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Myritonines A–C, Alkaloids from *Myrioneuron tonkinensis* Based on a Novel Hexacyclic Skeleton

Xiao-Hui Li,[†,‡,§] Yu Zhang,[†,§] Jia-Hui Zhang,[†] Xiao-Nian Li,[†] Ming-Ming Cao,[†] Ying-Tong Di,[†] Zong-Gen Peng,[∥] Jian-Dong Jiang,[∥] and Xiao-Jiang Hao*[,†]

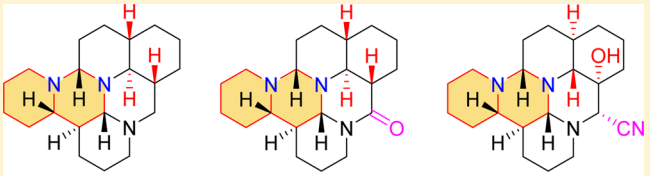
[†]State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, Yunnan, People's Republic of China

[‡]University of Chinese Academy of Sciences, Beijing 100039, People's Republic of China

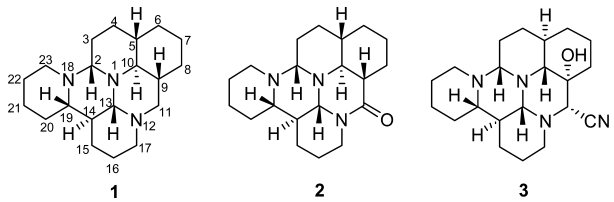
[∥]Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, People's Republic of China

Supporting Information

ABSTRACT: Myritonines A–C (**1**–**3**), three new alkaloids bearing an unprecedented heterohexacyclic skeleton, were isolated from *Myrioneuron tonkinensis*. Their structures were determined by a combination of spectroscopic data and single-crystal X-ray diffraction analysis. Compound **3** represents the first *Myrioneuron* alkaloid featuring a unique *trans*-decahydroquinoline motif and was also found to possess a rare cyano functionality. Compounds **1** and **2** showed inhibition against the hepatitis C virus in vitro.



Myrioneuron alkaloids are characteristic components containing a decahydroquinoline (*trans*- or *cis*-DHQ) motif elaborated specifically by plants of the genus *Myrioneuron* R. Br. (Rubiaceae).[1] The polycyclic structures are usually characterized by several contiguous stereogenic centers and thus have been attractive and challenging subjects of natural products and synthetic chemistry.[2] *Myrioneuron tonkinensis* Pitard. (Rubiaceae), occurring as an herb or subshrub, is distributed mainly in the southern area of mainland China. Its chemical constituents have not been reported previously. Previous investigations on *Myrioneuron faberi* have led to the isolation of a number of alkaloids, with some of these possessing novel structures and showing promising biological activities, such as myriberine A, and the first dimeric *Myrioneuron* alkaloid, myrifabine.[3] In view of this, *M. tonkinensis* was chosen as a research target, and three unprecedented alkaloids were obtained, myritonines A–C (**1**–**3**), from the mixed leaves and twigs. Compounds **1**–**3** represent a new class of *Myrioneuron* alkaloids possessing a novel hexacyclic skeleton with a characteristic extra C_5 unit conjugated with the parent skeleton. It is also noteworthy that compound **3** represents the first *Myrioneuron* alkaloid featuring a unique *trans*-decahydroquinoline motif possessing a rare cyano moiety. Herein, we report the structure elucidation and in vitro biological evaluation of these new compounds.



Myritonine A (**1**) was obtained as colorless needles. A molecular formula of $C_{20}H_{33}N_3$ was established by HREIMS at *m*/*z* 315.2679 [M^+] (calcd 315.2674), indicating six degrees of unsaturation. The ^{13}C NMR and DEPT data for **1** (Table 1) demonstrated the presence of 13 methylenes (three nitrogenated) and seven methines (four nitrogenated). Among these, two downfield signals (δ_C 79.4 and 79.0) were deduced as typical dinitrogenated methines, as found in the case of other *Myrioneuron* alkaloids.[2−4] Since all signals were sp^3 carbons, the six degrees of unsaturation were assumed to be representative of the presence of a hexacyclic system in **1**, as shown in Figure 1.

