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CHEMISTRY

Synthesis of Hybrid Compounds Derived from Diterpene Alkaloid Lappaconitine

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There has been growing interest in the design and synthesis of dimeric bases of different alkaloids after the structure and important pharmacological properties of dimeric alkaloids of isoquinoline (plant metabolites of genera *Thalictrum* and *Berberis*) [1] and indole types (from plants of genera *Vinca*, *Strychnos*, *Iboga*, and *Catharantus* [2, 3]) were established. Examples for modifications of morphinan alkaloids A–X are described that enable junction with the second molecule of alkaloid (A) through a linker (X) to form bivalent opioid ligands A–X–A. The latter show high selectivity in binding to receptors as compared with monovalent ligands A–X. Studies are in progress to transform semisynthetic alkaloid anhydrovinblastine [5], which differs from vinblastine by the modification of catharanthine unit and shows considerably larger cytotoxicity in human lung tumor cells H-460 and antitumor activity against certain kinds of carcinoma in animals [6]. The promise of hybrid molecules containing fragments of natural alkaloids as leader compounds for the development of pharmacologically valuable agents has been discussed [7].

Lappaconitine (**1**) used as hydrobromide as antiarrhythmic remedy [8] is one of promising alkaloids for synthetic transformations. The modification of lappaconitine molecule led to an increase in antiarrhythmic activity [9, 10].

In this paper, we describe the synthesis of hybrid alkaloids containing lappaconitine and indolizine fragments. It should be noted that substituted indolizines behave as agonists of neuronal acetylcholine receptors (N-AChRs) and are good candidates for therapeutics for the treatment of Alzheimer's and Parkinson's diseases and other problems of age-related neurodegeneration [11, 12]. To obtain dimeric compounds containing lappaconitine and indolizine fragments, we used the transformations of compound **3**, a product of the cross-coupling of 5'-iodolappaconitine (**2**) with 5-vinyl-2-methylpyridine [13]. Pyridinium salts **4**–**6** prepared by the reaction of compound **3** with phenacetyl bromide, 4-methoxyphenacetyl bromide, or 3,4-dichlorophenacetyl bromide were subjected to 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate in the presence of triethylamine. The reaction leads to compounds **7**–**9** in 50–55% yield (Scheme 1).

The composition and structure of compounds **7**–**9** were confirmed by elemental analysis data and IR, UV, and NMR spectra. The compounds show UV spectra typical for indolizines conjugated with benzene ring. For example, the spectrum of compound **7** shows absorption bands with maxima at 234, 250, 300, and 384 nm. The *E* configuration of the linking double bond in indolizinolappaconitines **7**–**9** was established by ^{1}H NMR data. The protons of the double bond (H-1a, H-1b) show resonances as doublets with spin–spin coupling constant of 15–17 Hz. A characteristic feature of the ^{1}H NMR spectra of these compounds is the downfield shift of the signals of the H-1b proton (for example, for compound **7** δ 7.53 ppm) as compared with its position in the spectrum of pyridine-substituted lappaconitine derivative **3** (δ 6.99 ppm).

Thus, in this work we obtained hybrid molecules containing fragments of diterpene and indolizine alkaloids interesting as biologically active compounds.

