Periglaucines A−D, Anti-HBV and -HIV-1 Alkaloids from *Pericampylus glaucus*

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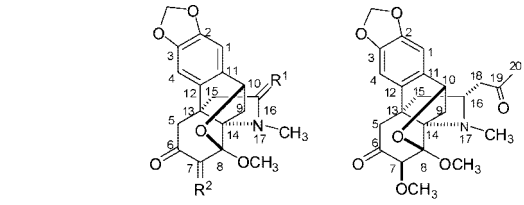
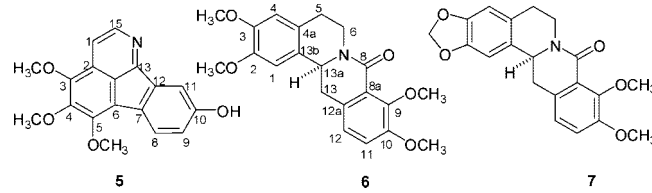
Four new hasubanane-type alkaloids, periglaucines A–D (**1**–**4**), and three known alkaloids, norruffscine (**5**), (−)-8-oxotetrahydropalmatine (**6**), and (−)-8-oxocanadine (**7**), were isolated from the aerial parts of *Pericampylus glaucus*. Their structures were elucidated on the basis of extensive NMR and EIMS data, and that of periglaucine A (**1**) was confirmed by single-crystal X-ray diffraction. Alkaloids **1**–**4** inhibited hepatitis B virus (HBV) surface antigen (HBsAg) secretion in Hep G2.2.15 cells. (−)-8-Oxotetrahydropalmatine (**6**) possessed a high selectivity index (SI = 22.4) for HBsAg secretion of the Hep G2.2.15 cell line with an IC_{50} value of 0.14 mM. Norruffscine (**5**) and (−)-8-oxotetrahydropalmatine (**6**) exhibited inhibitory activity against human immunodeficiency virus (HIV-1) with EC_{50} values of 10.9 and 14.1 μM in C8166 cells (SI = 45.7 and 18.8), respectively.

Plants of the Menispermaceae family are recognized to be rich in alkaloids that have diverse structures and significant biological activities. *Pericampylus glaucus* (Lam.) Merr. (Menispermaceae) is a climbing shrub that is widely distributed in the southwest of China.[1] The roots are employed in the treatment of laryngitis, cough, pulmonary disease, and boils by the local people, and the leaves are used for fractures and boar bites. Other medicinal uses include sedation, tetanus, and relieving rheumatic pains.[2] Several phytochemical investigations have led to the isolation of both alkaloids and other compounds from the genus;[3,4] however, the biologically active natural products from this species have not been reported to date.

In our recent study, a series of acutumine and rigid isoquinoline alkaloids were isolated from *Hypserpa nitida* (Menispermaceae)[5] and *Corydalis saxicola* (Menispermaceae),[6] respectively, which inhibited hepatitis B virus (HBV) surface antigen (HBsAg) and e antigen (HBeAg) secretion effectively in Hep G2.2.15 cells. These findings prompted us to further investigate the chemical constituents of *P. glaucus*. Our research on an ethanolic extract of the plant has yielded four new alkaloids, periglaucines A–D (**1**–**4**), along with three known alkaloids, norruffscine (**5**), (−)-8-oxotetrahydropalmatine (**6**), and (−)-8-oxocanadine (**7**). In this paper, we report the isolation and structural elucidation of alkaloids **1**–**4**. Alkaloids **1**–**7** were assayed for anti-HBV activity, and compounds **1**–**6** were evaluated for anti-HIV-1 activity *in vitro.*