Detailed 2D NMR (HSQC, $^1H-^1H$ COSY, and HMBC experiments) studies were used to establish the linkages of rings A–F in **1**. The $^1H-^1H$ COSY correlations of H-2/H_2-3/H_2-4/H-5/H_2-6(H-10)/H_2-7/H_2-8/H-9/H_2-11 coupled with HMBC correlations of H-13 (δ_H 3.52, d, J = 10.2 Hz) with C-2 (δ_C 79.0), C-10 (δ_C 59.2), and C-11 (δ_C 51.6) and of H_2-17 (δ_H 2.92, t, J = 13.2 Hz; 2.86, m) with C-13 (δ_C 79.4) confirmed the presence of subunit **a** and the linkages of rings A–D. The resonances for two methines at δ_H 3.16, δ_C 79.0 and δ_H 2.05, δ_C 30.2 were assigned as C-2 and C-14, respectively, which were used as the starting points to elucidate the parameters of rings E and F. HMBC correlations of H-2 (δ_H 3.16) to C-19 (δ_C 67.8), of H-19 (δ_H 1.48) to C-23 (δ_C 50.1), and of H_2-23 (δ_H 2.86; 1.51) to C-2 (δ_C 79.0) indicated that C-2, C-19, and C-23 are connected to one another via a nitrogen atom. The observation

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Table 1. ^{1}H and ^{13}C NMR Data for Compounds 1−3 (δ in ppm and J in Hz)[a]

	1		2		3	
no.	δ_C	δ_H (mult. J)	δ_C	δ_H (mult. J)	δ_C	δ_H (mult. J)
2	79.0	3.16 (s)	76.8	3.17 (d, 1.5)	80.9	2.70 (d, 10.0)
3a	28.5	2.07 (m)	28.0	2.09 (m)	29.7	1.89 (m)
3b		1.63 (m)		1.54 (m)		1.42 (m)
4a	26.5	1.45 (m)	24.4	1.57 (m)	30.2	1.44 (m)
4b		1.22 (m)		1.03 (m)		0.89 (m)
5	42.8	1.28 (m)	44.0	1.22 (m)	35.1	1.61 (m)
6a	33.2	1.50 (m)	31.9	1.45 (m)	32.6	1.46 (m)
6b		1.08 (m)		1.02 (m)		0.88 (m)
7a	26.8	1.54 (m)	26.1	1.65 (m)	20.5	1.86 (m)
7b		1.54 (m)		1.65 (m)		1.39 (m)
8a	30.3	1.46 (m)	26.8	2.65 (m)	34.3	1.81 (m)
8b		1.28 (m)		2.65 (m)		1.81 (m)
9	41.7	1.70 (m)	46.6	2.18 (td, 11.5, 2.0)	67.7	
10	59.2	2.71 (dd, 9.6, 3.0)	57.8	3.08 (t, 10.0)	66.4	2.07 (d, 10.0)
11a	51.6	2.70 (dd, 10.8, 5.4)	168.1		65.2	3.88 (s)
11b		2.36 (dd, 10.8, 3.6)				
13	79.4	3.52 (d, 10.2)	78.0	3.87 (d, 10.0)	81.8	2.66 (d, 8.5)
14	30.2	2.05 (m)	41.3	1.67 (m)	40.2	1.68 (m)
15a	28.3	1.80 (d, 12.6)	27.2	1.77 (m)	25.5	1.58 (m)
15b		0.79 (qd, 12.6, 4.8)		0.87 (m)		0.69 (m)
16a	19.9	1.59 (m)	25.4	1.37 (m)	24.5	1.45 (m)
16b		1.04 (m)		1.37 (m)		1.45 (m)
17a	54.2	2.92 (td, 13.8, 3.0)	43.4	2.36 (t, 12.5)	53.2	2.65 (d, 10.0)
17b		2.86 (m)		4.86 (dt, 12.5, 2.0)		2.58 (td, 10.0, 5.0)
19	67.8	1.48 (m)	66.0	2.07 (m)	62.8	1.91 (m)
20a	26.2	1.58 (m)	24.2	1.43 (m)	28.8	1.62 (m)
20b		1.27 (m)		1.16 (m)		1.16 (m)
21a	29.6	1.77 (m)	29.3	1.65 (m)	26.5	1.48 (m)
21b		1.13 (m)		1.03 (m)		1.48 (m)
22a	25.1	1.62 (m)	26.2	1.52 (m)	22.8	1.42 (m)
22b		1.07 (m)		1.52 (m)		1.14 (m)
23a	50.1	2.86 (m)	49.4	2.83 (m)	46.7	2.94 (m)
23b		1.51 (m)		1.48 (m)		1.93 (m)
24					116.4	