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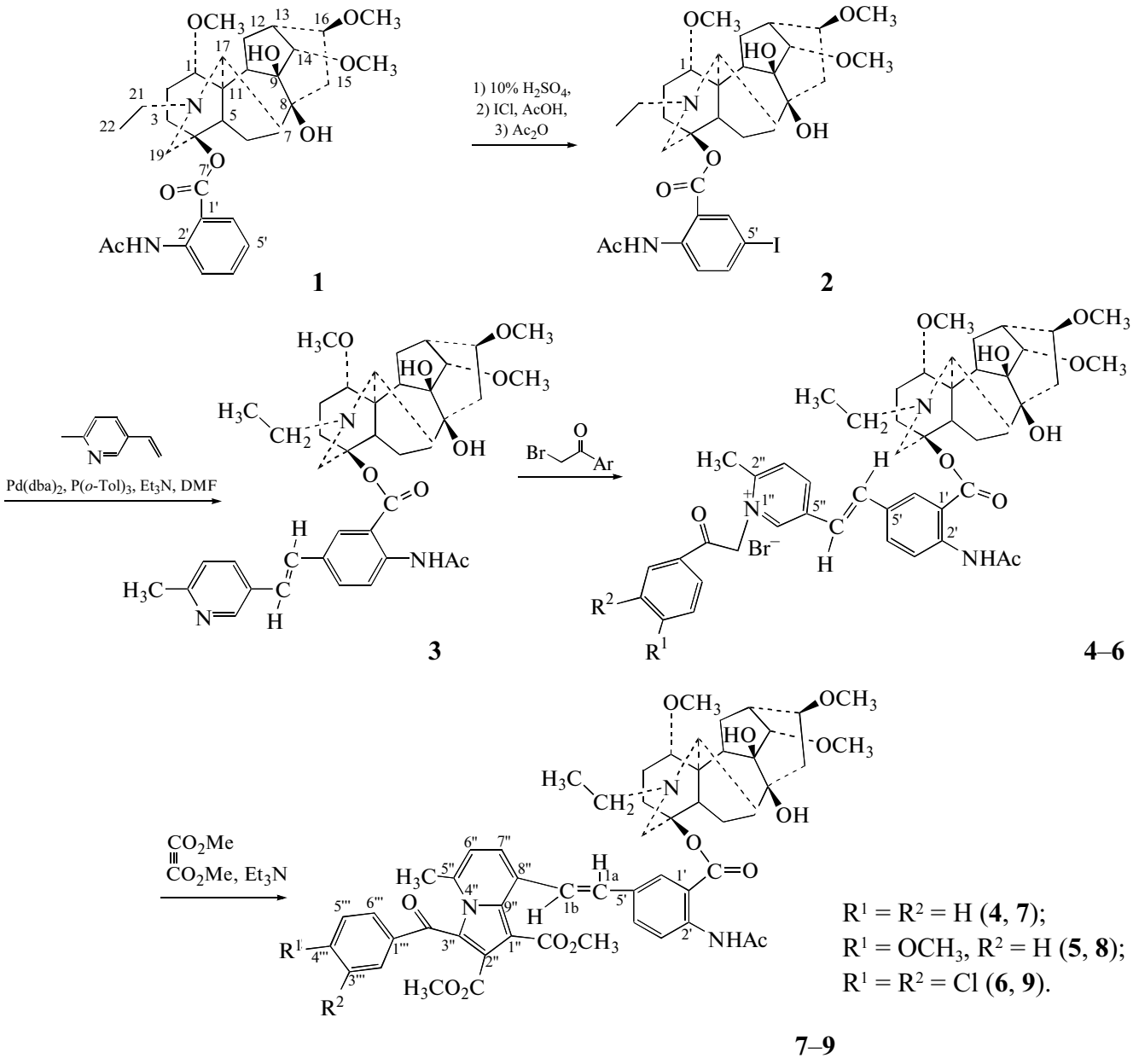

1 **2** **3** **4–6** **7–9**

Scheme 1.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-300 spectrometer operating at 300.13 and 75.47 MHz, respectively, in $CDCl_3$ solutions. Signal multiplicity in ^{13}C NMR spectra was determined by standard procedures in the *J*-modulation mode (JMOD). The 2D NMR ^{1}H–^{1}H (COSY) and ^{13}C–^{1}H (COSY *J* 125 Hz, COLOC *J* 7 Hz) spectra of the compounds were obtained on a Bruker DRX-500 spectrometer operating at 500.13 and 125.76 MHz for ^{1}H and ^{13}C, respectively, in $CDCl_3$ solutions with the use of standard Bruker software. IR spectra were recorded on a VECTOR-22 spectrophotometer as KBr pellets. Melting points were determined with a Kofler hot-stage apparatus. UV absorption spectra were recorded on a HP 8453 UV/Vis spectrophotometer in ethanol solutions.

Signal assignment of hydrogen atoms in ^{1}H NMR spectra and carbon atoms in ^{13}C NMR spectra was made by comparison with the corresponding spectra of lappaconitine (**1**) [14] as a key compound. since it is difficult to assign all signals in the NMR spectra of

compounds **7**–**9**, only characteristic signals are given. We failed to obtain ^{1}H and ^{13}C NMR spectra of salts **4**–**6** of quality acceptable for assignment because of low solubility of the salts.

The reaction course and purity of the obtained compounds was monitored by TLC on Silufol UV-254 plates using the chloroform–ethanol (20 : 1) system.

Silica gel precoated with 1% of K-35 fluorescent indicator was used as a loose-layer sorbent for preparative TLC. The plate size was 30 × 30 cm with 2-mm-thick sorbent layer.

