

Purine Alkaloids from the South China Sea Gorgonian *Subergorgia suberosa*

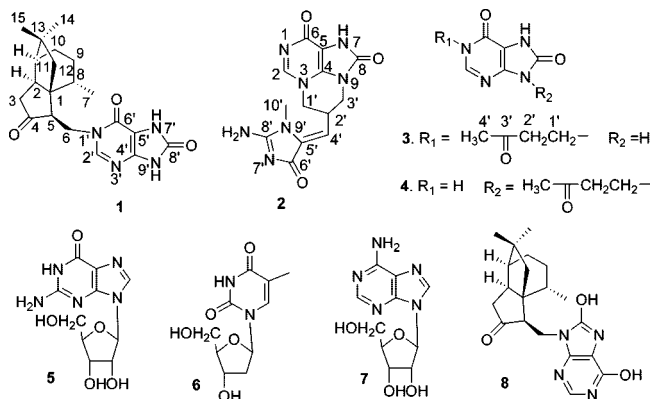
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Four new purine alkaloids, namely, 6-(1'-purine-6',8'-dionyl)suberosanone (**1**), 3,9-(2-imino-1-methyl-4-imidazolidinone-5-yl)isopropenylpurine-6,8-dione (**2**), 1-(3'-carbonylbutyl)purine-6,8-dione (**3**), and 9-(3'-carbonylbutyl)purine-6,8-dione (**4**), together with three known compounds, guanosine (**5**), thymidine (**6**), and adenosine (**7**), were isolated from the EtOH/CH<sub>2</sub>Cl<sub>2</sub> extracts of the South China Sea gorgonian *Subergorgia suberosa*. The structures of **1–4** were determined on the basis of extensive spectroscopic analysis, including 1D and 2D NMR data. Compounds **1–4** all showed weak cytotoxicity toward human cancer cell lines MDA-MB-231 and A435.

Nitrogen-containing compounds including alkaloids, nucleosides, and peptides are known to have an important role in medicinal chemistry on account of their widespread biological activity. Marine invertebrates such as sponges, soft corals, gorgonians, mollusks, coelenterates, and ascidians produce secondary metabolites of unprecedented structures; sponges and ascidians, in particular, produce nitrogen-containing compounds. However, there are few reports about alkaloids from gorgonians. The gorgonian *Subergorgia suberosa* was known to produce novel sesquiterpenes<sup>1–5</sup> and 9,11-secosteroids.<sup>6–8</sup> In our previous investigation on *S. suberosa*, a new sesquiterpene-alkaloid, 6-(9'-purine-6',8'-diolyl)suberosanone, was obtained.<sup>9</sup> Now, in our further chemical investigation on the EtOH/CH<sub>2</sub>Cl<sub>2</sub> extract of *S. suberosa*, four new purine alkaloids, 6-(1'-purine-6',8'-dionyl)suberosanone (**1**), 3,9-(2-imino-1-methyl-4-imidazolidinone-5-yl)isopropenylpurine-6,8-dione (**2**), 1-(3'-carbonylbutyl)purine-6,8-dione (**3**), and 9-(3'-carbonylbutyl)purine-6,8-dione (**4**), together with three known compounds, guanosine (**5**),<sup>10</sup> thymidine (**6**),<sup>10</sup> and adenosine (**7**),<sup>10</sup> were obtained. This paper deals with the isolation and structural elucidation of **1–4**.



The EtOH/CH<sub>2</sub>Cl<sub>2</sub> extract of *S. suberosa* was suspended in H<sub>2</sub>O and extracted with CHCl<sub>3</sub> and *n*-BuOH, respectively. The CHCl<sub>3</sub> and *n*-BuOH solubles were chromatographed over silica gel, and selected fractions were rechromatographed on Sephadex LH-20 and silica gel to yield compounds **1–7**. All of the compounds contained a purine skeleton.

