

## New Cytotoxic Naphthopyrane Derivatives from *Adenaria floribunda*

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Bioassay-guided fractionation of an EtOAc/MeOH extract of *Adenaria floribunda* young leaves using MCF-7, H-460, and SF-268 cancer cell lines yielded four new active compounds named adenaflorens A–D (1–4). Their chemical structures were determined by spectroscopic means. Adenafloren A (1) was the most cytotoxic.

The International Cooperative Biodiversity Group (ICBG) project of Panama uses an ecological approach, focused on young leaves, to discover novel, active compounds in tropical plants. We hypothesize that fresh young leaves rely more on chemical defense than do mature leaves and, thus, produce more bioactive molecules.<sup>1</sup>

The genus *Adenaria* (Lythraceae) is represented in Panama by one species, viz., *Adenaria floribunda* Kunth.<sup>2</sup> There is no phytochemical study nor any ethnomedical claims reported for this genus. In the course of an ICBG program for studying the Panamanian flora for its potential anticancer activity, the methanolic extract of the young leaves of *A. floribunda* showed cytotoxic activity against different human cell lines, while the extract from the mature leaves showed no activity. Bioassay-guided isolation of the EtOAc/MeOH extract of *A. floribunda* young leaves, using MCF-7, H-460, and SF-268 human cancer cell lines, led to the isolation of four new compounds, namely, adenaflorens A, B, C, and D. The structural determination and the cytotoxic activity of these compounds are discussed.

Compound 1 was obtained as orange crystals, and the molecular formula C<sub>25</sub>H<sub>30</sub>O<sub>5</sub> was determined from its HRFABMS, which showed a molecular ion peak [M + 1]<sup>+</sup> at 411.2176. The <sup>1</sup>H and <sup>13</sup>C NMR data (Table 1) demonstrated the presence of an aromatic proton at δ<sub>H</sub> 6.71 (δ<sub>C</sub> 99.7, C-10), a methylene group at δ<sub>H</sub> 2.81, 2.73 (δ<sub>C</sub> 43.6, C-3), a methine oxygen attached group at δ<sub>H</sub> 4.55 (δ<sub>C</sub> 73.2, C-2), two hydroxyl groups, one of them strongly hydrogen-bonded at δ<sub>H</sub> 15.90, 9.75 (5-OH and 6-OH), and a methyl group at δ<sub>H</sub> 1.53 (δ<sub>C</sub> 21.0, C-11), in addition to two prenyl groups connected to an aromatic system [δ<sub>H</sub> 3.45/δ<sub>C</sub> 23.0 (C-1), 5.28/123.1 (C-2), 131.4 (C-3), 1.73/25.7 (C-4), 1.85/17.9 (C-5)], [δ<sub>H</sub> 3.56/δ<sub>C</sub> 24.8 (C-1), 5.11/123.6 (C-2), 131.9 (C-3), 1.73/25.6 (C-4), 1.85/18.1 (C-5)] and an aromatic *O*-methyl group at δ<sub>H</sub> 3.78 (δ<sub>C</sub> 61.7). The <sup>1</sup>H–<sup>1</sup>H COSY correlations showed the methyl group (δ<sub>H</sub> 1.53) coupled with a methine proton (δ<sub>H</sub> 4.55), and the latter coupled with methylene protons (δ<sub>H</sub> 2.73, 2.81). The HMBC cross-peak connectivities demonstrated correlations for H-2/C-3, C-11; H-3/C-2, C-4, C-11; H-10/C-4a, C-5a, C-9, C-10a; and OH-6/C-6, C-5a, C-7. The above data indicated the presence of a 2,3-dihydronaphthopyranone skeleton<sup>3–6</sup> with an *O*-

