiabetic, antibacterial and anti-inflammatory activities.[2-7]

In the continuation of our study on *Knema* plants in Vietnam,[8-12] we reported herein the isolation and elucidation of six compounds including 8-hydroxy eridictyol (**1**), (2*S*)-7-hydroxy-3′,4′-methylene- dioxideflavan (**2**), sitostenone (**3**), protocatechuic acid **(4)**, 4-hydroxybenzoic acid **(5)**, and vanillin **(6)**. Their structures were determined by comparison of their NMR and MS spectral data with the reported literature.

2. MATERIALS AND METHODS

2.1. Plant materials

The plant stems were collected in Quangtri province, Vietnam in 2015. The plant was identified as *Knema saxatilis* de Wilde by Dr. Nguyen Quoc Binh, Vietnam Museum of Nature. A voucher specimen (VN-1672) was preserved at the Institute of Marine Biochemistry, VAST.

2.2. General experimental procedures

The ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra were obtained by a Bruker AM500

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FT-NMR spectrometer using TMS as an internal standard and chemical shift are expressed in ppm. The ESI-MS spectra were recorded on an Agilent 1260 LC/MS system. Column chromatography (CC) was carried out on silica gel (Merck, 230-400 mesh) or Sephadex® LH-20. Thin layer chromatography used precoated silica gel plates (Merck 60 F_{254}). Compounds were visualized by UV lamp (254 nm) or spraying with 10% sulfuric acid and heating.

2.3. Extraction and isolation

The dried, powdered plant materials of *K. saxatilis* (1.12 kg) were consecutively macerated (3L x 3 times, 1 day/time) with hexane, ethyl acetate and MeOH at room temperature. The organic extracts were combined and removed *in vacuo* to afford hexane (5 g), ethyl acetate (14.2 g) and MeOH residue (53 g), respectively.

The hexane and EtOAc residue (19 g) was subjected to a silica gel CC (4 cm size) and eluted using gradient solvents hexane/EtOAc (100:1 to 0:1, v/v) to afford 8 fractions (F1-F8). Fraction F2 (370 mg) was fractionated on silica gel CC (2 cm size), eluted with hexane/EtOAc (19:1, v/v) to afford three sub-fraction F2.1-F2.3. Sub-fraction F2.1 (80 mg) was purified by silica gel CC (1.5 cm size), eluted with hexane/CH_2Cl_2 to give **3** (7 mg). Fraction F5 (830 mg) was separated on silica gel CC (2.5 cm size) using hexane/EtOAc (19:1, v/v) as eluent to give five fractions F5.1-F.5.5. Fraction F5.1 (70 mg) was purified on silica gel CC (1.5 cm size) and eluted with CH_2Cl_2/MeOH (99/1, v/v) to yield **2** (3.5 mg). Fraction F5.2 (150 mg) was separated on silica gel CC (2 cm size), eluted with hexane/EtOAc (19:1, v/v) to afford four sub-fractions F5.2.1-F5.2.4. Sub-fraction F5.2.3 (30 mg) was further purified on silica gel CC (1 cm size) and eluted with CH_2Cl_2/MeOH (99/1, v/v) to yield **6** (4 mg). Fraction F7 (260 mg) was separated on Sephadex® LH-20 CC (2 cm size) using CH_2Cl_2/MeOH (2/8, v/v) as eluent to give four fraction F7.1-F7.4. Fraction F7.4 (15 mg) was purified on silica gel CC (1 cm size) and eluted with CH_2Cl_2/MeOH (99/1, v/v) to yield **5** (4 mg).

The MeOH residue (53 g) was fractionated on silica gel CC (4 cm size) and eluted using gradient solvents CH_2Cl_2/MeOH (100/1 to 0/1, v/v) to afford 12 fractions M1-M12. Fraction M6 (1.7 g) was purified on Sephadex® LH-20 (2.5 cm size) eluted with CH_2Cl_2/MeOH (1/9, v/v) to afford four sub-fraction M6.1-M6.4. Fraction M6.2 (110 mg) was purified on Sephadex® LH-20 CC (1.5 cm size) using CH_2Cl_2/MeOH (2/8, v/v) to give **4** (13 mg). Fraction M6.3 (70 mg) was separated on silica gel CC (1.5 cm size), eluted with CH_2Cl_2/acetone (8/2, v/v) to yield **1** (5 mg).