Results and Discussion

Compound **1** was obtained as colorless crystals from acetone with an optical rotation of $[\alpha]^{15}_{D}$ +78.0 (*c* 0.55, $CHCl_3$), and the molecular formula was determined to be $C_{20}H_{23}NO_6$ on the basis of the positive HRESIMS at *m/z* 374.1600 $[M + 1]^+$ (calcd for $C_{20}H_{24}NO_6$, 374.1603). Its IR absorption at 1733 cm^{-1} revealed the presence of a carbonyl group. In the ^1H NMR spectrum (Table 1), two singlet signals (δ_H 6.83 and 6.57) due to aromatic protons were observed, as well as signals of two *O*-methyl groups (δ_H 3.25, 3.23) and one *N*-methyl group (δ_H 2.53). The ^{13}C NMR spectrum displayed 20 carbon signals, corresponding to three primary, five secondary, four tertiary, and eight quarternary carbon atoms (Table 1). The signal at δ_C 205.6 indicated a ketone carbonyl group in the molecule and suggested that compound **1** was a hasubanane-type alkaloid. Comparison of the spectroscopic data with those of isolonganone[7] demonstrated that compound **1** possessed a skeleton similar to that of isolonganone except for different substituents on the aromatic ring. The proton signals at δ_H 6.83 (1H, s, H-1) and 6.57 (1H, s, H-4), along with a typical *O*-CH_2-*O* signal at δ_H 5.93, indicated that the *O*-CH_2-*O* unit should be linked at C-2 and C-3. This was supported by the correlations H-17/C-2 and H-17/C-3 in its HMBC spectrum (Figure 1). The structure of compound **1** was confirmed by an X-ray crystallographic study as depicted in Figure 2. Thus, the structure of compound **1** was established as (7α,8*β*,10*β*)-8,10-epoxy-7,8-dimethoxy-2,3-[methylenebis(oxy)]-17-methyl-6-oxohasubanan, and it was named periglaucine A.

Compound **2** had the same molecular formula as periglaucine A (**1**), as determined by the positive HRESIMS at *m/z* 374.1605 $[M + 1]^+$ (calcd 374.1603). The IR absorption spectrum was very similar to that of **1**. Comparison of the NMR data with those of **1** indicated that the compounds differed in structure only slightly. The main differences in the ^{13}C NMR spectrum (Table 1) were observed in signals ascribed to C-5, C-6, C-7, and C-8, especially C-7, which suggested that **2** was probably a stereoisomer of **1** due

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Table 1. ^{1}H NMR and ^{13}C NMR Data for Periglaucines A–D (**1**–**4**)[a]

	1[b]		**2**[b]		**3**[c]		**4**[b]	
position	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1	6.83 s	108.7	6.81 s	108.7	6.64 s	107.6	6.79 s	108.7
2		148.5		148.6		148.3		148.6
3		146.1		146.2		146.1		146.0
4	6.57 s	106.0	6.58 s	106.1	6.52 s	105.6	6.57 s	105.9
5	3.67 d (12.0)	47.3	3.25 d (12.7)	50.3	2.63 s	45.1	3.28 d (12.6)	51.4
	2.35 d (12.0)		2.52 d (12.7)				2.53 d (12.7)	
6		205.6		203.1		204.3		202.8
7	3.43s	82.0	4.24 s	89.4	3.65 s	80.3	4.24 s	89.4
8		106.2		108.0		104.3		107.9
9	1.59 d (10.8)	29.6	1.55 d (10.8)	30.0	1.65 d (10.9)	34.8	1.57 d (10.9)	28.8
10	4.71 d (6.2)	76.5	4.78 d (6.1)	77.4	4.73 d (6.0)	75.2	4.80 d (6.3)	77.1
11		135.9		135.8		133.9		135.7
12		135.4		135.6		131.3		135.4
13		53.6		53.8		47.4		52.3
14		74.0		76.7		71.0		77.4
15	2.03 m	38.0	1.97 m	37.8	3.46 d (12.4)	46.3	2.03 m	44.8
			2.11 m		2.35 d (12.4)			
16	3.29 m	53.8	3.42 m	54.4		171.7	3.02 m	61.5
18							2.68 m 3.04 m	51.0
19								207.7
20							2.13 s	30.5
O-CH_2-O	5.93 s	102.0	5.93 d (4.0)	102.0	5.93 d (3.1)	101.4	5.93 s	101.9
7-OCH_3	3.23 s	58.0	3.35 s	59.3	3.29 s	58.2	3.35 s	59.2
8-OCH_3	3.25 s	47.8	3.43 s	51.8	3.32 s	48.0	3.43 s	51.8
N-CH_3	2.53 s	37.9	2.86 s	38.5	3.07 s	28.1	3.07 s	36.7

[a] Chemical shifts are expressed in δ (ppm), and coupling constants (J) are expressed in Hz. [b] NMR data are measured in CD_3COCD_3. [c] NMR data are measured in $CDCl_3$.

