Paliasanines A−E, 3,4-Methylenedioxyquinoline Alkaloids Fused with a Phenyl-14-oxabicyclo[3.2.1]octane Unit from Melochia umbellata var. deglabrata

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Paliasanines A−E, 3,4-Methylenedioxyquinoline Alkaloids Fused with a Phenyl-14-oxabicyclo[3.2.1]octane Unit from *Melochia umbellata* var. *deglabrata*

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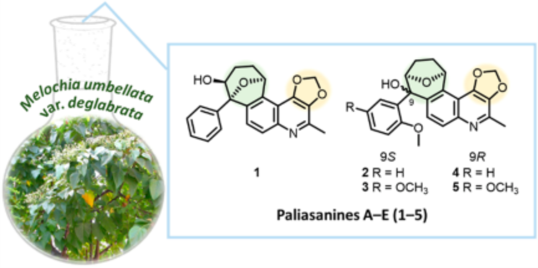
ABSTRACT: Five new quinoline alkaloids, paliasanines A−E (**1**−**5**), and 17 known compounds (**6**−**22**) were isolated from a methanol extract of *Melochia umbellata* var. *deglabrata* leaves. Their chemical structures were elucidated by analysis of HRMS and 1D and 2D NMR spectroscopic data. Compounds **1**−**5** are the first naturally occurring 3,4-methylenedioxyquinolines incorporating an oxabicyclo[3.2.1]octane unit. Compounds **6** and **7** displayed selective cytotoxicity (IC_{50} 5.9−8.4 μM) against A549 and MCF-7 cell lines, while compounds **1**−**5** were not active. Compounds **1**−**3** did not exhibit an anti-HIV effect in MT4 cells, although the related quinolone derivative waltherione A exhibited significant activity. These preliminary results indicate that the 3-methoxy-4-quinolone skeleton might be preferred for both antiproliferative and anti-HIV activities.



Paliasanines A–E (1–5)

The genus *Melochia* (Malvaceae) contains 57 species,[1] widely distributed in tropical and subtropical areas worldwide as perennial herbs, shrubs, or small trees.[2] *M. umbellata* (Houtt.) Stapf var. *deglabrata* Koord. & Valeton, found in South Sulawesi, Indonesia,[3,4] is known traditionally as "Paliasa". A decoction of the leaves has been used for the treatment of fever, hepatitis, hypercholesterolemia, diabetes, hypertension, and cancer.[3−5]

Phytochemical investigations of several related species, including *M. chamaedrys*,[6,7] *M. corchorifolia*,[8−14] *M. odorata*,[15,16] *M. pyramidata*,[17−19] and *M. tomentosa*,[20−26] led to the isolation of cyclopeptides,[6,8,11,14,15,18,24] isatins,[19,20] pyridines/pyridones,[9,14] and quinolinone/quinolone alkaloids,[6,7,12,13,15,23] as well as other constituents[6,8,9,22,25] with diverse biological activities, such as anti-HIV,[16] antimicrobial,[7] antifungal,[8,15] cytotoxic,[4] and nematicidal effects.[27] For *M. umbellata*, only a few compounds, including kaemferol-3-galactoside from the leaves[28] and waltherione C, cleomiscosin,[4] and stigmasterol glycoside[29] from the heartwood and root wood, have been reported. As a continuation of our phytochemical investigation of Indonesian medicinal plants,[30] reported are the isolation, structure elucidation, and biological evaluation of five new compounds (**1**−**5**) together with 17 known compounds (**6**−**22**) from *M. umbellata* var. *deglabrata*.

■ RESULTS AND DISCUSSION

A MeOH extract of *M. umbellata* var. *deglabrata* was partitioned and purified using normal- and reversed-phase silica gel chromatographic systems, to afford five new quinoline alkaloids, paliasanines A−E (**1**−**5**), and 17 known compounds, including four quinolone alkaloids[31−35] [waltherione A (**6**), 5′-methoxywaltherione A (**7**), antidesmone (**8**), and waltherione F (**9**)], three cyclopeptides[36,37] [frangufoline (**10**), sanjoinenine (**11**), and lotusanine A (**12**)], six ionones[38−43] [blumenol A (**13**), (3*S*,5*R*,6*S*,7*E*)-3,5,6-trihydroxy-7-megastigmen-9-one (**14**), (−)-dehydrovomifoliol (**15**), (9*S*)-9-hydroxy-4-megastigmen-3-one (**16**), (3*R*,6*R*,7*E*)-3-hydroxy-4,7-megastigmadien-9-one (**17**), and (−)-3-hydroxy-β-ionone (**18**)], a monoterpene lactone[44] [(−)-loliolide (**19**)], and three lignans[45,46] [(+)-eudesmine (**20**), (+)-magnolin (**21**), and (+)-yangambin (**22**)], as summarized in Figure 1.

Compound **1** was isolated as a pale yellow, amorphous powder with a molecular formula of $C_{22}H_{20}NO_4$ owing to a protonated molecular ion at *m*/*z* 362.1375 [M + H]$^+$ (calcd 362.1392), as determined by HRMS. Fourteen indices of hydrogen deficiency were calculated. The ^{1}H NMR spectroscopic data (Table 1) indicated a methyl group at δ_H 2.68 (3H, s), two methylene protons at δ_H 0.68 (1H, m), 1.99 (1H, m),

