Alkaloids from the Roots of *Aconitum pseudo-laeve* var. *erectum*[⊥]

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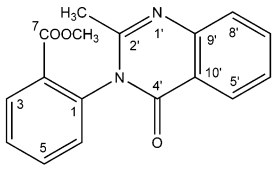
One new quinazoline (**1**) and two new norditerpenoid (**2** and **3**) alkaloids along with 10 known compounds were isolated from the roots of *Aconitum pseudo-laeve* var. *erectum*. The new alkaloids were assigned as 2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoic acid methyl ester (**1**), 18-*O*-2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoyllycoctonine (**2**), and 14-*O*-acetyl-8-*O*-methyl-18-*O*-2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoylcammaconine (**3**). The structures of the new alkaloids were established by spectroscopic methods. This is the first report of the 2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoyl ester group being found as an acyl substituent in norditerpenoid alkaloids (compounds **2** and **3**).

Aconitum pseudo-laeve var. *erectum* Nakai (Ranunculaceae) is a species found in the alpine regions of Korea, Japan, and mainland China. The roots of *A. pseudo-laeve* var. *erectum* are used as an analgesic and antispasmodic agent in traditional Korean folk medicine, and a decoction of the roots is used to treat neuralgic and rheumatic conditions.[1] In addition, the root has been used to treat the common cold.[2] *Aconitum* species containing highly toxic diterpene and norditerpene alkaloids have attracted considerable attention on account of their complex structures, interesting chemistry, and noteworthy physiological effects.[3] Previous studies on this plant have led to the isolation of norditerpene alkaloids, lycoctonine, septentriodine,[4] avadhardine,[5] and anthranilic acid amides[5−7] together with sterols,[8] glycerol 1-hexadecanoate,[6] and the flavonoid astragalin.[8] The acute toxicity of the H_2O and MeOH extracts of the roots of *A. pseudo-laeve* var. *erectum*, which are expressed as LD_{50} values in mice, was reported to be 1.23 and 0.77 g/kg, respectively.[5] Lycaconitine was isolated from this plant and found to be effective in multidrug-resistant cancers.[9]

As part of an ongoing phytochemical investigation of *Aconitum* plants in Korea,[10,11] the present study examined the roots of *A. pseudo-laeve* var. *erectum* and resulted in the isolation of one new quinazoline alkaloid, 2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoic acid methyl ester (**1**), along with two new norditerpene alkaloids, 18-*O*-2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoyllycoctonine (**2**) and 14-*O*-acetyl-8-*O*-methyl-18-*O*-2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoylcammaconine (**3**), as well as 10 known compounds. The known compounds were identified as β-sitosterol,[8] stigmasta-4-en-3-one,[8] stigmasta-4-en-3,6-dione,[8] β-sitosterol glucoside,[8] methyl *N*-(2-acetaminobenzoyl)anthranilate,[6] methyl *N*-acetylanthranilate,[7] lycoctonine,[4] inuline,[12] acobretine E,[13] and methyl *N*-(3-carbamoylpropionyl)anthranilate.[5] This paper reports the isolation and structural elucidation of compounds **1**−**3**.

Compound **1** was obtained as an amorphous powder. The HREIMS showed a molecular ion peak $[M]^+$ at *m*/*z* 294.1003 (calcd 294.1004), which corresponds to the molecular formula $C_{17}H_{14}N_2O_3$. The IR spectrum of **1** showed absorption bands at 1718 (ester), 1689 (C═O), 1595, 1570, 1469 (aromatic), 1282 (C−O), and 1089 (C−O−C) cm^{-1}. The UV absorbances at 227, 231, 266, 273, 306, and 316 nm indicated the presence of a quinazolinone derivative.[14,15]



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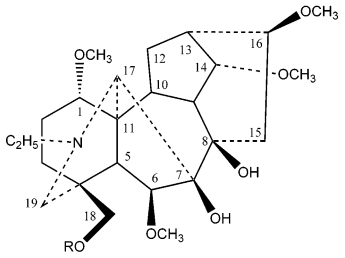
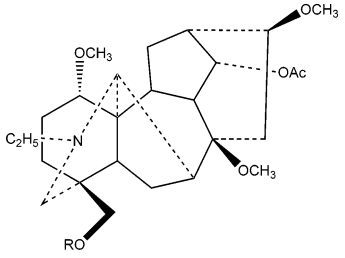