[a]Compound **1** was measured in pyridine-d_5 at 600 MHz (^{1}H) and 150 MHz (^{13}C), and compounds **2** and **3** were measured in pyridine-d_5 at 500 MHz (^{1}H) and 125 MHz (^{13}C); overlapped.

of ^{1}H−^{1}H COSY correlations of H_2-23/H_2-22/H_2-21/H_2-20/H-19/H-14 suggested the presence of a piperidine ring E fused with a hexahydropyrimidine ring F, which was confirmed by the key HMBC correlations of H-13 (δ_H 3.52) and H-14 (δ_H 2.05) to C-19 (δ_C 67.8). Thus, the gross structure of **1**, which shares the same basic skeleton with a monomeric partner found in the dimeric alkaloid myrifabine,[3b] was elucidated as shown.

The relative configuration of **1** was elucidated from a ROESY experiment (Figure 1B) and the values of the ^{1}H−^{1}H vicinal coupling constants. The cross-peaks of H-2/H-13, H-2/H-19, and H-13/H-19 in the ROESY spectrum revealed that H-2, H-13, and H-19 are cofacial, and these were defined arbitrarily as having a β-orientation. Thus, H-10 and H-14 were designated

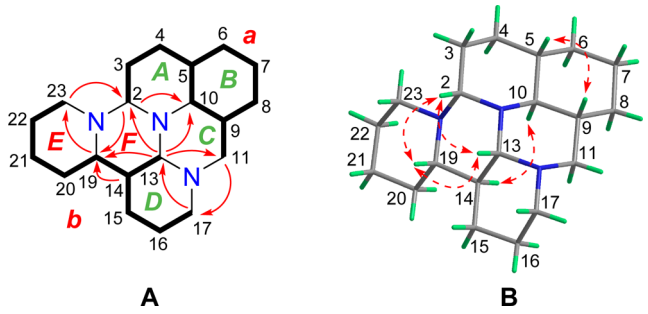

Figure 1. ^{1}H−^{1}H COSY (A, bold −), selected HMBC (A, →), and ROESY (B, ↔) correlations of **1**.

as α-oriented due to the correlations of H-10/H-14 and the coupling constants of H-13 ($^3J_{H-C-C-H}$ = 10.2 Hz).[3b] The observation of a correlation between H-5 and H-9 indicated the presence of a *trans*-decahydroquinoline (*trans*-DHQ) motif in **1** rather than the more usual *cis*-decahydroquinoline (*cis*-DHQ) motif found commonly in *Myrioneuron* alkaloids. A single-crystal X-ray diffraction experiment (Figure 2) confirmed its relative configuration.

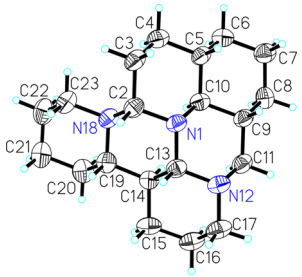

Figure 2. Single-crystal X-ray structure of **1**.

