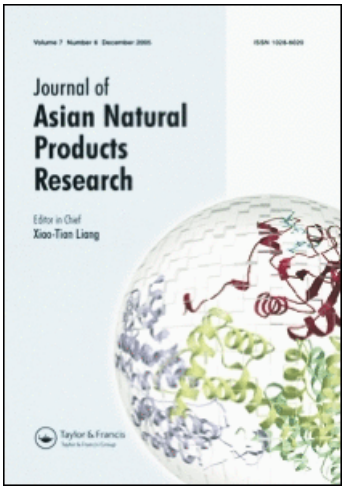

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Synthesis and antimicrobial activity of 3-octyloxy-8-alkyljatrorrhizine derivatives

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By introducing octyloxy to C-3 and alkyl groups to C-8 of jatrorrhizine, a series of 3-octyloxy-8-alkyljatrorrhizine derivatives were synthesized and their antimicrobial activities were evaluated *in vitro*. The results indicated that the derivatives exhibited high antimicrobial activities, especially against Gram-positive bacteria. The 3-octyloxy-8-butyljatrorrhizine displayed the highest antimicrobial activity in all compounds. Their structure–activity relationships were discussed.

Keywords: jatrorrhizine; 3-octyloxy-8-alkyljatrorrhizine derivatives; antimicrobial activity

1. Introduction

Jatrorrhizine (**1**) is a kind of quaternary protoberberine alkaloid (QPA) and is one of the active constituents of *Coptis chinensis* Franch. (*Ranunculaceae*), a traditional Chinese herbal medicine [1]. It has antimicrobial [2], hypoglycemic [3], antiarrhythmic [4], and antioxidant [5] activities and low host toxicity [6]. Substituted derivatives of QPA in the A, C, or D ring exhibit changes in their pharmacological effects. Iwasa *et al.* [7] reported that dioxymethylene replacement at the C-2 and C-3 positions in the A ring, as well as 8-alkyl- or 13-alkyl-substitution [8,9] increased, but 13-hydroxy-substituted derivatives decreased their antibacterial activity [10]. Duk *et al.* [11] reported that benzyl introduced to 13-C of berberine and berberrubine increased the antifungal activities. The antimicrobial activities of 8-alkylberberine derivatives increased with the aliphatic chain elongation and then decreased gradually when the alkyl chain exceeds eight carbon atoms [12]. In our previous study, 3-alkoxyjatrorrhizine derivatives were synthesized and their antimicrobial activities and toxicity were tested *in vitro*. The antimicrobial activities of the substituted derivatives were 32–1000 times higher than that of jatrorrhizine (**1**), which increased as the aliphatic chain was elongated and then decreased slightly when the alkyl chain exceeded eight carbon atoms. 3-Octyloxyjatrorrhizine (**2**) displayed the highest antimicrobial activity of all 3-alkoxyjatrorrhizine derivatives [13]. In this study, we synthesized a series of 3-octyloxy-8-alkyljatrorrhizine derivatives by introducing alkyl groups in C-8 and octyloxy to C-3 of jatrorrhizine and their antimicrobial activities were evaluated *in vitro* to study their structure–activity relationships.