2 R = MOQB



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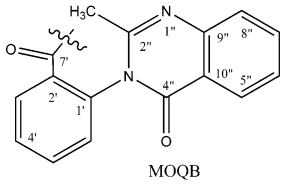

MOQB

The ^1H NMR spectrum exhibited signals at δ_H 2.19 (3H, s, CH_3) and 3.69 (3H, s, OCH_3), and eight aromatic protons (δ_H 7.49−8.22). The $^1H-^1H$ COSY spectrum revealed two sets of 1,2-disubstituted benzene ring systems, indicating that **1** is a 2-methyl-3-aryl-4(3*H*)-quinazolinone derivative.[14−16] The ^{13}C NMR spectrum of compound **1** showed 17 signals, including one methoxy, one methyl, eight methines, and seven quaternary carbons. The $^1H-^{13}C$ correlations were obtained from the HMQC spectrum, while the long-range correlations were determined using the HMBC spectrum. Figure 1 shows the HMBC correlations of H-3 with 7-

[⊥] Dedicated to Dr. Norman R. Farnsworth of the University of Illinois at Chicago for his pioneering work on bioactive natural products.

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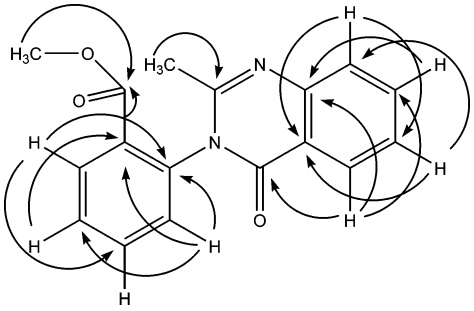

Figure 1. HMBC correlations of compound **1**.

C═O and C-1, H-6 with C-4 and C-2, CH_3-2′ with C-2′, and H-5′ with C-4′, which were used to position the vinyl methyl and carbomethoxyphenyl groups in the 4(3*H*)-quinazolinone moiety. On the basis of the above spectroscopic data, the structure of compound **1** was determined as 2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)-benzoic acid methyl ester. Although compound **1** was previously reported to be a byproduct of imidate synthesis, this is the first report of it being isolated as a natural product.[16]

Compound **2** was isolated as an amorphous powder. The HREIMS showed a molecular ion peak $[M]^+$ at *m*/*z* 729.3463 corresponding to the molecular formula $C_{41}H_{51}N_3O_9$. The spectroscopic data of compound **2** were similar to those of inuline.[12] A comparison of the ^1H and ^{13}C NMR spectra of compound **2** with those of inuline clearly showed the new alkaloid to be a lycoctonine derivative possessing a 2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)-benzoyl (MOQB) ester group [δ_H 8.22 (dd, J = 1.5, 7.8 Hz, H-3′), 7.71 (td, J = 0.6, 7.5 Hz, H-4′), 7.82 (td, J = 1.5, 8.6 Hz, H-5′), 7.45 (dd, J = 1.2, 8.1 Hz, H-6′), 8.16 (ddd, J = 0.6, 1.5, 8.0 Hz, H-5″), 7.55 (ddd, J = 1.2, 7.2, 8.1 Hz, H-6″), 7.88 (ddd, J = 1.8, 7.2, 9.0 Hz, H-7″), 7.71 (td, J = 1.2, 7.5 Hz, H-8″), 2.23 (s, CH_3-2″); δ_C 138.4 (C-1′), 129.8 (C-2′), 133.4 (C-3′), 131.2 (C-4′), 135.6 (C-5′), 131.4 (C-6′), 166.4 (C-7′), 156.5 (C-2″), 163.7 (C-4″), 127.8 (C-5″), 128.2 (C-6″), 136.3 (C-7″), 127.8 (C-8″), 148.7 (C-9″), 122.0 (C-10″), 24.2 (CH_3-2″)] at C-18, instead of an anthranoyl group. A HMBC experiment showed that the proton signals at δ_H 3.99 and 4.10 (1H each, d, J = 11.4 Hz), which were assigned to the nonequivalent C-18 methylene protons, correlated with three-bond connectivities with a carbonyl carbon signal at δ_C 166.4. Therefore, the structure of compound **2** was determined to be 18-*O*-2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoyllycoctonine.

