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NEW ACYL DERIVATIVES OF *N*-DEACETYLLAPPACONITINE

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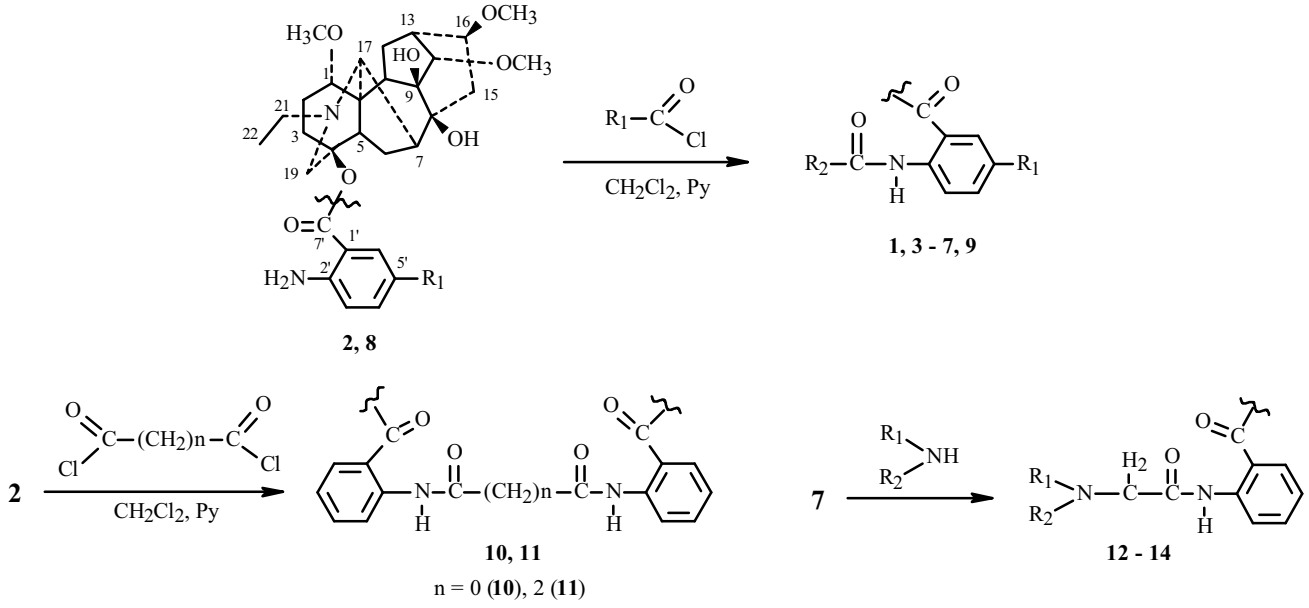
New N-*acylates of the norditerpenoid alkaloid* N-*deacetyllappaconitine that were modified in the aromatic ring and are interesting as potential pharmacologically valuable compounds were prepared.*

Key words: diterpenoid alkaloids, *N*-deacetyllappaconitine, *N*-deacetyl-5′-bromolappaconitine, glycylamides.

The C_{18}-bisnorditerpenoid alkaloid lappaconitine (**1**), which is produced by several species of the plant genus *Aconitum*, is a rather common plant metabolite [1, 2]. It is of interest because its hydrobromide salt (Allapinine preparation) (**1**) is an effective antiarrhythmic agent [3-5] that also exhibits psychotropic [6] and analgesic [7] activity. The principal metabolite of this alkaloid is *N*-deacetyllappaconitine (**2**) [8]. Alkaloid **2** was isolated from several *Aconitum* species (*A. septentrionale*, *A. leucostomum*, *A. orientale*) [9-12] and possesses antiarrhythmic, local anesthetic, analgesic, sedative, and anti-inflammatory activity [12-16]. The antiproliferative activity of certain C_{19}-norditerpenoid alkaloids was recently reported [17-19]. Therefore, the investigation of synthetic transformations of diterpenoid alkaloids in order to discover new derivatives that combine high biological activity and reduced toxicity is timely. Recent studies have shown the promise of this approach [16, 20, 21]. Herein we describe the synthesis of derivatives of *N*-deacetyllappaconitine modified in the aromatic ring.



