Chaetoglobosins Q, R, and T, Three Further New Metabolites from *Chaetomium globosum*

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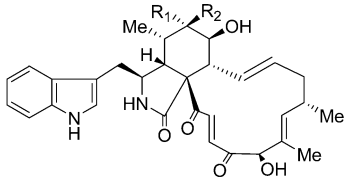
Nine cytotoxic metabolites, including three novel compounds, chaetoglobosins Q (**1**), R (**2**), and T (**3**), have been isolated from cultures of the fungus *Chaetomium globosum*. The structures were elucidated primarily from NMR spectroscopic data.

Chaetoglobosins are a family of secondary metabolites belonging to the general group of cytochalasins. The name "cytochalasin" originates from the Greek word *cytos* (cell) and *chalasis* (relaxation) and refers to the cytological effects of the metabolites. The cytochalasins are remarkable in their biological activity, which includes the inhibition of movement and cytoplasmic cleavage of mammalian cells. Much of the biological activity can be accounted for by an interaction with the common target protein actin. These biological activities are unprecedented by any other group of compounds.[1] Chaetoglobosins contain an indolyl group in place of the phenyl group found in the cytochalasins.[2]

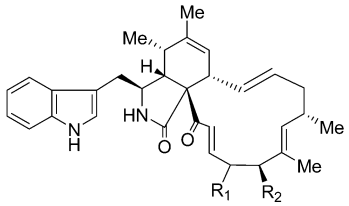
Some 30 or so chaetoglobosins or analogues have now been reported, with most being produced by fungi of the genus *Chaetomium*. Chaetoglobosins A, B, C, D, E, F, G, and J show cytotoxicity against HeLa cells with IC_{50} values in the range 3.2−20 μg/mL.[3] Most chaetoglobosins induce polynucleation in HeLa cells. Apart from cytotoxicity, some chaetoglobosins (A, C, and O) also show phytotoxicity against alfalfa seedlings.[4] Chaetoglobosin A, the most widely studied metabolite in the chaetoglobosin family, has been reported to exhibit strong cytotoxicity against other human cancer cell lines,[5] antibacterial activity against *Helicobacter pylori* and *Staphylococcus aureus*,[6] and antifungal activity toward a series of plant pathogens.[7] We report here the isolation and structural elucidation of three new members of the chaetoglobosin family, Q (**1**), R (**2**), and T (**3**).[8]

In the course of general studies on cytotoxic compounds from New Zealand terrestrial and saline fungi, one isolate, identified as *Chaetomium globosum* (CANU N60), gave an extract that showed significant activity against the P388 murine leukemia cell line. Bioassay- and ^{1}H NMR-guided fractionation of the EtOAc extract by RP C18 column chromatography, followed by normal-phase chromatography (Diol), afforded nine compounds (**1**−**9**). On the basis of the molecular formulas determined by high-resolution MS and the NMR data, it was concluded that compounds **4**, **5**, **6**, **7**, **8**, and **9** were identical to chaetoglobosins A, B, D,[9] and J[10] and prochaetoglobosins I and II,[11] respectively. Prochaetoglobosins I and II had been isolated previously by Oikawa et al. after treating *Chaetomium subaffine* with specific cytochrome P-450 inhibitors, but this report is the first record as natural metabolites.

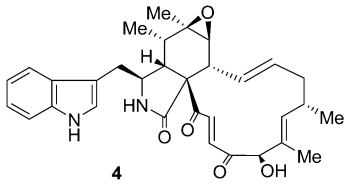
On the basis of analysis of the HRESMS and the ^{13}C NMR data the molecular formula of chaetoglobosin Q (**1**) was determined as $C_{32}H_{38}N_2O_6$. The IR spectrum showed characteristic absorptions at 3080−3240 cm^{-1} (NH and OH groups) and at 1691, 1683 cm^{-1} (carbonyl groups). The ^{1}H NMR spectrum and HSQC data disclosed the presence of four methyl groups (two secondary, one allylic, and one tertiary), two methylenes, seven methines, including two oxymethines, two *trans* −CH=CH− groups, and a trisub-