General procedure for the preparation of pyridinium salts (4–6). A solution of 355 mg (0.5 mmol) of compound **3** and 0.55 mmol of appropriate phenacetyl bromide in 20 mL of dry acetone was stirred at ambient temperature for 48 h. The resulting precipitate was filtered off, washed with dry acetone, and dried in air to constant weight.

(*E*)-5''-{2'-Acetamido-1'-[(8,9-dihydroxy-1α,14α,16β-trimethoxy-20-ethylaconitan-4β-yl)oxycarbonyl]styr-5'-yl}-2''-methyl-1''-(2-oxo-2-phenylethyl)pyridinium bromide (4). According to the general procedure, the reaction of 351 mg (0.5 mmol) of compound **3** and 110 mg (0.5 mmol) of phenacetyl bromide afforded 330 mg (73% yield) of compound **4**, mp 235–237°C. IR (ν, cm^{-1}): 570, 689, 760, 784, 853, 970, 1040, 1083, 1129, 1206, 1231, 1300, 1371, 1410, 1450, 1523, 1588, 1631, 1694, 2046, 2842, 2938, 3411.

For $C_{48}H_{56}BrN_3O_9$ anal. calcd. (%): N, 3.11.

Found (%): N, 2.80.

(*E*)-5''-{2'-Acetamido-1'-[(8,9-dihydroxy-1α,14α,16β-trimethoxy-20-ethylaconitan-4β-yl)oxycarbonyl]styr-5'-yl}-1''-[2-(4'''-methoxyphenyl)-2-oxoethyl]-2''-methylpyridinium bromide (5). According to the general procedure, the reaction of 701 mg (1 mmol) of compound **3** and 252 mg (1.1 mmol) of 4ðmethoxyphenacetyl bromide afforded 654 mg (70% yield) of compound **5**, mp 216–217°C. IR (ν, cm^{-1}): 567, 696, 790, 837, 970, 1023, 1082, 1128, 1173, 1206, 1240, 1369, 1422, 1460, 1514, 1600, 1630, 1685, 2822, 2930, 3410.

For $C_{49}H_{58}BrN_3O_{10}$ anal. calcd. (%): N, 3.01.

Found (%): N, 3.35.

(*E*)-5''-{2'-Acetamido-1'-[(8,9-dihydroxy-1α,14α,16β-trimethoxy-20-ethylaconitan-4β-yl)oxycarbonyl]styr-5'-yl}-1''-[2-(3''',4'''-dichlorophenyl)-2-oxoethyl]-2'''-methylpyridinium bromide (6). According to the general procedure, the reaction of 351 mg (0.5 mmol) of compound **3** and 147 mg (0.55 mmol) of 2-bromo-3',4'-dichloroacetophenone afforded 337 mg (70% yield) of compound **6**, mp 243–245°C. IR (ν, cm^{-1}): 556, 676, 751, 834, 966, 1032, 1086, 1147, 1219, 1270, 1376, 1412, 1450, 1515, 1587, 1692, 2822, 2928, 3401.

For $C_{48}H_{54}Cl_2BrN_3O_9$ anal. calcd. (%): N, 4.73; Cl 7.99.

Found (%): N, 4.84; Cl 8.88.

General procedure for the preparation of compounds 7–9. A solution of 0.22 mmol of dimethyl acetylenedicarboxylate and 0.5 mL of triethylamine in 10 mL of methylene chloride was added dropwise to a solution of 0.2 mmol of appropriate pyridinium salt (**4–6**) in 10 mL of dry methylene chloride over 10 min. The resulting dark red solution was stirred for 1 h at ambient temperature, treated with aqueous ammonia to pH ~ 11 and stirred for 10 min, treated with concentrated sulfuric acid to pH ~ 3 and stirred for 10 min, aqueous ammonia was added again to pH ~ 11. The organic layer was separated and dried with $MgSO_4$. The solvent was removed, the residue was chromatographed on a SiO_2 plate (chloroform–ethanol as eluent), and the yellow-orange zone showing intense fluorescence in UV light was collected. The substance was extracted with ethanol. The solvent was removed, and the residue as a brown powder was dried in vacuum to constant weight.