Compound **1** had the molecular formula C<sub>20</sub>H<sub>26</sub>N<sub>4</sub>O<sub>3</sub> as deduced from NMR spectra and HRESIMS. Its <sup>13</sup>C NMR spectrum showed the presence of three methyls (δ<sub>C</sub> 16.3, 26.6, 33.9), five methylenes

(δ<sub>C</sub> 26.4, 27.3, 40.2, 40.3, 47.1), four methines (δ<sub>C</sub> 35.6, 43.1, 48.9, 53.2), two quaternary carbons (δ<sub>C</sub> 55.9, 39.1), and a ketone carbon (δ<sub>C</sub> 216.4), along with five low-field carbons [δ<sub>C</sub> 116.6 (C), 137.9 (CH), 151.1 (C), 153.3 (C), 156.6 (C)]. The <sup>1</sup>H NMR spectrum displayed three methyl groups at δ<sub>H</sub> 0.73 (3H, d, *J* = 7.0 Hz), 1.07 (3H, s), and 1.11 (3H, s) and a proton at δ<sub>H</sub> 7.63 (1H, s). According to HSQC, HMBC, and <sup>1</sup>H–<sup>1</sup>H COSY experiments, all of the <sup>1</sup>H and <sup>13</sup>C NMR signals of **1** were assigned (Table 1). These <sup>1</sup>H and <sup>13</sup>C NMR data were very similar to those of 6-(9'-purine-6',8'-diolyl)suberosanone (**8**) (Table 1), which was previously isolated from the same species,<sup>9</sup> and indicated that **1** should also be a suberosanone-type sesquiterpene linked to a purine-6,8-dione group. Actually, purine-8-one derivatives have previously been isolated from many marine organisms, such as gorgonians,<sup>11</sup> ascidians,<sup>12</sup> and sponges.<sup>13</sup>

The only obvious difference between them was the chemical shift values of five low-field carbons [δ<sub>C</sub> 137.9 (CH, C-2'), 156.6 (C, C-4'), 116.6 (C, C-5'), 151.1 (C, C-6'), 153.3 (C, C-8') in **1**, and δ<sub>C</sub> 140.6 (CH, C-2'), 150.2 (C, C-4'), 108.1 (C, C-5'), 155.8 (C, C-6'), 151.9 (C, C-8') in **8**], which might be caused by the location of the connection between the 6',8'-purinedione moiety and the suberosanone moiety. This was supported by the HMBC data. In the HMBC spectrum of **1**, correlations of δ<sub>H</sub> 4.17 (1H, dd, *J* = 4.9, 14.4 Hz, H-6a) and 3.87 (1H, dd, *J* = 8.8, 14.4 Hz, H-6b) with C-6'/C-2' suggested the connection of the 6',8'-purinedione moiety with the suberosanone moiety by a C(6)–N(1') bond instead of a C(6)–N(9') bond.

The relative configuration of **1** was deduced from a 2D NOE experiment. The NOESY spectrum of **1** showed correlations of H-9a (δ<sub>H</sub> 1.85, 1H, m) with Me-14 (δ<sub>H</sub> 1.11, 3H, s); Me-15 (δ<sub>H</sub> 1.07, 3H, s) with H-9b (δ<sub>H</sub> 1.20, 1H, m), H-3b (δ<sub>H</sub> 2.22, 1H, dd, *J* = 6.9, 19.8 Hz), and H-11 (δ<sub>H</sub> 1.70, 1H, m); and H-3a (δ<sub>H</sub> 2.62, 1H, dd, *J* = 12.0, 19.8 Hz) with H-2 (δ<sub>H</sub> 2.40, 1H, dd, *J* = 6.9, 12.0 Hz). In addition, to form a five-membered ring across the six-membered ring, the C1–C12 and C11–C13 bonds had to both be axial, leaving H-11 equatorial. These suggested the β-orientation of Me-15 and α-orientation of H-2, H-11, and Me-14. Meanwhile, NOE correlations of Me-7 (δ<sub>H</sub> 0.73, 3H, d, *J* = 7.0 Hz) with H-2 and H-5 (δ<sub>H</sub> 3.12, 1H, dd, *J* = 4.9, 8.8 Hz) indicated that Me-7 and H-5 were α-oriented. On the basis of the above data, the structure of **1** was elucidated as 6-(1'-purine-6',8'-dionyl)suberosanone. Therefore, in compound **8** H-2 should also be in the α-orientation.