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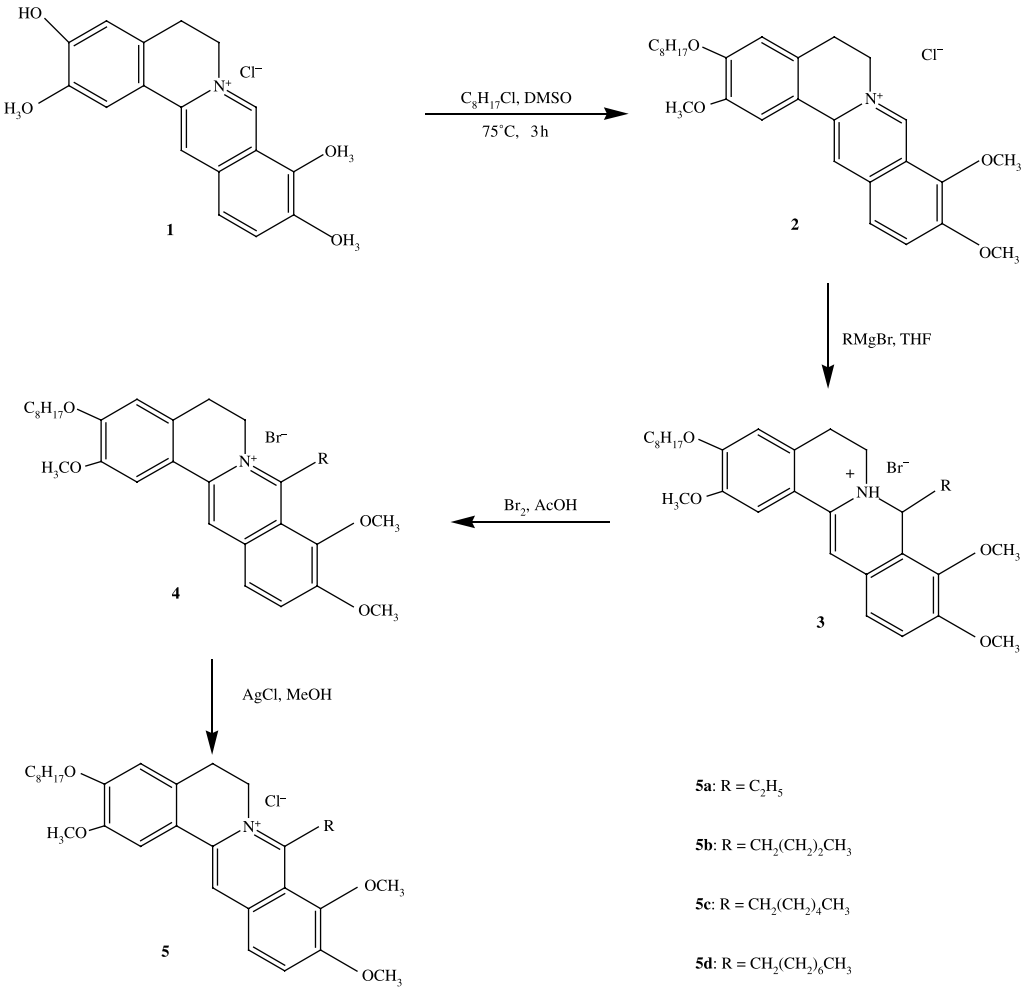

Scheme 1. Synthetic route for compounds **5a**–**d**.

2. Results and discussion

The 3-octyloxy-8-alkyljatrorrhizine derivatives were synthesized successfully (Scheme 1). The yield of the derivatives was decreased from 77.9 to 47.4% as the aliphatic chain length increased. The ^{1}H NMR spectrum showed that the proton signals at δ 9.89 were disappeared and some new proton signals of CH_2/CH_3 appeared. The compounds were deeply analyzed by the ^{13}C NMR, gCOSY, DEPT, and HMQC spectra. The results showed that the alkyl group was attached in position C-8.

The antimicrobial activities of the compounds **5a**–**c** were higher than that of 3-octyloxyjatrorrhizine (**2**) and displayed more potency against bacteria than fungus (Table 1). The antimicrobial activities of compounds **5a**–**d** did not increase as the aliphatic chain length increased. The compound 3-octyloxy-8-butyljatrorrhizine (**5b**) showed the strongest activity against the microbes tested. The antimicrobial activities of compound 3-octyloxy-8-octyljatrorrhizine were even lower than compound 3-octyloxyjatrorrhizine (**2**), which was not similar to the

Table 1. The minimum inhibitory concentration of compounds **2**, **5a–d** (μg/ml).

Compound	No.	Gram-positive bacteria				Gram-negative bacteria		Fungi
		S. aureus	*B. subtilis*	*M. tetragenus*	*B. megaterium*	*E. coli*	*S. enteritidis*	*C. tropicalis*
Berberine	Control	250	125	125	125	250	500	1000
Jatrorrhizine	**1**	320	640	–	–	320	640	–
3-Octyloxy-jatrorrhizine	**2**	0.1563	1.25	20	20	0.625	1.25	80
3-Octyloxy-8-ethyljatrorrhizine	**5a**	0.0781	0.3125	5	10	0.625	0.625	40
3-Octyloxy-8-butyljatrorrhizine	**5b**	0.0391	0.1563	1.25	1.25	0.3125	0.625	20
3-Octyloxy-8-hexyljatrorrhizine	**5c**	0.0781	0.625	2.5	2.5	1.25	5	80
3-Octyloxy-8-octyljatrorrhizine	**5d**	0.625	1.25	20	20	2.5	5	160

The given values are means of three experiments. "–" showed no values given. Tween-80 was used as a blank and berberine as positive control.

