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Cytotoxic Pentacyclic and Tetracyclic Aromatic Sesquiterpenes from *Phomopsis archeri*

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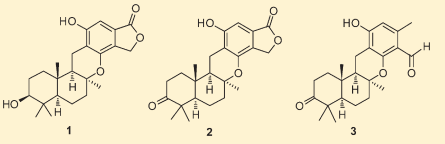
Supporting Information

ABSTRACT: Three new sesquiterpenes, named phomoarcherins A−C (**1**−**3**), and four known compounds, kampanol A (**4**), *R*-mevalonolactone, ergosterol, and ergosterol peroxide, were isolated from the endophytic fungus *Phomopsis archeri*. These structures were established on the basis of spectroscopic evidence. The structure and absolute configuration of **1** were confirmed by X-ray crystallographic analysis of its *p*-bromobenzoate derivative (**1a**). Compounds **1**−**4** showed cytotoxicity against five cholangiocarcinoma cell lines (0.1−19.6 μg/mL), while **1** and **2** exhibited weak cytotoxicity against the KB cell line with IC_{50} values of 42.1 and 9.4 μg/mL, respectively. In addition, compound **2** showed antimalarial activity against *Plasmodium falciparum* with an IC_{50} value of 0.79 μg/mL.



Natural products from endophytic fungi have been reported to inhibit or kill a wide variety of harmful microorganisms including phytopathogenic fungi, bacteria, viruses, and protozoans that affect humans and animals.[1] Endophytic fungi in the genus *Phomopsis* are a rich source of bioactive metabolites.[2] Previous investigations of secondary metabolites from *Phomopsis* species resulted in the isolation of phomopsichalasin,[3] phenochalasins,[4] phomalactones,[5] dicarandrols,[6] phomoxanthones,[7] phomopsidin,[8] phomopsins,[9] phomoenamide,[10] phomoeuphorbins,[11] benzophomosin A, xylarinol A,[12] and oblongolides.[13] However, no phytochemical investigation of *Phomopsis archeri* has been reported. As part of our work on bioactive constituents from fungi, we noted that the EtOAc extract of the endophytic fungus *P. archeri* isolated from the cortex stem of *Vanilla albidia* showed antimalarial activity against *Plasmodium falciparum* (IC_{50} 5.0 μg/mL). We report herein the isolation, characterization, and bioactivities of three new sesquiterpenes (**1**−**3**) and four known compounds.

RESULTS AND DISCUSSION

Separation of hexane, EtOAc, and MeOH extracts gave three new pentacyclic and tetracyclic aromatic sesquiterpenes (**1**−**3**) and four known compounds. The known compounds were identified by physical and spectroscopic data measurements (IR, NMR, 2D NMR, MS, and specific rotation) as well as by comparing the data obtained with published values, as kampanol A (**4**)[14] {$[\alpha]^{25}_{D}$ −13.4 (*c* 1.02, $CHCl_3$)}, *R*-mevalonolactone[15] {$[\alpha]^{25}_{D}$ −29.0 (*c* 0.2, EtOH)}, ergosterol,[16] and ergosterol peroxide.[17] Kampanol A was first isolated from the fungus *Stachybotrys kampalensis*. It has been shown to be a specific inhibitor of Ras protein farnesyltransferase, and it has been expected to be a promising new lead for novel anticancer agents.[14] In addition, the tetracyclic analogue of kampanol A has been synthesized for bioactivity evaluation.[18]

Compound **1** was obtained as a white solid, and its molecular formula $C_{23}H_{30}O_5$ was determined from HRESITOFMS, *m*/*z* 387.2168 $[M + H]^+$, indicating nine degrees of unsaturation. The UV spectrum exhibited absorption maxima at 263 and 309 nm. The IR spectrum showed absorption bands for hydroxy (3420 cm^{-1}), lactone carbonyl (1744 cm^{-1}), and aromatic (1618 cm^{-1}) groups. The ^{13}C NMR, HSQC, and DEPT spectra revealed 23 signals attributable to four methyls, six methylenes (including an oxymethylene), four methines (including an aromatic), and nine quaternary carbons (including three oxygenated carbons). The ^1H and ^{13}C NMR spectra of **1** (Table 1) were similar to those of kampanol A,[14] except that the acetyl group at C-3 was displaced by a hydroxyl group [δ_H 3.19 (*J* = 11.2, 4.4 Hz, H-3)]. The COSY spectrum showed correlations of H-1/H-2/H-3, H-5/H-6/H-7, and H-9/H-11, indicating three partial units of a sesquiterpene. The HMBC spectrum demonstrated

