Two New Cryptoporic Acid Derivatives from the Fruiting Bodies of *Cryptoporus sinensis*

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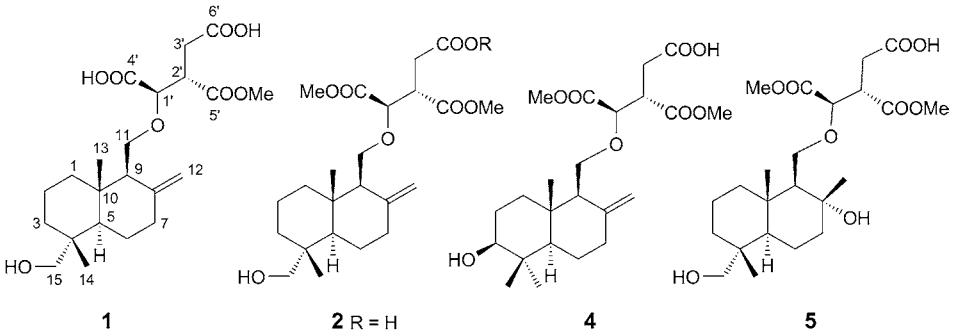
Two new drimane-type sesquiterpenoid ethers of isocitric acid, cryptoporic acids N (**1**) and O (**6**), were isolated from the fruiting bodies of *Cryptoporus sinensis*. Their structures were established by means of spectroscopic methods, including 1D- and 2D-NMR. The cytotoxic activity against a panel of cell lines (A549, MCF-7, PC-3, and PANC-1) was evaluated for all cryptoporic acid derivatives **1**–**12** isolated.

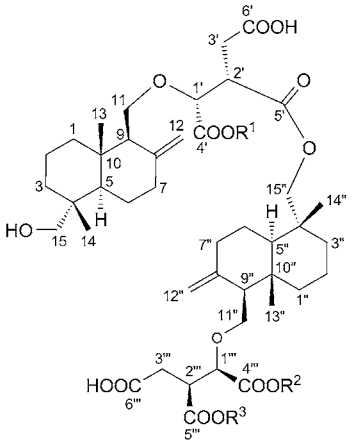
Introduction. – The fruiting bodies of *C. sinensis* have been used for the treatment of asthma and bronchitis in China as a herbal medicine for a long time [1]. In our previous phytochemical investigations on *C. sinensis*, four new drimane-type sesquiterpenoid ethers of isocitric acid, named cryptoporic acids J–M (**4**, **5**, **7**, and **8**), together with the six known cryptoporic acids **2**, **3**, **9**, **10**, **11**, and **12**, which showed nitric oxide production inhibition in macrophages, were isolated [2]. Cryptoporic acid derivatives are unusual in structure; namely, they are drimane-type sesquiterpenoid linked to an isocitric acid moiety *via* an ether bond. Cryptoporic acids also exhibited interesting biological activities, such as strong superoxide-release inhibition and antitumor-promotion activity [3–5]. To search for further new cryptoporic acid derivatives from this fungus, we re-examined the fruiting bodies of *C. sinensis*, which led to the isolation of the two new cryptoporic acid derivatives **1** and **6**. In addition, the cytotoxic activity against a panel of cell lines (A549, MCF-7, PC-3, and PANC-1) was evaluated for all cryptoporic acid derivatives **1**–**12** (*Fig. 1*). Herein, the isolation, structure elucidation, and biological activities of the new compounds **1** and **6** are described.

Results and Discussion. – *Structure Elucidation*. Cryptoporic acid N[1]) (**1**) was obtained as colorless oil. The molecular formula was established as $C_{22}H_{34}O_8$ on the basis of HR-TOF-MS data (*m*/*z* 449.2158 ([*M* + Na]$^+$)). The ^{1}H-NMR spectrum of **1**

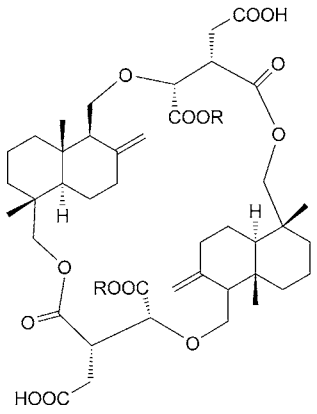
[1]) Arbitrary atom numbering; for systematic names, see *Exper. Part.*