1 $R_1 = CH_3$ $R_2 = OH$
2 $R_1 = OH$ $R_2 = CH_3$



3 $R_1 = H_2$ $R_2 = OH$
7 $R_1 = O$ $R_2 = OH$
8 $R_1 = H_2$ $R_2 = H$
9 $R_1 = O$ $R_2 = H$



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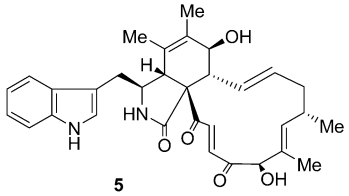

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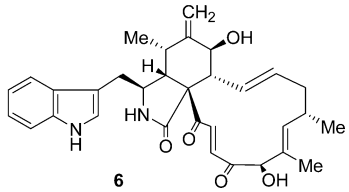

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Table 1. Cytotoxic and Antimicrobial Activities of **1**−**9**[a]

activity	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
IC_{50} P388 (μg/mL)	2.19		1.58	1.94	3.45	4.92	2.47	3.99	3.99
antimicrobial				Bs (3) Cr (5)	Bs (1)	Bs (3)	Bs (2)	Tm (2)	Tm (2)

[a] P388 = murine leukemia cell line. Bs = *Bacillus subtilis*. Cr = *Cladosporium resinae*. Tm = *Trichophyton mentagrophytes*. Bs (*X*) or Cr (*X*): *X* mm inhibition at a concentration of 15 μg/disk. Tm (*X*): *X* mm inhibition at a concentration of 30 μg/disk.

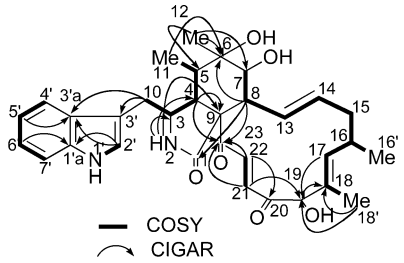

Figure 1. Key 2D NMR correlations for chaetoglobosin Q (**1**).

stituted olefin. The presence of a 3-substituted indolyl group was also deduced from analysis of the NMR data and was supported by UV data. The identity of the remaining carbons was revealed by an APT experiment: two conjugated ketones (δ_C 196.0 and 201.1), an amide (δ_C 171.6), two aliphatic quaternary carbons (δ_C 63.2, 72.5), and an olefinic carbon (δ_C 132.8).

Close inspection of the COSY data for **1** led to the partial structural units shown in boldface in Figure 1. The assignments of C-1′a, C-3′, and C-3′a in the indolyl group were determined by long-range correlations in the CIGAR spectrum, mainly from H-2′ and H-6′ to C-1′a and from H-2′ and H-5′ to C-3′a (Figure 1). Connectivity from the indolyl group relied on long-range correlations from H-10a and H-10b to C-3′ and from H-10b to C-3′a. The assignments of C-6 and C-12 were made by long-range correlations from H-11 to C-6 and from H-12 to C-5, C-6, and C-7.

The chemical shifts (δ_H 3.69, δ_C 53.8) for C-3 implied linkage to an amide group. The long-range correlations of H-2 to C-4 and H-2, H-4 to C-9, and H-8 to C-1 and C-6 along with the COSY data established the central core (C-1 to C-12). The connectivity from C-18 to C-23 was based on the long-range correlations of H-17 and H-18′ to C-19, H-21 to C-19, and H-22 to C-20 and C-23, respectively. The final element of connectivity, C-23 to C-9, was established by observation of the long-range correlation of H-4 and H-8 to C-23. The assigned planar structure (Figure 1) was in keeping with that found for the co-occurring and previously assigned chaetoglobosins (**4**−**9**).[9,10]

The relative stereochemistry of **1** was assigned by a combination of NOESY data, interpretation of *vicinal* coupling constants, and reference to the X-ray diffraction analysis of chaetoglobosin A (**4**).[12] The observation of a positive NOE between H-5 and H-8 and the lack of an observable NOE from H-4 to H-8 established that the cyclohexane ring was in a boat conformation, as found in chaetoglobosin A (**4**).[12] This was confirmed by an NOE correlation between H-7 and H-3. The relative configuration of the substituents on the cyclohexane ring (C-4 to C-9) (**1**) followed from observation of NOEs from H-7 to H-12 and from H-3 to H-11 and H-12 together with the large *vicinal* coupling constant between H-7 and H-8 (10.5 Hz) and the smaller *vicinal* coupling constant between H-4 and H-5 (4.5 Hz). The relative configuration of the 13-membered ring of **1** was initially based on chemical shift correlations with chaetoglobosins A, B, D, and J (**4**−**7**), which are structurally and stereochemically invariant from C-9−C-23. These assignments were supported by NOE correlations from H-15a to H-16′, H-17 to H-16′ and H-19, H-19 to H-17 and H-22, and H-18′ to H-16. These data are entirely in keeping with the suggested configuration and stereochemistry when the conformation of the 13-membered ring, as reported for the X-ray structural analysis of chaetoglobosin A (**4**), is adopted.[12]