8-Hydroxy eriodictyol (1) white solid, $[\alpha]_D^{25}$ –50° (*c* 0.3, MeOH); ESI-MS: *m/z* 305 $[M+H]^+$. ^{1}H-NMR (500 MHz, $CDCl_3$+ CD_3OD) δ (ppm): 6.94 (1H, d, *J* = 2.0 Hz, H-2'), 6.85 (1H, d, *J* = 8.0 Hz, H-5'), 6.81 (1H, dd, *J* = 2.0 Hz, 8.0 Hz, H-6'), 5.97 (1H, s, H-6), 5.27 (1H, dd, *J* = 12.5 Hz, 3.0 Hz, H-2), 3.06 (1H, dd, *J* = 17.0 Hz, 12.5 Hz, H-3a), 2.73 (1H, dd, *J* = 17.0 Hz, 3.0 Hz, H-3b). ^{13}C-NMR (125 MHz, $CDCl_3$+ CD_3OD) δ (ppm): 196.2 (C-4), 166.9 (C-7), 163.7 (C-9), 163.3 (C-5), 145.3 (C-4′), 144.9 (C-3′), 130.4 (C-1′), 126.0 (C-8), 118.5 (C-6′), 115.3 (C-5′), 113.5 (C-2′), 102.5 (C-10), 96.6 (C-6), 79.1 (C-2), 43.1 (C-3).

(2*S*)-7-hydroxy-3′,4′-methylenedioxideflavan (**2**) white solid, $[\alpha]^{25}_D$: -14.2 (c 0.4; $CHCl_3$). ESI-MS: *m/z* 271 $[M+H]^+$. ^{1}H-NMR (500MHz, $CDCl_3$), δ (ppm): 6.92 (1H, d, *J* = 8.0 Hz, H-5), 6.91 (1H, s, H-2′), 6.87 (1H, d, *J* = 8.5 Hz, H-6′), 6.81 (1H, d, *J* = 8.5 Hz, H-5′), 6.39 (1H, d, 8.0 Hz H-6), 6.38 (1H, s, H-8), 5.95 (1H, s, H-7′), 4.95 (1H, dd, *J* = 10 Hz, H-2), 2.88 and 2.70 (2H, m, H-4), 2.13 and 2.03 (2H, m, H-3).^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 155.8 (C-9), 154.9 (C-7), 147.7 (C-3′), 147.2 (C-4′), 135.6 (C-1′), 130.1 (C-5), 119.6 (C-6′), 114.1

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(C-10), 108.2 (C-5′), 108.0 (C-6), 106.7 (C-2′), 103.5 (C-8), 101.1 (C-7′), 77.8 (C-2), 30.0 (C-4), 24.4 (C-3).

Sitostenone (**3**) white solid. ESI-MS m/z 413 $[M+H]^+$. ^{1}H-NMR (500MHz, $CDCl_3$), δ (ppm): 5.72 (1H, s, H-40), 1.17 (3H, s, H-19), 0.91 (3H, d, J = 6.5 Hz, H-21), 0.84 (3H, t, J = 7.5 Hz, H-29), 0.83 (3H, d, J = 7.0 Hz, H-27), 0.81 (3H, d, J = 7.0 Hz, H-26), 0.70 (3H, s, H-18). **^{13}C-NMR** (125 MHz, $CDCl_3$), δ (ppm): 199.6 (C-3), 171.7 (C-5), 123.7 (C-4), 56.0 (C-14), 55.9 (C-17), 53.8 (C-9), 45.9 (C-24), 42.4 (C-13), 39.6 (C-12), 38.6 (C-10), 36.1 (C-20), 35.7 (C-1), 35.6 (C-8), 34.0 (C-2), 33.9 (C-22), 33.0 (C-6), 32.1 (C-7), 29.2 (C-25), 28.2 (C-16), 26.1 (C-23), 24.2 (C-15), 23.1 (C-28), 21.0 (C-11), 19.8 (C-26), 19.0 (C-27), 18.7 (C-21), 17.4 (C-19), 12.0 (C-29), 11.9 (C-18).