(*E*)-8''-{2'-Acetamido-1'-[(8,9-dihydroxy-1α,14α,16β-trimethoxy-20-ethylaconitan-4β-yl)oxycarbonyl]styr-5'-yl}-3''-benzoyl-1'',2''-dimethoxycarbonyl-5''-methylindolizin (7). According to the above procedure, the reaction of 250 mg (0.28 mmol) of compound **4** and 44 mg (0.31 mmol) of dimethyl acetylenedicarboxylate gave 147 mg (55%) of compound **7**, mp 142–143°C. ^{1}H NMR ($CDCl_3$, δ, ppm, *J*, Hz): 1.12 (t, 3H, H-22, *J* = 2), 2.22 (s, 3H, C$\underline{H}_3$CO), 2.33 (s, 3H, CH_3 at C-5''), 3.01 (s, 1H, H-17), 3.28 and 3.29 (both s, 6H, OCH_3 at C-1 and C-14, respectively), 3.38 (m, 6H, OCH_3 at C-16 and $COOCH_3$ at C-1'' or C-2''), 3.81 (s, 3H, $COOCH_3$ at C-1'' or C-2''), 6.68 (d, 1H, H-6'', *J* = 8.0), 6.96 (d, 1H, H-1a, *J* = 17.0), 7.32 (d, 1H, H-7'', *J* = 8.0), 7.47 (m, 2H, H-3''', H-5'''), 7.53 (d, 1H, H-1b, *J* = 17.0), 7.55 (m, 1H, H-4'''), 7.75 (dd, 1H, H-4', *J* = 7.5, 2.3), 7.89 (d, 2H, H-2''', H-6''', *J* = 8.2), 7.95 (d, 1H, H-6', *J* = 2.3), 8.70 (d, 1H, H-3', *J* = 7.5), 11.07 (s, 1H, N$\underline{H}$ at C-2'). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.45 (C-22), 22.60 (NHCO$\underline{C}H_3$), 24.07 (C-6), 25.49 ($\underline{C}H_3$ at C-5''), 25.80 (C-12), 26.70 (C-2), 31.75 (C-3), 36.19 (C-13), 44.67 (C-15), 47.51 (C-7), 47.87 (C-5), 48.91 (C-21), 49.78 (C-10), 50.90 (C-11), 51.78 (COO$\underline{C}H_{33}$ at C-1'' or C-2''), 52.65 (COO$\underline{C}H_3$ at C-1'' or C-2''), 55.44 (C-19), 56.03 (OCH_3 at C-16), 56.49 (OCH_3 at C-1), 57.84 (OCH_3 at C-14), 61.46 (C-17), 75.52 (C-8), 78.47 (C-9), 82.78 (C-16), 83.11 (C-1), 84.95 (C-4), 90.01 (C-14), 107.33 (C-1''), 115.88 (C-1'), 115.92 (C-1a), 120.61 and 121.02 (C-3', C-6''), 132.53 (C-3''), 123.97 (C-1b), 126.18 (C-5'), 128.31 (C-8''), 128.51 (C-7''), 129.61 (C-6'), 129.61 (C-3''', C-5'''),

130.18 (C-2‴, C-6‴), 130.18 (C-4‴), 131.21 (C-2″), 133.17 (C-1‴), 133.32 (C-4′), 135.30 (C-9″), 138.68 (C-5″), 141.14 (C-2′), 163.48 (C$\underline{\text{O}}$OCH$_3$ at C-1″ or C-2″), 164.06 (C$\underline{\text{O}}$OCH$_{33}$ at C-1″ or C-2″), 166.25 (C-7′), 167.13 (NHC$\underline{\text{O}}$CH$_3$), 188.11 (CO at C-3″). IR (ν, cm^{-1}): 650, 696, 727, 754, 789, 839, 892, 914, 967, 1000, 1035, 1086, 1100, 1120, 1147, 1231, 1377, 1515, 1588, 1620, 1690, 1703, 1710, 2928, 2932, 3401.

UV (ethanol, λ_{max}, nm (logε): 234 (4.40), 250 (4.40), 300 (4.21), 384 (3.88).

For $C_{54}H_{59}N_3O_{13} \cdot CHCl_3$ anal. calcd. (%): C, 61.25; H, 5.38; N, 3.90.

Found (%): C, 61.10; H, 5.77; N, 3.45.