1 **2** R = H, **3** R = Me **4** **5**



	R^1	R^2	R^3
6[1])	Me	H	H
7	Me	H	Me
8	H	H	Me
9	Me	Me	Me
10	Me	Me	H



11 R = H
12 R = Me

Fig. 1. *Compounds* **1**–**12** *isolated from* Cryptoporus sinensis

(*Table 1*) exhibited two quaternary Me signals at δ(H) 0.76 (*s*, Me(14)) and 0.81 (*s*, Me(13)), one MeO group at δ(H) 3.68 (*s*, MeO–C(5′)), two geminal olefinic H-atoms at δ(H) 4.78 and 4.83 (2 br. *s*, CH_2(12)), as well as eight signals between δ(H) 2.56 and 4.10. The ^{13}C-NMR spectrum evidenced an olefinic bond at δ(C) 108.5 and 148.4, three oxygenated C-atoms at δ(C) 69.0, 72.0, and 79.9, and three C=O C-atoms at δ(C) 173.4, 174.0, and 175.3. The C-atom skeleton of **1** showed close resemblance to that of cryptoporic acid B (**2**) by comparing their ^{1}H- and ^{13}C-NMR spectra [6]. The complete assignment was performed by analyses of ^{1}H,^{1}H-COSY, HMQC, and HMBC data. In the HMBC spectrum, the correlations between δ(H) 0.76 (Me(14)) and δ(C) 36.5, 38.9, 49.0, and 72.0, between δ(H) 0.81 (Me(13)) and δ(C) 39.6, 40.0, 49.0, and 56.8 confirmed the location of the two Me groups. The existence of an O-bearing CH_2 group

Table 1. *^{1}H- and ^{13}C-NMR* (500 and 125 MHz, resp.) *Data of Compound* **1**[1]) *in CD_3OD.* δ in ppm, J in Hz.

	δ(H)	δ(C)
CH_2(1)	1.21 – 1.25, 1.51 – 1.58 (2*m*)	40.0
CH_2(2)	1.56 – 1.66 (*m*)	19.6
CH_2(3)	1.36 – 1.38, 1.54 – 1.62 (2*m*)	36.5
C(4)		38.9
H–C(5)	1.19 – 1.21 (*m*)	49.0
CH_2(6)	1.36 – 1.39, 1.64 – 1.70 (2*m*)	24.7
CH_2(7)	2.11 – 2.14, 2.36 – 2.39 (2*m*)	38.4
C(8)		148.4
H–C(9)	2.03 – 2.04 (*m*)	56.8
C(10)		39.6
CH_2(11)	3.59 (*dd*, J = 10.0,3.6), 3.93 – 3.97 (*m*)	69.0
CH_2(12)	4.78, 4.83 (2 br. *s*)	108.5
Me(13)	0.81 (*s*)	16.3
Me(14)	0.76 (*s*)	18.2
CH_2(15)	3.02, 3.37 (2*d*, J = 11.1)	72.0
H–C(1′)	4.10 (*d*, J = 4.9)	79.9
H–C(2′)	3.36 – 3.38 (*m*)	45.8
CH_2(3′)	2.59 (*dd*, J = 17.2, 4.8), 2.76 (*dd*, J = 17.2, 9.6)	33.2
C(4′)		174.0
C(5′)		173.4
C(6′)		175.3
*Me*O–C(5′)	3.68 (*s*)	52.5

at C(4) was verified by the long-range correlations CH_2(15)/δ(C) 18.2, 36.5, 38.9, and 49.0 in combination with the ^{1}H,^{1}H-COSY data. Furthermore, the correlations CH_2(12)/δ(C) 38.4 and 56.8 confirmed the existence of an exocyclic C=C bond. All these data established a drimenol structure as the sesquiterpenoid portion of **1**. An isocitric moiety was confirmed by the HMBC cross-peaks H–C(1′)/δ(C) 174.0 (C(4′)) and 173.4 (C(5′)), H–C(2′)/δ(C) 174.0 (C(4′)), 173.4 (C(5′)), and 175.3 (C(6′)), H–C(3′)/δ(C) 173.4 (C(5′)) and 175.3 (C(6′)), and MeO–C(5′)/δ(C) 173.4 (C(5′)). The connection between the isocitrate and drimenol moiety was determined by the HMBC cross-peaks δ(H) 4.10 (*d*, J = 4.9, H–C(1′)) and δ(C) 69.0 (C(11)). The relative configuration of **1** was established by NOESY analyses (*Fig. 2*). The absolute configurations of C(1′) and C(2′) in the isocitrate moiety were proposed to be either (1′*S*,2′*R*) or (1′*R*,2′*S*) by comparing the signals of H–C(1′) and H–C(2′) with those of the four diastereoisomers of cryptoporic acid A methyl ester synthesized recently [7]. Further comparison of the optical rotation value of **1** ($[\alpha]_D^{25} = +38.2$) and with that of cryptoporic acid I ($[\alpha]_D^{18} = +43.0$) confirmed the (1′*R*,2′*S*) configuration of **1** [8]. Thus, the structure was finally identified as **1** and named cryptoporic acid N.