R_1 = H (**2 - 7**), Br (**8, 9**); R_2 = CH_3 (**1**), Ph (**3, 9**), C(=CH_2)CH_3 (**4**), CH=$CHCH_3$ (**5**), CH=CHPh (**6**), CH_2Cl (**7**)
R_1 = R_2 = Et (**12**); R_1 + R_2 = -$(CH_2)_2O(CH_2)_2$- (**13**), -$(CH_2)_2$-N(CH_3)-$(CH_2)_2$- (**14**)

Scheme 1

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TABLE 1. Chemical Shifts of C Atoms in ^{13}C NMR Spectra of New *N*-Deacetyllappaconitine Derivatives, δ, ppm

Atom	**3**	**4**	**5**	**6**	**7**	**9**	**10**	**11**	**12**	**13**	**14**
C-1	83.64	84.16	84.11	84.48	83.83	83.65	83.82	83.84	83.68	83.80	84.13
C-2	26.31	26.39	25.71	26.59	26.26	26.28	26.37	29.46	26.76	26.44	26.92
C-3	31.29	31.38	31.34	31.64	31.25	31.30	31.26	31.68	31.70	31.57	31.98
C-4	84.21	83.80	83.69	83.99	84.36	85.21	84.35	84.25	84.17	83.70	83.98
C-5	47.90	48.09	48.04	48.36	48.34	47.71	48.32	48.06	48.58	48.15	48.56
C-6	23.61	23.69	22.14	23.91	23.68	23.64	23.67	23.90	24.01	23.74	24.03
C-7	47.11	47.18	47.10	47.35	47.17	47.13	47.16	47.33	47.44	47.12	47.62
C-8	75.08	75.25	75.08	75.42	75.25	75.16	75.24	75.38	75.56	75.24	75.49
C-9	78.08	78.15	78.07	78.32	78.16	78.12	78.15	78.29	78.46	78.16	78.45
C-10	49.34	49.38	49.36	49.59	49.38	49.34	49.37	49.22	49.79	49.52	49.85
C-11	50.48	50.55	50.46	50.74	50.56	50.52	50.54	50.71	50.84	50.55	50.86
C-12	25.74	25.83	24.76	26.00	25.80	25.80	25.78	25.99	26.17	25.83	26.16
C-13	35.79	35.89	35.78	36.07	35.88	35.87	35.86	36.08	36.28	35.97	36.27
C-14	89.62	89.73	89.62	89.92	89.73	89.67	89.72	89.88	90.09	89.77	90.06
C-15	44.28	44.47	44.30	44.66	44.43	44.39	44.41	44.60	44.44	44.47	44.72
C-16	82.41	82.50	82.41	82.67	82.48	82.45	82.47	82.64	82.83	82.50	82.79
C-17	60.93	61.10	61.01	61.35	61.05	60.99	61.03	61.32	61.54	61.10	61.48
C-19	55.02	55.06	55.00	55.29	54.82	55.02	54.81	55.28	55.46	55.36	55.57
C-21	48.46	48.55	48.54	48.80	48.56	48.50	48.55	48.82	48.29	48.55	48.87
C-22	13.05	13.14	13.06	13.37	13.18	13.10	13.17	13.25	13.34	13.03	13.43
1-OCH_3	56.03	56.14	56.05	55.92	56.20	56.12	56.12	56.32	56.00	56.02	56.37
14-OCH_3	57.40	57.52	57.40	57.72	57.49	57.49	57.48	57.69	57.80	57.49	57.77
16-OCH_3	55.62	55.71	55.00	55.91	55.70	55.68	55.69	55.91	56.00	55.70	55.97
C-1′	115.81	115.83	115.37	115.69	117.17	117.41	117.16	115.62	117.29	116.50	116.61
C-2′	141.38	141.27	141.41	141.68	139.25	140.51	139.24	141.33	140.55	140.33	140.79
C-3′	119.92	119.92	119.90	120.29	120.06	121.71	120.05	120.09	120.45	120.06	120.25
C-4′	133.94	133.94	133.86	134.24	133.76	136.76	133.75	134.07	133.63	133.66	133.96
C-5′	120.05	121.99	121.77	122.27	123.43	114.50	123.42	122.05	122.25	122.19	122.36
C-6′	130.70	130.70	130.63	130.95	130.95	132.97	130.94	130.83	130.75	130.62	130.86
C-7′	167.18	166.48	167.00	167.18	166.26	166.08	166.25	167.05	166.16	166.21	166.40
NHC=O	165.18	167.11	163.96	164.01	158.01	165.23	158.00	170.29	172.03	169.28	169.88

*For **3**: C (2″,6″) - 126.94; C (3″,5″) - 128.27; C (4″) - 131.35; C (1″) - 134.45; **4**: ($\underline{C}H_3C$=) - 18.27; ($\underline{C}H_2$=) - 120.55; $\underline{C}(CH_3)=CH_2$ - 140.44; **5**: ($\underline{C}H_3$) - 17.36; C(2″) - 126.21; C (1″) - 140.70; **6**: C (7″) - 121.87; C (2″,6″) - 127.90; C (3″,5″) - 128.59; C (4″) - 129.68; C(1″) - 134.52; C (8″) - 142.06; **7**: $\underline{C}H_2Cl$ - 43.15; **9**: C (2″,6″) - 126.39; C (3″,5″) - 126.98; C (4″) - 131.61; C (1″) - 134.15; **11**: $\underline{C}H_2$ - 32.61; **12**: $\underline{C}H_2$×2 - 48.89; $\underline{C}H_3$×2 - 11.99; $NH\underline{C}H_2(C=O)$ - 58.97; **13**: C (2″,6″) - 53.42; C (3″,5″) - 66.42; $NH\underline{C}H_2(C=O)$ - 62.61; **14**: ($\underline{C}H_3N$) - 45.84; C (2″,6″) - 53.04; C (3″,5″) - 54.63; $NH\underline{C}H_2(C=O)$ - 62.35.