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Table 1. ^{1}H NMR and ^{13}C NMR Data for Compounds 1−3 ($CDCl_3$)

	1		2		3	
position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	H_β 1.88, brd (12.8)[a]	38.0 t[b]	H_β 2.13, m	38.3 t	H_β 2.11, m	38.1 t
	H_α 1.05, td (12.8, 2.8)		H_α 1.55, m		H_α 1.54, m	
2	1.63, m	26.8 t	H_β 2.57, m	34.1 t	H_β 2.54, m	34.1 t
			H_α 2.54, m		H_α 2.42, m	
3	3.19, dd (11.2, 4.4)	78.7 d		217.3 s		217.2 s
4		38.7 s		47.3 s		47.3 s
5	0.90, d (11.2)	52.2 d	1.52, t (8.4)	54.3 d	1.48, m	54.2 d
6	1.51, m	17.8 t	H_β 1.84, m	19.0 t	H_β 1.80, td (11.2, 4.8)	19.0 t
			H_α 1.49, m		H_α 1.59, m	
7	H_β 2.12, d (10.4)	40.2 t	H_β 2.21, brd (14.0)	39.6 t	2.24, dd (11.2, 2.8)	39.7 t
	H_α 1.57, m		H_α 1.63, td (13.6, 4.0)			
8		76.2 s		76.1 s		76.0 s
9	1.39, d (8.0)	48.5 d	1.53, m	47.5 d	1.47, m	47.1 d
10		38.1 s		37.7 s		37.6 s
11	H_β 2.80, d (19.2)	18.3 t	H_β 2.86, dd (19.2, 8.0)	18.6 t	2.73, d (6.0)	17.4 t
	H_α 2.67, dd (19.2, 8.0)		H_α 2.82, dd (19.2, 8.0)			
12	1.13, s	26.9 q	1.22, s	26.9 q	1.25, s	26.7 q
13	0.98, s	28.4 q	1.12, s	26.7 q	1.12, s	26.7 q
14	0.73, s	15.6 q	1.04, s	21.7 q	1.04, s	21.6 q
15	0.61, s	14.0 q	0.82, s	14.0 q	0.82, s	14.0 q
1′		117.6 s		116.8 s		106.8 s
2′		156.4 s		155.5 s		158.1 s
3′	6.71, s	100.7 d	6.98, s	101.9 d	6.20, s	110.3 d
4′		123.9 s		124.5 s		141.5 s
5′		126.2 s		126.9 s		117.0 s
6′		149.9 s		149.9 s		160.7 d
7′		173.2 s		172.3 s	10.47, s	191.0 d
8′	5.13, AB_q (15.3)	68.5 t	5.19, AB_q (14.8)	68.3 t	2.51, s	21.8 q
2′-OH	9.40, brs		7.02, brs		6.48, brs	

[a] Figures in parentheses are coupling constants in Hz. [b] Multiplicities were deduced from DEPT and/or HSQC experiments.

correlations of H-3 to C-1, C-5, C-13, and C-14; H-5 to C-4, C-6, C-9, and C-15; H_3-15 to C-1, C-5, and C-10; H-9 to C-10, C-11, and C-1′; H_3-12 to C-7, C-8, and C-9; H_2-11 to C-8, C-9, C-1′, C-2′, and C-6′; and H_2-8 to C-4′, C-5′, C-6′, and C-7′, establishing the pentacyclic skeleton (ABCDE ring system) of **1**. The NOESY spectrum exhibited correlation of those protons in **1** indicating
a *trans*-fused decalin ring. Finally, the absolute configuration of **1** was confirmed by the X-ray crystallographic analysis of its *p*-bromobenzoate derivative (**1a**) based on its anomalous dispersion data with the Flack parameter of 0.054(8), (Figure 1). This is the first report of the absolute configurations of a pentacyclic skeleton, which are 3*S*, 5*R*, 8*S*, 9*R*, and 10*S*. According to the above data, structure **1** was elucidated as a new pentacyclic aromatic sesquiterpene and was named phomoarcherin A.