Cryptoporic acid O[1]) (**6**) was obtained as a colorless oil. The molecular formula was established as $C_{43}H_{64}O_{15}$ on the basis of HR-TOF-MS which showed a quasimolecular-ion peak ($[M + Na]^+$) at m/z 843.4146. The ^{1}H- and ^{13}C-NMR spectrum of **6** (*Table 2*) showed signals corresponding to four Me groups, one MeO, four olefinic H-atoms, four O-bearing CH_2, two ester C=O, and four COO groups. Its ^{1}H- and ^{13}C-NMR spectra

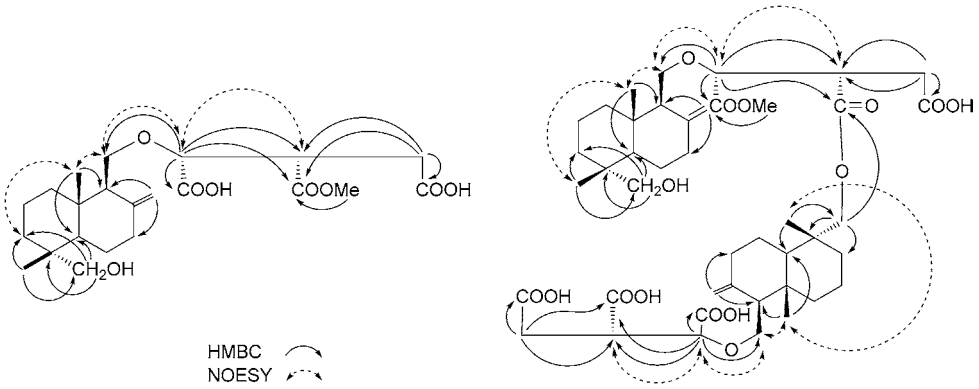


Fig. 2. *Selected HMBC and NOESY correlations of compounds* **1** *and* **6**

Table 2. *^{1}H- and ^{13}C-NMR* (500 and 125 MHz, resp.) *Data of Compound* **6**[1]) *in CD_3OD.* δ in ppm, J in Hz.

	δ(H)	δ(C)		δ(H)	δ(C)
CH_2(1)	1.18–1.24, 1.69–1.81 (2*m*)	39.8	CH_2(1″)	1.24–1.31, 1.69–1.81 (2*m*)	40.2
CH_2(2)	1.51–1.74 (*m*)	19.8[a])	CH_2(2″)	1.51–1.74 (*m*)	19.6[a])
CH_2(3)	1.22–1.30, 1.60–1.68 (2*m*)	36.6	CH_2(3″)	1.30–1.35, 1.46–1.60 (2*m*)	37.0
C(4)		39.1	C(4″)		38.2
H–C(5)	1.45–1.60 (*m*)	49.3	H–C(5″)	1.45–1.60 (*m*)	49.3
CH_2(6)	1.29–1.39, 1.55–1.68 (2*m*)	25.0[b])	CH_2(6″)	1.29–1.39, 1.55–1.68 (2*m*)	24.9[b])
CH_2(7)	2.05–2.15, 2.33–2.40 (2*m*)	38.6	CH_2(7″)	2.05–2.15, 2.33–2.40 (2*m*)	38.6
C(8)		148.5[c])	C(8″)		148.3[c])
H–C(9)	2.06–2.14 (*m*)	56.8	H–C(9″)	2.00–2.04 (*m*)	57.2
C(10)		39.8	C(10″)		39.8
CH_2(11)	3.57–3.61, 3.92–3.97 (2*m*)	69.6[d])	CH_2(11″)	3.55–3.59, 3.93–3.99 (2*m*)	69.2[d])
CH_2(12)	4.81, 4.79 (2*s*)	108.9[e])	CH_2(12″)	4.81, 4.79 (2*s*)	108.7[e])
Me(13)	0.80 (*s*)	16.4	Me(13″)	0.79 (*s*)	16.5
Me(14)	0.74 (*s*)	18.3	Me(14″)	0.83 (*s*)	18.2
CH_2(15)	2.99 (*d*, J = 11.1), 3.35–3.38 (*m*)	72.1	CH_2(15″)	3.59, 3.88 (2*d*, J = 10.9)	74.3
H–C(1′)	4.13–4.14 (*m*)	80.1	H–C(1‴)	4.11–4.13 (*m*)	80.0
H–C(2′)	3.39–3.44 (*m*)	46.3	H–C(2‴)	3.35–3.38 (*m*)	45.9
CH_2(3′)	2.56–2.58 (*m*), 2.80 (*dd*, J = 17.2, 9.8)	33.8	CH_2(3‴)	2.52–2.54 (*m*), 2.73 (*dd*, J = 17.2, 9.8)	33.3
C(4′)		172.8	C(4‴)		175.3
C(5′)		172.6	C(5‴)		173.2
C(6′)		175.8	C(6‴)		175.8
*Me*O–C(4′)	3.78 (*s*)	52.7			