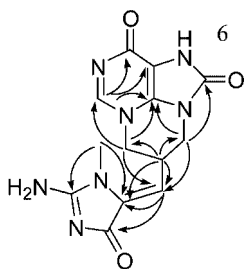
The molecular formula C<sub>13</sub>H<sub>13</sub>N<sub>7</sub>O<sub>3</sub> of **2** was deduced from its NMR spectra and ESIMS. The compound was conferred by the HRFABMS (positive ions) with a peak at *m/z* 316.1076 [M + H]<sup>+</sup> (calculated value: *m/z* 316.1080). Its <sup>13</sup>C NMR spectrum showed

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**Table 1.** NMR Data for Compound **1**<sup>a</sup>

no.	<b>1</b> in DMSO- <i>d</i> <sub>6</sub> <sup>1</sup> H NMR	<sup>13</sup> C NMR	HMBC	NOESY	<b>8</b> in CDCl <sub>3</sub> <sup>13</sup> C NMR
1		55.9	H-2, 3, 5, 6, 7, 8, 12		56.7
2	2.40 (dd, 6.9, 12.0),	43.1	H-3, 5, 8, 11	H-3a, 7	44.0
3a	2.62 (dd, 12.0, 19.8)	40.2	H-2, 5, 11	H-2	40.8
3b	2.22 (dd, 6.9, 19.8)			H-15	
4		216.4	H-2, 3, 5, 6		216.5
5	3.12 (dd, 4.9, 8.8)	53.2	H-2, 3, 6	H-2, 7	52.4
6	4.17 (dd, 4.9, 14.4), 3.87(dd, 8.8, 14.4)	40.3	H-5, 2'		41.3
7	0.73 (d, 7.0)	16.3	H-8, 9	H-2, 5	16.7
8	1.58 (m)	35.6	H-2, 7, 9, 10	H-9b	36.6
9a	1.85 (m)	26.4	H-7, 8, 10, 11	H-14	27.0
9b	1.20 (m)			H-15	
10	1.52 (m)	27.3	H-8, 9, 11		27.9
11	1.70 (m)	48.9	H-2, 3, 10, 14, 15		49.7
12	1.60 (d, 14.4), 1.44(d, 14.4)	47.1	H-2, 11, 14, 15		48.5
13		39.1	H-11, 12, 14, 15		39.7
14	1.11 (s)	26.6	H-15	H-9a	27.0
15	1.07 (s)	33.9	H-14	H-9b	34.4
2'	7.63 (s)	137.9	H-6		140.6
4'		156.6	H-2'		150.2
5'		116.6	H-2'		108.1
6'		151.1	H-2', 6		155.8
8'		153.3			151.9

<sup>a</sup> Chemical shift values  $\delta$  are in ppm, and coupling constant values  $J$  in Hz.

**Figure 1.** Key HMBC correlations of **2**.

nine low-field carbons [ $\delta_C$  107.8 (C), 117.4 (CH), 131.8 (C), 136.9 (C), 139.0 (C), 150.3 (C), 154.3 (C), 155.4 (C), 162.4 (C)], together with one methyl ( $\delta_C$  28.5), two methylenes ( $\delta_C$  42.4, 46.2), and one methine ( $\delta_C$  28.2). The <sup>1</sup>H NMR spectrum displayed one methyl at  $\delta_H$  3.24 (3H, s), two methylenes at  $\delta_H$  3.82 (1H, dd,  $J = 9.0$ , 12.9 Hz), 4.25 (1H, dd,  $J = 4.2$ , 12.9 Hz), 4.29 (1H, dd,  $J = 8.8$ , 12.9 Hz), and 4.62 (1H, dd,  $J = 4.4$ , 12.9 Hz), one methine at  $\delta_H$  4.48 (1H, m), and two protons at  $\delta_H$  5.95 (1H, d,  $J = 9.5$  Hz) and 8.83 (1H, s). These <sup>13</sup>C and <sup>1</sup>H NMR data were correspondingly assigned by 2D NMR spectra, including HSQC, HMBC, and <sup>1</sup>H–<sup>1</sup>H COSY. Comparison of the NMR spectral data of **2** with those of **1** suggested that **2** also should be a purine-6,8-dione derivative.