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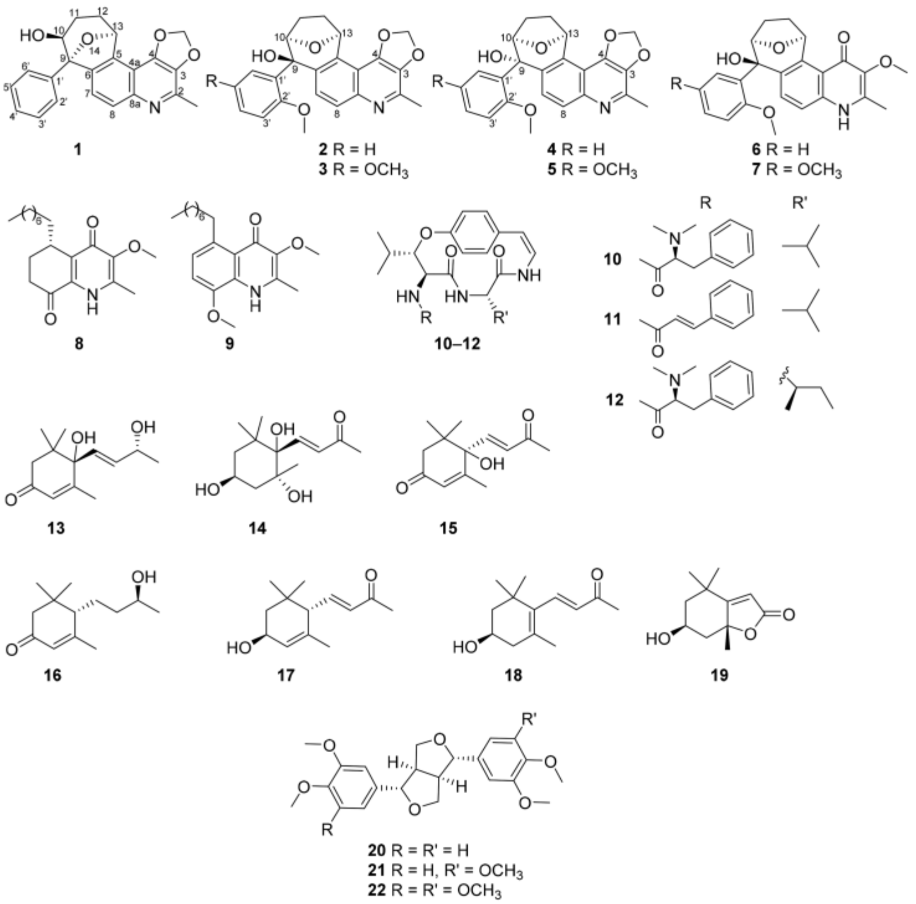

Figure 1. Structures of compounds **1**–**22**.

Table 1. ^{1}H NMR Data of Compounds **1**–**5**

	δ_H (J in Hz)				
position	**1**[a]	**2**[a]	**3**[a]	**4**[b]	**5**[c]
7	7.45 d (8.6)	7.59 d (8.9)	7.59 d (8.9)	7.12 d (8.7)	7.14 d (9.2)
8	7.93 d (8.6)	7.86 d (8.9)	7.86 d (8.9)	7.60 d (8.7)	7.61 d (9.2)
10	4.42 m	4.77 dd (2.1,7.9)	4.76 dd (2.1, 7.9)	4.49 brs	4.47 brs
11a	0.68 m	2.07 m	2.07 m	1.5−1.71 m	1.67 m (2H)
11b	1.99 m	2.49 m	2.49 m		
12a	1.76 dd (5.8, 13.4)	1.98 t (10.3)	1.97 t (9.8)	1.86 m	1.83 m
12b	2.21 m	2.22 m	2.22 m	2.09 m	2.09 m
13	5.78 d (2.8)	5.92 d (6.2)	5.91 d (6.2)	5.82 d (6.9)	5.82 d (6.8)
2′	7.76 d (7.6)				
3′	7.45 t (6.7)	6.99 d (8.3)	6.90 d (8.9)	6.93 overlap	6.87 d (8.7)
4′	7.39 t (7.4)	7.24 ddd (8.3, 7.4, 1.4)	6.74 dd (3.1, 8.9)	7.26 ddd (8.5, 7.1, 1.4)	6.83 dd (2.8, 8.7)
5′	7.45 t (6.7)	6.76 ddd (7.7, 7.4 1.4)		6.93 overlap	
6′	7.76 d (7.6)	6.39 dd (7.7, 1.4)	5.99 d (3.1)		
CH_3-2	2.68 s	2.66 s	2.66 s	2.51 s	2.51 s
OMe-2′		4.03 s	3.98 s	3.34 s	3.27 brs
OMe-5′			3.53 s		3.66 s
OCH_2O	6.26 d (18.2)	6.23 d (18.4)	6.24 d (18.4)	6.29 d (16.3)	6.28 d (14.2)
OH	1.59 d (5.5)	5.11 s	5.15 s	5.51s	5.44 brs

[a] $CDCl_3$ at 600 MHz. [b] DMSO-d_6, 400 MHz at 60 °C. [c] DMSO-d_6, 400 MHz at 80 °C.