According to our results, the reaction of *N*-deacetyllappaconitine (**2**) with benzoic, metacrylic, crotonic, cinnamic, and 2-chloroacetic acid chlorides in anhydrous CH_2Cl_2 in the presence of pyridine gives the corresponding *N*-acyl derivatives of *N*-deacetyllappaconitine (**3-7**) (yields 72-86%). The reaction of *N*-deacetyl-5′-bromolappaconitine (**8**) [22] with benzoylchloride under analogous conditions gives **9** (Scheme 1). The reaction of **2** with oxalylchloride or succinyldichloride (0.5 eq) produced aconitane-type bivalent ligands **10** and **11** (yields 65-71%). Monosubstituted products were not formed via reaction of **2** with oxalylchloride or succinyldichloride. A minor impurity of starting alkaloid in the products was removed by washing the resulting precipitate with ethanol. Aconitane-type bivalent ligands joined through the $C^{2'}$ positions were prepared for the first time. We prepared previously dimeric compounds with two lappaconitine moieties joined through the $C^{5'}$ positions using the Glaser reaction and oxidative coupling of 5′-ethynyllappaconitine [23].

Compound **7**, which contains a chloroacetamide in the aromatic ring, was next used to prepare anthranilate glycylamides. Thus, reaction of *N*-deacetyllappaconitine chloroacetate (**7**) with diethylamine, morpholine, or *N*-methylpiperazine occurred upon storing a mixture of the reagents in anhydrous THF and gave the corresponding *N*-substituted glycylamides **12-14** (yields 61-74%).

The compositions and structures of the synthesized compounds (**3-7** and **9-14**) were confirmed by mass, IR, PMR, and ^{13}C NMR spectra and elemental analyses. Thus, IR spectra of all compounds contained absorption bands at 1675-1693 cm^{-1} (1-amide band and conjugated carbonyl), 3297-3305 cm^{-1} (*trans*-associated NH), and 3400-3540 cm^{-1} (OH). Resonances of H and C atoms in NMR spectra of **3-7** and **9-14** were assigned based on 2D NMR spectra of **7** and **11-14** and taking into account literature data for lappaconitine [24]. Table 1 lists the ^{13}C NMR spectra. The principal differences in the ^{13}C NMR spectra were the differences in the chemical shifts of $C^{1'}$, $C^{2'}$, and the amide C atom. The same set of principal resonances for C atoms were observed for dimeric structures **10** and **11**.

Thus, several new derivatives of **2** modified in the anthranilate moiety were synthesized. Compounds **3**, **6**, **9**, and **12-14** are potentially interesting in view of literature reports [25, 26] of the activity of anthranilic amides as inhibitors of Xa-factor, i.e., the compounds are promising for developing antithrombolytic agents. Furthermore, biarylanthranilates are becoming more and more interesting as agonists of niacin receptors. The compounds are promising for creating preparations for treating cardiovascular diseases [27].

EXPERIMENTAL

NMR spectra in $CDCl_3$ were recorded on a Bruker AV-300 instrument at operating frequency 300.13 MHz (^1H) and 75.47 MHz (^{13}C). The multiplicity of resonances in ^{13}C NMR spectra were determined by standard methods for recording spectra with J-modulation (JMOD). 2D NMR ^1H—^1H (COSY) and ^{13}C—^1H (COSY) spectra (COSY 125 Hz, COLOC 7 Hz) of **7**, **11**, **12**, **13**, and **14** in $CDCl_3$ were recorded on a Bruker DRX-500 instrument at operating frequency 500.13 MHz (^1H) and 125.76 MHz (^{13}C) using standard Bruker programs. IR spectra in KBr disks were recorded on a Vector-22 instrument. Mass spectra were recorded in a Finnigan MAT 8200 high-resolution mass spectrometer at ionizing potential 70 eV. Molecular weights of dimeric **10** and **11** in CH_3OH were determined by HPLC-MSD. We used an Agilent 1100 Series instrument and LC/MSD with direct introduction of the solution into the solvent flow (CH_3OH). Samples were ionized by electrospray at atmospheric pressure (API-ES). The solvent flow was 0.3 mL·min^{-1}; carrier gas (N_2) flow, 10 L·min^{-1}; temperature 340°C. The N_2 pressure in the sprayer was 30 psi.