Protocatechuic acid (4): brown solid. ESI-MS *m/z* 155 $[M+H]^+$. ^{1}H-NMR (500MHz, $CDCl_3$+ CD_3OD), δ (ppm): 7.41 (1H, d, J = 1.5 Hz, H-2), 7.41 (1H, dd, J = 8.5 Hz, J =1.5 Hz, H-6), 6.76 (1H, d, J = 8.5 Hz, H-5). ^{13}C-NMR (125 MHz, $CDCl_3$+ CD_3OD), δ (ppm): 169.4 (COOH); 149.6 (C-4); 144.0 (C-3), 123.2 (C-1), 121.6 (C-6); 116.4 (C-5); 114.5 (C-2).

4-Hydroxybenzoic acid (5): brown solid. ESI-MS *m/z* 139 $[M+H]^+$. ^{1}H-NMR (500MHz, CD_3OD), δ (ppm): 7.85 (2H, d, J = 8.5 Hz, H-2, H-6), 6.76 (2H, d, J = 8.5 Hz, H-3, H-5). ^{13}C-NMR (125 MHz, CD_3OD), δ (ppm): 169.9 (COOH), 163.1 (C-4), 133.0 (C-2, C-6), 122.6 (C-1), 116.0 (C-3, C-5).

Vanillin (**6**): pale yellow solid. ESI-MS *m/z* 153 $[M+H]^+$. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ (ppm): 9.83 (1H, s, CHO), 7.43 (2H, m, H-2, H-6), 7.04 (1H, d, J = 8.5 Hz, H-5), 6.26 (1H, OH), 3.97 (3H, s, OMe). **^{13}C-NMR** (125 MHz, $CDCl_3$), δ (ppm): 190.8 (CHO), 151.8 (C-3), 147.2 (C-4), 129.8 (C-1), 127.4 (C-6), 114.4 (C-5), 108.8 (C-2), 56.0 (OMe).

3. RESULTS AND DISCUSSION

Compound **1** was isolated as a white solid. The ESI-MS spectrum revealed a pseudo-molecular ion peak at *m/z* 305 $[M+H]^+$, suggested the molecular formula of **1** is $C_{15}H_{12}O_7$ (M= 304). The ^{1}H NMR spectrum showed signals of a flavanone structure with three protons of an ABX system at δ_H 6.94 (1H, d, J = 2.0 Hz, H-2'), 6.85 (1H, d, J = 8.0 Hz, H-5'), 6.81 (1H, dd, J = 2.0 Hz, 8.0 Hz, H-6'), an aromatic singlet at δ_H 5.97 (1H, s, H-6). In addition, signals of benzopyranone moiety were observed with a signal at δ_H 5.27 (1H, dd, J = 12.5 Hz, 3.0 Hz, H-2) and 2 protons at δ_H 3.06 (1H, dd, J = 17.0 Hz, 12.5 Hz, H-3a) and 2.73 (1H, dd, J = 17.0 Hz, 3.0 Hz, H-3b). The ^{13}C-NMR showed 15 carbon signals of a flavanone including a carbonyl carbon at δ_C 196.2 (C-4), 12 aromatic carbons ranging from 166.9 to 96.6 ppm, an oxymethine carbon at δ_C 79.1 (C-2) and a methylene group at δ_C 43.1 (C-3). In the HMBC spectrum, the correlations of H-6 (δ_H 5.97) to C-7 (δ_C 166.9), C-5 (δ_C 163.3) and C-10 (δ_C 102.5) were observed, suggested a hydroxyl group was substituted at C-8 (Fig. 2). Based on above spectral evidences, compound **1** was identified as 8-hydroxy eriodictyol. The analytical NMR data of **1** are in accordance with those published.[13]