Myritonine B (**2**), isolated as colorless prisms, showed a molecular formula of $C_{20}H_{31}N_3O$, as established by HREIMS at m/z 329.2463 [M$^+$] (calcd 329.2467), indicating seven degrees of unsaturation. The ^{1}H and ^{13}C NMR spectra of **2** (Table 1) were closely related to those of **1**, with the exception of the replacement of a nitrogenated methylene carbon with a carbonyl group that resonated at δ_C 168.1 in **2**. The HMBC correlations of H-9 (δ_H 2.18), H-10 (δ_H 3.08), H-13 (δ_H 3.87), and H_2-17 (δ_H 2.36, 4.86) with the carbonyl carbon (δ_C 168.1) revealed that the carbonyl group could be assigned as C-11. The planar structure of **2** was thus constructed as shown in Figure 3. The relative configuration of this alkaloid was identical with that of **1**, based on their same ROESY correlations, which was confirmed by a single-crystal X-ray diffraction experiment (Figure 4).

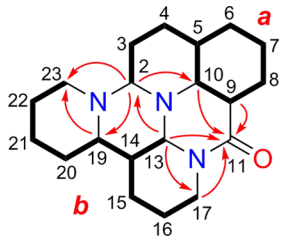

Figure 3. ^{1}H−^{1}H COSY (bold −) and selected HMBC (→) correlations of **2**.

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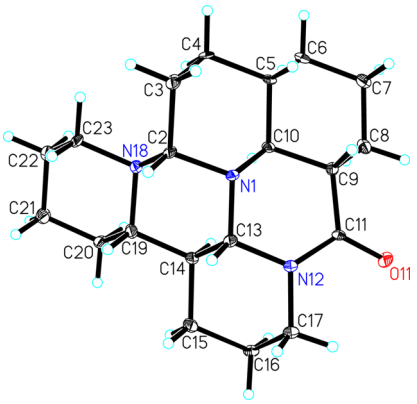

Figure 4. Single-crystal X-ray structure of **2**.

The molecular formula, $C_{21}H_{32}N_4O$, of myritonine C (**3**), purified as a colorless oil, was established by HREIMS at *m/z* 356.2578 [M$^+$] (calcd 356.2576). The IR absorption at 3428 cm^{-1} indicated the presence of a hydroxy group. Analysis of the combined ^{1}H and ^{13}C NMR data (Table 1) established that **3** possesses 12 methylenes, seven methines, and two quaternary carbons (δ_C 67.7, 116.4) and also indicated this compound to have the same basic skeleton as that of **1**. A characteristic nitrile functionality was suggested by the presence of only one quaternary carbon signal that appeared at δ_C 116.4 in the olefinic region.[5,6] The key HMBC correlation of H-11 (δ_H 3.88) to C-24 (δ_C 116.4) suggested a cyano group as being attached to C-11. The HMBC correlations of H-7b (δ_H 1.39, m), H$_2$-8 (δ_H 1.81, m), H-10 (δ_H 2.07, d, *J* = 10.0 Hz), and H-11 (δ_H 3.88, s) to C-9 (δ_C 67.7) indicated that a hydroxy group was located at C-9. The other parts of **3** were determined as being the same as those of **1**, as confirmed by the 2D NMR (HSQC, ^{1}H−^{1}H COSY, and HMBC) data (Figures S25−28, Supporting Information). Thus, the planar structure of **3** was established as shown (Figure 5A).

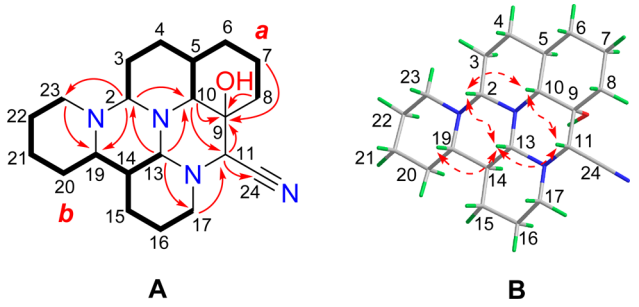

Figure 5. ^{1}H−^{1}H COSY (A, bold −), selected HMBC (A, →), and ROESY (B, ↔) correlations of **3**.