Compound **2** was isolated as colorless needles, and its molecular formula was deduced as $C_{23}H_{28}O_5$ from HRESITOFMS, m/z 385.2015 $[M + H]^+$, indicating 10 degrees of unsaturation. The UV spectrum exhibited maximum absorptions at 262 and 309 nm. The IR spectrum displayed absorption bands of hydroxy (3202 cm^{-1}), lactone carbonyl (1754 cm^{-1}), nonconjugate carbonyl (1681 cm^{-1}), and aromatic (1618 cm^{-1}) groups. The ^{1}H and ^{13}C NMR spectra of **2** were similar to those of **1**, except for the hydroxyl group at C-3, which was displaced by a carbonyl group (δ_C 217.3). The HMBC data confirmed the location of the ketone at C-3 by showing correlation of H-1 to C-3, H-5 to C-3, and H_3-13 and H_3-14 to C-3. The complete interpretation of the NMR data of **2** was established as a result of conclusive DEPT, COSY, HSQC, HMBC, and NOESY experiments (Table 1). Thus the structure of **2** was deduced as a new pentacyclic aromatic sesquiterpene and named phomoarcherin B.

Compound **3** was obtained as a white solid, and it was assigned the molecular formula $C_{23}H_{30}O_4$, from HRESITOFMS, m/z 393.2047 $[M + Na]^+$, indicating nine degrees of unsaturation. The UV spectrum showed the absorption maximum at 242 nm. The IR spectrum showed the presence of hydroxy (3244 cm^{-1}), carbonyl (1698 cm^{-1}), aromatic aldehyde (1647 cm^{-1}), and aromatic (1588 cm^{-1}) groups. The ^{13}C NMR and DEPT spectral data revealed the presence of six sp^2 quaternary (including a carbonyl group), two sp^2 methine (including an aldehyde group), three sp^3 quaternary, two sp^3 methine, five methylene, and five methyl carbons. The ^{1}H and ^{13}C NMR spectra of **3** (Table 1) were similar to those of **2**, except for the absence of a lactone ring (E), which was replaced by methyl (δ_H 2.51, δ_C 21.8) and aldehyde (δ_H 10.47, δ_C 191.0) groups at C-4′ and C-5′, respectively. The HMBC correlations of H-3′ to C-1′, C-2′, C-5′, and C-8′; H_3-8′

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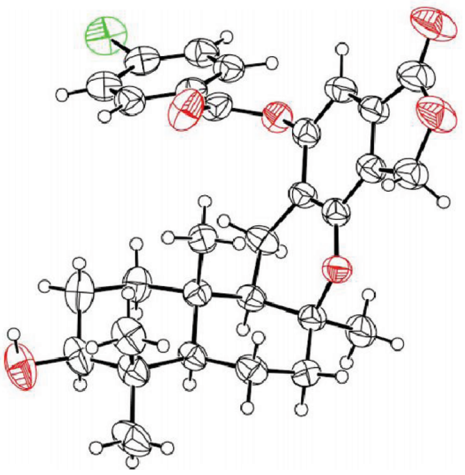
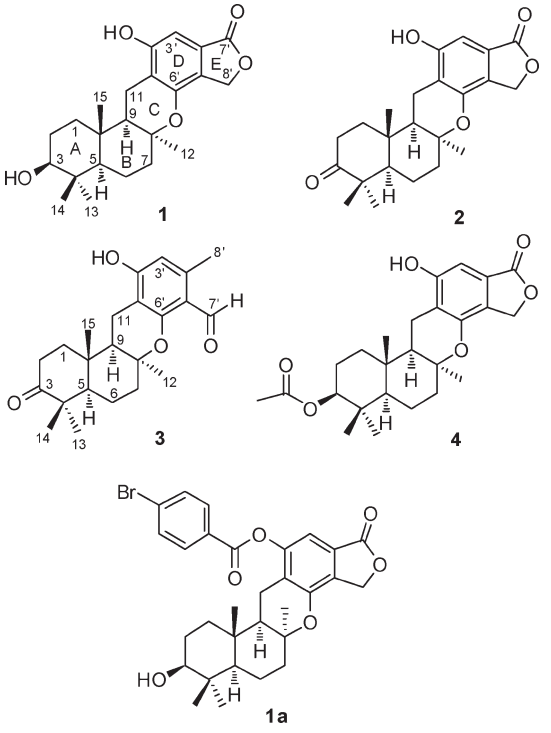