8-alkylberberine derivatives and 3-alkoxyjatrorrhizine derivatives [12,13]. We may conclude that by introducing the suitable alkyl groups to jatrorrhizine can increase the antibacterial activity.

3. Experimental

3.1 General experimental procedures

Melting points were determined on an RD-2C electrothermal melting point apparatus and are uncorrected. The UV spectra were recorded on a Hitachi U-1800 spectrophotometer. The IR spectra were carried out on a Perkin-Elmer one IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA 600 (600 MHz) using TMS as the internal standard and DMSO-d_6 as solvent. TLC analysis was used to confirm the purity of the compounds, which was performed on silica gel-GF254 thin layers and developed with a moving phase of $CHCl_3$/MeOH (3:1) and C_6H_6/EtOAc/MeOH/i C_3H_7OH/NH_3 (6:3:1.5:1.5:0.5).

3.2 Synthesis of 3-octyloxyjatrorrhizine

Jatrorrhizine was extracted and purified from *Rhizoma coptidis* according to Ref. [14]. The purity of jatrorrhizine used to synthesize its derivatives was up to 98%. The 3-octyloxyjatrorrhizine was synthesized according to our previous report [13]. The octyl bromate (18 mmol) in DMSO (20 ml) was slowly added to the suspension of jatrorrhizine (15 mmol) and KOH (16.5 mmol) in DMSO (20 ml). After 3 h of reflux at 75°C, the above reactants were poured into 100 ml of cool water and the 3-octyloxyjatrorrhizine bromates would be precipitated immediately. The crude 3-octyloxyjatrorrhizine was washed with distilled water and ethyl acetate thrice, respectively, and be recrystallized thrice from MeOH at −20°C gave 3-octyloxyjatrorrhizine **2** (5.35 g) in 73.4% yield.

3.3 Synthesis of 3-octyloxy-8-alkyljatrorrhizine derivatives

The 3-octyloxy-8-alkyljatrorrhizine derivatives were synthesized according to Ref. [15].

Grignard reagents prepared from Mg turnings (8.8 mmol) and the corresponding alkyl bromides (8 mmol) in absolute THF (10 ml) were slowly added to the suspension of dry 3-octyloxyjatrorrhizine chloride (2 mmol) in absolute THF (10 ml) under N_2 at 0°C. After 2 h of reflux, the 3-octoxyl-8-alkyl-dihydrojatrorrhizine bromides (**3**) were obtained. A mixture of hydrobromides, Br_2 (1.8 mmol) and THF (30 ml), was heated at 50°C; no further change in the composition of the reaction mixture was evident by TLC. After cooling, the precipitates were filtered and washed with 10% $Na_2S_2O_5$ solution and H_2O, respectively. The crude 3-octyloxy-8-alkyljatrorrhizine bromides were obtained, which were crystallized from MeOH. Thereafter, these bromides were added into hot MeOH containing AgCl (1.8 mmol) and converted into corresponding chlorides. Melting points, UV, IR, ^{1}H and ^{13}C NMR, and TLC were used to identify the structures of **5a**–**d**.

*3.3.1 3-Octyloxy-8-ethyljatrorrhizine (**5a**)*

R_f = 0.32, yield: 77.9%; mp 146–150°C; UV (CH_3OH) λ_{max} (nm): 435, 350, 243; IR (KBr) ν_{max} (cm^{-1}): 3075 (CH_{Ar}), 2923 and 2854 (CH), 1604 (Ar), 1520 (C=N), 1469 and 1354 (C—H), 1243–1038 (C—O), 734 ($(-CH_2-)_n$, $n \geqq 4$); ^{1}H and ^{13}C NMR spectral data were shown in Table 2. Elemental analysis: Found: C, 70.10%; H, 7.78%; N, 2.72%; Cl, 6.91%; calcd for $C_{30}H_{40}NClO_4$: C, 70.11%; H, 7.79%; N, 2.73%; Cl, 6.91%.