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1.76 (1H, dd, J = 5.8, 13.4 Hz), and 2.21 (1H, m), and two methine protons at δ_H 4.42 (1H, m) and 5.78 (1H, d, J = 2.8 Hz). The proton signals between δ_H 7.39 and 7.93 indicated seven aromatic protons. The proton signals at δ_H 6.26 (2H, d, J = 18.2 Hz) and δ_H 1.59 (d, J = 5.5 Hz) were characterized as methylenedioxy and hydroxy groups, respectively. The ^{13}C NMR (Table 2) and HMBC spectroscopic data included 22 distinct carbon signals due to a methyl group (δ_C 19.4), two methylene carbons (δ_C 27.5 and 27.2), a methylenedioxy carbon (δ_C 102.7), two oxygenated methine carbons (δ_C 68.6 and 78.5), and an oxygenated tertiary carbon (δ_C 88.7), as well as 15 aromatic carbons [δ_C 109.6−147.5 (overlapped carbons at δ_C 127.6 and 128.6)]. The 2D structure of **1** was defined from an analysis of the 1D and 2D NMR data (Figure 2). A quinoline system with a methyl group attached at C-2 was defined from the HMBC correlations of the methyl protons at δ_H 2.68 with the carbons at δ_C 144.1 (C-2) and 140.3 (C-3), δ_H 7.45 (H-7) with δ_C 145.8 (C-8a) and 135.6 (C-5), and δ_H 7.93 (H-8) with δ_C 109.6 (C-4a) and 138.7 (C-6). A seven-membered ring with an ether linkage between C-9 and C-13 (an 8-oxabicyclo[3.2.1]octane) was indicated by $^1H-^1H$ COSY correlations of H-10/H$_2$-11/H$_2$-12/H-13 (Figure 2, bold lines) and a HMBC correlation between δ_H 5.78 (d, J = 2.8 Hz, H-13) and δ_C 88.7 (C-9). The fusion of the seven-membered ring to C-5 and C-6 of the quinoline was suggested by the HMBC correlations of H$_2$-12 with δ_C 135.6 (C-5) and of H-10/H-13 with δ_C 138.7 (C-6). The methylenedioxy moiety was assigned at C-3 and C-4 owing to a cross-correlation of δ_H 6.26 with δ_C 140.3 (C-3) and 147.5 (C-4). $^1H-^1H$ COSY correlations indicated connectivity of the H-2′−H-6′ vicinal protons in a monosubstituted phenyl ring, and the HMBC correlations of H-2′ and H-6′ with δ_C 88.7 (C-9) suggested that it was linked to C-9 of the tricyclic skeleton. The relative configuration of **1** was deduced from the ^1H NMR and NOESY data (Figure 3). In the most stable chair conformation of the six-membered ring containing C-9−C-13 and O-14, the fused quinoline ring is in a 1,3-diaxial arrangement, while the hydrogen at C-13 and phenyl at C-9 are in equatorial positions (Figure 3, **1a** and **1b**). In the ^1H NMR spectrum, H-13 (δ_H 5.78) appeared as a doublet with J = 2.8 Hz, consistent with an equatorial orientation. The axial position of H-10 (δ_H 4.42) was supported by a NOESY correlation of H-10 with H-12$_{ax}$ (δ_H 2.21). The correlations of H-11$_{eq}$ (δ_H 1.99) with H-12$_{ax}$ (δ_H 2.21) and H-12$_{eq}$ (δ_H 1.76) and of H-12$_{eq}$ (δ_H 2.21) with H-13 (δ_H 5.78), H-11$_{ax}$ (δ_H 0.68), and H-11$_{eq}$ (δ_H 1.99) were also consistent with the assigned structure. The relatively high field shift of H-11$_{ax}$ (δ_H 0.68) is likely due to the anisotropic effect of the quinoline π-system. The structure of paliasanine A (**1**) was defined as 10-hydroxy-2-methyl-3,4-methylenedioxy-9-phenyl-14-oxabicyclo[3.2.1]octa[*f*]quinoline. The (10*S*,13*R*) absolute configuration was determined by comparison of the experimental and calculated ECD spectra (Figure 4).

Compound **1** is the first characterized natural product with a phenyl oxabicyclo-octane unit fused at C-5 and C-6 of a 3,4-methylenedioxyquinoline. Only six related 3-alkoxy-4-quinolones have been found as secondary metabolites, waltheriones A−E and helicterone A, in three *Waltheria* species,[32,33,47−50] three *Melochia* species,[4,6,15] *Triumfetta grandidens*,[31] and *Helicteres angustifolia*.[51] The absolute configurations of these

Table 2. ^{13}C NMR Data of Compounds 1−5

position	1[a]	2[a]	3[a]	4[b]	5[c]
2	144.1	143.5	143.4	142.6	142.6
3	140.3	140.3	140.2	140.3	140.3
4	147.5	148.5	148.4	148.6	148.6
4a	109.6	110.92	110.8	111.2	111.2
5	135.6	134.2	134.2	132.9	133.1
6	138.7	133.0	132.7	135.6	135.2
7	122.9	128.7	128.5	129.4	129.3
8	128.5	128.3	128.3	127.1	127.2
8a	145.8	145.5	145.5	144.9	145.0
9	88.7	78.0	77.9	75.6	75.6
10	68.6	80.7	80.6	83.9	83.9
11	27.5	22.6	22.6	24.2	24.2
12	27.2	33.9	33.8	32.0	32.0
13	78.5	75.1	75.0	74.2	74.2
1′	139.0	133.9	135.2	131.3	132.7
2′	127.6	156.3	150.4	157.4	151.6
3′	128.6	110.97	111.4	112.8	113.8
4′	128.4	128.8	112.0	129.4	114.1
5′	128.6	120.9	153.2	120.9	153.7
6′	127.6	131.8	118.9	130.2	116.6
CH_3-2	19.4	19.3	19.2	19.4	19.3
OCH_2O	102.7	102.2	102.2	102.9	102.9
OMe-2′		55.6	55.8	55.8	56.4
OMe-5′			55.4		56.0

[a] $CDCl_3$ at 150 MHz. [b] DMSO-d_6 on 100 MHz at 60 °C. [c] DMSO-d_6, 100 MHz at 80 °C.

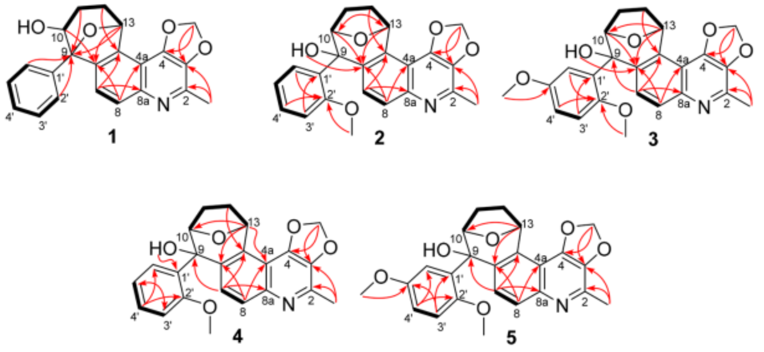

Figure 2. $^1H-^1H$ COSY (bold lines) and selected key HMBC (arrows) correlations of compounds **1**−**5**.