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates using $CHCl_3$:EtOH (20:1).

Compounds **2** and **8** were prepared by acid hydrolysis of lappaconitine and 5′-bromolappaconitine by the literature methods [28, 22], respectively.

General Method for Synthesizing 3-7. A solution of **2** (0.542 g, 1 mmol) in dry CH_2Cl_2 (10 mL) was treated with the corresponding acid chloride (1.1 mmol) and pyridine (0.5 mL, distilled), stirred at room temperature for 2 h, washed with NH_4OH (25%) and water, dried over anhydrous $MgSO_4$, and evaporated. The resulting compound was dissolved in benzene and evaporated to remove pyridine. The workup was repeated three times. The resulting amorphous solid was dried in vacuo (oil pump).

1-[4β-(8β,9β-Dihydroxy-1α,14α,16β-trimethoxy-20-ethylaconitan-4-yl)]-2-benzamidobenzoate (3). Yield 78%, mp 140-142°C, $C_{37}H_{46}N_2O_8$. IR spectrum (ν, cm^{-1}): 704, 757, 1081, 1100, 1495, 1530, 1589, 1607, 1676, 3256, 3304, 3485.

PMR spectrum (δ, ppm, J/Hz): 1.11 (3H, t, J = 7, CH_3), 1.63 (1H, ddd, J_1 = 15.6, J_2 = 7.3, J_3 = 1.5, H_b-6), 1.84 (1H, m, H_b-3), 1.95-2.02 (3H, m, H-3,10,15), 2.12-2.17 (2H, m, H-2,12), 2.26 (1H, m, H-2), 2.32-2.58 (6H, m, H-5,6,12,13,15,19,21), 2.62-2.70 (2H, m, H-3,21), 2.99 (1H, s, H-17), 3.17 (1H, dd, J_1 = 10.8, J_2 = 5.8, H_a-1), 3.30 (1H, m, H-16), 3.27, 3.28, 3.38 (9H, 3H each, all s, 1-, 16-, and 14-OCH_3, respectively), 3.41 (1H, d, J = 5.5, H-14), 3.57 (1H, d, J = 11.2, H_a-19), 7.05 (1H, ddd, J_1 = 8.0, J_2 = 8.2, J_3 = 1.5, H-5′), 7.40-7.55 (4H, m, H-4′,3″,4″,5″), 7.95 (1H, dd, J_1 = 8.0, J_2 = 1.8, H-6′), 7.99 (1H, dd, J = 8.2, H-2″,6″), 8.85 (1H, dd, J_1 = 8.3, J_2 = 1.5, H-3′), 11.98 (1H, s, NH).

1-[4β-(8β,9β-Dihydroxy-1α,14α,16β-trimethoxy-20-ethylaconitan-4-yl)]-2-metacrylamidobenzoate (4). Yield 86%, mp 132-134°C, $C_{34}H_{46}N_2O_8$. IR spectrum (ν, cm^{-1}): 700, 1086, 1100, 1143, 1265, 1525, 1588, 1600, 1631, 1682, 2819, 3258, 3303, 3526.

PMR spectrum (δ, ppm, J/Hz): 1.10 (3H, t, J = 7, CH_3), 1.60 (1H, dd, J_1 = 15.4, J_2 = 7.5, H_b-6), 1.82 (1H, m, H_b-3), 1.95-2.02 (3H, m, H-7,10,15), 2.06 (3H, s, CH_3 on C-4″), 2.04-2.17 (2H, m, H-2,12), 2.26 (1H, m, H-2), 2.32-2.41 (3H, m, H-5,6,12), 2.48-2.70 (6H, m, H-3,21,13,15,19,21), 2.99 (1H, s, H-17), 3.17 (1H, dd, J_1 = 10.2, J_2 = 5.6, H_a-1), 3.30 (1H, m, H-16), 3.27, 3.29, 3.39 (9H, 3H each, all s, 1-, 16-, 14-OCH_3, respectively), 3.42 (1H, d, J = 5.6, H-14), 3.55 (1H, d, J = 11.2,

H_a-19), 5.49 (1H, s, H-3″), 5.94 (1H, s, H-3″), 7.02 (1H, dd, J_1 = 8.0, J_2 = 8.3, H-5′), 7.49 (1H, ddd, J_1 = 8.0, J_2 = 8.3, J_3 = 1.6, H-4′), 7.92 (1H, dd, J_1 = 8.0, J_2 = 1.6, H-6′), 8.73 (1H, d, J_1 = 8.3, H-3′), 11.53 (1H, s, NH).

(*E*)-1-[4*β*-(8*β*,9*β*-Dihydroxy-1*α*,14*α*,16*β*-trimethoxy-20-ethylaconitan-4-yl)]-2-but-2-enamidobenzoate (5). Yield 80%, mp 124-126°C, $C_{34}H_{46}N_2O_8$. IR spectrum (ν, cm^{-1}): 700, 1086, 1100, 1143, 1266, 1525, 1588, 1600, 1631, 1682, 2819, 3258, 3303, 3526.