Compound **3** was assigned a molecular formula of $C_{42}H_{51}N_3O_8$, which was established by HREIMS (*m*/*z* 725.3608 $[M]^+$; calcd for $C_{42}H_{51}N_3O_8$, 725.3674), as well as from ^{13}C NMR spectroscopic data and DEPT experiments. The ^1H NMR spectrum of compound **3** displayed resonance signals characteristic of a MOQB norditerpenoid alkaloid, including methyl protons of the alkaloid *N*-ethyl group (δ_H 1.01), the methyl group of the MOQB ester group (δ_H 2.22), three methoxyl groups (δ_H 3.04, 3.20, 3.30), an acetoxyl group (δ_H 1.98), downfield resonances for the methine proton at C-14 (δ_H 4.71), C-18 methylene protons (δ_H 3.78, 3.96), and low-field aromatic protons for the MOQB ester group [δ_H 8.20 (m, H-3′,5″), 7.70 (td, J = 1.2, 7.5 Hz, H-4′), 7.81 (td, J = 1.5, 7.8 Hz, H-5′), 7.43 (dd, J = 0.9, 7.8 Hz, H-6′), 7.58 (m, H-6″), 7.90 (tt, J = 1.5, 8.4 Hz, H-7″), 7.75 (m, H-8″), 2.22 (s, CH_3-2″); δ_C 138.3 (C-1′), 130.1 (C-2′), 133.4 (C-3′), 131.2 (C-4′), 135.4 (C-5′), 131.3 (C-6′), 166.5 (C-7′), 156.4 (C-2″), 163.8 (C-4″), 127.9 (C-5″), 128.3 (C-6″), 136.4 (C-7″), 127.9 (C-8″), 148.7 (C-9″), 122.0 (C-10″), 24.0 (CH_3-2″)]. The $^1H-^1H$ COSY spectrum of compound **3** revealed an oxygenated methine proton vicinal to the methylene protons in a $-CH(O)-CH_2-CH_2-$ fragment, confirming the presence of a methoxy group at C-1. The HMBC experiment showed that the signal at δ_H 4.71 (t, J = 4.8 Hz), which was assigned to the C-14 methine proton, had three-bond connectivities with an acetoxyl C═O (δ_C 173.2), a quaternary carbon (δ_C 79.0), and an oxygenated methine carbon (δ_C 84.7) signal, which were assigned to the C-14 OAc and the C-8 and C-16 methoxyls, respectively. The MOQB ester at C-18 in compound **3** was established by a three-bond correlation in the HMBC spectrum. The configurations at C-1, C-14, and C-16 were established from the similarity of the ^1H and ^{13}C NMR data of **3** to those reported for 8-ethoxysachaconitine[17] and 14-*O*-acetyl-8-*O*-methyltalatizamine.[18] Therefore, the structure of compound **3** was determined to be 14-*O*-acetyl-8-*O*-methyl-18-*O*-2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoylcammaconine. Compounds **2** and **3** are the first examples of the MOQB ester group being found as a substituent in norditerpenoid alkaloids.

Experimental Section

General Experimental Procedures. Optical rotations were determined using a JASCO P-1020 polarimeter. IR and UV spectra were recorded on a JASCO FT/IR-5300 and a Hitachi U-3210 spectrometer, respectively. NMR spectra were obtained using either a Varian Gemini 2000 instrument (300 MHz) or a Bruker AM-500 (500 MHz), and the chemical shifts were referenced to TMS. EIMS were measured using a Hewlett-Packard 5989B spectrometer. FABMS were run in a 3-nitrobenzyl alcohol matrix in the positive-ion mode using a JEOL 700 mass spectrometer. TLC was performed on silica gel $60F_{254}$ (Merck).