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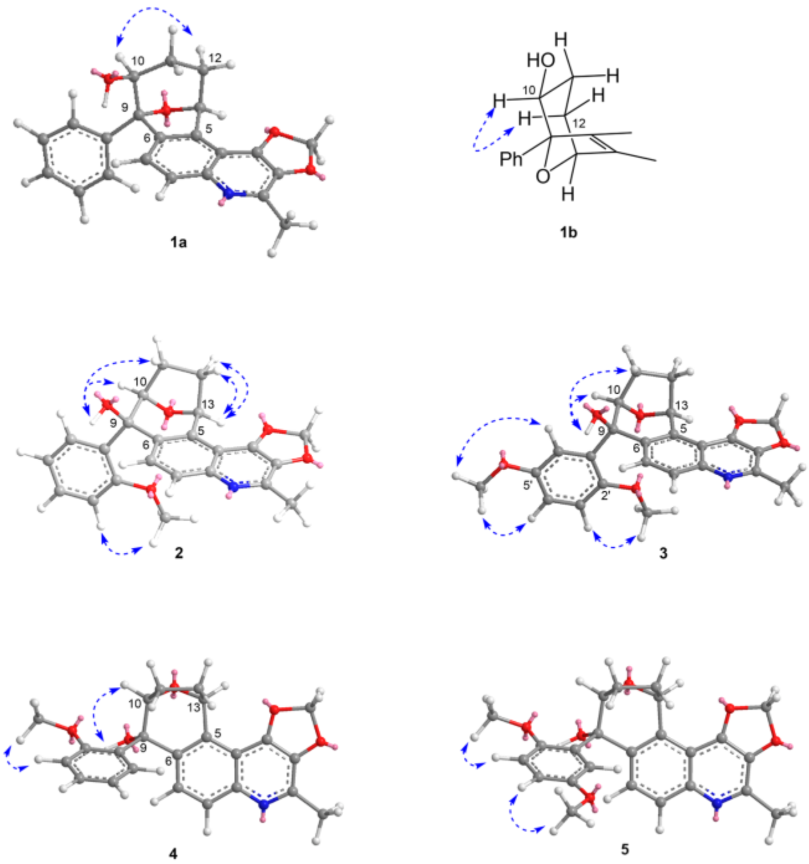

Figure 3. Key NOESY correlations (dotted arrows) of compounds **1**−**5**.

six compounds have not been established. In addition, no other natural quinolines with 3,4-methylenedioxy substitution have been found, although quinolines with methylenedioxy at other positions have been reported. Examples include a 2,3-methylenedioxy-4,7-dimethoxyquinoline found in *Acronychia laurifolia*[52] and a 7,8-methylenedioxyquinoline alkaloid found in *Ptelea trifoliata*.[53]

Compound **2** was obtained as a white, amorphous powder. The molecular formula was assigned from the HRMS protonated molecular ion at *m*/*z* 392.1479 [M + H]$^+$ (calcd 392.1498) as $C_{23}H_{22}NO_5$, which indicated 14 indices of hydrogen deficiency. Compounds **2** and **1** showed similar ^{1}H and ^{13}C NMR spectroscopic data, except for the signals around the phenyl ring as well as at C-9 and C-10 (Tables 1 and 2). Both compounds were assigned as 3,4-methylenedioxyquinolines fused with a phenyl-substituted oxabicyclo-octane ring. However, an *ortho*-methoxyphenyl group was attached at C-9 in **2** rather than the unsubstituted phenyl in **1**, as an additional methoxy group (δ_H 4.03) showing HMBC correlations with C-2′ (δ_C 156.3) (Figure 2) and NOESY correlations with H-3′ (δ_H 6.99) (Figure 3) were observed. The HMBC correlations of H-10 (δ_H 4.77, dd, $J = 2.1$, 7.9 Hz) with C-13 (δ_C 75.1) and of H-13 (δ_H 5.92, d, $J = 6.2$ Hz) with C-10 (δ_C 80.7) suggested an ether bridge connecting C-10 and C-13, in contrast to the linkage between C-9 and C-13 in **1**. The relative configurations at C-9, C-10, and C-13 were established from NOESY data; a key correlation between OH at C-9 and H-11β indicated a β-oriented OH (Figure 3). From these data and ECD calculations (Figure 4), the structure of paliasanine B (**2**) was defined as (9*S*,10*R*,13*S*)-9-hydroxy-2-methyl-3,4-methylenedioxy-9-(2-methoxyphenyl)-14-oxabicyclo[3.2.1]octa[*f*]-quinoline.

Compound **3** was purified as a white solid. The HRMS showed a protonated ion at *m*/*z* 422.1607 [M + H]$^+$ (calcd 422.1604) corresponding to the molecular formula $C_{24}H_{24}NO_6$, which was 30 amu higher than that of **2**, suggesting an additional methoxy substituent. The ^{1}H and ^{13}C NMR spectroscopic data of **3** (Tables 1 and 2) were slightly different from those of **2**, particularly the proton and carbon signals of the phenyl ring. Two methoxy signals at δ_H 3.98/δ_C 55.8 and δ_H 3.53/δ_C 55.4 suggested a dimethoxyphenyl ring located at C-9. With no vicinal coupling between C-5′ and C-6′ and HMBC correlations between the methoxy protons and the two aromatic carbons at δ_C 150.4/153.2, the two methoxy moieties were assigned at C-2′ and C-5′. This assignment was supported by NOESY correlations between the methoxy protons and H-3′ and H-4′/C-6′, respectively. The specific rotations, $[\alpha]_D^{25}$ −74.6 ($CHCl_3$, *c* 0.12) for **2** and −72.7 ($CHCl_3$, *c* 0.12) for **3** indicated the same absolute configurations at C-9, C-10, and C-13, which was also supported by ECD

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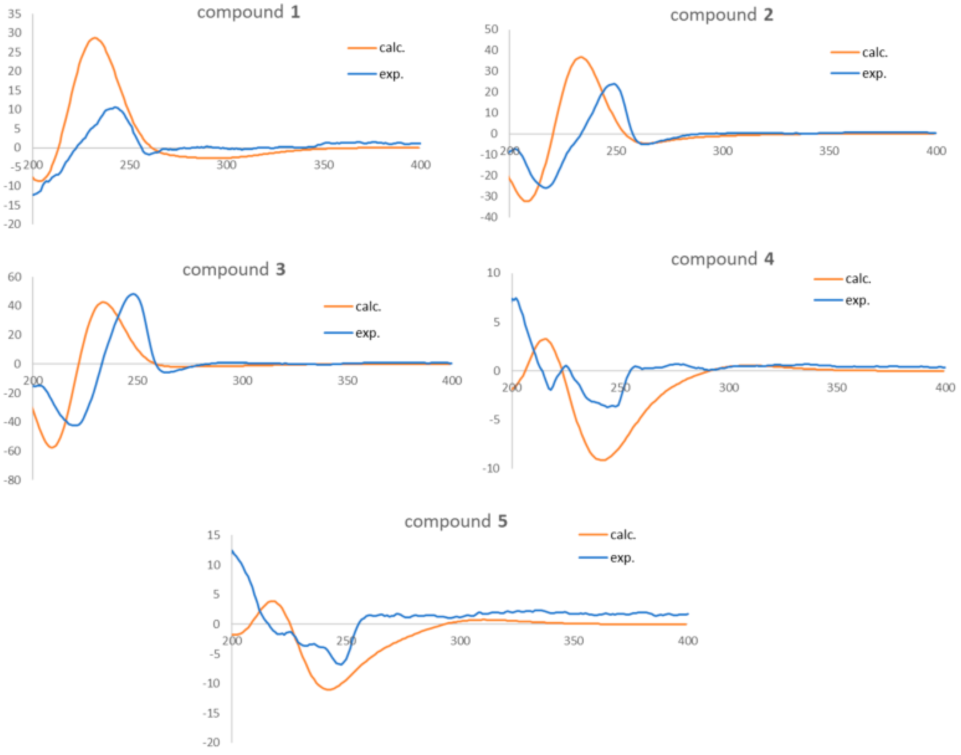