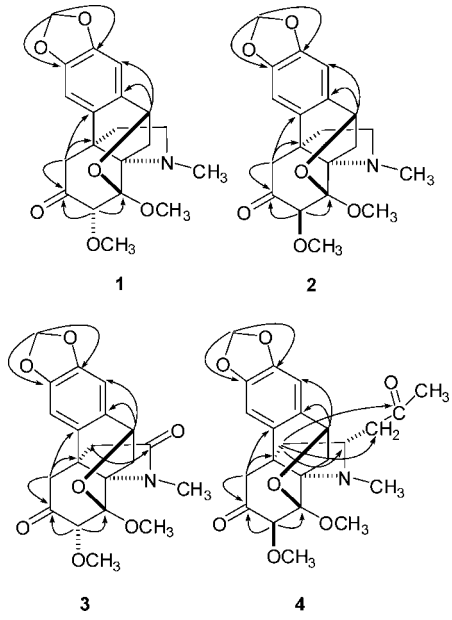

Figure 1. Selected HMBC correlations of periglaucines A–D (**1**–**4**).

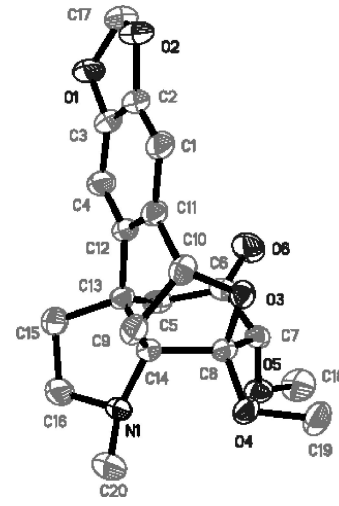

Figure 2. X-ray crystal structure of periglaucine A (**1**).

to a β-oriented methoxy group at C-7. This assumption was supported by comparison of its NMR data with those of the known compound langanone.[7] The correlations observed in the ^{1}H–^{1}H COSY and HSQC spectra, in combination with the HMBC data (Figure 1), allowed the assignments of all resonances in the ^{13}C NMR spectrum. Thus, compound **2** was determined to be (7β,8β,10β)-8,10-epoxy-7,8-dimethoxy-2,3-[methylenebis(oxy)]-17-methyl-6-oxohasubanan and was given the name periglaucine B.

Compound **3** was obtained as a white powder with an optical rotation of $[\alpha]^{24}_D$ +131.7 (*c* 0.12, MeOH), and the molecular formula was deduced as $C_{20}H_{21}NO_7$ by HRESIMS. The IR spectrum exhibited strong absorption signals at 1731 and 1697 cm^{-1}, indicating the presence of two carbonyl groups. As shown in Table 1, the ^{1}H NMR spectrum exhibited proton signals similar to those of **1**, except for the downfield shifted signal of H-15 and the absence of the signal of H-16. The ^{13}C NMR spectrum showed one more carbonyl group (δ_C171.7, indicative of an amide or ester) when compared with the spectrum of **1**. Considering the coupling constant for H-15 (J = 12.4 Hz), as well as the chemical shift for C-15 downshifted to δ_C 46.3, the additional carbonyl unit was assigned to C-16. The assignment was further supported by the long-range correlation between H-15 and C-16 in the HMBC spectrum of compound **3**. Consequently, compound **3** was deduced to be (7α,8β,10β)-8,10-epoxy-7,8-dimethoxy-2,3-[methylenebis(oxy)]-17-methyl-6,16-dioxohasubanan, and it was named periglaucine C.