Compound **2** was obtained as a white solid. The ESI-MS showed a protonated molecular ion peak *m/z* 271 $[M+H]^+$, corresponding to $C_{16}H_{14}O_4$ (M= 270) molecular formula. The ^{1}H NMR spectrum revealed signals of a flavan structure with signal of two ABX systems at δ_H 6.91 (1H, s, H-2′), 6.87 (1H, d, J = 8.5 Hz, H-6′), 6.81 (1H, d, J = 8.5 Hz, H-5′) and 6.92 (1H, d, J = 8.0 Hz, H-5), 6.39 (1H, d, 8.0 Hz H-6), 6.38 (1H, s, H-8), a methylenedioxide group at δ_H 5.95 (1H, s, H-7′)

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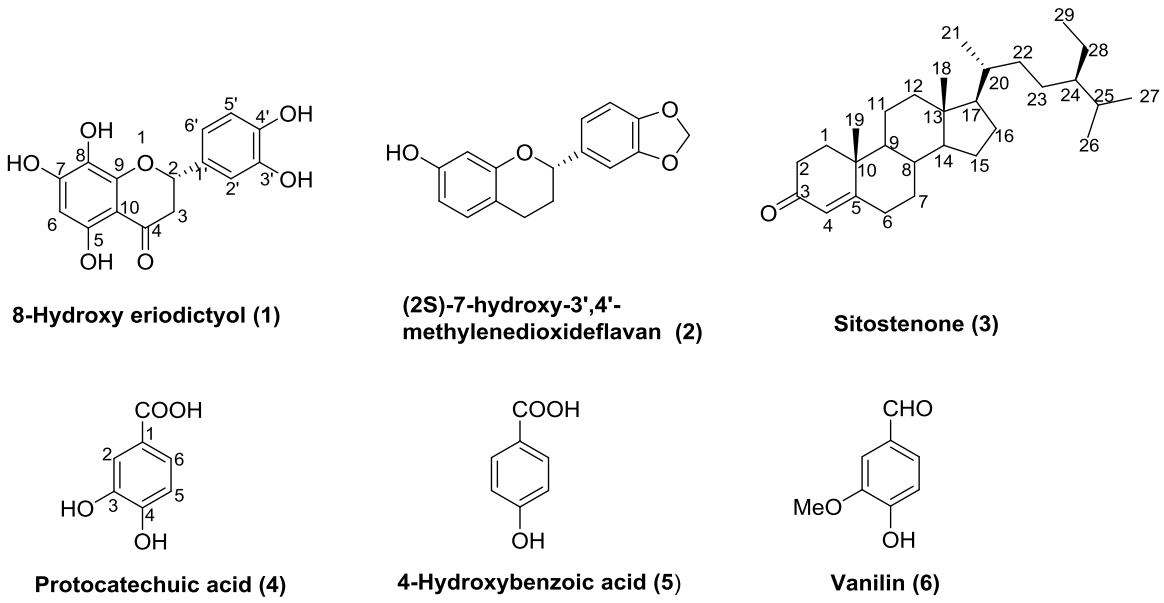

Figure 1. Chemical structures of isolated compounds **1-6** from *K. saxatilis* stems.

and signals of pyrane ring at δ_H 4.95 (1H, dd, J = 10 Hz, H-2), 2.88 and 2.70 (2H, m, H-4), 2.13 and 2.03 (2H, m, H-3). The ^{13}C-NMR showed 16 carbon signals of a flavan including 12 aromatic carbons ranging from 155.9 to 103.5 ppm, an methylenedioxide carbon at δ_C 101.1 (C-7′) and 3 signals at δ_C 77.8 (C-2), 30.0 (C-4) and 24.4 (C-3). In the HMBC spectrum, the correlations of H-7′ to C-3′ and C-4′; H-3, H-6, H-8 to C-10 were observed (Fig. 2). Compound **2** was determined as (2*S*)-7-hydroxy-3′,4′-methylenedioxideflavan by comparision of NMR and optical rotation data with those reported in the literature.[14-15] Compound **2** has been isolated from *K. pachycarpa* [16] and *K. laurina* stem barks.[17]

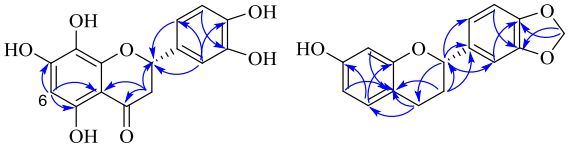

Figure 2. Key HMBC correlations of compound **1-2**.