Figure 4. Measured and calculated ECD of compounds **1**−**5**.

calculations (Figure 4). Accordingly, the structure of paliasanine C (**3**) was defined as (9*S*,10*R*,13*S*)-9-hydroxy-2-methyl-3,4-methylenedioxy-9-(2,5-dimethoxyphenyl)-14-oxabicyclo[3.2.1]octa[*f*]quinoline.

Compound **4** was isolated as a pale yellow solid. The molecular formula was established as $C_{23}H_{22}NO_5$, the same as that of **2**, from the HRMS protonated ion at *m/z* 392.1504 [M + H]$^+$ (calcd 392.1498). The 1D and 2D NMR spectra of **4** were measured at 60 °C, because clear data were not obtained at room temperature (Figures S28a and S28b, Supporting Information). Although the H-6′ signal did not appear clearly in the ^{1}H NMR spectrum of **4**, it was assumed to be a peak around 7.45 ppm, which correlated with C-4′ (Figure 2). The presence of C-6′ was assigned from HMBC correlations (Figure 2). Except for the chemical shifts of C-6′, C-9, C-10, and C-1′ (Table 2), the ^{13}C NMR data of **4** were similar to those of **2**, indicating that **4** and **2** are isomers. Unlike **2**, compound **4** did not show a NOESY correlation between OH and H-11*β* (Figure 3), which suggested that compound **4** has an OH-9*α* substituent. This assignment was further supported by ECD calculations, suggesting a (9*R*,10*R*,13*S*) absolute configuration (Figure 4). The structure of paliasanine D (**4**) was defined as (9*R*,10*R*,13*S*)-9-hydroxy-2-methyl-3,4-methylenedioxy-9-(2-methoxyphenyl)-14-oxabicyclo[3.2.1]octa[*f*]quinoline.

Compound **5** was obtained as a white solid with the same molecular formula ($C_{24}H_{24}NO_6$) as **3**, according to a protonated ion at *m/z* 422.1606 [M + H]$^+$ (calcd 422.1604) in the HRMS spectrum. The ^{1}H and ^{13}C NMR data of **5** were measured at 80 °C to provide clearer spectra (Figures S37a and b, Supporting Information). The ^{13}C NMR data of **5** were similar to those of **4**, except for the chemical shifts of the phenyl carbons. Comparison of the 1D and 2D spectroscopic data of **5** to those of **3** and **4** suggested that compounds **5** and **3** are stereoisomers and compounds **5** and **4** have the same configurations at C-9, C-10, and C-13. The value of the specific rotation, $[\alpha]_D^{25}$ −13.4 ($CHCl_3$, *c* 0.12), of **5** was close to that of **4**, $[\alpha]_D^{25}$ −4.7 ($CHCl_3$, *c* 0.12). The NOESY correlations (Figure 3) and ECD calculations (Figure 4) also supported the same absolute configurations. The structure of paliasanine E (**5**) was defined as (9*R*,10*R*,13*S*)-9-hydroxy-2-methyl-3,4-methylenedioxy-9-(2,5-dimethoxyphenyl)-14-oxabicyclo[3.2.1]octa[*f*]quinoline.

Compounds **1**−**14**, **16**, and **19** were evaluated for antiproliferative activity against five human tumor cell lines, A549 (lung cancer), MDA-MB-231 [triple-negative breast cancer: estrogen receptor (ER), progesterone receptor (PR), and HER2 negative], MCF-7 (ER positive and HER2 negative), KB (HeLa derivative), and KB-VIN (P-gp-overexpressing MDR KB-subline). Compounds **1**−**5**, which are quinoline alkaloids with 3,4-methylenedioxy substitution, did not display cytotoxic effects against the evaluated cancer cell lines. However, compounds **6** and **7**, which are quinolone alkaloids without a methylenedioxy moiety, demonstrated moderate and selective antiproliferative activities (IC_{50} 5.9−8.4 *μ*M) against MCF-7 and A549 cell lines. The methylenedioxy group and/or the difference between quinoline and quinolone systems could affect the activity toward both cell lines (**2** vs **6** and **3** vs **7**). The orientation of the OH did not significantly

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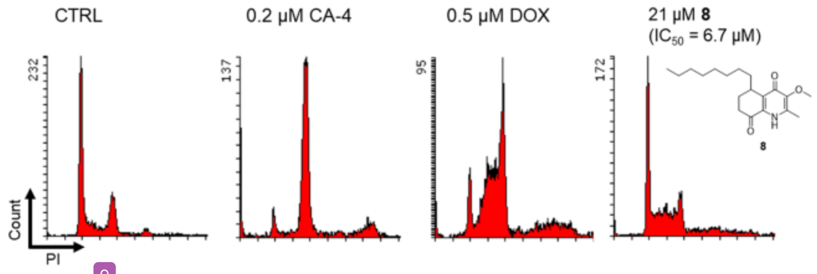

Figure 5. Effect of compound **8** on cell cycle progression. MDA-MB-231 cells were treated for 24 h with the test compound. DMSO was used as a vehicle control (CTRL). Combretastatin A-4 (CA-4) or doxorubicin (DOX) was used as a positive control for induction of cell cycle arrest in the G2/M or S/G2 phase, respectively.

influence the activity (**2** vs **4** and **3** vs **5**). Among all compounds tested, antidesmone (**8**) demonstrated the most potent activity, with IC_{50} values of 6.4−8.4 μM against A549, MDA-MB-231, MCF, and KB-VIN. It also exhibited 2-fold greater activity against the MDR (KB-VIN, IC_{50} = 8.6 μM) than the non-MDR (KB, IC_{50} = 17.7 μM) tumor cell line (Table S1, Supporting Information). However, waltherione F (**9**), which has an OCH_3 substituent rather than the 8-oxo moiety found in **8**, showed greatly reduced potency. The impact of compound **8** on cell cycle progression in MDA-MB-231 cells was assessed by flow cytometry (Figure 5). Compared with the vehicle control, compound **8** induced S phase accumulation, suggesting it probably impacted S phase progression. However, the effect on cell cycle progression was not obvious compared with those of the known cell cycle inhibitors combretastatin A-4 (CA-4) and doxorubicin (DOX).