Chaetoglobosin R (**2**) had the same molecular formula, $C_{32}H_{38}N_2O_6$, as **1**, as concluded from the HRESMS and carbon count. The ^1H and ^{13}C NMR spectra of **1** and **2** were closely correlated. From the molecular formula and the spectral data it could be concluded that **2** was isomeric with **1**, with the differences centered on the C-6 to C-8 region of the cyclohexane moiety. From analysis of the COSY, HSQC, and CIGAR spectra the identical planar structure (Figure 1) could be deduced for **2**. In the NOESY experiments, H-7 showed NOE correlations only to H-3, while H-5 showed correlations with H-4, H-11, and H-12, which established that chaetoglobosin R (**2**) was the C-6 epimer of chaetoglobosin Q (**1**).

Chaetoglobosin T (**3**) had the molecular formula $C_{32}H_{38}N_2O_3$ (HRESMS). Comparison of the NMR spectra with that for **1** revealed that the 6,7-diol (δ_C 72.5 and 71.4) in **1** had been replaced by a trisubstituted olefin (δ_H 5.34; δ_C 140.1 and 126.6) in **3**. Furthermore, the C-20 conjugated ketone resonance (δ_C 201.1) had been replaced by a methylene signal (δ_C 35.4, δ_H 2.48). As a consequence, the chemical shift of C-19 in **3** had moved to higher field (δ_C 76.9). The assignment of C-20 (H-20) was supported by the appearance of a doublet of triplets for H-21 (δ_H 6.80) in the ^1H NMR spectrum and COSY correlations observed between H-20/H-21/H-19. On these grounds, **3** was proposed as a reduced analogue of **1**. This was confirmed by a series of 2D NMR (COSY, HSQC, and CIGAR) experiments. The stereochemistry of **3** was deduced from NOESY spectral analysis. The principal NOEs were H-5 to H-8, H-3 to H-11, H-7 to H-12, H-14 to H-8, H-16 to H-18′, and H-19 to H-17, H-22. These observations implied that the stereochemistry of **3** was the same as that of chaetoglobosin A (**4**).[9]

As far as we are aware, chaetoglobosins Q (**1**) and R (**2**) are the only examples of chaetoglobosins with the C-6 and C-7 *vicinal* diol system. Chatoglobosins Q (**1**) and R (**2**), as well as B (**5**) and D (**6**), are clearly related to chaetoglobosin A (**4**): for **1** and **2** by the S_N1-type hydrolytic opening of the epoxide ring of chaetoglobosin A (**4**) and in the case of **5** and **6** by an E1-type elimination from the equivalent carbocation. The possibility that **1** and **2** are artifacts of the isolation process was examined. Careful extraction of the fermentation broth under neutral conditions followed by LC/MS on the extract established the presence of **1**, **2**, **5**, and **6** as well as other members of the chaetoglobosin family. A parallel experiment established the hydrolytic stability of chaetoglobosin A (**4**) in the fermentation broth. From this it was concluded that chaetoglobosins Q and R were most probably of natural origin.[13]

The cytotoxic and antimicrobial activities of compounds **1**−**9** were evaluated, and the results are shown in Table

1. These data indicate that chaetoglobosins A, B, D, J, Q, and T and prochaetoglobosins I and II (**1**, **3**−**9**) showed significant cytotoxicity against the P388 murine leukemia cell line, whereas chaetoglobosin R (**2**) was inactive. Chaetoglobosins A, B, D, and J and prochaetoglobosins I and II (**4**−**9**) were also noted as being antimicrobial against *Bacillus subtilis*, *Cladosporium resinae*, and *Trichophyton mentagrophytes*.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a Perkin-Elmer 341 polarimeter. UV spectra were recorded on a GBC UV/VIS 920 spectrometer and IR spectra on a Shimadzu FTIR-8201 PC spectrometer. NMR spectra were recorded on a Varian (UNITY INOVA) AS-500 spectrometer (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR), with tetramethylsilane (TMS) as an internal reference. HRESMS were determined using a Micromass LCT TOF mass spectrometer. Column chromatography used J. T. Baker 40 μM Prep LC Bakerbond Octadecyl (RP C18), 40 μM Prep LC Bakerbond Diol (COHCOH), and Sephadex LH-20 (Pharmacia Biotech AB). Solvents used for extraction and isolation were distilled prior to use.