**Table 1.** <sup>1</sup>H and <sup>13</sup>C NMR Spectral Data for Compounds 1 and 2 in CDCl<sub>3</sub>

position	1		2	
	C	H (mult., J Hz)	C	H (mult., J Hz)
2	73.2 d	4.55 (dq, 10.4, 6.2, 4.0)	169.2 s	
3	43.6 t	2.81 (dd, 17.3, 10.4), 2.73 (dd, 17.3, 4.0)	106.5 d	6.03 (s)
4	198.5 s		184.4 s	
4a	102.9 s		103.2 s	
5	164.5 s		161.7 s	
5a	107.3 s		108.8 s	
6	155.2 s		154.3 s	
7	117.0 s		117.3 s	
8	160.9 s		159.3 s	
9	119.4 s		119.0 s	
9a	138.3 s		125.9 s	
10	99.7 d	6.71 (s)	99.5 d	7.16 (s)
10a	153.9 s		151.3 s	
11	21.0 q	1.53 (d, 6.2)	21.3 q	2.41 (s)
1	23.0 t	3.45 (d, 6.5)	23.1 t	3.45 (d, 6.6)
2	123.1 d	5.28 (tq, 6.5, 1.3)	123.0 d	5.32 (tq, 6.6, 1.3)
3	131.4 s		132.0 s	
4	25.7 q	1.73 (s)	25.7 q	1.70 (s)
5	17.9 q	1.85 (s)	17.9 q	1.84 (s)
1	24.8 t	3.56 (d, 5.5)	25.0 t	3.64 (d, 5.5)
2	123.6 d	5.11 (tq, 5.5, 1.3)	123.6 d	5.12 (tq, 5.5, 1.3)
3	131.9 s		132.5 s	
4	25.6 q	1.73 (s)	25.6 q	1.70 (s)
5	18.1 q	1.85 (s)	18.1 q	1.90 (s)
OMe	61.7 q	3.78 (s)	61.8 q	3.79 (s)
5-OH		15.90 (s)		16.21 (s)
6-OH		9.75 (s)		10.11 (s)

methyl and two prenyl groups. The two prenyl groups were positioned at C-7 and C-9, as indicated from HMBC correlations, CH<sub>2</sub> (δ<sub>H</sub> 3.45, H-1) showed correlations with carbons at δ<sub>C</sub> 117.0, 155.2, and 160.9 (C-7, C-6, and C-8), while CH<sub>2</sub> (δ<sub>H</sub> 3.56, H-1) showed correlations with carbons at δ<sub>C</sub> 119.4, 160.9, and 138.3 (C-9, C-8, and C-9a). The methoxyl group was positioned at C-8, as indicated from HMBC, and the methoxyl protons (δ<sub>H</sub> 3.78) showed correlations with a carbon at δ<sub>C</sub> 160.9 (C-8). In the NOESY experiment, H-3a (δ<sub>H</sub> 2.81) showed correlation with H-2 (δ<sub>H</sub> 4.55), while H-3b (δ<sub>H</sub> 2.73) showed correlations with both H-2 and Me-11. The absolute configuration at the C-2 stereogenic center of 1 was not ascertained directly, but its [α]<sub>D</sub> value (−86.7) is opposite of that reported for a closely related compound possessing 2*S* absolute stereochemistry, as was established from CD data.<sup>6</sup> Consequently, we suggest a 2*R* configuration for 1. Thus, structure 1

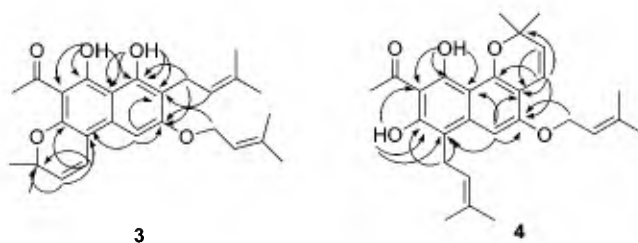
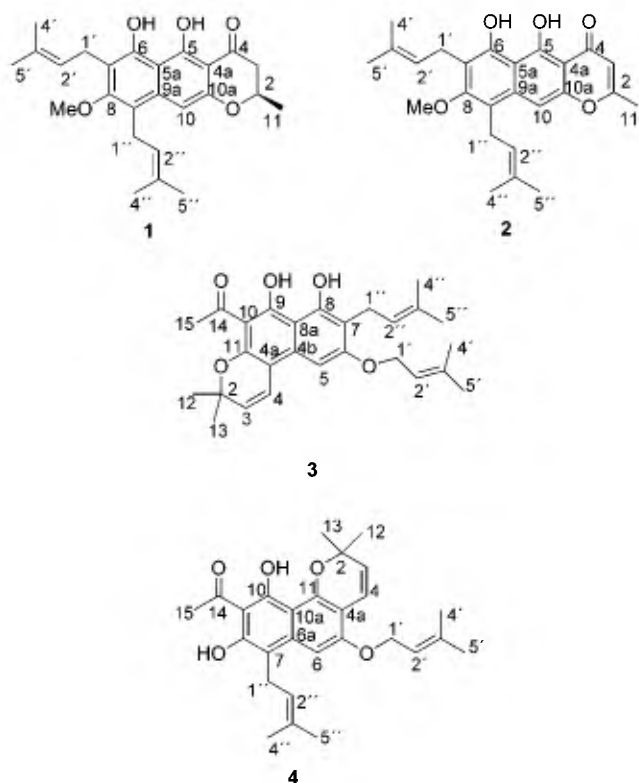
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was assigned to the new compound adenaflorin A.