(*E*)-8″-{2′-Acetamido-1′-[(8,9-dihydroxy-1α,14α,16β-trimethoxy-20-ethylaconitan-4β-yl)oxycarbonyl]styr-5′-yl}-3″-(4‴-methoxybenzoyl)-1″,2″-dimethoxycarbonyl-5″-methylindolizin (8). The reaction of 550 mg (0.59 mmol) of compound **5** and 92 mg (0.65 mmol) of dimethyl acetylenedicarboxylate gave 297 mg (55%) of compound **8**, mp 155–157°C. ^{1}H NMR ($CDCl_3$, δ, ppm, *J*, Hz): 1.11 (t, 3H, H-22, *J* = 2), 2.22 (s, 3H, C$\underline{\text{H}}_3$CO), 2.32 (s, 3H, CH$_3$ at C-5″), 3.00 (s, 1H, H-17), 3.28 and 3.29 (both s, 6H, OCH$_3$ at C-1 and C-14, respectively), 3.38 (s, 3H, OC$\underline{\text{H}}_3$ at C-16), 3.44 (s, 3H, OC$\underline{\text{H}}_3$ at COOC$\underline{\text{H}}_3$ at C-1″ or C-2″), 3.81 (s, 3H, COOC$\underline{\text{H}}_3$ at C-1″ or C-2″), 3.85 (s, 3H, OC$\underline{\text{H}}_3$ at C-4‴), 6.62 (d, 1H, H-6″, *J* = 7.4), 6.92 (d, 2H, H-3‴, H-5‴, *J* = 7.2), 6.96 (d, 1H, H-a, *J* = 16.1), 7.26 (d, 1H, H-7″, *J* = 7.4), 7.53 (d, 1H, H-b, *J* = 16.1), 7.74 (dd, 1H, H-4′, *J* = 7.0, 2.0), 7.84 (d, 2H, H-2‴, H-6‴, *J* = 7.2), 7.94 (d, 1H, H-6′, *J* = 2.0), 8.70 (d, 1H, H-3′, *J* = 7.0), 11.06 (s, 1H, N$\underline{\text{H}}$ at C-2′). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.45 (C-22), 22.19 (NHCO$\underline{\text{C}}$H$_3$), 24.11 (C-6), 25.46 (C$\underline{\text{H}}_3$ at C-5″), 26.17 (C-12), 26.75 (C-2), 31.84 (C-3), 36.31 (C-13), 44.70 (C-15), 47.60 (C-7), 48.33 (C-5), 48.88 (C-21), 49.86 (C-10), 50.98 (C-11), 51.81 (COO$\underline{\text{C}}$H$_3$ at C-1″ or C-2″), 52.60 (COO$\underline{\text{C}}$H$_3$ at C-1″ or C-2″), 55.46 (O$\underline{\text{C}}$H$_3$ at C-4‴), 55.51 (C-19), 56.03 (O$\underline{\text{C}}$H$_3$ at C-16), 56.43 (O$\underline{\text{C}}$H$_3$ at C-1), 57.84 (O$\underline{\text{C}}$H$_3$ at C-14), 61.41 (C-17), 75.53 (C-8), 78.50 (C-9), 82.85 (C-16), 83.10 (C-1), 85.02 (C-4), 90.08 (C-14), 107.27 (C-1″), 113.82 (C-1a), 115.54 (C-6″), 115.97 (C-1′), 120.50 (C-7″), 120.64 (C-3′), 122.40 (C-2″), 124.06 (C-1b), 128.34 (C-8″), 129.01 (C-5′), 129.91 (C-6′), 130.14 (C-3‴, C-5‴), 131.25 (C-4′), 131.30 (C-3″), 131.96 (C-2‴, C-6‴), 132.17 (C-1‴), 132.70 (C-9″), 135.11 (C-5″), 141.14 (C-2′), 163.80 (C$\underline{\text{O}}$OCH$_3$ at C-1″), 163.80 (C$\underline{\text{O}}$OCH$_3$ at C-2″), 166.46 (C-4‴), 167.15 (C-7′), 168.84 (NHC$\underline{\text{O}}$CH$_3$), 187.27 (CO at C-3″). IR (ν, cm^{-1}): 649, 755, 789, 838, 892, 916, 967, 1031, 1086, 1115, 1167, 1239, 1379, 1513, 1550, 1597, 1620, 1630, 1690, 1710, 1723, 2928, 3437. UV (ethanol, λ_{max}, nm (logε): 229 (4.55), 252 (4.29), 301 (4.50), 382 (4.04).

For $C_{55}H_{61}N_3O_{14} \cdot CHCl_3$ anal. calcd. (%): C, 60.67; H, 5.60; N, 3.79.

Found (%): C, 60.21; H, 6.00; N, 3.93.