Compound **4** was isolated as a white powder. The EIMS gave a molecular ion peak at *m*/*z* 429, consistent with a molecular formula of $C_{23}H_{27}NO_7$ (HRESIMS). Its IR spectrum indicated the presence of two carbonyl groups (1737 and 1711 cm^{-1}), which were in agreement with two ketone carbonyl signals (δ_C 202.8 and 207.7) in the ^{13}C NMR spectrum (Table 1). NMR analyses suggested that compound **4** was also a hasubanane-type alkaloid. Comparison of the ^{13}C NMR data with those of **2** indicated that compound **4** was

Table 2. Anti-HBV Activity of Compounds **1**–**7**[a]

		HBsAg[b]		HBeAg[c]	
compound	CC_{50} (mM)	IC_{50} (mM)	SI[d]	IC_{50} (mM)	SI
1	2.96	1.04	2.85	3.41	<1
2	0.64	0.47	1.36	3.09	<1
3	2.36	1.72	1.37	>3.69	<1
4	2.06	0.67	3.07	3.01	<1
5	>3.88	0.93	>4.17	>3.88	
6	3.00	0.14	22.40	>7.47	<1
7	>3.40	>3.40		>3.40	
3TC[e]	30.00	11.70	2.56	25.90	1.16

[a] All values are the mean of two independent experiments. [b] HBsAg: HBV surface antigen. [c] HBeAg: HBV e antigen. [d] CC_{50} = cytostatic concentration; the concentration to inhibit Hep G2.2.15 cell proliferation by 50%, IC_{50} = 50% inhibition concentration against HBV synthesis, SI = CC_{50}/IC_{50}. [e] 3TC: Lamivudine, an antiviral agent used as a positive control.

Table 3. Anti-HIV-1 Activity of Compounds **1**–**6**[a]

compound	EC_{50} (μM)[b]	CC_{50} (μM)[c]	SI[d]
1	204.00	>536	4.03
2	388.60	>536	1.61
3	162.50	>516	3.29
4	334.10	>466	1.65
5	10.90	493	45.74
6	14.10	307	18.80
AZT[e]	0.0108	5091	471 388

[a] All data represent mean values for two separate experiments. [b] EC_{50} = effective concentration required to protect C8166 cells against the cytopathogenicity of HIV-1 by 50%. [c] CC_{50} = cytostatic concentration; the concentration required to reduce C8166 cell proliferation by 50%. [d] Selectivity index: CC_{50}/EC_{50} ratio. [e] AZT was used as a positive control.

an analogue of **2**, which contained three additional carbon signals [δ_C 207.7 (C-19), 51.0 (C-18), and 30.5 (C-20)]. The long-range correlations between H-15/C-16, H-15/C-18, and H-15/C-19 in the HMBC spectrum (Figure 1) demonstrated that the new methylene group (C-18) was linked with C-16 and C-19. Accordingly, the additional methyl group (C-20) was linked with the carbonyl carbon (C-19). On the basis of the above analyses, a propan-2-one moiety was attached at C-16. Furthermore, a cross-peak between H-16 and H-9 was observed in the NOESY spectrum (Figure S24, Supporting Information) of compound **4**, which suggested a β-H was located at C-16. Thus, the structure of compound **4** was proposed to be (7β,8β,10β)-8,10-epoxy-7,8-dimethoxy-2,3-[methylenebis(oxy)]-16-propan-2-one-17-methyl-6-oxohasubanan, and it was named periglaucine D.

Three known compounds were identified as norruffscine (**5**),[8] (−)-8-oxotetrahydropalmatine (**6**),[9] and (−)-8-oxocanadine (**7**)[10] by comparison of their ^{1}H and ^{13}C NMR spectroscopic data with those reported in the literature (Supporting Information).

Anti-HBV Assay. Compounds **1**–**7** were evaluated for their anti-HBV activity in the HBV-transfected Hep G 2.2.15 cell line. Results including their activity and cytotoxicities are shown in Table 2. (−)-8-Oxotetrahydropalmatine (**6**) showed an IC_{50} value of 0.14 mM in inhibiting HBV surface antigen secretion with a high selectivity index (SI = 22.4) in Hep G2.2.15 cells and is deserving of further anti-HBV study. The hasubanane-type alkaloids **1**–**4** were found to possess weak to moderate activity against HBsAg secretion, with IC_{50} values of 0.47–1.72 mM and CC_{50} values of 0.64–2.96 mM, respectively, which led to SI values of 1.36–3.07.