Plant Material. The whole plant of *A. pseudo-laeve* var. *erectum* was collected on Mt. Gyerhyong, Korea, in August 2002, and was identified by one of the authors (K.-H.B.), from Chungnam National University, where a voucher specimen (CNU 624) has been deposited.

Extraction and Isolation. The powdered roots of *A. pseudo-laeve* var. *erectum* (1.5 kg) were extracted with MeOH seven times at room temperature. The MeOH extracts were combined and evaporated to dryness under reduced pressure. This extract was partitioned with 3% aqueous NH_4OH and $CHCl_3$. The $CHCl_3$ extract (45 g) was separated by chromatography on a silica gel column into seven fractions (I−VII) with a gradient of MeOH in $CHCl_3$. The precipitate (200 mg) obtained by decantation from fraction I was chromatographed over silica gel (cyclohexane−EtOAc, 40:1) to give β-sitosterol (20 mg) and stigmasta-4-en-3-one (20 mg). The rest of fraction I (9.3 g) was purified over a silica gel column, with hexane−EtOAc (10:1) as the solvent system, yielding stigmasta-4-en-3,6-dione (25 mg), β-sitosterol glucoside (15 mg), and methyl *N*-(2-acetaminobenzoyl)anthranilate (30 mg). Fraction III was chromatographed on silica gel using cyclohexane−EtOAc−diethylamine (10:1:0.2) for elution, which afforded five fractions (III-1−III-5). Fraction III-1 (0.19 g) was further purified by a silica gel column, with cyclohexane−EtOAc−diethylamine (20:1:0.2), to give methyl *N*-acetylanthranilate (15 mg). Fraction III-3 (0.2 g) was further chromatographed over a silica gel column (cyclohexane−EtOAc−diethylamine, 10:1.5:1) and yielded 10 mg of compound **2**. Fraction III-5 (0.4 g) was subjected to repeated column chromatography over silica gel with cyclohexane−EtOAc−diethylamine (5:1:0.2) and purified on silica gel with cyclohexane−EtOAc (40:1) to yield lycoctonine (80 mg). Fraction IV (1.5 g) was subjected to silica gel column chromatography using cyclohexane−EtOAc−diethylamine (10:1.1:0.2) for elution, giving fractions IV-1−IV-10. Fractions IV-1 and IV-3 were chromatographed on a silica gel column using benzene−EtOAc−diethylamine (30:1:0.2) as solvents, giving compound **3** (15 mg) and acobretine E (18 mg), respectively. Fraction V (1.2 g) was further purified by silica gel column chromatography with cyclohexane−EtOAc−diethylamine (30:1:0.2) to afford 10 mg of compound **1**. Fraction VI (1.2 g) was purified over a silica gel column, with benzene−EtOAc−diethylamine (30:1:0.2) as the solvent system, resulting in nine subfractions (VI-1−VI-9). Inuline (25 mg) and methyl *N*-(3-carbamoylpropionyl)anthranilate (25 mg) were isolated from fractions VI-2 and VI-7 by recrystallization from MeOH, respectively.

2-(2-Methyl-4-oxo-4*H*-quinazoline-3-yl)benzoic acid methyl ester [3-(2-carbomethoxyphenyl)-2-methyl-4(3*H*)-quinazolinone] (1): amorphous powder (MeOH); IR (KBr) ν_{max} 3429, 1718 (ester), 1689 (CO), 1595, 1570, 1469 (aromatic C═C), 1379, 1346, 1282, 1089, 777 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 227 (4.23), 231 (4.24), 266 (3.87), 273 (3.85), 306 (3.50), 316 (3.42) nm; ^1H NMR (300 MHz, CD_3OD) δ 2.19 (3H, s, CH_3-2′), 3.69 (3H, s, $COOCH_3$), 7.49 (1H, dd, J = 1.2, 7.8 Hz, H-6), 7.53 (1H, ddd, J = 0.9, 7.3, 8.4 Hz, H-6′), 7.70 (1H, br d, J = 7.5 Hz, H-8′), 7.70 (1H, ddd, J = 1.2, 7.8, 7.8 Hz, H-4), 7.83 (1H, ddd, J =