Compounds **1**−**3** were evaluated for anti-HIV activity in MT4 cells. However, these three tested compounds were not active, although the related analogue waltherione A (**6**) inhibited HIV P24 formation at 1.7 μM.[16]

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured on a JASCO P-2200 digital polarimeter in $CHCl_3$. NMR spectra were recorded on JEOL JNM-ECS400 and JNM-ECA600 NMR spectrometers with tetramethylsilane as an internal standard, and chemical shifts are stated as δ values. HRMS data were measured on a JMS-700 (FAB) or JMS-T100TD (DART) mass spectrometer. UV spectra were recorded on a Tecan SPARK 10M in CH_3CN−H_2O (1:1) except for compound **2** in CH_3CN. IR spectra were measured neat on a Shimadzu IRSprit. Preparative HPLC was performed on a GL Science recycling system using InertSustain C_{18} (5 μm, 20 × 250 mm) and chiral ART Cellulose-SC (5 μm, 250 × 10.0 mm) columns. Analytical and preparative TLC were carried out on precoated silica gel 60 F_{254} plates (0.25 or 1 mm thickness; Merck) and an NH_2 silica gel 60 F_{254} plate (0.5 mm; Wako). Column chromatography was conducted with silica gel 60 N (Spherical, 63-210 μm, neutral; Kanto Chemical). Analytical and reversed-phase preparative TLC were performed on silica gel 60 RP-18 F254S (0.25 mm, Merck).

Plant Material. *Melochia umbellata* var. *deglabrata* leaves were collected at Makassar, South Sulawesi, Indonesia, in January 2018 and identified by Djoko Santoso, Department of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Gadjah Mada. A voucher specimen has been deposited in the Pharmacognosy-Phytochemistry Laboratory, Hasanuddin University (2018_AR_FFUH_01).

Extraction and Isolation. Air-dried and powdered *M. umbellata* leaves (1.32 kg) were extracted with MeOH (×3, each 8.0 L) at room temperature for 48 h. After removing the solvent in vacuo, a MeOH extract residue (300 g) was obtained, which was partitioned with *n*-hexane (×10, each 250 mL) assisted by ultrasound irradiation for 15 min to give *n*-hexane-soluble (74.2 g) and -insoluble (226 g) fractions. The *n*-hexane-soluble fraction was partitioned between *n*-hexane and MeOH−H_2O (4:1) to yield *n*-hexane (52.8 g) and MeOH−H_2O (21.3 g) extracts. The *n*-hexane-insoluble fraction was partitioned with EtOAc (×6, each 350 mL) aided by an ultrasonic irradiation for 15 min, to afford EtOAc-soluble (10.2 g) and -insoluble (216 g) fractions.

The MeOH−H_2O extract (21.3 g) was fractionated using normal-phase silica gel column chromatography (CC) eluting with *n*-hexane−acetone (5:1, 1:1, 1:2, 1:3, 1:5 v/v), EtOAc, and MeOH to give eight pooled fractions (A−H). Fraction F (701 mg) was subjected to reversed-phase MPLC, eluting with MeOH−H_2O (4:1, v/v) and acetone, to yield three subfractions (F1, F2, and F3). Subfraction F1 (510 mg) was further separated by normal-phase silica gel CC with *n*-hexane−EtOAc (3:1, 2:1, 1:1, 1:2, 1:5, v/v), EtOAc, and MeOH to furnish 145 subfractions (each 20 mL). These fractions were combined according to the similarity of their TLC profiles into nine subfractions (F1-A−F1-I). Compound **1** (4.4 mg) was isolated from subfraction F1-B by reversed-phase preparative TLC eluting with MeOH−H_2O (4:1). Combined subfractions F1-C and F1-D (22.3 mg) were purified with semipreparative HPLC RP-18 eluting with CH_3CN−MeOH−H_2O (1:2:1) to yield compounds **1** (2.1 mg), **3** (2.2 mg), **9** (1.4 mg), and **10** (5.8 mg). Subfraction F1-F (144 mg) was further separated by normal-phase silica gel CC eluting with $CHCl_3$−acetone (9:1 and 8:1, v/v) and MeOH to give three subfractions [F1-F1 (compound **12**, 13.1 mg), F1-F2, and F1-F3]. Subfraction F1-F2 (116 mg) was purified by semipreparative RP-18 HPLC eluting with MeOH−H_2O (4:1, v/v), to yield compounds **8** (73.7 mg), **1** (4.2 mg), and **5** (1.8 mg). Subfraction F1-G (215 mg) was subjected to normal-phase silica gel CC eluting with *n*-hexane−acetone (3:1, 2:1, v/v) and MeOH to provide five subfractions (F1-G1−F1-G5). Compounds **4** (9.1 mg) and **13** (4.2 mg) were isolated by semipreparative RP-18 HPLC from subfractions F1-G2 (13.1 mg) and F1-G3 (40.0 mg), respectively, with a mobile phase of CH_3CN−MeOH−H_2O (1:2:1, v/v). Fraction E (708 mg) was fractionated by reversed-phase MPLC with MeOH−H_2O (4:1, v/v) and acetone 100% v/v to afford four subfractions (E1−E4, each 300 mL). Repeated chromatography of subfraction E1 (371 mg) with normal-phase silica gel CC eluting with *n*-hexane−acetone (4:1, 3:1, 2:1, v/v) and MeOH 100% v/v afforded seven subfractions (E1-A−E1-G). Subfraction E1-C (20.8 mg) was purified successively by semipreparative RP-18 HPLC, eluting with CH_3CN−MeOH−H_2O (1:1:1, v/v), normal-phase preparative TLC, eluting with $CHCl_3$−MeOH (50:1, v/v), and reversed-phase preparative TLC, eluting with CH_3CN−MeOH−H_2O (1:2:1, v/v), to give compounds **15** (1.5 mg) and **16** (1.2 mg). Subsequently, MeOH was added separately to subfractions E1-D (96.7 mg) and E1-E (129 mg), to give compounds **2** (19.9 mg) and **3** (20.4 mg), respectively, as MeOH-insoluble solids. The MeOH-soluble portion of E1-E (102 mg) was further separated by normal-phase silica gel CC eluting with $CHCl_3$−acetone (25:1, 20:1, 15:1, 10:1, v/v) and MeOH to provide four subfractions (SM-1−SM-4). Repeated chromatography of SM-1 using normal-phase preparative TLC, eluting with $CHCl_3$−acetone (20:1, v/v), and