Anti-HIV-1 Assay. Alkaloids **1**–**6** were assayed for their anti-HIV-1 activity. The hasubanane-type alkaloids **1**–**4** displayed weak activity or were inactive in the syncytium assay. Norruffscine (**5**) and (−)-8-oxotetrahydropalmatine (**6**) showed activity with EC_{50} values of 10.9 and 14.1 μM against HIV-1 in the C8166 cell line (Table 3), resulting in SI values of 45.7 and 18.8, respectively. Isoquinoline alkaloids were found previously to inhibit HIV-1 in the literature.[11] Our findings that compounds **5** and **6**, the rigid isoquinoline alkaloids, showed potent anti-HIV-1 activity adds to information regarding isoquinoline alkaloids.

Experimental Section

General Experimental Procedures. Melting points were measured on a XRC-1 melting instrument (Sichuan University, Sichuan, China) and are uncorrected. Optical rotations were determined on a SEPA-300 polarimeter. UV spectra were measured on a Shimadzu UV-210A spectrophotometer. IR (KBr) spectra were recorded on a Bio-Rad FTS-135 spectrometer. 1D and 2D NMR spectra were recorded on Bruker AM-400 NMR and DRX-500 spectrometers, respectively, with TMS as internal standard. EIMS (70 eV) was recorded on a VG Autospec-3000 spectrometer. Positive HRESIMS were recorded on an API Qstar Pulsar spectrometer. Silica gel (200–300 mesh and H) and alumina (neutral) for column chromatography were obtained from the Qingdao Meigao Chemical Company, Ltd., and Shanghai Wusi Chemical Reagents Company, Ltd., respectively. Sephadex LH-20 was purchased from Pharmacia Fine Chemical Co. Ltd., Germany.

Plant Material. The aerial parts of *P. glaucus* were collected in Xishuangbanna, Yunnan Province, P. R. China, in July 2005, and identified by senior engineer Mr. Jing-Yun Cui, Xishuangbanna Tropical Botanical Garden, Chinese Academy of Sciences. A voucher specimen (2005-07-02) has been deposited in the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany.

Extraction and Isolation. Dried and finely powdered plant material (13 kg) was extracted with 90% EtOH (104 L × 3) under reflux for 2 h each time. The extract was concentrated under vacuum to give a residue, which was acidified to pH 2 with 5% HCl and partitioned between H_2O and EtOAc, and then the aqueous layer was basified to pH 10 with NH_4OH and extracted with EtOAc. The EtOAc fraction was evaporated to give an alkaloid fraction (42 g). The alkaloid fraction was subjected to column chromatography (CC) on silica gel (500 g, 200–300 mesh) and eluted with petroleum ether/Me_2CO/Et_2NH mixtures of increasing polarities (15:1:1, 10:1:1, 5:1:1, 1:1:1, and 0:1:0) to give seven fractions (1–7). Fraction 2 (1.4 g) was separated by silica gel CC (45 g, 200–300 mesh) and medium-pressure silica gel CC (70 g, silica gel H), eluted with petroleum ether/Me_2CO (90:10) and petroleum ether/EtOAc (90:10), respectively. It was then purified using Sephadex LH-20 to obtain compounds **3** (10 mg) and **6** (30 mg). Fraction 4 (3.5 g) was subjected to silica gel CC (100 g, 200–300 mesh), eluted with $CHCl_3$/Me_2CO (99:1), to afford three fractions (4a–4c). Fraction 4c (1.5 g) was subjected to medium-pressure silica gel CC (70 g, silica gel H) eluted with petroleum ether/Me_2CO (90:10) to obtain six fractions (4ca–4cf). Fraction 4cc (120 mg) was successively purified by silica gel CC eluted with petroleum ether/Me_2CO (90:10) to afford fraction 4ccb and then Sephadex LH-20 chromatography eluted with 100% MeOH to give compound **2** (25 mg). Fraction 4cf (135 mg) was treated the same as fraction 4cc to provide compound **4** (33 mg). Fraction 6 (1.2 g) was separated by CC on silica gel (25 g, 200–300 mesh) and silica gel H (30 g, medium-pressure) to obtain fractions 6a–6c. Fraction 6b (130 mg) was subjected to CC over silica gel to obtain fractions 6ba–6bc. Fraction 6bb was purified by silica gel CC (20 g, 200–300 mesh) using petroleum ether/EtOAc (70:30) to give **7** (40 mg). Compound **1** (35 mg) was isolated from fraction 6bc (82 mg) by low-pressure silica gel CC (20 g, silica gel H). Fractions 6c and 7 (3.3 g) were combined and chromatographed through a column of alumina (100 g, neutral), eluted with petroleum ether/ Me_2CO (90:10), and further purified by low-pressure silica gel CC (40 g, silica gel H) and medium-pressure silica gel CC (30 g, silica gel H) to afford compound **5** (22 mg).