[a])–[e]) Signals are interchangeable.

were quite similar to those of cryptoporic acid F, except for the loss of a MeO group [9]. Compound **6** was deduced to be a dimer, like cryptoporic acid F, which was supported by the ^{1}H,^{1}H-COSY, HMQC, and HMBC data. The substitution by four Me groups was

determined by the HMBC cross-peaks Me(14)/C(3), C(4), C(5), and C(15), Me(13)/C(5), C(9), and C(10), Me(14″)/C(3″), C(4″), C(5″), and C(15″), and Me(13″)/C(5″), C(9″), and C(10″). The HMBC H–C(1′) (δ(H) 4.13–4.14 (*m*))/C(11) and H–C(1‴) (δ(H) 4.11–4.13 (*m*))/C(11″) connected the isocitrate moieties to the drimenol substructures *via* an ether linkage. The position of the MeO group in the isocitrate moiety was deduced from the HMBC MeO (δ(H) 3.78)/C=O (δ(C) 172.8 (C(4′))). The ester connection between the OH group at C(15‴) and the C(5′)OOH group was confirmed by the HMBC from CH_2(15″) (δ(H) 3.59 and 3.88 (2*d*, $J = 10.9$)) to C(5′) (δ(C) 172.6). The relative configuration of **6** was established by NOESY analyses (*Fig. 2*). The absolute configurations of C(1′), C(1‴), C(2′), and C(2‴) in the isocitrate moieties were determined to be (1′*R*,1‴*R*,2′*S*,2‴*S*) in the same way as described for cryptoporic acid L [2]. On the basis of the above data, the structure of **6** was determined and named cryptoporic acid O.

Biological Study. The cytotoxic activity against a panel of cell lines (A549, MCF-7, PC-3, and PANC-1) was evaluated for the isolated cryptoporic acids (*Table 3*). Compounds **2** and **8** exhibited moderate cytotoxicity against PC-3 with an IC_{50} of 79.4 ± 6.6 and 83.0 ± 8.6 μM, respectively. Compound **9** inhibited the growth of PC-3, PANC-1, A549, and MCF-7 with an IC_{50} of 74.0 ± 6.8, 73.8 ± 8.4, 77.0 ± 6.2, and 93.4 ± 7.1 μM, respectively. Compound **12** showed inhibitory activity to PC-3 and PANC-1 with an IC_{50} of 78.5 ± 4.2 and 63.1 ± 3.6 μM, respectively. Compounds **1**, **3**–**7**, **10**, and **11** presented weak cytotoxicity to all cell lines with an IC_{50} larger than 100 μM.