Figure 1. X-ray crystal structure of compound **1a**.



to C-3′ and C-5′; and an aldehyde proton (H-7′) to C-5′ confirmed the connectivity of these groups. The HMBC spectrum also showed correlations of H_3-15 to C-1, C-5, C-9, and C-10; H_3-12 to C-7, C-8, and C-9; and H_3-13 and H_3-14 to C-3, C-4, and C-5, permitting completion of the decalin ring system (A and B). Further analysis of its 2D NMR data led to the identification of a decalin (A and B), a tetrahydropyran (C), and an aromatic ring (D) in **3**. Relevant HMBC cross-peaks indicated that ring C was fused to the decalin moiety at C-8 and C-9, and ring D was joined to C at C-1′ and C-6′ (Figure 2). The relative configuration of **3** was deduced on the basis of NOESY correlations between H-9 and H-5, H-11, and H_3-12, indicating that these protons are on the same face of the ring system. Those of H-6, H_3-14, and H_3-15 are placed on the opposite face of the ring system, thereby establishing the relative configuration of **3**. Thus, the structure of **3** was as indicated, and it was named phomoarcherin C.

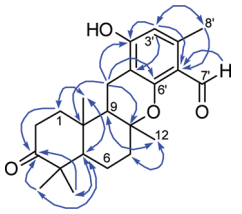


Figure 2. Key HMBC correlations (H→C) for compound **3**.

The isolated compounds **1**−**4** were tested for their bioactivities, and results are given in Table 2. Compounds **1**−**4** exhibited cytotoxicity against five cholangiocarcinoma cell lines, with IC_{50} values ranging from 0.1 to 19.6 μg/mL. Among these, **2** showed significant cytotoxicity against two cholangiocarcinoma cell lines, KKU-M139 (0.1 μg/mL) and KKU-M156 (2.0 μg/mL), which are close to the control drug, ellipticine. Compounds **1** and **2** showed weak cytotoxicity against the KB cell line with IC_{50} values of 42.1 and 9.4 μg/mL, respectively. In addition, **2** demonstrated activity against *P. falciparum* with an IC_{50} value of 0.79 μg/mL and also showed weak activity against *Mycobacterium tuberculosis* (MIC 50 μg/mL). The results showed that pentacyclic and tetracyclic aromatic sesquiterpenes **1**−**4** are cytotoxic to the cancer cell lines tested. The most active compound in the series was compound **2**, which contained a ketone function at C-3 and an aromatic lactone ring.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined using a Gallenkamp melting point apparatus and were uncorrected. UV spectra were measured on an Agilent 8453 UV−visible spectrophotometer. IR spectra were taken on a Perkin-Elmer Spectrum One spectrophotometer. NMR spectra were recorded in $CDCl_3$ on a Varian Mercury Plus 400 spectrometer, using residual $CHCl_3$ as an internal standard. HRESITOFMS were recorded on a Micromass Q-TOF-2 spectrometer. Column chromatography (CC) and preparative TLC were carried out on silica gel 60 (230−400 mesh) and PF_{254}, respectively.

Fungal Material. The fungus *P. archeri* was collected from cortex stem of *Vanilla albidia* in Pathumthani Province, Thailand, in 2008, and was identified by one of the authors (K.S.). A voucher specimen (no. Pac01) was deposited at the Department of Plant Pest Management, King Mongkut's Institute of Technology Ladkrabang, Bangkok, Thailand. The fungus was cultured in conical flasks (1 L, 70 flasks) with potato dextrose broth (200 mL/flask) and incubated in standing conditions at 25−28 °C for 4 weeks. The culture broth was filtered to give a wet mycelial mat and then air-dried at room temperature.