*3.3.2 3-Octyloxy-8-butyljatrorrhizine (**5b**)*

R_f = 0.34, yield: 64.0%; mp 143–147°C; UV (CH_3OH) λ_{max} (nm): 438, 350, 243; IR (KBr) ν_{max} (cm^{-1}): 3071 (CH_{Ar}), 2929 and 2856 (CH), 1605 (Ar), 1520 (C=N), 1463 and 1352 (CH), 1283–1016 (C—O), 730 ($(-CH_2-)_n$, $n \geqq 4$); ^{1}H and ^{13}C NMR data were shown in Table 2. Elemental analysis: Found: C, 70.92%; H, 8.12%; N, 2.58%; Cl, 6.57%; calcd for $C_{32}H_{44}NClO_4$: C, 70.91%; H, 8.13%; N, 2.59%; Cl, 6.56%.

*3.3.3 3-Octyloxy-8-hexyljatrorrhizine (**5c**)*

R_f = 0.37, yield: 63.0%; mp 137–141°C; UV (CH_3OH) λ_{max} (nm): 439, 352, 243; IR (KBr) ν_{max} (cm^{-1}): 3071 (CH_{Ar}), 2927 and 2855 (CH), 1605 (Ar), 1519 (C=N), 1466 and 1349 (CH), 1278–1018 (C—O), 724 ($(-CH_2-)_n$, $n \geqq 4$); ^{1}H and ^{13}C NMR spectral data were shown in Table 2. Elemental analysis: Found: C, 71.65; H, 8.42; N, 2.45; Cl, 6.24; calcd for $C_{34}H_{48}NClO_4$: C, 71.64; H, 8.43; N, 2.46; Cl, 6.23.

*3.3.4 3-Octyloxy-8-octyljatrorrhizine (**5d**)*

R_f = 0.39, yield: 47.4%; mp 133–137°C; UV (CH_3OH) λ_{max} (nm): 441, 353, 243; IR (KBr) ν_{max} (cm^{-1}): 3072 (CH_{Ar}), 2926 and 2854 (CH), 1605 (Ar), 1520 (C=N), 1466 and 1349 (CH), 1282–1020 (C–O), 724 ($(-CH_2-)_n$, $n \geqq 4$); ^{1}H and ^{13}C NMR spectral data were shown in Table 2. Elemental analysis: Found: C, 72.31; H, 8.68; N, 2.33; Cl, 5.95; calcd for $C_{36}H_{52}NClO_4$: C, 72.30; H, 8.70; N, 2.34; Cl, 5.94.

3.4 Antimicrobial activity

The compounds of **2**, **5a**–**d** were investigated *in vitro* for antimicrobial activity against Gram-positive (G+) bacteria, Gram-negative (G−) bacteria, and a fungus. The minimum inhibitory concentration was evaluated by using the two-fold serial dilution test [16]. Compounds **2**, **5a**–**d** were dissolved in H_2O containing 1% Tween-80 and diluted to different concentrations from 0.0012 to 160 μg/ml with liquid medium. The mixtures of serious dilutions of compounds and the microbes (2×10^8 cfu/ml) in broth medium were incubated at 37°C for 24 h for bacteria and at 25°C for 48 h for the fungus. Microbial growth was examined by measuring the absorbance at 655 nm with a spectrophotometer [17]. The H_2O/Tween-80 was used as a blank and berberine as positive control. All experiments were run in triplicate.

Table 2. ^{1}H and ^{13}C NMR spectral data of compounds **5a–d** (DMSO-d_6; δ in ppm, 600 MHz).