Fungal Identification. *Chaetomium globosum* strain No. CANU N60 was isolated from saline sand, Pegasus Bay, Canterbury, New Zealand, and has been deposited in the culture collection of the School of Biological Sciences, University of Canterbury.

Morphological and cultural characteristics: colonies on malt extract agar (MEA) 58−67 mm in diameter (7 days, 25 °C), with buff aerial mycelium; reverse pale. Colonies on 25% glycerol nitrate agar (G25N) 2−3 mm diameter (7 days, 25 °C). No growth at 5 °C. At 37 °C, colonies 15−16 mm in diameter (MEA, 7 days).

Ascomata maturing at 7−10 days, brown, superficial, spherical or ovate, ostiolate, 145−238 × 173−252 μm; ascomatal hairs numerous, unbranched, undulate or coiled, septate, pale greenish brown; asci clavate, 22−33 × 11−17 μm, 8 spored, evanescent; ascospores limoniform, brownish when mature, containing numerous droplets, 6−8 × 7−9 μm, with an apical germ pore. After comparing the characteristics of this strain with descriptions by von Arx et al.[14] and Pitt and Hocking[15] strain No. N60 was identified as C*haetomium globosum* Kunze.

Fermentation and Isolation. The isolate was grown on potato dextrose agar (GibcoBRL) for 5 days at 25 °C. Mycelial disks (8 mm in diameter) were then cut from the outer regions of the colony and used for broth (1/2 MEB) inoculation (malt extract (Oxoid) (8.5 g) and meat peptone (GibcoBRL) (1.5 g) in distilled H_2O (1 L)). Two liters of 1/2 MEB were inoculated and incubated at 26 °C in the dark for four weeks on a rotary shaker at 180 rpm. The culture was filtered through Celite 545 under suction, and the mycelium and filtrate were extracted separately with EtOAc. The extracts were dried over $MgSO_4$ and evaporated under reduced pressure to yield a yellowish brown extract (234 mg) from the filtrate and a brownish red extract (294 mg) from the mycelium. The two extracts were assayed against the P388 cell line, and each showed significant activity. Since the HPLC profiles of the two extracts were identical, the extracts were combined before chromatography. Initial chromatography of the extract (528 mg) was on RP C18 eluting with a gradient system from 10% MeOH/H_2O to 100% MeOH, then to 100% CH_2Cl_2. Fractions 5−8 (70%−90% MeOH/H_2O) each showed activity against the P388 cell line and were each further chromatographed on Diol. Fraction 5 (52.3 mg) was chromatographed using an EtOAc/petroleum ether gradient system to give chaetoglobosins D (**6**) (5.0 mg) and Q (**1**) (5.1 mg). Fraction 6 (116.5 mg) was purified using a CH_2Cl_2/EtOAc gradient to afford chaetoglobosins R (**2**) (4.9 mg) and B (**5**) (4.9 mg). Fraction 7 (78.5 mg) was eluted from Diol with a gradient system from 100% CH_2Cl_2 to 100%EtOAc. Subfraction 7.5 (25.3 mg) was chaetoglobosin A (**4**) (5% CH_2Cl_2/EtOAc). Subfraction 7.8 (2.6 mg) on LH-20 (2 g) using 100% MeOH as the eluent gave chaetoglobosin T (**3**) (1.5 mg). Fraction 8 (15.2 mg) yielded prochaetoglobosins I (**8**) (3.0 mg) and II (**9**) (3.1 mg) and chaetoglobosin J (**7**) (7.9 mg) eluting off Diol with 80%, 90% EtOAc/petroleum ether and 100% EtOAc, respectively.