Extraction and Isolation. The air-dried mycelial mat (225 g) was ground and extracted successively at room temperature with hexane (500 mL × 3), EtOAc (500 mL × 3), and MeOH (500 mL × 3) to give crude hexane (16.3 g), EtOAc (16.4 g), and MeOH (13.2 g) extracts. CH_2Cl_2 (100 mL) was added to the hexane extract to give ergosterol (200 mg). The EtOAc extract was subjected to flash CC, eluted with a gradient system of hexane−EtOAc and EtOAc−MeOH. On the basis of their TLC characteristics, the fractions that contained the same major compounds were combined to give 10 fractions, P_1−P_{10}. Fraction P_5 was purified by flash CC over silica gel, eluted with a gradient system of hexane−EtOAc, to give six subfractions, $P_{5.1}$−$P_{5.6}$. Subfraction $P_{5.4}$ was chromatographed on flash CC, eluted with CH_2Cl_2, to give a white solid of **4** (10.2 mg) and **3** (7.5 mg). Fraction P_7 was further subjected to flash CC, eluted with a gradient system of hexane−EtOAc, to give 10 subfractions, $P_{7.1}$−$P_{7.10}$. Subfraction $P_{7.6}$ was purified by crystallization from EtOAc to give a white solid of **1** (700 mg). Fraction P_8 was

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Table 2. Biological Activities of Compounds 1−4

compound	antimalarial IC_{50}(μg/mL)	anti-TB MIC (μg/mL)	cytotoxicity (IC_{50}, μg/mL)					
			KKU-100[a]	KKU-M139[b]	KKU-M156[c]	KKU-M213[d]	KKU-M214[e]	KB[f]
1	>20	>200	>20	>20	>20	16.6 ± 0.10	>20	42.1
2	0.79	50.0	8.0 ± 0.08	0.1 ± 0.12	2.0 ± 0.22	>20	5.0 ± 0. 21	9.4
3	nd[g]	nd	8.9 ± 0.0	8.9 ± 0	18.0 ± 0.15	15.4 ± 0.17	18.8 ± 0.18	nd
4	nd	nd	>20	>20	>20	19.6 ± 0.14	>20	nd
dihydro-artemisinin	0.0044							
isoniazid		0.23−0.46						
ellipticine			7.11 ± 0.09	1.21 ± 0.03	2.02 ± 0.11	0.30 ± 0.001	0.21 ± 0 0.04	0.19

[a] Poorly differentiated adenocarcinoma. [b] Squamous carcinoma. [c] Moderately differentiated adenocarcinoma. [d] Adenosquamous carcinoma. [e] Moderately differentiated denocarcinoma. [f] Human epidermoid carcinoma of the mouth. [g] nd = not determined.

rechromatographed on flash CC, eluted with a gradient system of hexane−EtOAc, to give 10 subfractions, $P_{8.1}$−$P_{8.10}$. Crystallization of subfraction $P_{8.5}$ from 2% MeOH−CH_2Cl_2 gave colorless needles of **2** (600 mg). Fraction P_9 was chromatographed on flash CC, eluted with a gradient system of CH_2Cl_2−EtOAc, to give 10 subfractions, $P_{9.1}$−$P_{9.10}$. Subfraction $P_{9.7}$ was further subjected to flash CC, eluted with an isocratic system of 50% EtOAc−hexane, to yield a yellow-brown, viscous liquid of mevalonolactone (32.6 mg). The MeOH extract was fractionated by flash CC, eluted with a gradient system of hexane−CH_2Cl_2 and CH_2Cl_2−MeOH, to provide eight fractions, PM_1−PM_8. Fraction PM_6 was chromatographed on a silica gel CC, eluted with a gradient system of hexane−EtOAc, to yield an additional amount of **1** (300.1 mg) and ergosterol peroxide (36 mg).