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Table 3. Antiproliferative Data of Selected Isolated Compounds

compound	cell line (IC_{50} μM)[a]				
	A549	MDA-MB-231	MCF-7	KB	KB-VIN
6	6.6 ± 0.03	>10	8.0 ± 0.3	>10	>10
7	5.9 ± 0.2	>10	8.2 ± 0.7	>10	>10
8	8.4 ± 0.3	6.7 ± 0.01	6.4 ± 0.2	>10	8.6 ± 0.3
12	9.5 ± 0.4	>10	>10	>10	>10
1–5, 9–11, 13, 14, 16, 19	>10	>10	>10	>10	>10
PXL (nM)[b]	6.5 ± 0.3	8.6 ± 0.3	13.5 ± 0.7	7.7 ± 0.2	2353 ± 47.6

[a] Antiproliferative activity stated as IC_{50} values for each cell line, the concentration of compound that caused 50% reduction relative to untreated cells evaluated by the SRB assay, mean ± SD (n = 6). [b] The IC_{50} of paclitaxel (PXL) is stated in nM.

semipreparative RP-18 HPLC, eluting with $CH_3CN–MeOH–H_2O$ (1:2:1, v/v), yielded compounds **9** (6.4 mg) and **21** (8.0 mg). In the same manner, compound **22** (2.3 mg) was isolated from subfraction E1-F via silica gel normal-phase CC, eluting with *n*-hexane–acetone (3:1, 2:1, v/v) and MeOH, and reversed-phase preparative TLC, eluting with $CH_3CN–MeOH–H_2O$ (1:1:1, v/v). Fraction D (1.05 g) was subjected to reversed-phase MPLC, eluting with $MeOH–H_2O$ (4:1, v/v), MeOH, and acetone, to give six subfractions (D1–D6). Subfraction D1 (289 mg) was subjected to normal-phase silica gel CC, eluting with *n*-hexane–acetone (3:1, 2:1, v/v) and MeOH, to yield six subfractions (D1-A–D1-F). Repeated CC of subfraction D1-B with normal-phase silica gel eluting with the same solvent system, semipreparative RP-18 HPLC, eluting with $MeOH–H_2O$ (3:1, v/v), and normal-phase preparative TLC, eluting with *n*-hexane–acetone (2:1, v/v), gave a mixture of compounds **17** and **18** (3.2 mg). Subfraction D2 (272.8 mg) was separated by normal-phase silica gel CC, eluting with *n*-hexane–acetone (4:1, 3:1, 2:1 v/v) and MeOH, to provide six subfractions (D1-A–D1-F). Recrystallization of subfraction D1-D (107.9 mg) with MeOH afforded compound **11** (23.4 mg).

The EtOAc-soluble extract (10.2 g) was fractionated by normal-phase CC, eluting with *n*-hexane–EtOAc (5:1, 3:1, 1:1, 1:3, 1:5, 1:10, 1:25, 1:50, 1:100, v/v), EtOAc, and MeOH, to give 11 fractions (FA–FK). Fraction FF (460 mg) was further subjected to reversed-phase MPLC, by elution with $MeOH–H_2O$ (4:1, v/v), MeOH, and acetone, to yield five subfractions (FF-1–FF-5). Repeated chromatography of subfraction FF-1 with normal-phase CC, eluting with *n*-hexane–acetone (3:1, 2:1, 1:1, v/v) and MeOH, afforded eight subfractions (FF-1A–FF-1H). Compounds **19** (8.8 mg) and **14** (2.9 mg) were isolated from subfraction FF-1C (26.1 mg) by reversed-phase preparative TLC, eluting with $MeOH–H_2O$ (4:1, v/v), and normal-phase preparative TLC, eluting with $CHCl_3$–acetone (15:1, v/v). Normal-phase preparative TLC of subfraction FF-1D eluting with $CHCl_3$–acetone (15:1, v/v) yielded compounds **20** (1.7 mg), **21** (3.8 mg), **22** (2.4 mg), and **2** (3.5 mg). Fraction FI (198 mg) was fractionated by reversed-phase MPLC, eluting with $MeOH–H_2O$ (1:1, 2:1, 4:1, v/v) and acetone, to give seven subfractions (FI-1–FI-7). Repeated chromatography of subfraction FI-1 (44.8 mg) with normal-phase CC, eluting with *n*-hexane–acetone (1:2, 1:4, v/v), EtOAc, and MeOH, afforded six subfractions (FI-1A–FI-1F). Subfraction FI-1B (10.3 mg) was separated by NH_2 silica gel preparative TLC, eluting with $CHCl_3–MeOH$ (98:2, v/v), to afford three isolates (a, b, and c). Repeated chromatography of isolate b on semipreparative HPLC chiral ART eluting with *n*-hexane–isopropyl alcohol (15:1, v/v) for 70 min and then isopropyl alcohol (100%) yielded compounds **6** (1.8 mg) and **7** (3.6 mg).

*Paliasanine A (**1**):* pale yellow, amorphous powder; $[\alpha]_D^{25}$ −165.6 ($CHCl_3$, *c* 0.21); UV ($CH_3CN–H_2O$ = 1:1) λ_{max} (log ε) 249 (1.86), 342 (0.96) nm; IR ν_{max} 3373, 2921, 2851, 1651, 1608, 1530, 1433, 1385, 1345, 1325, 1159, 1094, 1064, 1022, 983, 951, 756 cm^{-1}; ECD (0.8 μg/mL, CH_3CN) $\Delta\varepsilon_{242}$ +7.47, $\Delta\varepsilon_{260}$ − 1.22; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz), see Tables 1 and 2; HRMS *m/z* 362.1375 $[M + H]^+$ (calcd for $C_{22}H_{20}NO_4$, 362.1392).