Table 1. ^{13}C NMR Chemical Shifts for Compounds **2** and **3** (norditerpenoid moiety) in CD_3OD

carbon	**2**	**3**	carbon	**2**	**3**
1	84.9	86.0	15	34.8	36.5
2	27.0	27.3	16	84.3	84.7
3	32.7	33.1	17	65.8	62.3
4	38.2	38.7	18	71.4	71.6
5	51.6	46.5	19	53.2	53.4
6	91.8	24.9	CH_2CH_3	52.0	49.9
7	89.6	41.0	CH_2CH_3	14.3	13.7
8	78.6	79.0	$OCOCH_3$		173.2
9	44.5	44.2			21.3
10	46.7	45.7	OCH_3-1	56.1	56.5
11	50.0	50.0	OCH_3-6	56.3	
12	29.6	29.8	OCH_3-8		48.1
13	39.0	39.7	OCH_3-14	57.9	
14	85.2	77.1	OCH_3-16	58.8	56.4

Table 2. ^{13}C NMR Chemical Shifts for Compounds **1**−**3** (acyl moiety) in CD_3OD

carbon	**1**	carbon	**2**	**3**
1	139.0	1′	138.4	138.3
2	129.2	2′	129.8	130.1
3	133.1	3′	133.4	133.4
4	131.2	4′	131.2	131.2
5	135.5	5′	135.6	135.4
6	131.4	6′	131.4	131.3
7	166.3	7′	166.4	166.5
2′	156.6	2″	156.5	156.4
4′	164.1	4″	163.7	163.8
5′	127.7	5″	127.8	127.9
6′	128.0	6″	128.2	128.3
7′	136.2	7″	136.3	136.4
8′	127.4	8″	127.8	127.9
9′	148.7	9″	148.7	148.7
10′	121.6	10″	122.0	122.0
CH_3-2′	23.8	CH_3-2″	24.2	24.0
$COOCH_3$	52.9			

1.5, 7.8, 7.8 Hz, H-5), 7.86 (1H, ddd, J = 1.5, 7.2, 8.4 Hz, H-7′), 8.16 (1H, ddd, J = 0.6, 1.5, 8.1 Hz, H-5′), 8.22 (1H, dd, J = 1.5, 7.8 Hz, H-3); ^{13}C NMR (75.5 MHz, CD_3OD), see Table 2; FABMS *m*/*z* 295 $[M + H]^+$; EIMS *m*/*z* 294 $[M]^+$ (26), 279 $[M - CH_3]^+$ (5), 261 $[M - (H_2O + CH_3)]^+$ (27), 235 $[M - CH_3COO]^+$ (100), 144 (11), 116 (18), 90 (31), 77 (72); HREIMS *m*/*z* 294.1003 $[M]^+$ (calcd for $C_{17}H_{14}N_2O_3$, 294.1004).