PMR spectrum (δ, ppm, J/Hz): 1.08 (3H, t, J = 7, CH_3), 1.56 (1H, dd, J_1 = 15.4, J_2 = 7.5, H_b-6), 1.78 (1H, m, H_b-3), 1.89 (1H, dd, J_1 = 10.4, J_2 = 2.5, H-15), 1.98 (1H, m, H-10), 2.12 (1H, m, H-12), 2.12 (3H, s, C-4″), 2.20-2.36 (2H, m, H-2,7), 2.39-2.71 (10H, m, H-2,3,5,6,12,13,15,19,21,21), 2.96 (1H, s, H-17), 3.12 (1H, dd, J_1 = 11.2, J_2 = 5.6, H_a-1), 3.30 (1H, m, H-16), 3.25, 3.27, and 3.40 (9H, 3H each, all s, 1-, 16-, and 14-OCH_3, respectively), 3.39 (1H, d, J = 5.4, H-14), 3.55 (1H, d, J = 11.2, H_a-19), 5.98 (1H, dd, J_1 = 16.1, J_2 = 1.3, H-3″), 6.97 (1H, ddd, J_1 = 8.2, J_2 = 8.4, J_3 = 1.5, H-5′), 7.27 (1H, d, J = 16.1, H-2″), 7.45 (1H, ddd, J_1 = 8.2, J_2 = 8.4, J_3 = 1.8, H-4′), 7.92 (1H, dd, J_1 = 8.3, J_2 = 1.8, H-6′), 8.72 (1H, dd, J_1 = 8.4, J_3 = 1.5, H-3′), 11.11 (1H, s, NH).

1-[4*β*-(8*β*,9*β*-Dihydroxy-1*α*,14*α*,16*β*-trimethoxy-20-ethylaconitan-4-yl)]-2-but-2-cinnamamidobenzoate (6). Yield 80%, mp 138-140°C, $C_{39}H_{48}N_2O_8$. IR spectrum (ν, cm^{-1}): 700, 760, 1088, 1100, 1144, 1264, 1319, 1526, 1588, 1605, 1631, 1681, 2819, 3298, 3306, 3400, 3527.

PMR spectrum (δ, ppm, J/Hz): 1.09 (3H, t, J = 7, CH_3), 1.60 (1H, dd, J_1 = 15.6, J_2 = 7.8, H_b-6), 1.80 (1H, m, H_b-3), 1.92 (1H, m, H-15), 2.01 (1H, m, H-10), 2.06-2.20 (3H, m, H-12,2,7), 2.30-2.70 (10H, m, H-2,3,5,6,12,13,15,19,21,21), 3.00 (1H, s, H-17), 3.17 (1H, dd, J_1 = 11.0, J_2 = 6.0, H_a-1), 3.30 (1H, m, H-16), 3.27, 3.28, and 3.39 (9H, 3H each, all s, 1-, 16-, and 14-OCH_3, respectively), 3.42 (1H, d, J = 5.9, H-14), 3.60 (1H, d, J = 11.0, H_a-19), 6.60 (1H, d, J_1 = 16.2, CH=), 7.04 (1H, ddd, J_1 = 8.2, J_2 = 8.0, J_3 = 1.5, H-5′), 7.39 (3H, m, H-2″,4″,6″), 7.50 (1H, ddd, J_1 = 8.2, J_2 = 8.4, J_3 = 1.8, H-4′), 7.59 (2H, m, H-3″,5″), 7.73 (1H, d, J = 16.2, CH=), 7.94 (1H, dd, J_1 = 8.0, J_2 = 1.8, H-6′), 8.82 (1H, dd, J_1 = 8.4, J_3 = 1.5, H-3′), 11.36 (1H, s, NH).

1-[4*β*-(8*β*,9*β*-Dihydroxy-1*α*,14*α*,16*β*-trimethoxy-20-ethylaconitan-4-yl)]-2-(2-chloroacetamido)benzoate (7). Yield 72%, mp 93-95°C, $C_{32}H_{43}ClN_2O_8$. IR spectrum (ν, cm^{-1}): 758, 1088, 1100, 1144, 1268, 1526, 1590, 1606, 1691, 3258, 3305, 3474.