Compound **3** was obtained as a white solid, The ESI-MS spectrum exhibited a protonated ion at *m/z* 413 $[M+H]^+$, corresponding to $C_{29}H_{48}O$ (M = 412) molecular formula. The ^{1}H-NMR spectrum showed characteristic signals of a steroid with 6 methyl group including 2 singlets at δ_H 1.17 (3H, s, H-19), 0.70 (3H, s, H-18), 3 doublets at δ_H 0.91 (3H, d, J = 6.5 Hz, H-21), 0.83 (3H, d, J = 7.0 Hz, H-27) and 0.81 (3H, d, J = 7.0 Hz, H-26) and a triplet at δ_H 0.84 (3H, t, J = 7.5 Hz, H-29), an olefinic proton at δ_H 5.71 (1H, s, H-4). The ^{13}C-NMR showed 29 carbon signals including 6 methyl groups at δ_C 19.8, 19.0, 18.7, 17.4, 12.0 , 11.9 (C-26, C-27, C-21, C-19, C-29, C-18); a carbonyl signal at δ_C 199.6 (C-3) and 2 olefinic carbons at δ_C 171.6 (C-5) and 123.7 (C-4). Compound **3** was identified as stigmast-4-en-3-one or sitostenone.[18]

Compound **4** was isolated as a brown solid. The ESI-MS spectrum exhibited a protonated molecular ion peak at *m/z* 155 $[M+H]^+$ corresponding to the molecular formula of $C_7H_6O_4$ (M = 154). The ^{1}H NMR spectrum revealed signals of an ABX system with 3 protons at δ_H 7.41 (1H, d, J = 1.5 Hz, H-2), 7.41 (1H, dd, J = 1.5 Hz, J =8.5 Hz, H-6), 6.76 (1H, d, J = 8.5 Hz, H-5). The ^{13}C-NMR showed 7 carbon signals with a carboxylic signal at δ_C 169.4 (COOH) and six aromatic carbons. Comparing NMR spectral data,[19] **4** was determined as protocatechuic acid.

Compound **5** was isolated as a brown solid. The ESI-MS spectrum showed a pseudo-molecular ion peak at *m/z* 139 $[M+H]^+$ suggested

the molecular formula of **1** is $C_7H_6O_3$ (M= 138). The ^{1}H NMR spectrum displayed signals of an A_2B_2 system with 4 protons at δ_H 7.85 (2H, d, *J* = 8.5 Hz, H-2, H-6), 6.76 (2H, d, *J* = 8.5 Hz, H-3, H-5). The ^{13}C-NMR also showed 7 carbon signals with a carboxylic signal at δ_C 169.9 (COOH) and six aromatic carbons. Compound **5** was assigned as 4-hydroxybenzoic acid by comparison of NMR data with those reported in the previous paper.[19]

Compound **6** was isolated as a pale yellow solid. The ESI-MS spectrum exhibited a protonated molecular ion peak at *m/z* 153 $[M+H]^+$ corresponding to the molecular formula of $C_8H_8O_3$ (M = 152). The ^{1}H NMR spectrum revealed signals of an aldehyde group at δ_H 9.83 (1H, s, CHO), 3 protons of an ABX system at δ_H 7.43 (2H, m, H-2, H-6), 7.04 (1H, d, *J* = 8.5 Hz, H-5), and a methoxy group at δ_H 3.97 (3H, s, OMe). The ^{13}C-NMR showed 8 carbon signals including a carbonyl carbon at δ_C 190.8 (CHO), six aromatic carbons and a methoxy group at δ_C 56.0 (OMe). Compound **6** was identified as vanillin by comparison NMR spectral data with published paper.[20]

4. CONCLUSION

Six known compounds have been isolated and elucidated as 8-hydroxy eriodictyol (**1**), (2*S*)-7-hydroxy-3′,4′-methylenedioxideflavan (**2**), sitostenone (**3**), protocatechuic acid **(4)**, 4-hydroxybenzoic acid **(5)**, and vanillin **(6)** from stems of *K. saxatilis* including. Compounds **1** and **3-6** were found for the first time from *Knema* genus.

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