Detailed analysis of the ROESY spectrum of **3** indicated the conformations of rings A−F occurred in chair conformations like those of compounds **1** and **2**. The cross-peaks of H-2/H-10, H-10/H-11, H-11/H-13, and H-13/H-19 suggested that H-2, H-10, H-11, H-13, and H-19 are all cofacial and were assigned arbitrarily as *β*-oriented. In turn, H-14 and OH-9 were located in axial positions and, hence, were *α*-oriented. The vicinal coupling constants of H-13 ($^3J_{H-C-C-H}$ = 8.5 Hz) and H-10 ($^3J_{H-C-C-H}$ = 10.0 Hz) confirmed the *α*-orientation of H-14 and H-5.[3b] Accordingly, the relative configuration of **3** was elucidated as shown in Figure 5B.

It is noteworthy that compound **3** features an uncommon *trans*-decahydroquinoline (*trans*-DHQ) motif within the *Myrioneuron* alkaloid category. The basic C_5 building blocks derived putatively from L-lysine perhaps underwent an alternative pathway during the formation of the core decahydroquinoline ring (Scheme 1),[1,3b] and the cyano moiety might have originated from acetyl-CoA through the Mannich reaction as a key step.[7,8]

Myritonines A−C (**1**−**3**) were tested for cytotoxicity against the A-549, MCF-7, SMMC-7721, SW-480, and HL-60 human cancer cell lines using the MTT method with cisplatin as the positive control.[9] Alkaloids **1**−**3** exhibited no cytotoxicity against these five cell lines, having IC_{50} values greater than 10 *μ*M. These alkaloids were tested also for anti-HCV activity, and **1** and **2** showed inhibitory effects on the hepatitis C virus (HCV) life cycle with a therapeutic index (CC_{50}/EC_{50}) of greater than 12.0 and 11 in vitro, respectively (see Table S1, Supporting Information).[3a,c]

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured with a JASCO P-1020 polarimeter. UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. ECD spectra were recorded with an Applied Photophysics Chirascan spectrometer. A Tensor 27 spectrophotometer was used for IR spectra that were obtained with KBr pellets. 1D and 2D NMR spectra were performed on Bruker AM-400, DRX-500, and Bruker AV-600 spectrometers with tetramethylsilane as an internal standard. Mass spectra were taken on VG Auto Spec-3000 or API-Qstar-Pulsar instruments. Column chromatography (CC) was performed using silica (200−300 mesh and 300−400 mesh, Qingdao Marine Chemical, Inc., Qingdao, People's Republic of China) and Sephadex LH-20 (40−70 *μ*m, Amersham Pharmacia Biotech AB, Uppsala, Sweden).

Plant Material. The leaves and stems of *M. tonkinensis* were collected from Guangxi Province, People's Republic of China, in July 2013. The plant samples were identified by Yunbiao Liao of Kunming Botanical Garden, Kunming Institute of Botany, Chinese Academy of Science (CAS). A voucher specimen (KIB H20130715) was deposited at the State Key Laboratory of Phytochemistry and Plant Resource in West China, Kunming Institute of Botany, Chinese Academy of Science (CAS).

Extraction and Isolation. The air-dried, powdered leaves and stems (50 kg) of *M. tonkinensis* were extracted three times with methanol under reflux at 50 °C, and the combined extract was removed under vacuum to afford a viscous residue. The crude extract (3.7 kg) was chromatographed over silica gel (100−200 mesh, $CHCl_3$−MeOH, 1:0 → 0:1) to obtain three major fractions (Fr. 1−3). Fr. 1 (10.0 g) was chromatographed on a silica gel containing column, eluted with a gradient of petroleum ether−Me_2CO (9:1 to 5:5) to yield four subfractions (Fr. 1A−1D). Subfraction 1A (1.2 g) was purified using Sephadex LH-20 (MeOH) and further purified using a silica gel column (petroleum ether−EtOAc, 8:2) to afford **1** (4 mg) and **2** (5 mg). Compound **3** (5 mg) was isolated from subfraction 1C (2.8 g) by repeated silica gel column chromatography, eluted with a gradient of $CHCl_3$−Me_2CO (from 20:1 to 5:1), and further purified by passage over a Sephadex LH-20 (MeOH) column.