PMR spectrum (δ, ppm, J/Hz): 1.10 (3H, t, J = 7, CH_3), 1.60 (1H, dd, J_1 = 15.2, J_2 = 7.5, H_b-6), 1.80 (1H, m, H_b-3), 1.97-2.02 (2H, m, H-7,15), 2.12-2.17 (3H, m, H-2,10,12), 2.25-2.31 (1H, m, H-2), 2.34-2.40 (4H, m, H-5,13,15,21), 2.54-2.70 (5H, m, H-3,6,12,19,21), 3.02 (1H, s, H-17), 3.19 (1H, dd, J_1 = 10.6, J_2 = 6.0, H_a-1), 3.30 (1H, m, H-16), 3.28, 3.29, and 3.39 (9H, 3H each, all s, 1-, 16-, and 14-OCH_3, respectively), 3.42 (1H, d, J = 5.2, H-14), 3.60 (1H, d, J = 11.4, H_a-19), 4.15 [2H, s, (C$\underline{H_2}$)Cl], 7.01 (1H, ddd, J_1 = 8.0, J_2 = 8.0, J_3 = 1.2, H-5′), 7.50 (1H, ddd, J_1 = 8.1, J_2 = 8.0, J_2 = 1.8, H-4′), 7.92 (1H, dd, J_1 = 8.0, J_2 = 1.8, H-6′), 8.63 (1H, dd, J_1 = 8.1, J_2 = 1.2, H-3′), 11.78 (1H, s, NH).

1-[4*β*-(8*β*,9*β*-Dihydroxy-1*α*,14*α*,16*β*-trimethoxy-20-ethylaconitan-4-yl)]-2-benzamido-5-bromobenzoate (9) was prepared by the aforementioned method by reacting **8** (1 mmol, 0.621 g) and benzoylchloride (1.1 mmol, 0.154 g). Yield 77%, mp 121-123°C, $C_{37}H_{45}BrN_2O_8$. IR spectrum (ν, cm^{-1}): 704, 757, 1083, 1100, 1291, 1310, 1494, 1515, 1580, 1603, 1680, 2819, 3200, 3254, 3304, 3325, 3495.

PMR spectrum (δ, ppm, J/Hz): 1.12 (3H, t, J = 7, CH_3), 1.64 (1H, ddd, J_1 = 15.6, J_2 = 7.3, J_3 = 1.5, H_b-6), 1.88 (1H, m, H_b-3), 1.96-2.05 (3H, m, H-7,10,15), 2.10-2.19 (2H, m, H-2,12), 2.28 (1H, m, H-2), 2.30-2.72 (9H, m, H-3,5,6,12,13,15,19,21,21), 3.01 (1H, s, H-17), 3.17 (1H, dd, J_1 = 10.8, J_2 = 5.8, H_a-1), 3.26, 3.27, and 3.30 (9H, 3H each, all s, 1-, 16-, and 14-OCH_3, respectively), 3.32 (1H, m, H-16), 3.40 (1H, d, J = 5.3, H-14), 3.58 (1H, d, J = 11.4, H_a-19), 7.45-7.54 (2H, m, H-3″,5″), 7.63 (1H, dd, J_1 = 9.0, J_2 = 2.2, H-4′), 7.78 (1H, m, H-4″), 7.97 (1H, dd, J = 2.2, H-6′), 8.01 (2H, dd, J_1 = 8.6, J_2 = 2.0, H-2″,6″), 8.81 (1H, d, J = 9.0, H-3′), 11.96 (1H, s, NH).

***N*′,*N*^{4}-bis{2-[2-(8*β*,9*β*-Dihydroxy-1*α*,14*α*,16*β*-trimethoxy-20-ethylaconitan-4*β*-yl)oxacarbonyl]phenyl}oxalamide (10).** A solution of **2** (1 mmol, 0.542 g) in dry CH_2Cl_2 (10 mL) was treated with oxalylchloride (0.5 mmol, 0.062 g) and pyridine (0.5 mL, distilled), stored at room temperature with stirring for 2 h, washed with NH_4OH (25%) and water, dried over anhydrous $MgSO_4$, and evaporated. The resulting compound was dissolved in benzene and evaporated to remove pyridine. The workup was repeated three times. The resulting white powder was washed twice with ethanol (10 mL). Yield 65%, mp 228-230°C. IR spectrum (ν, cm^{-1}): 756, 1084, 1090, 1094, 1141, 1269, 1509, 1583, 1603, 2819, 3245, 3297, 3334, 3534.

PMR spectrum (δ, ppm, J/Hz): 1.07 (6H, t, J = 7, 2 ×CH_3), 1.62 (2H, dd, J_1 = 15.4, J_2 = 7.6, H_b-6), 1.74 (2H, m, H_b-3), 1.94 (2H, m, H-12), 2.02-2.54 [24H (12×2), m, H-2,2,5,7,10,12,13,15,15,19,21,21), 2.60-2.68 (4H, m, H-3,6), 2.98 (2H, br.s, H-17), 3.16 (2H dd, J_1 = 10.8, J_2 = 6.8, H_a-1), 3.30 (2H, m, H-16), 3.28, 3.29, and 3.39 (2×9H, 6H each, all s, 1-, 16-, and