Phomoarcherin A (***1***)*:*. white solid; mp 246−248 °C; $[\alpha]^{25}_D$ −23.7 (*c* 1.02, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 263 (4.77), 309 (3.45) nm; IR (KBr) ν_{max} 3420, 2968, 1744, 1618, 1467 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; HRESITOFMS *m*/*z* 387.2168 $[M + H]^+$ (calcd for $C_{23}H_{31}O_5$ + H, 387.2171).

Phomoarcherin B (***2***)*:*. colorless needles; mp 253−255 °C; $[\alpha]^{25}_D$ −44.7 (*c* 1.02, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 262 (5.19), 309 (4.57) nm; IR (KBr) ν_{max} 3202, 2966, 2940, 2902, 1754, 1681, 1618, 1458 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; HRESITOFMS *m*/*z* 385.2015 $[M + H]^+$ (calcd for $C_{23}H_{29}O_5$ + H, 385.2015).

Phomoarcherin C (***3***)*:*. white solid; mp 245−246 °C; $[\alpha]^{25}_D$ −3.2 (*c* 1.02, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 242 (4.03) nm; IR (KBr) ν_{max} 3244, 2951, 1698, 1647, 1588, 1451 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; HRESITOFMS *m*/*z* 393.2047 $[M + Na]^+$ (calcd for $C_{23}H_{30}O_4$ + Na, 393.2042).

Preparation of p-Bromobenzoate Derivative ***1a***. To solution of **1** (10 mg, 0.026 mmol) in CH_2Cl_2 (5 mL) and pyridine (0.5 mL) was added *p*-bromobenzoyl chloride (7 mg, 0.032 mmol), and the mixture was stirred at room temperature for 2 h. The solution was evaporated to dryness, and the residue was purified by preparative TLC using CH_2Cl_2−MeOH (95:5) as eluent, to give a colorless solid of **1a** (6.0 mg, 40.8%).

X-ray Crystal Data of 1a. *Crystal data of* ***1a***:. $C_{30}H_{33}BrO_6$, MW = 569.47, monoclinic, $P2_1$, a = 10.1410(1) Å, b = 12.8570(3) Å, c = 20.6150(5) Å, β = 96.978(1)°, V = 2667.93(9) Å^3, D_x = 1.418 g/cm^3, Z = 4, F(000) = 1184. A total of 17 663 reflections, of which 9764 were unique reflections (8542 observed, $|F_o| > 4\sigma|F_o|$), were measured at room temperature from a 0.20 × 0.15 × 0.10 mm^3 colorless crystal using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) on a Bruker-Nonius kappaCCD diffractometer. The crystal structure was solved by direct methods using SIR-97, and then all atoms except hydrogen atoms were refined anisotropically by a full-matrix least-squares methods on F^2 using SHELXL-97 to give a final *R*-factor of 0.0562 (R_w = 0.1922 for all data).

Crystallographic data of compound **1a** have been deposited at the Cambridge Crystallographic Data Centre under the reference number CCDC 790981. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

Antimalarial Assay. Antimalarial activity was evaluated against the parasite *P. falciparum* (K1, multidrug-resistant strain), using the method of Trager and Jensen.[19] Quantitative assessment of activity in vitro was determined by means of the microculture radioisotope technique based upon the method described by Desjardins et al.[20] The inhibitory concentration (IC_{50}) represents the concentration that causes 50% reduction in parasite growth as indicated by the in vitro uptake of [^{3}H]-hypoxanthine by *P. falciparum*. The standard compound was dihydroartemisinin (Table 2).

Antimycobacterial Assay. Antimycobacterial activity was assessed against *M. tuberculosis* H37Ra using the microplate Alamar Blue assay (MABA).[21] The standard drug isoniazid was used as the reference compound (Table 2).

Cytotoxicity Assay. Cytotoxic assays against five cholangiocarcinoma (KKU-100, KKU-M139, KKU-M156, KKU-M213, KKU-M214) and human epidermoid carcinoma (KB) cell lines were performed employing the colorimetric method as described by Skehan and co-workers.[22] The reference substance was ellipticine (Table 2).

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra for compounds **1**−**3**, X-ray crystallographic tables of atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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