18-*O*-2-(2-Methyl-4-oxo-4*H*-quinazoline-3-yl)benzoyllycoctonine (2): amorphous powder (MeOH); $[\alpha]^{21}_D$ +64.97° (*c* 3.5, MeOH); IR (KBr) ν_{max} 3437, 1722 (ester), 1686 (CO), 1607, 1572, 1489, 1471 (aromatic C═C), 1381, 1292, 1269, 1119, 1088, 775 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.97 (3H, t, J = 7.2 Hz, CH_2CH_3), 1.41 (1H, br s, H-5), 1.52 (1H, dd, J = 6.6, 15.3 Hz, H-15a), 2.23 (3H, s, CH_3-2″), 2.50 (1H, br s, H-19), 2.54 (1H, dd, J = 9.0, 15.3 Hz, H-15b), 2.81 (1H, br s, H-17), 2.91 (1H, dd, J = 4.8, 6.6 Hz, H-9), 3.14 (1H, dd, J = 6.6, 9.0 Hz, H-16), 3.19 (3H, s, OCH_3-1), 3.24 (3H, s, OCH_3-6), 3.28 (3H, s, OCH_3-16), 3.36 (3H, s, OCH_3-14), 3.61 (1H, t, J = 4.5 Hz, H-14), 3.73 (1H, br s, H-6), 3.99, 4.10 (1H each, J = 11.4 Hz, H-18), 7.45 (1H, dd, J = 1.2, 8.1 Hz, H-6′), 7.55 (1H, ddd, J = 1.2, 7.2, 8.1 Hz, H-6″), 7.71 (1H, td, J = 0.6, 7.5 Hz, H-4′), 7.71 (1H, td, J = 1.2, 7.5 Hz, H-8″), 7.82 (1H, td, J = 1.5, 8.6 Hz, H-5′), 7.88 (1H, ddd, J = 1.8, 7.2, 9.0 Hz, H-7″), 8.16 (1H, ddd, J = 0.6, 1.5, 8.0 Hz, H-5″), 8.22 (1H, dd, J = 1.5, 7.8 Hz, H-3′); ^{13}C NMR (75.5 MHz, CD_3OD), see Tables 1 and 2; EIMS *m*/*z* 729 $[M]^+$ (21), 701 $[M - CO]^+$ (32), 700 $[M - (CO + H)]^+$ (76), 684 $[M - (CO + OH)]^+$ (100), 668 $[M - (CH_3OH + CO + H)]^+$ (67), 436 [norditerpene moiety (467) − $CH_3O]^+$ (21), 406 $[436 - 2CH_3]^+$ (58), 281 (100), 263 $[MOQB]^+$ (100), 235 (100), 146 (57), 71 (89); HREIMS *m*/*z* 729.3463 $[M]^+$ (calcd for $C_{41}H_{51}N_3O_9$, 729.3625); HRFABMS *m*/*z* 730.3698 $[M + H]^+$ (calcd for $C_{41}H_{52}N_3O_9$, 730.3703).

14-*O*-Acetyl-8-*O*-methyl-18-*O*-2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoylcammaconine (3): amorphous powder (MeOH); $[\alpha]^{21}_D$ −10.4° (*c* 1.3, MeOH); IR (KBr) ν_{max} 3437, 1726 (ester), 1686 (CO), 1609, 1572, 1491, 1471 (aromatic C═C), 1379, 1292, 1252, 1115, 1088, 775 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.01 (3H, t, J = 7.2 Hz, CH_2CH_3), 1.98 (3H, s, OAc), 2.22 (3H, s, CH_3-2″), 2.71 (1H, br s, H-17), 2.79 (1H, dd, J = 6.6, 9.9 Hz, H-1), 3.04, 3.20, 3.30 (3H each, s, OCH_3), 4.71 (1H, t, J = 4.8 Hz, H-14), 3.78, 3.96 (1H each, J = 11.1 Hz, H-18), 7.43 (1H, dd, J = 0.9, 7.8 Hz, H-6′), 7.58 (1H, m, H-6″), 7.70 (1H, td, J = 1.2, 7.5 Hz, H-4′), 7.75 (1H, m, H-8″), 7.81 (1H, td, J = 1.5, 7.8 Hz, H-5′), 7.90 (1H, tt, J = 1.5, 8.4 Hz, H-7″), 8.20 (2H, m, H-3′, 5″); ^{13}C NMR (75.5 MHz, CD_3OD), see Tables 1 and 2; FABMS *m*/*z* 726 $[M + H]^+$; EIMS *m*/*z* 726 $[M + H]^+$ (16), 695 $[M - OCH_3]^+$ (100), 634 $[M - (CH_3COOH + OCH_3)]^+$ (34), 633 $[M - (CH_3COOH + CH_3OH)]^+$ (76), 432 [norditerpene moiety (463) − $CH_3O]^+$ (100), 400 $[432 - CH_3OH]^+$ (40), 282 (97), 263 $[MOQB]^+$ (100), 236 (93), 121 (49), 71 (75); HREIMS *m*/*z* 725.3608 $[M]^+$ (calcd for $C_{42}H_{51}N_3O_8$, 725.3674).

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