Chaetoglobosin Q (1): pale yellow solid; $[\alpha]_D^{20}$ −100° (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ϵ) 217 (4.81), 289 (4.05) nm; IR ($CHCl_3$) ν_{max} 3689, 3535, 3080−3240 (br), 2360, 1691, 1683, 1602, 1193 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.26 (1H, br s, H-1′), 8.17 (1H, d, J = 16.5, H-22), 7.50 (1H, d, J = 7.5, H-4′), 7.37 (1H, d, J = 8.5, H-7′), 7.22 (1H, t, J = 7.5), 7.14 (1H, t, J = 7.5, H-5′), 7.00 (1H, d, J = 2.5, H-2′), 6.72 (1H, d, J = 16.5, H-21), 5.82 (1H, br s, H-2), 5.76 (1H, dd, J = 14.5, 10.5, H-13), 5.63 (1H, d, J = 10.0, H-17), 5.41 (1H, m, H-14), 5.09 (1H, d, J = 3.5, H-19), 3.95 (1H, d, J = 4.5, H-19′), 3.69 (1H, m, H-3), 3.23 (1H, dd, J = 14.0, 11.5, H-10a), 3.19 (1H, d, J = 10.5, H-7), 2.99 (1H, t, J = 4.5, H-4), 2.54 (1H, br m, H-16), 2.52 (1H, dd, J = 14.5, 10.5, H-10b), 2.38 (1H, t, J = 10.5, H-8), 2.33 (1H, m, H-15a), 2.24 (1H, m, H-5), 2.06 (1H, m, H-15b), 1.39 (3H, s, H-12), 1.36 (3H, d, J = 8.5, H-11), 1.35-(3H, s, H-18′), 1.01 (3H, d, J = 4.5, H-16′); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.1 (C, C-20), 196.0 (C, C-23), 171.6 (C, C-1), 136.7 (C, C-1a), 138.1 (CH, C-14), 126.8 (C, C-3′a), 140.3 (CH, C-17), 122.8 (CH, C-2′), 122.9 (CH, C-6′), 137.4 (CH, C-22), 120.2 (CH, C-5a), 132.8 (C, C-18), 127.7 (CH, C-13), 118.4 (CH, C-4′), 132.5 (CH, C-21), 111.7 (C, C-3′), 111.8 (CH, C-7′), 72.5 (C, C-6), 71.4 (CH, C-7), 81.4 (CH, C-19), 63.2 (C, C-9), 53.8 (CH, C-3), 45.0 (CH, C-4), 45.9 (CH, C-8), 38.2 (CH, C-5), 42.0 (CH_2, C-15), 35.4 (CH_2, C-10), 32.5 (CH, C-16), 25.1 (CH_3, C-12), 21.1 (CH_3, C-16′), 15.2 (CH_3, C-11), 10.9 (CH_3, C-18′); HRESMS m/z 547.2796 [M + H$^+$] (calcd for $C_{32}H_{39}N_2O_6$, 547.2808).

Chaetoglobosin R (2): pale yellow solid; $[\alpha]_D^{20}$ −100° (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ϵ) 220 (4.46), 282 (3.73), 291 (3.67) nm; IR ($CHCl_3$) ν_{max} 3689, 3544, 3060−3240 (br), 2360, 1695, 1685, 1602, 1188 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.34 (1H, br s, H-1′), 8.22 (1H, d, J = 16.5, H-22), 7.58 (1H, d, J = 7.5, H-4′), 7.35 (1H, d, J = 8.5, H-7′), 7.18 (1H, t, J = 7.5, H-6′), 7.10 (1H, t, J = 7.5, H-5′), 6.97 (1H, d, J = 2.0, H-2′), 6.65 (1H, d, J = 17.0, H-21), 6.26 (1H, br s, H-2), 5.67 (1H, dd, J = 15.0, 10.0, H-13), 5.62 (1H, d, J = 9.5, H-17), 5.32 (1H, m, H-14), 5.09 (1H, s, H-19), 4.19 (1H, m, H-3), 3.54 (1H, d, J = 11.5, H-7), 3.21 (1H, br d, J = 14.5, H-10a), 2.78 (1H, dd, J = 7.0, 4.0, H-4), 2.49 (1H, br m, H-16), 2.47 (1H, dd, J = 14.5, 10.5, H-10b), 2.32 (1H, m, H-15a), 2.05 (1H, m, H-15b), 2.04 (1H, m, H-8), 1.92 (1H, dd, J = 7.5, 4.0, H-5), 1.34 (3H, s, H-18′), 1.32 (3H, d, J = 7.5, H-11), 1.16 (3H, s, H-12, H-12), 0.99 (3H, d, J = 7.0, H-16′); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.1 (C, C-20), 197.1 (C, C-23), 171.9 (C, C-1), 136.6 (C, C-1′a), 127.1 (C, C-3′a), 140.5 (CH, C-17), 137.2 (CH, C-14), 122.9 (CH, C-2′), 122.6 (CH, C-6′), 137.7 (CH, C-22), 120.0 (CH, C-5′), 119.0 (CH, C-4′), 132.7 (C, C-18), 127.4 (CH, C-13), 132.0 (CH, C-21), 111.9 (C, C-3′), 111.6 (CH, C-7′), 76.1 (C, C-6), 74.7 (CH, C-7), 81.4 (CH, C-19), 63.7 (C, C-9), 53.9 (CH, C-3), 46.1 (CH, C-4), 48.7 (CH, C-8), 38.0 (CH, C-5), 42.1 (CH_2, C-15), 35.1 (CH_2, C-10), 32.5 (CH, C-16), 22.3 (CH_3, C-12), 21.1 (CH_3, C-16′), 13.4 (CH_3, C-11), 10.8 (CH_3, C-18′); HRESMS m/z 547.2805 [M + H$^+$] (calcd for $C_{32}H_{39}N_2O_6$, 547.2808).