*Paliasanine B (**2**):* white, amorphous powder; $[\alpha]_D^{25}$ −74.6 ($CHCl_3$, *c* 0.12); UV (CH_3CN) λ_{max} (log ε) 247 (0.14), 343 (0.07) nm; IR ν_{max} 3516, 3000, 2945, 1640, 1607, 1582, 1563, 1520, 1486, 1466, 1336, 1289, 1240, 1190, 1159, 1146, 1107, 1057, 1024, 987, 910, 832 cm^{-1}; ECD (1.7 μg/mL, CH_3CN) $\Delta\varepsilon_{217}$ − 37.35, $\Delta\varepsilon_{249}$ + 34.29, $\Delta\varepsilon_{263}$ − 7.34; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz), see Tables 1 and 2; HRMS *m/z* 392.1479 $[M + H]^+$ (calcd for $C_{23}H_{22}NO_5$, 392.1498).

*Paliasanine C (**3**):* white, amorphous solid; $[\alpha]_D^{25}$ −72.7 ($CHCl_3$, *c* 0.12); UV ($CH_3CN–H_2O$ = 1:1) λ_{max} (log ε) 247 (1.24), 298 (0.87), 343 (0.72) nm; IR ν_{max} 3508, 2935, 2843, 1640, 1609, 1496, 1445, 1425, 1389, 1335, 1220, 1187, 1159, 1110, 1047, 1022, 910 cm^{-1}; ECD (1.6 μg/mL, CH_3CN) $\Delta\varepsilon_{220}$ −53.27, $\Delta\varepsilon_{248}$ +60.41, $\Delta\varepsilon_{264}$ −7.43; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz), see Tables 1 and 2; HRMS *m/z* 422.1607 $[M + H]^+$ (calcd for $C_{24}H_{24}NO_6$, 422.1604).

*Paliasanine D (**4**):* white, amorphous solid; $[\alpha]_D^{25}$ −4.7 ($CHCl_3$, *c* 0.12); UV ($CH_3CN–H_2O$ = 1:1) λ_{max} (log ε) 245 (1.13), 341 (0.36) nm; IR ν_{max} 3408, 3356, 2925, 1720, 1637, 1522, 1490, 1459, 1425, 1379, 1339, 1279, 1243, 1162, 1070, 1053, 1022, 897, 829, 756 cm^{-1}; ECD (2.4 μg/mL, CH_3CN) $\Delta\varepsilon_{218}$ −3.86, $\Delta\varepsilon_{225}$ +1.17, $\Delta\varepsilon_{244}$ −7.48; ^1H NMR (DMSO-d_6, 400 MHz at 60 °C) and ^{13}C NMR (DMSO-d_6, 100 MHz at 60 °C), see Tables 1 and 2; HRMS *m/z* 392.1504 $[M + H]^+$ (calcd for $C_{23}H_{22}NO_5$, 392.1498).

*Paliasanine E (**5**):* white, amorphous solid; $[\alpha]_D^{25}$ −13.4 ($CHCl_3$, *c* 0.12); UV ($CH_3CN–H_2O$ = 1:1) λ_{max} (log ε) 298 (2.36), 342 (1.67) nm; IR ν_{max} 3394, 2918, 2850, 1719, 1609, 1560, 1493, 1420, 1379, 1339, 1273, 1222, 1156, 1104, 1046, 1022, 977, 829 cm^{-1}; ECD (CH_3CN) $\Delta\varepsilon_{248}$ −3.47; ^1H NMR (DMSO-d_6, 400 MHz at 80 °C) and ^{13}C NMR (DMSO-d_6, 100 MHz at 80 °C), see Tables 1 and 2; HRMS *m/z* 422.1606 $[M + H]^+$ (calcd for $C_{24}H_{24}NO_6$, 422.1604).

Calculated ECD Spectra. Conformational analysis for each compound was performed in a preliminarily manner by CONFLEX8 with the MMFF94 force field. The conformers obtained were further optimized in CH_3CN by a density functional theory (DFT) approach with the B3LYP functional and 6-31(d) basis set. Each ECD spectrum was calculated by the time-dependent DFT (TDDFT) method with the CAM-B3LYP functional and TZVP basis set. The calculation was completed using the conformers within 2 kcal/mol predicted in CH_3CN. The solvent effect was introduced by the conductor-like polarizable continuum model (CPCM). The DFT optimization and TDDFT-ECD calculation were achieved using Gaussian09 (Gaussian, Inc., Wallingford, CT, USA). The calculated spectrum was displayed by GaussView 5.0.920 with the peak half-width at half-height being 0.333 eV. The Boltzmann-averaged spectrum at 298.15K was calculated using Excel 2016 (Microsoft Co., Redmond, WA, USA). The calculations were reoptimized according to a literature procedure.[54]

Antiproliferative Activity Assay. In vitro antiproliferative activity assays using several human tumor cell lines, including A549, MDA-MB-231, MCF-7, KB, and KB VIN, were performed as previously described.[55]

Flow Cytometry. MDA-MB-231 cells were seeded in a 12-well plate 24 h prior to treatment with the test compounds. Compound **8** was used at 3-fold IC_{50} concentration. After a 24 h treatment of each compound, harvested cells were fixed for 24 h in 70% EtOH at −20

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°C. Fixed cells were stained with propidium iodide reagent containing RNase (BD Biosciences) and subjected to flow cytometry analysis (BD Biosciences, LSRFortessa).

Multicycle Viral Replication in an MT4 Cellular Assay. In vitro antiviral activity against HIV-1 was evaluated with acutely infected MT4 cells, as previously described.[30]

Cytotoxicity Assay (MT4 Cells). The cytotoxicity of isolated compounds against MT4 cells was evaluated by a CytoTox-Glo cytotoxicity assay (Promega), as previously described.[30]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.0c00454.

1D and 2D NMR spectra for **1**−**5** (PDF)

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Notes

The authors declare no competing financial interest.

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