The HMBC spectrum of **2** showed correlations of  $\delta_H$  8.83 (1H, s, H-2) with  $\delta_C$  107.8 (C), 139.0 (C), and 155.4 (C) that supported the presence of the purine-6,8-dione substructure (Figure 1). The HMBC spectrum showed correlations of  $\delta_H$  4.29 (1H, dd,  $J = 8.8$ , 12.9 Hz, H-1'a), 4.62 (1H, dd,  $J = 4.4$ , 12.9 Hz, H-1'b), 3.82 (1H, dd,  $J = 9.0$ , 12.9 Hz, H-3'a), and 4.25 (1H, dd,  $J = 4.2$ , 12.9 Hz, H-3'b) with  $\delta_C$  28.2 (CH, C-2') and 117.4 (CH, C-4'),  $\delta_H$  4.48 (1H, m, H-2') with  $\delta_C$  46.2 (CH<sub>2</sub>, C-1'), 42.4 (CH<sub>2</sub>, C-3'), 117.4 (CH, C-4'), and 131.8 (C, C-5'), and  $\delta_H$  5.95 (1H, d,  $J = 9.5$  Hz, H-4') with C-1'/C-3'/C-5'. The <sup>1</sup>H–<sup>1</sup>H COSY spectrum showed correlations of H-2' with H-1'a/H-1'b/H-3'a/H-3'b/H-4', suggesting the presence of a 1-isopentene group. HMBC correlations of H-1'a/H-1'b/H-3'a/H-3'b with C-4 ( $\delta_C$  139.0, C), H-1'a/H-1'b with C-2 ( $\delta_C$  136.9, C), and H-3'a/H-3'b with C-8 ( $\delta_C$  150.3, C) indicated that the 1-isopentene group was attached to the purine-6,8-dione substructure by two C–N bonds, C-1' with N(3) and C-3' with N(9). HMBC correlation of H-4' with C-6' ( $\delta_C$  162.4, C) and  $\delta_H$  3.24 (3H, s, Me-10') with C-5' and C-8' ( $\delta_C$  154.3, C), and comparison of the NMR data [ $\delta_C$  131.8 (C), 154.3 (C), 162.4 (C),

28.5 (CH<sub>3</sub>)] of the heteroatom in **2** with those of other alkaloids that contained an imidazole ring,<sup>14–16</sup> together with the amounts of nitrogen and oxygen atoms in the molecular formula of **2**, indicated the presence of a 2-imino-5-isopropenyl-1-methyl-4-imidazolidinone unit. On the basis of the above data, the structure of **2** was determined as shown.

The molecular formula of **3** was determined as C<sub>9</sub>H<sub>10</sub>N<sub>4</sub>O<sub>3</sub> by analysis of its NMR spectra and ESIMS. Its <sup>13</sup>C NMR spectrum also showed five low-field carbons [ $\delta_C$  143.1 (CH), 151.1 (C), 107.4 (C), 157.0 (C), 153.1 (C)], together with one methyl ( $\delta_C$  29.7), two methylenes ( $\delta_C$  41.8, 43.7), and one carbonyl group ( $\delta_C$  205.9, s). The <sup>1</sup>H NMR spectrum displayed one methyl at  $\delta_H$  2.04 (3H, s), two methylenes at  $\delta_H$  4.58 (2H, t,  $J = 6.45$  Hz) and 3.22 (2H, t,  $J = 6.45$  Hz), and one proton at  $\delta_H$  8.09 (1H, s). Comparison of the NMR spectral data of **3** with those of **1** and HMBC correlations of  $\delta_H$  8.09 (1H, s) with  $\delta_C$  151.1 (C), 107.4 (C), and 157.0 (C) in the HMBC spectrum of **3** proved the presence of a 6,8-purinedione substructure in **3**. HMBC correlations of  $\delta_H$  4.58 (2H, t,  $J = 6.45$  Hz), 3.22 (2H, t,  $J = 6.45$  Hz), and 2.04 (3H, s) with  $\delta_C$  205.9 (C), in addition to <sup>1</sup>H–<sup>1</sup>H COSY correlations of  $\delta_H$  4.58 with  $\delta_H$  3.22, suggested the presence of a CH<sub>3</sub>–CO–CH<sub>2</sub>CH<sub>2</sub>– unit. Meanwhile, HMBC correlations of  $\delta_H$  4.58 with  $\delta_C$  157.0 (C, C-6) and 143.1 (CH, C-2) suggested that the CH<sub>3</sub>–CO–CH<sub>2</sub>CH<sub>2</sub>– unit was attached to the 6,8-purinedione substructure by a C–N(1) bond. So, the structure of **3** was determined to be 1-(3'-carbonylbutyl)purine-6,8-dione.