Chaetoglobosin T (3): white solid; $[\alpha]_D^{20}$ −80° (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ϵ) 220 (4.39), 283 (3.58), 290 (3.54) nm; IR ($CHCl_3$) ν_{max} 3691, 3481, 2360, 2341, 1697, 1685, 1604, 1463 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (1H, br s, H-1′), 7.51 (1H, d, J = 7.5, H-4′), 7.36 (1H, d, J = 7.5, H-7′), 7.19 (1H, t, J = 7.5, H-6′), 7.12 (1H, t, J = 7.5, H-5′), 6.99 (1H, d, J = 2.5, H-2′), 6.89 (1H, d, J = 16.0, H-22), 6.80 (1H, m, H-21), 5.96 (1H, m, H-13), 5.67 (1H, br s, H-2), 5.34 (1H, br s, H-7), 5.22 (1H, d, J = 8.0, H-17), 5.10 (1H, m, H-14), 4.38 (1H, m, H-19), 3.30 (1H, m, H-3), 3.03 (1H, dd, J = 14.0, 10.5, H-10a), 2.99 (1H, t, J = 5.0, 4.0, H-4), 2.67 (1H, m, H-8), 2.58 (1H, dd, J = 13.5, 10.0, H-10b), 2.50 (1H, dd, J = 7.5, 4.0, H-5), 2.48 (2H, m, H-20), 2.47 (1H, br m, H-16), 2.21 (1H, m, H-15a), 1.90 (1H, m, H-15b), 1.75 (3H, s, H-12), 1.52 (3H, d, J = 1.0, H-18′), 1.34 (3H, d, J = 7.5, H-11), 0.95 (3H, d, J = 7.0, H-16′); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.7 (C, C-23), 174.0 (C, C-1), 136.6 (C, C-1′a), 140.1 (C, C-6), 127.0 (C, C-3′a), 142.5 (CH, C-21), 122.8 (CH, C-2′), 137.1 (CH, C-17), 126.6 (CH, C-7),

132.3 (CH, C-14), 130.3 (CH, C-13), 122.5 (CH, C-6′), 133.3 (C, C-18), 119.9 (CH, C-5′), 118.7 (CH, C-4′), 112.0 (C, C-3′), 128.4 (CH, C-22), 111.6 (CH, C-7′), 76.9 (CH, C-19), 66.0 (C, C-9), 54.0 (CH, C-3), 50.7 (CH, C-4), 46.7 (CH, C-8), 34.9 (CH, C-5), 41.3 (CH_2, C-15), 35.0 (CH_2, C-10), 32.3 (CH, C-16), 35.4 (CH_2, C-20), 20.3 (CH_3, C-12), 21.4 (CH_3, C-16′), 14.6 (CH_3, C-11), 9.9 (CH_3, C-18′); HRESMS *m*/*z* 499.2955 [M + H^+] (calcd for $C_{32}H_{39}N_2O_3$, 499.2961).

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