Periglaucine A (1): colorless crystals (acetone); mp 197–199 °C; $[\alpha]^{15}_D$ +78.0 (*c* 0.55, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 205 (4.57), 293 (3.73), 328 (2.95) nm; IR (KBr) ν_{max} 1733, 1616, 1503, 1484, 1454, 1421, 1370, 1336, 1265, 1250, 1196, 1155, 1087, 1066, 1024, 964, 911, 864, 753 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; EIMS *m*/*z* 373 $[M]^+$ (2), 342 (2), 270 (2), 242 (9), 228 (100), 213 (3), 198 (5), 170 (15); HRESIMS *m*/*z* 374.1600 (calcd for $C_{20}H_{24}NO_6$, 374.1603).

Periglaucine B (2): white powder; $[\alpha]^{22}_D$ +90.1 (*c* 0.37, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 241 (3.60), 294 (3.61) nm; IR (KBr) ν_{max} 1736, 1619, 1503, 1486, 1371, 1335, 1260, 1207, 1170,1087, 1037, 932, 804, 754, 649 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; EIMS *m*/*z* 373 $[M]^+$ (2), 342 (1), 270 (3), 242 (12), 228 (100), 213 (6), 198 (8), 170 (21); HRESIMS *m*/*z* 374.1605 (calcd for $C_{20}H_{24}NO_6$, 374.1603).

Periglaucine C (3): white powder; $[\alpha]^{24}_D$ +131.7 (*c* 0.12, MeOH); UV ($CHCl_3$) λ_{max} (log ϵ) 228 (2.30), 244 (3.56), 294 (3.66) nm; IR (KBr) ν_{max} 1731, 1697, 1618, 1504, 1487, 1420, 1384, 1335, 1317, 1249, 1198, 1087, 1037, 965, 931, 884 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m*/*z* 387 $[M]^+$ (3), 271 (2), 268 (3), 241 (100), 212 (10), 185 (11), 154 (3), 115 (7); HRESIMS *m*/*z* 410.1219 (calcd for $C_{20}H_{21}NO_7Na$, 410.1215).

Periglaucine D (4): white powder; $[\alpha]^{24}_D$ +76.1 (*c* 0.20, MeOH); UV ($CHCl_3$) λ_{max} (log ϵ) 222 (3.33), 242 (3.58), 294 (3.68) nm; IR (KBr) ν_{max} 1737, 1711, 1619, 1503, 1486, 1445, 1372, 1338, 1259, 1170, 1115, 1087, 1038, 933, 868, 805, 734, 651 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m*/*z* 429 $[M]^+$ (1), 398 (1), 326 (3), 298 (18), 283 (25), 240 (6), 226 (100), 211 (8), 196 (11), 168 (16); HRESIMS *m*/*z* 430.1870 (calcd for $C_{23}H_{28}NO_7$, 430.1865).

X-ray Crystallographic Study of Periglaucine A (1). The crystal structure data: $\lambda = 0.71073$ Å, $T = 571(2)$ K, space group $P2_1$, $a = 11.2062(13)$ Å, $b = 12.5950(14)$ Å, $c = 12.8803(15)$ Å, $V = 1818.0(4)$ $Å^3$, $Z = 4$, $D_c = 1.357$ $g \cdot cm^{-3}$, crystal size $0.45 \times 0.29 \times 0.10$ mm. The crystallographic data have been deposited in the Cambridge Crystallographic Date Centre (deposition number: 658178), and the data can be obtained free of charge from the Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/deposit.

***In Vitro* Anti-HBV and Anti-HIV-1 Assays.** The anti-HBV and anti-HIV-1 assays were performed according to previous reports.[12–14] (Supporting Information).

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Supporting Information Available: ^1H, ^{13}C NMR, HSQC, HMBC, ^1H–^1H COSY, and EIMS spectra of compounds **1**–**4**, and CIF data for the crystal study of compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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