(*E*)-8″-{2′-Acetamido-1′-[(8,9-dihydroxy-1α,14α,16β-trimethoxy-20-ethylaconitan-4β-yl)oxycarbonyl]styr-5′-yl}-3″-(3‴,4‴-dichlorobenzoyl)-1″,2″-dimethoxycarbonyl-5″-methylindolizin (9). The reaction of 550 mg (0.59 mmol) of compound **6** and 92 mg (0.65 mmol) of dimethyl acetylenedicarboxylate gave 297 mg (52%) of compound **9**, mp 155–157°C. ^{1}H NMR ($CDCl_3$, δ, ppm, *J*, Hz): 1.12 (t, 3H, H-22, *J* = 2), 2.23 (s, 3H, C$\underline{\text{H}}_3$CO), 2.30 (s, 3H, CH$_3$ at C-5″), 3.00 (s, 1H, H-17), 3.28 and 3.29 (both s, 6H, OC$\underline{\text{H}}_3$ at C-1 and C-14, respectively), 3.39 (s, 3H, OC$\underline{\text{H}}_3$ at C-16), 3.51 (s, 3H, COOCH$_3$ at C-1″ or C-2″), 3.82 (s, 3H, COOC$\underline{\text{H}}_3$ at C-1″ or C-2″), 6.72 (d, 1H, H-6″, *J* = 6.8), 6.97 (d, 1H, H-1a, *J* = 16.0), 7.35 (d, 1H, H-7″, *J* = 8.0), 7.53 (d, 1H, H-b, *J* = 16.0), 7.54 (d, 1H, H-5‴, *J* = 7.2), 7.71 (dd, 1H, H-6‴, *J* = 7.2, 2.2), 7.74 (dd, 1H, H-4′, *J* = 7.8, 2.0), 7.95 (d, 1H, H-6′, *J* = 2.0), 8.03 (1H, H-2‴, *J* = 2.2), 8.71 (d, 1H, H-3′, *J* = 7.8), 11.07 (s, 1H, N$\underline{\text{H}}$ at C-2′). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.37 (C-22), 22.67 (NHCO$\underline{\text{C}}$H$_3$), 23.99 (C-6), 25.17 (C$\underline{\text{H}}_3$ at C-5″), 25.42 (C-12), 26.62 (C-2), 31.69 (C-3), 36.10 (C-13), 44.63 (C-15), 47.41 (C-7), 48.25 (C-5), 48.83 (C-21), 49.69 (C-10), 50.82 (C-11), 51.99 (COO$\underline{\text{C}}$H$_3$ at C-1″ or C-2″), 52.66 (COO$\underline{\text{C}}$H$_3$ at C-1″ or C-2″), 55.35 (C-19), 55.95 (O$\underline{\text{C}}$H$_3$ at C-16), 56.41 (O$\underline{\text{C}}$H$_3$ at C-1), 57.76 (OCH$_3$ at C-14), 61.38 (C-17), 75.46 (C-8), 78.38 (C-9), 82.70 (C-16), 83.96 (C-1), 84.89 (C-4), 89.93 (C-14), 107.60 (C-1″), 115.80 (C-1′), 116.29 (C-1a), 120.54 (C-3′), 121.36 (C-6″), 122.62 (C-2″), 123.56 (C-1b), 124.01 (C-5‴), 128.42 (C-8″), 128.56 (C-7″), 129.90 (C-6′), 130.45 (C-6‴), 130.53 (C-3‴), 130.99 (C-5′), 131.00 (C-4′), 131.13 (C-2‴), 133.17 (C-3‴), 133.45 (C-1‴), 135.11 (C-9″), 137.80 (C-4‴), 138.19 (C-5″), 141.15 (C-2′), 163.82 (C$\underline{\text{O}}$OCH$_3$ at C-1″), 163.82 (C$\underline{\text{O}}$OCH$_3$ at C-2″), 167.02 (C-7′), 168.84 (NHC$\underline{\text{O}}$CH$_3$), 185.29 (CO at C-3″).

IR (ν, cm^{-1}): 676, 751, 966, 1031, 1086, 1106, 1127, 1147, 1219, 1270, 1290, 1376, 1515, 1550, 1587, 1598, 1623, 1692, 1700, 2928, 3401.

UV (ethanol, λ_{max}, nm (logε): 225 (4.42), 257 (4.30), 305 (4.14), 405 (3.62).

For $C_{54}H_{57}ClN_3O_{13} \cdot CHCl_3$ anal. calcd. (%): C, 57.70; H, 5.19; N, 3.67; Cl, 15.52.

Found (%): C, 58.07; H, 5.55; N, 3.92; Cl, 15.31.

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