Table 3. *Cytotoxicity of Cryptoporic Acid Derivatives from* Cryptoporus sinensis

	IC_{50} [μM]			
	PC-3	PANC-1	A549	MCF-7
1	> 100	> 100	> 100	> 100
2	79.4 ± 6.6	> 100	> 100	> 100
3	> 100	> 100	> 100	> 100
4	> 100	> 100	> 100	> 100
5	> 100	> 100	> 100	> 100
6	> 100	> 100	> 100	> 100
7	> 100	> 100	> 100	> 100
8	83.0 ± 8.6	> 100	> 100	> 100
9	74.0 ± 6.8	73.8 ± 8.4	77.0 ± 6.2	93.4 ± 7.1
10	> 100	> 100	> 100	> 100
11	> 100	> 100	> 100	> 100
12	78.5 ± 4.2	63.1 ± 3.6	> 100	> 100
Cisplatin	26.8 ± 3.2	26.2 ± 2.4	19.8 ± 2.8	33.2 ± 3.6

HPLC Analysis of the Fruiting-Body Extract. The cryptoporic acid derivatives isolated from the fruiting-body extract of *C. sinensis* are all methylated metabolites. To verify that all these methylated metabolites are authentic natural products, a portion of air-dried fruiting bodies were extracted with AcOEt, and the resulting extract was subjected to reversed-phase HPLC analysis with a linear gradient of MeOH (*A*) and H_2O (0.4‰ CF_3COOH; *B* in H_2O) from 60 to 80% *A* within 20 min, then from 80 to 100% *A* within further 20 min. Compounds **1**–**12** were all identified on the HPLC plot

of the crude extract by comparison of their retention times with those of the pure compounds, indicating that these compounds are indeed naturally occurring metabolites.

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Experimental Part

General. TLC: silica gel *60 F_{254}* (SiO_2); visualized by spraying with 10% H_2SO_4 soln. and heating. Column chromatography (CC): *LH-20* (*Amersham Biosciences*) and *ODS* (*Lobar*, 40–63 μm; *Merck*). Prep. HPLC: *Agilent 1200* system and *ODS* column (*RP-8*, 250 × 10 mm, 5 μm *YMC Pak*); UV detector; flow rate 2.5 ml/min. Optical rotations: *P-1020* digital polarimeter (*Jasco*). IR Spectra: *Magna 750* FT-IR spectrometer (*Nicolet*); $\tilde{\nu}_{max}$ in cm^{-1}. ^{1}H-, ^{13}C-, and 2D-NMR: *Bruker-AV-500* spectrometer; at 500 (^{1}H) and 125 MHz (^{13}C); δ in ppm rel. to Me_4Si as an internal standard, *J* in Hz. ESI-MS: *Bruker-Esquire 2000* spectrometer; in *m*/*z*. HR-TOF-MS: *Bruker-microTOF-Q* instrument; in *m*/*z*.

Plant Material. The fruiting bodies of *Cryptoporus sinensis* were collected from the Yunnan Province of China in March 2010, and identified by Prof. *Xiaoqing Zhang*, Institute of Microbiology, Chinese Academy of Sciences. A voucher specimen (LHW-2010-01) was deposited with the Institute of Microbiology, Chinese Academy of Sciences.

Extraction and Isolation. Dried and powdered fruiting bodies of *C. sinensis* (5.0 kg) were extracted 3 × with EtOH (30 l) at r.t. (for 1 h each time) to give 420 g of crude extract. The residue was dissolved in H_2O (3000 ml) and partitioned with $CHCl_3$ to yield a $CHCl_3$ fraction (*CS-C*, 120.8 g). A portion of *CS-C* (20 g) was roughly separated by CC (SiO_2, CH_2Cl_2/MeOH 1:0 → 0:1): *Frs. CS-C1 – CS-C10*. *Frs. CS-C2* and *CS-C9* contained metabolites different from those described in our earlier report by HPLC analysis [2]. *Fr. CS-C2* (5.6 g) was first applied to CC (*ODS*, gradient MeOH/H_2O 40, 50, 60, 70, 80, 90, and 100%): *Frs. CS-C2.1 – CS-C2.8*). *Fr. CS-C2.4* (1.5 g) was subjected to CC (SiO_2, $CHCl_3$/acetone 1:0 → 0:1): *Frs. CS-C2.4.1 – CS-C2.4.13*. *Fr. CS-C2.4.13* was first separated by CC (*LH-20*, MeOH): *Frs. CS-C.2.4.13.1 – CS-C2.4.13.5*. *Fr. CS-C2.4.13.2* was further purified by reversed-phase HPLC (80% MeOH in 0.4‰ CF_3COOH/H_2O): **1** (7.6 mg; t_R 6.1 min). *CS-C9* (3.8 g) was subjected to CC (*ODS*, gradient MeOH/H_2O 40, 50, 60, 70, 80, 90, and 100%): *Frs. CS-C9.1 – CS-C9.16*. *Fr. CS-C9.13* was further purified by reversed-phase HPLC (55% MeCN in 0.4‰ CF_3COOH/H_2O): **2** (9.8 mg; t_R 20.1 min).