Compound **4** showed the same molecular formula of C<sub>9</sub>H<sub>10</sub>N<sub>4</sub>O<sub>3</sub> as **3**, which was deduced from the NMR and ESIMS data of **4**. Comparison of overall <sup>1</sup>H and <sup>13</sup>C NMR spectral data revealed similarity between **4** and **3**. The only obvious difference between them was the chemical shifts of low-field carbons. HMBC correlations of  $\delta_H$  4.66 (2H, t,  $J = 7.5$  Hz), 3.15 (2H, t,  $J = 7.5$  Hz), and 2.09 (3H, s) with  $\delta_C$  206.5 (C) and <sup>1</sup>H–<sup>1</sup>H COSY correlations of  $\delta_H$  4.66 with  $\delta_H$  3.15 also suggested the presence of a CH<sub>3</sub>–CO–CH<sub>2</sub>CH<sub>2</sub>– unit. However, HMBC correlations of  $\delta_H$  4.66 with  $\delta_C$  152.2 (C, C-8) and 150.1 (C, C-4) suggested that the CH<sub>3</sub>–CO–CH<sub>2</sub>CH<sub>2</sub>– unit should be attached to the 6,8-purinedione substructure by a C–N(9) bond instead of a C–N(1) bond. So, the structure of **4** was determined to be 9-(3'-carbonylbutyl)purine-6,8-dione.

In total, four new purine alkaloids, **1–4**, were isolated from the South China Sea gorgonian *S. suberosa*. It was rare to find alkaloids

from gorgonians. These compounds represented mix biogenesis and definitely indicated elements of novelty in gorgonian natural products.

In cytotoxicity bioassays, compounds **1–4** all showed weak cytotoxicity toward human cancer cell lines MDA-MB-231 and A435. However, in our previous report, **8** had moderate cytotoxicity against the MDA-MB-231 cell line with an  $IC_{50}$  of 8.87  $\mu\text{g}/\text{mL}$ .<sup>9</sup> The location of the connection between the 6',8'-purinedione moiety and the suberosanone moiety in the isomers **1** and **8** could significantly affect their cytotoxic activity.

## Experimental Section

**General Experimental Procedures.** The procedures were the same as previously reported.<sup>9</sup>

**Animal Material.** The material was the same as previously reported.<sup>9</sup>

**Extraction and Isolation.** The frozen specimen was extracted with EtOH/CH<sub>2</sub>Cl<sub>2</sub> (2:1) three times at room temperature, and the solution was evaporated *in vacuo*. The residue was suspended in H<sub>2</sub>O and extracted with CHCl<sub>3</sub> and *n*-BuOH three times, respectively. The CHCl<sub>3</sub> and *n*-BuOH layers were concentrated *in vacuo* to afford 50 and 8 g of residues, respectively. The CHCl<sub>3</sub> extract was subjected to column chromatography (CC) on silica, using CHCl<sub>3</sub>/Me<sub>2</sub>CO (from 10:0 to 0:10) as eluent. By combining the fractions with TLC (GF<sub>254</sub>) monitoring, eight fractions were obtained. Fraction 7 was chromatographed over Sephadex LH-20 eluting with CHCl<sub>3</sub>/MeOH (1:1), then repeatedly subjected to CC on Si gel, eluted with CHCl<sub>3</sub>/MeOH (from 8:2 to 7:3) to yield **1** (8 mg), **3** (3 mg), and **4** (4 mg). The *n*-BuOH extract was subjected to CC on Si gel, using CHCl<sub>3</sub>/MeOH (from 9:1 to 0:10) as eluent, to give five fractions. Fraction 2 was subjected to CC on Si gel, eluted with CHCl<sub>3</sub>/MeOH (from 8:2 to 7:3), to yield **5** (8 mg), **6** (9 mg), and **7** (9 mg). Fraction 3 was subjected to CC on Si gel, eluted with CHCl<sub>3</sub>/MeOH (1:1), to yield **2** (7 mg).

**6-(1'-Purine-6',8'-diolyl)suberosanone (1):** white powder;  $[\alpha]_{\text{D}}^{20} +27.3$  (c 0.2, CHCl<sub>3</sub>); UV (MeOH)  $\lambda_{\text{max}}$  212, 265 nm; IR (KBr) 3502, 3115, 1739, 1710, 1672, 1659  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) data, see Table 1; <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) data, see Table 1; HRESIMS  $m/z$  369.1918 [M - H]<sup>-</sup> (calcd for C<sub>20</sub>H<sub>25</sub>N<sub>4</sub>O<sub>3</sub> 369.1926).