Myritonine A (1): colorless needle crystals; $[\alpha]_D^{20}$ −13.8 (*c* 0.07, MeOH); UV (MeOH) λ_{max} (log ε) 203 (3.14) nm; IR (KBr) ν_{max} 3428, 2924, 2851, 1630, 1445, 1384, 1347 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HREIMS *m/z* 315.2679 [M]$^+$ (calcd for $C_{20}H_{33}N_3$, 315.2674).

Myritonine B (2): colorless prism; $[\alpha]_D^{20}$ −77.0 (*c* 0.04, MeOH); UV (MeOH) λ_{max} (log ε) 204 (3.84) nm; ECD (0.0032 M, MeOH) λ_{max} ($\Delta\varepsilon$) 202 (−4.0), 231 (+1.3) nm; IR (KBr) ν_{max} 3443, 2925, 1656, 1632, 1440, 1384, 1128 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HREIMS *m/z* 329.2463 [M]$^+$ (calcd for $C_{20}H_{31}N_3O$, 329.2467).

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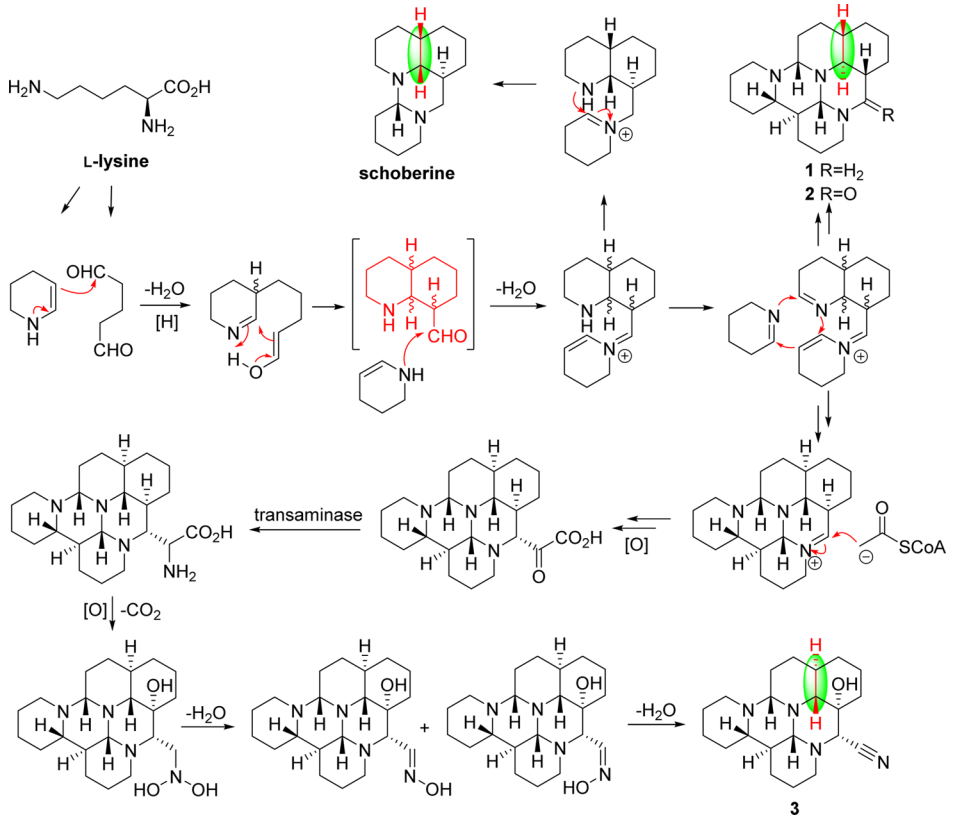
Scheme 1. Proposed Biosynthetic Pathway of 1−3



*Myritonine C (**3**):* colorless oil; $[\alpha]_D^{20}$ −10.0 (*c* 0.08, MeOH); UV (MeOH) λ_{max} (log ε) 203 (3.56) nm; ECD (0.0022 M, MeOH) λ_{max} ($\Delta\varepsilon$) 218 (+0.84), 241 (−0.48) nm; IR (KBr) ν_{max} 3428, 2933, 2857, 1632, 1446, 1385, 1307 cm^{-1}; ^1H and ^{13}C NMR data see Table 1; HREIMS *m*/*z* 356.2578 $[M]^+$ (calcd for $C_{21}H_{32}N_4O$, 356.2576).