Cryptoporic Acid N (=*(1*R,*2*S*)-1-{[(1*S,*4a*R,*5*R,*8a*S*)-Decahydro-5-(hydroxymethyl)-5,8a-dimethyl-2-methylenenaphthalen-1-yl]methoxy}propane-1,2,3-tricarboxylic Acid 2-Methyl Ester*; **1**): Colorless oil. $[\alpha]_D^{25} = +38.2$ ($c = 0.79$, MeOH). IR (neat): 3413, 2931, 1726, 1641, 1589, 1440, 1408, 1236, 1120, 1039, 892. ^{1}H- and ^{13}C-NMR (MeOH): *Table 1*. ESI-MS (pos.): 449 ($[M+Na]^+$). ESI-MS (neg.): 425 ($[M-H]^-$). HR-TOF-MS (pos.): 449.2158 ($[M+Na]^+$, $C_{22}H_{34}NaO_8^+$; calc. 449.2154).

Cryptoporic Acid O (=*(1*R,*2*S*)-1-{[(1*S,*4a*R,*5*R,*8a*S*)-5-{[(2*S,*3*R*)-2-(Carboxymethyl)-3-{[(1*S,*4a*R,*5*R,*8a*S*)-decahydro-5-(hydroxymethyl)-5,8a-dimethyl-2-methylenenaphthalen-1-yl]methoxy}-4-methoxy-1,4-dioxobutoxy}methyl]decahydro-5,8a-dimethyl-2-methylenenaphthalen-1-yl}methoxy}propane-1,2,3-tricarboxylic Acid*; **6**): Colorless oil. $[\alpha]_D^{25} = +40.1$ ($c = 0.98$, MeOH). IR (neat): 2934, 1726, 1441, 1386, 1205, 1133, 1029, 893. ^{1}H- and ^{13}C-NMR (MeOH): *Table 2*. ESI-MS (pos.): 843 ($[M+Na]^+$). ESI-MS (neg.): 819 ($[M-H]^-$). HR-TOF-MS (pos.): 843.4146 ($[M+Na]^+$, $C_{43}H_{64}NaO_{15}^+$; calc. 843.4137).

Cytotoxicity Assay. A549, MCF-7, PC-3, and PANC-1 cells were seeded in 96-well microtiter plates at 1200 cells/well. After 24 h, the compounds were added to the cells. After 48 h of drug treatment, cell viability was determined by measuring the metabolic conversion of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl-2*H*-tetrazolium bromide) into purple formazan crystals by active cells. MTT-Assay results were read with a microplate reader (*Bio-Rad*) at 570 nm. All compounds were tested at five concentrations (100, 75, 50, 25, and 12.5 μM) and were dissolved in 100% DMSO to give a final DMSO concentration of 0.1% in each well. Each concentration of the compounds was tested in three parallel wells. IC_{50} Values were calculated with *Microsoft Excel* software.

HPLC Analysis of the Fruiting-Body Extract. Dried and powdered fruiting bodies of *C. sinensis* (5.0 kg) were extracted 3 × with EtOH (30 l) at r.t. to give 420 g of crude extract. A portion of the resulting extract was subjected to reversed-phase HPLC analysis (detection at 210 nm, gradient of MeOH (*A*) and 0.4‰ CF_3COOH/H_2O soln. (*B*), *i.e.*, 60–80% *A* from 0–20 min, 80–100% *A* from 20–40 min; flow rate 1 ml/min). Compounds **1**–**12** were all identified in the HPLC of the crude extract by comparing their retention times with those of pure compounds under the same chromatographic conditions. The retention times of compounds **1**–**12** were 7.2 (**1**), 10.1 (**2**), 12.6 (**3**), 8.8 (**4**), 6.3 (**5**), 21.3 (**6**), 19.8 (**7**), 16.6 (**8**), 22.1 (**9**), 20.7 (**10**), 13.2 (**11**), and 21.6 min (**12**).

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