**3,9-(2-Imino-1-methyl-4-imidazolidinon-5-yl)isopropenylpurine-6,8-dione (2):** white powder; UV (MeOH)  $\lambda_{\text{max}}$  213, 264, 310 nm; IR (KBr) 3504, 3110, 1738, 1708, 1675, 1648  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O + 0.5 N HCl)  $\delta_{\text{H}}$  8.83 (1H, s, H-2), 5.95 (1H, d,  $J = 9.5$  Hz, H-3'), 4.62 (1H, dd,  $J = 4.4, 12.9$  Hz, H-1'b), 4.48 (1H, m, H-2'), 4.29 (1H, dd,  $J = 8.7, 12.9$  Hz, H-1'a), 4.25 (1H, dd,  $J = 4.2, 12.9$  Hz, H-5'b), 3.82 (1H, dd,  $J = 9.0, 12.9$  Hz, H-5'a), 3.24 (3H, s, NMe); <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O + 0.5 N HCl)  $\delta_{\text{C}}$  162.4 (s, C-6'), 155.4 (s, C-6), 154.3 (s, C-8'), 150.3 (s, C-8), 139.0 (s, C-4), 136.7 (d, C-2), 131.8 (s, C-5'), 117.4 (d, C-4'), 46.2 (t, C-1'), 42.4 (t, C-3'), 28.5 (q, C-10'), 28.2 (d, C-2'); ESIMS(+)  $m/z$  316 [M + H]<sup>+</sup>; HRFABMS  $m/z$  316.1076 [M + H]<sup>+</sup> (calcd for C<sub>13</sub>H<sub>14</sub>N<sub>7</sub>O<sub>3</sub> 316.1080).

**1-(3'-Carbonylbutyl)purine-6,8-dione (3):** white powder; UV (MeOH)  $\lambda_{\text{max}}$  212, 264 nm; IR (KBr) 3501, 3115, 1740, 1710, 1670, 1658  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, Pyr-*d*<sub>5</sub>)  $\delta_{\text{H}}$  8.09 (1H, s, H-2), 4.58 (2H, t,  $J = 6.45$  Hz, H-1'), 3.22 (2H, t,  $J = 6.45$  Hz, H-2'), 2.04 (3H, s, H-4'); <sup>13</sup>C NMR (125 MHz, Pyr-*d*<sub>5</sub>)  $\delta_{\text{C}}$  205.9 (s, C-3'), 157.0 (s, C-6), 153.1 (s, C-8), 151.1 (s, C-4), 143.1 (d, C-2), 107.4 (s, C-5),

43.7 (t, C-2'), 41.8 (t, C-1'), 29.7 (q, C-4'); ESIMS(-)  $m/z$  221 [M - H]<sup>-</sup>; HRFABMS  $m/z$  221.0750 [M - H]<sup>-</sup> (calcd for C<sub>9</sub>H<sub>9</sub>N<sub>4</sub>O<sub>3</sub> 221.0753).

**9-(3'-Carbonylbutyl)purine-6,8-dione (4):** white powder; UV (MeOH)  $\lambda_{\text{max}}$  212, 264 nm; IR (KBr) 3501, 3115, 1740, 1710, 1670, 1658  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, Pyr-*d*<sub>5</sub>)  $\delta_{\text{H}}$  8.27 (1H, s, H-2), 4.66 (2H, t,  $J = 7.5$  Hz, H-1'), 3.15 (2H, t,  $J = 7.5$  Hz, H-2'), 2.09 (3H, s, H-4'); <sup>13</sup>C NMR (125 MHz, Pyr-*d*<sub>5</sub>)  $\delta_{\text{C}}$  206.5 (s, C-3'), 156.3 (s, C-6), 152.2 (s, C-8), 150.1 (s, C-4), 140.6 (d, C-2), 108.7 (s, C-5), 42.0 (t, C-2'), 38.3 (t, C-1'), 29.7 (q, C-4'); ESIMS(-)  $m/z$  221 [M - H]<sup>-</sup>; HRFABMS  $m/z$  221.0749 [M - H]<sup>-</sup> (calcd for C<sub>9</sub>H<sub>9</sub>N<sub>4</sub>O<sub>3</sub> 221.0753).

**Biological Assays.** Human breast carcinoma MDA-MB-231 and liver carcinoma A435 cell lines were purchased from the American Type Culture Collection (ATCC, Rockville, MD). Cytotoxicity assays were measured by MTT methods as described previously.<sup>13</sup>

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**Supporting Information Available:** This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References and Notes

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