X-ray Crystal Structure Analysis of Compounds 1 and 2. Colorless needle crystals of **1** and **2** were recrystallized from acetone. Intensity data were collected on a Bruker Apex Duo diffractometer equipped with an Apex II CCD using Cu Kα radiation. Cell refinement and data reduction were performed with Bruker SAINT software. The structure was solved by direct methods using SHELXL-97. Refinements were performed with SHELXL-97 using full-matrix least-squares, with anisotropic displacement parameters for all the non-hydrogen atoms. The H atoms were placed in calculated positions and refined using a riding model. Molecular graphics were computed with PLATON.

*Compound **1**:* $C_{20}H_{33}N_3$, M = 315.49, orthorhombic, a = 5.4602(4) Å, b = 17.7085(15) Å, c = 18.1951(15) Å, V = 1759.3(2) Å^3, T = 296(2) K, space group $P212121$, Z = 4, μ(Cu Kα) = 0.532 mm^{-1}, 17 349 reflections measured, 3128 independent reflections (R_{int} = 0.2608). The final R_1 values were 0.1025 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.2308 ($I > 2\sigma(I)$). The final R_1 values were 0.2542 (all data). The final $wR(F^2)$ values were 0.3376 (all data). The goodness of fit on F^2 was 0.876. Flack parameter = −3.1(15). Crystallographic data (excluding structure factor tables) for compound **1** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication (deposit number CCDC1419710).

*Compound **2**:* $C_{20}H_{31}N_3O$, M = 329.48, orthorhombic, a = 5.3218(4) Å, b = 14.7425(8) Å, c = 21.8252(14) Å, V = 1712.33(19) Å^3, T = 100(2) K, space group $P212121$, Z = 4, μ(Cu Kα) = 0.617 mm^{-1}, 15 068 reflections measured, 3074 independent reflections (R_{int} = 0.1156). The final R_1 values were 0.0727 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.2060 ($I > 2\sigma(I)$). The final R_1 values were 0.0922 (all data). The final $wR(F^2)$ values were 0.2251 (all data). The goodness of fit on F^2 was 1.215. Flack parameter = 0.6(6). Crystallographic data (excluding structure factor tables) for compound **2** were deposited with the Cambridge Crystallographic Data Center as supplementary publication (deposit number CCDC 1419709). Copies of the data can be obtained free of charge by application to the CCDC, 12 Union Road, Cambridge CB 1EZ, UK [fax: Int. +44 (0) (1223) 336 033; e-mail: deposit@ccdc.cam.ac.uk].

Cytotoxicity Assays. Compounds **1**−**3** were tested in vitro for their cytotoxicities against proliferation of five human tumor cell lines, HL-60 (premyelocytic leukemia), SMMC-7721 (hepatocellular carcinoma), A-549 (lung adenocarcinoma), MCF-7 (breast cancer), and SW480 (colon adenocarcinoma), using the MTT assay.[9] Cytotoxicity evaluations were performed according to the previously described protocol, with cisplatin used as positive control.[10]

Anti-HCV Assays. The anti-HCV activity evaluations were performed according to the previously described protocol, with VX-950 used as positive control.[3a,c]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.5b01130.

MS, HREIMS, IR, UV, ECD, and NMR spectra of new compounds **1**−**3** (PDF)

X-ray crystallographic data of **1** (CIF)

X-ray crystallographic data of **2** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*Tel/Fax: 86-871-65223070. E-mail: haoxj@mail.kib.ac.cn (X.-J. Hao).

Author Contributions

§X.-H. Li and Y. Zhang contributed equally.

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Notes

The authors declare no competing financial interest.

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