	5a		**5b**		**5c**		**5d**	
No.	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	7.64 (s, 1H)	109.2	7.63 (s, 1H)	109.1	7.63 (s, 1H)	109.8	7.63 (s, 1H)	109.9
2	–	150.7	–	150.7	–	151.5	–	151.5
3	–	148.7	–	148.6	–	149.4	–	149.4
4	7.12 (s, 1H)	111.3	7.11 (s, 1H)	111.2	7.11 (s, 1H)	111.9	7.11 (s, 1H)	112.0
5	3.18 (t, 2H, $J = 6.0$ Hz)	26.1	3.17 (t, 2H, $J = 6.0$ Hz)	26.2	3.17 (t, 2H, $J = 6.0$ Hz)	27.0	3.17 (t, 2H, $J = 6.0$ Hz)	27.0
6	4.84 (t, 2H, $J = 6.0$ Hz)	49.5	4.82 (t, 2H, $J = 6.0$ Hz)	49.6	4.81 (t, 2H, $J = 6.0$ Hz)	50.4	4.81 (t, 2H, $J = 6.0$ Hz)	50.4
8	–	162.0	–	160.9	–	161.6	–	161.7
9	–	152.2	–	152.2	–	153.0	–	153.0
10	–	145.5	–	145.4	–	146.2	–	146.2
11	8.20 (d, 1H, $J = 9.0$ Hz)	125.1	8.20 (d, 1H, $J = 9.0$ Hz)	125.0	8.20 (d, 1H, $J = 9.0$ Hz)	125.8	8.20 (d, 1H, $J = 9.0$ Hz)	125.8
12	8.04 (d, 1H, $J = 9.0$ Hz)	124.4	8.05 (d, 1H, $J = 9.0$ Hz)	124.5	8.05 (d, 1H, $J = 9.0$ Hz)	125.3	8.05 (d, 1H, $J = 9.0$ Hz)	125.2
13	8.87 (s, 1H)	119.6	8.88 (s, 1H)	119.7	8.87 (s, 1H)	120.4	8.87 (s, 1H)	120.3
2-OCH_3	3.93 (s, 3H)	56.1	3.93 (s, 3H)	56.1	3.93 (s, 3H)	56.9	3.93 (s, 3H)	56.9
3-OC_8H_{17}								
1′	4.06 (t, 2H)	68.3	4.05 (t, 2H)	68.3	4.05 (t, 2H)	69.1	4.05 (t, 2H)	69.1
2′	1.77 (m, 2H)	28.6	1.76 (m, 2H)	28.5	1.75 (m, 2H)	29.3	1.77 (m, 2H)	29.4
3′	1.44 (m, 2H)	25.4	1.42 (m, 2H)	25.4	1.44 (m, 2H)	26.2	1.43 (m, 2H)	26.2
4′	1.28–1.35 (m, 2H)	28.6	1.28–1.34 (m, 2H)	28.6	1.28–1.38 (m, 2H)	29.4	1.28–1.38 (m, 2H)	29.4
5′	1.28–1.35 (m, 2H)	28.5	1.28–1.34 (m, 2H)	28.6	1.28–1.38 (m, 2H)	29.4	1.28–1.38 (m, 2H)	29.4
6′	1.28–1.35 (m, 2H)	31.1	1.28–1.34 (m, 2H)	31.2	1.28–1.38 (m, 2H)	31.9	1.28–1.38 (m, 2H)	32.0
7′	1.28–1.35 (m, 2H)	22.0	1.28–1.34 (m, 2H)	22.0	1.28–1.38 (m, 2H)	22.8	1.28–1.38 (m, 2H)	22.8
8′	0.87 (t, 3H)	13.9	0.87 (t, 3H)	13.9	0.88 (t, 3H)	14.7	0.88 (t, 3H)	14.7
9-OCH_3	4.07 (s, 3H)	61.5	4.07 (s, 3H)	61.4	4.07 (s, 3H)	62.2	4.07 (s, 3H)	62.2
10-OCH_3	4.07 (s, 3H)	56.9	4.07 (s, 3H)	56.9	4.06 (s, 3H)	57.7	4.06 (s, 3H)	57.7
8-R								
1″	3.78 (br, 2H)	25.6	3.78 (br, 2H)	32.0	3.77 (br, 2H)	33.0	3.78 (br, 2H)	33.0
2″	1.47 (t, 3H)	12.3	1.80 (m, 2H)	29.8	1.80 (m, 2H)	29.7	1.80 (m, 2H)	30.1
3″			1.62 (m, 2H)	22.5	1.60 (m, 2H)	26.2	1.59 (m, 2H)	26.2
4″			1.03 (t, 3H)	13.6	1.28–1.38 (m, 2H)	28.6	1.41 (m, 2H)	29.3
5″					1.28–1.38 (m, 2H)	22.8	1.28–1.38 (m, 2H)	28.6
6″					0.93 (t, 3H)	14.7	1.28–1.38 (m, 2H)	31.9
7″							1.28–1.38 (m, 2H)	22.8
8″							0.88 (t, 3H)	14.7

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