14-OCH_3, respectively), 3.40 (2H, d, J = 5.0, H-14), 3.69 (2H, d, J = 11.2, H_a-19), 7.12 (2H, ddd, J_1 = 8.2, J_2 = 7.8, J_3 = 1.0, H-5′), 7.51 (2H, ddd, J_1 = 8.2, J_2 = 8.4, J_3 = 1.5, H-4′), 7.98 (2H, dd, J_1 = 7.8, J_2 = 1.5, H-6′), 8.83 (2H, dd, J_1 = 8.4, J_2 = 1.0, H-3′), 12.05 (2H, s, NH). Scanning of positive ions of **10** (Agilent instrument) in the range *m/z* 1200-1250 found an ion with *m/z* 1138.6 $[M + H]^+$. $[C_{62}H_{82}N_4O_{16} + H]^+$, calc. MW = 1138.6.

***N′,N*⁴-bis{2-[2-(8β,9β-Dihydroxy-1α,14α,16β-trimethoxy-20-ethylaconitan-4β-yl)oxacarbonyl]phenyl}succinamide (11)** was prepared by the aforementioned method by reacting **2** with succinyldichloride. Yield 71%, mp 240-242°C. IR spectrum (ν, cm^{-1}): 757, 1088, 1095, 1099, 1144, 1270, 1522, 1589, 1606, 1683, 1701, 2820, 3245, 3297, 3316, 3397, 3463.

PMR spectrum (δ, ppm, J/Hz): 1.12 [6H (2×3), t, J = 7, CH_3], 1.57 (2H, dd, J_1 = 15.6, J_2 = 7.8, H_b-6), 1.76 (2H, m, H_b-3), 1.94 (2H, dd, J_1 = 14.5, J_2 = 7.9, H_b-12), 1.97-2.70 [28H (14×2), m, H-2,2,3,5,6,7,10,12,13,15,15,19,21,21), 2.86 [4H, s, 2×(CH_2)], 2.98 (2H, s, H-17), 3.20 (2H, dd, J_1 = 10.5, J_2 = 6.6, H_a-1), 3.29 (2H, m, H-16), 3.27, 3.29, and 3.40 (9×2, 3H each, all s, 1-, 16-, and 14-OCH_3, respectively), 3.42 (2H, d, J = 4.9, H-14), 3.58 (2H, d, J = 11.6, H_a-19), 6.99 (2H, ddd, J_1 = 8.2, J_2 = 8.0, J_3 = 1.5, H-5′), 7.45 (2H, ddd, J_1 = 8.0, J_2 = 8.3, J_3 = 1.2, H-4′), 7.89 (2H, dd, J_1 = 8.2, J_2 = 1.2, H-6′), 8.64 (2H, dd, J_1 = 8.3, J_2 = 1.5, H-3′), 11.16 (2H, s, NH). Scanning of positive ions of **11** (Agilent instrument) in the range 1200-1250 found an ion with *m/z* 1165.6 $[M + H]^+$. $[C_{64}H_{86}N_4O_{16} + H]^+$, calc. MW 1166.6.

General Method for Preparing 12-14. A solution of **7** (0.3 mmol, 0.186 g) in dry anhydrous THF (10 mL) was treated with the amine (0.45 mmol) and stored at room temperature with stirring until the starting material disappeared (TLC). The THF was distilled off. The solid was dissolved in benzene, washed with water, dried over anhydrous $MgSO_4$, and evaporated to afford **12-14** as amorphous solids.

1-[4β-(8β,9β-Dihydroxy-1α,14α,16β-trimethoxy-20-ethylaconitan-4-yl)]-2-[(2-diethylamino)acetamido]benzoate (12). Yield 62%, mp 136-138°C, $C_{36}H_{53}N_3O_8$. IR spectrum (ν, cm^{-1}): 758, 1087, 1117, 1143, 1265, 1516, 1582, 1693, 2819, 3200, 3299, 3463.

PMR spectrum (δ, ppm, J/Hz): 1.03 (6H, t, J = 7, 2-CH_3), 1.08 (3H, t, J = 7, CH_3), 1.59 (1H, dd, J_1 = 15.6, J_2 = 7.8, H_b-6), 1.76 (1H, m, H_b-3), 1.94 (1H, dd, J_1 = 14.5, J_2 = 7.9, H_b-12), 1.97-2.02 (2H, m, H-7,15), 2.07 (1H, dd, J_1 = 12.8, J_2 = 4.2, H-10), 2.12-2.17 (1H, m, H-2), 2.25-2.31 (1H, m, H-2), 2.34-2.40 (3H, m, H-5,13,15), 2.44-2.60 (4H, m, H-12,21,19,21), 2.62 [4H, q, ($C\underline{H}_2$)$_2$-Et], 2.60-2.68 (2H, m, H-3,6), 3.05 (1H, s, H-17), 3.16 [2H, s, ($C\underline{H}_2$)N], 3.18 (1H, dd, J_1 = 10.5, J_2 = 6.6, H_a-1), 3.29 (1H, m, H-16), 3.28, 3.29, and 3.39 (9H, 3H each, all s, 1-, 16-, and 14-OCH_3, respectively), 3.42 (1H, d, J = 4.9, H-14), 3.61 (1H, d, J = 11.6, H_a-19), 7.01 (1H, ddd, J_1 = 8.1, J_2 = 8.0, J_3 = 1.5, H-5′), 7.46 (1H, ddd, J_1 = 8.1, J_2 = 8.3, J_2 = 2.0, H-4′), 7.86 (1H, dd, J_1 = 8.0, J_2 = 2.0, H-6′), 8.71 (1H, dd, J_1 = 8.3, J_2 = 1.5, H-3′), 12.05 (1H, s, NH).