**Figure 1.** Selected HMBC correlations of **3** and **4**.

**Table 2.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR Spectral Data for Compounds **3** and **4** in  $\text{CDCl}_3$

position	<b>3</b>		<b>4</b>	
	C	H (mult., $J$ Hz)	C	H (mult., $J$ Hz)
2	77.1 s		79.7 s	
3	125.1 d	5.75 (d, 8.0)	126.7 d	5.53 (d, 8.1)
4	118.8 d	6.67 (d, 8.0)	117.3 d	6.69 (d, 8.1)
4a	105.1 s		106.2 s	
4b	135.0 s			
5	93.2 d	6.58 (s)	156.7 s	
6	161.6 s		96.2 d	6.59 (s)
6a			139.0 s	
7	113.0 s		110.7 s	
8	157.2 s		156.6 s	
8a	105.0 s			
9	168.7 s		106.9 s	
10	105.1 s		160.5 s	
11	149.9 s		151.4 s	
12	27.2 q	1.50 (s)	27.5 q	1.58 (s)
13	27.2 q	1.50 (s)	27.5 q	1.58 (s)
14	203.6 s		205.0 s	
15	32.0 q	2.77 (s)	34.1 q	2.75 (s)
1	65.0 t	4.61 (d, 6.2)	65.1 t	4.59 (d, 6.3)
2	119.7 d	5.53 (tq, 6.2, 1.3)	119.3 d	5.49 (tq, 6.3, 1.3)
3	137.7 s		138.0 s	
4	25.7 q	1.75 (s)	25.8 q	1.79 (s)
5	18.3 q	1.79 (s)	18.2 q	1.74 (s)
1	21.9 t	3.41 (d, 6.5)	23.6 t	3.52 (d, 6.4)
2	122.7 d	5.26 (tq, 6.5, 1.3)	123.4 d	5.11 (tq, 6.4, 1.3)
3	131.1 s		131.3 s	
4	25.8 q	1.64 (s)	25.7 q	1.72 (s)
5	17.8 q	1.77 (s)	18.0 q	1.88 (s)
8-OH		10.0 (s)		13.10 (s)
9-OH		15.87 (s)		
10-OH				11.14 (s)

Compound **2** was isolated as orange-yellow crystals. The molecular formula corresponding to  $\text{C}_{25}\text{H}_{28}\text{O}_5$  was deduced from HRFABMS, which showed a molecular ion peak  $[\text{M} + 1]^+$  at 409.2032, i.e., 2 atomic mass units less than **1**.  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (Table 1) were similar to those of **1**. The appearance of an olefinic proton at  $\delta_{\text{H}}$  6.03 ( $\delta_{\text{C}}$  106.5, C-3) and the deshielded methyl group at  $\delta_{\text{H}}$  2.41 ( $\delta_{\text{C}}$  21.3, C-11) indicated the presence of a (C-2/C-3) double bond. This fact was supported by HMBC correlations; H-3 ( $\delta_{\text{H}}$  6.03) showed correlations with carbons at  $\delta_{\text{C}}$  169.2, 103.2, and 21.3 (C-2, C-4a, and C-11). All the foregoing data with other data of COSY 45, HMQC, and HMBC supported the structure of **2** as the new compound adenaflorin B.