1-[4β-(8β,9β-Dihydroxy-1α,14α,16β-trimethoxy-20-ethylaconitan-4-yl)]-2-[(2-morpholino)acetamido]benzoate (13). Yield 74%, mp 183-186°C, $C_{36}H_{51}N_3O_9$. IR spectrum (ν, cm^{-1}): 706, 732, 817, 841, 861, 926, 1103, 1120, 1558, 1597, 1615, 3348.

PMR spectrum (δ, ppm, J/Hz): 1.10 (3H, t, J = 7, CH_3), 1.60 (1H, dd, J_1 = 15.4, J_2 = 8.0, H_b-6), 1.79 (1H, m, H_b-3), 1.90-2.20 (6H, m, H-2,3,7,10,12,15), 2.25 (1H, m, H-2), 2.30-2.40 (3H, m, H-5,13,15), 2.42 (1H, m, H-21), 2.53 (2H, m, H-19,21), 2.60 [4H, m, ($C\underline{H}_2$)–N–($C\underline{H}_2$)], 2.68 (1H, m, H-6), 3.00 (1H, s, H-17), 3.15 [2H, s, ($C\underline{H}_2$)N], 3.18 (1H, m, H-1), 3.28 (1H, m, H-16), 3.27, 3.28, and 3.39 (9H, 3H each, all s, 1-, 16-, and 14-OCH_3, respectively), 3.40 (1H, d, J = 5.4, H-14), 3.59 (1H, d, J = 11.4, H_a-19), 3.83 [2H, m, ($C\underline{H}_2$)–O–($C\underline{H}_2$)], 7.03 (1H, ddd, J_1 = 8.2, J_2 = 8.0, J_3 = 1.5, H-5′), 7.48 (1H, ddd, J_1 = 8.1, J_2 = 8.0, J_2 = 1.9, H-4′), 7.91 (1H, dd, J_1 = 8.2, J_2 = 1.9, H-6′), 8.72 (1H, dd, J_1 = 8.1, J_2 = 1.5, H-3′), 12.08 (1H, s, NH).

1-[4β-(8β,9β-Dihydroxy-1α,14α,16β-trimethoxy-20-ethylaconitan-4-yl)]-2-{2-[4-methylpiperazin-1-yl]acetamido}benzoate (14). Yield 61%, mp 118-120°C, $C_{37}H_{54}N_4O_8$. IR spectrum (ν, cm^{-1}): 756, 1038, 1086, 1147, 1293, 1517, 1582, 1692, 3200, 3338, 3462.

PMR spectrum (δ, ppm, J/Hz): 1.10 (3H, t, J = 7, CH_3), 1.59 (1H, dd, J_1 = 15.2, J_2 = 8.1, H_b-6), 1.78 (1H, m, H_b-3), 1.90-2.18 (6H, m, H-2,3,7,10,12,15), 2.25 (3H, s, N–$C\underline{H}_3$), 2.26-2.40 (4H, m, H-2,5,13,15), 2.48 (1H, m, H-21), 2.53-2.72 [13H, m, H-3,6,12,19,21,(CH_2)$_4$], 2.98 (1H, s, H-17), 3.14 [2H, s, ($C\underline{H}_2$)N], 3.15 (1H, m, H-1), 3.26 (1H, m, H-16), 3.27, 328, and 3.38 (9H, 3H each, all s, 1-, 16-, and 14-OCH_3, respectively), 3.40 (1H, d, J = 5.2, H-14), 3.64 (1H, d, J = 11.1, H_a-19), 7.01 (1H, ddd, J_1 = J_2 = 7.8, J_3 = 1.2, H-5′), 7.46 (1H, ddd, J_1 = 7.8, J_2 = 8.0, J_2 = 2.0, H-4′), 7.89 (1H, dd, J_1 = 7.8, J_2 = 2.0, H-6′), 8.73 (1H, dd, J_1 = 8.0, J_2 = 1.2, H-3′), 12.08 (1H, s, NH).

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