Compound **3** was isolated as orange-yellow crystals. HRFABMS gave a molecular ion peak  $[\text{M} + 1]^+$  at  $m/z$  437.2335 corresponding to the molecular formula  $\text{C}_{27}\text{H}_{32}\text{O}_5$ . The IR spectra showed absorption at  $3225\text{ cm}^{-1}$  for one or more hydroxyl groups and at  $1661\text{ cm}^{-1}$  for a conjugated carbonyl functionality, which also appeared at  $\delta_{\text{C}}$  203.6 (C-14) in the  $^{13}\text{C}$  NMR spectrum of **3**. The NMR data of **3** (Table 2) showed signals of an aromatic proton at  $\delta_{\text{H}}$  6.58 ( $\delta_{\text{C}}$  93.2, C-5), two olefinic protons, *cis* coupled, at  $\delta_{\text{H}}$  5.75, 6.67 ( $J = 8.0\text{ Hz}$ ,  $\delta_{\text{C}}$  125.1, 118.8; C-3, C-4), and two methyl groups at  $\delta_{\text{H}}$  1.50 [6H,  $\delta_{\text{C}}$  27.2 (2C), C-12, C-13] attached to a carbon-bearing oxygen at  $\delta_{\text{C}}$  77.1 (C-2). The HMBC cross-peak connectivities (Figure 1) showed correlations of H-3/C-2, C-4a; H-4/C-2, C-11; and H-5/C-4a, C-7, C-6. The aforementioned data, with unambiguous analysis of other DEPT 135, COSY 45, HMBC, and NOESY data, indicated the presence of a 2*H*-naphtho[3,4-*b*]pyran-3-ene skeleton. The rest of the molecule showed signals attributable to an acetyl group ( $\delta_{\text{C}}/\delta_{\text{H}}$  32.0/2.77, 203.6) and two prenyl groups, one *O*-attached [ $\delta_{\text{H}}$  4.61/ $\delta_{\text{C}}$  65.0 (C-1), 5.53/119.7 (C-2), 137.7 (C-3), 1.75/25.7 (C-4), 1.79/18.3 (C-5)], [ $\delta_{\text{H}}$  3.41/ $\delta_{\text{C}}$  21.9 (C-1), 5.26/122.7 (C-2), 131.1 (C-3), 1.64/25.8 (C-4), 1.77/17.8 (C-5)]. The HMBC NMR experiment was employed to determine the positions of the two prenyl

groups; H-1 protons showed correlations with C-7, C-6, and C-8, while the *O*-attached prenyl group was positioned at C-6, as evidenced by correlations of H-1/C-6. The acetyl group was located at C-10 on the basis of the strong hydrogen-bonded hydroxyl group ( $\delta_{\text{H}}$  15.87) and NOESY correlations between Me-12, Me-13, and Me-15. On the basis of the above spectral data, structure **3** was assigned to the new compound adenaflorin C.

Compound **4** was isolated as orange crystals and was deduced to have the molecular formula  $\text{C}_{27}\text{H}_{32}\text{O}_5$  by the HRFABMS ( $m/z$  437.2314 for  $[\text{M} + 1]^+$ ). The NMR data of **4** (Table 2) were almost identical with those of **3**, except for the position of the pyran ring. The chemical shift of 10-OH ( $\delta_{\text{H}}$  11.14) and the appearance of the second hydroxyl group at  $\delta_{\text{H}}$  13.10 instead of  $\delta_{\text{H}}$  10.0 (8-OH in **3**) indicated that the pyran ring was located at C-1, C-2 of the naphthyl group. This fact was supported by HMBC cross-peaks (Figure 1), which demonstrated correlations for H-4/C-4a, C-11, C-5; H-6/C-5, C-6a, C-4a, C-10a, C-7; H-1/C-7, C-8; H-1/C-5, 8-OH/C-8, C-9, C-7; and 10-OH/C-10, C-9, C-10a. In the NOESY spectra, correlations observed between H-6/H-1, H-1; Me-12, Me-13/10-OH; and Me-15/10-OH, 8-OH. All these spectral data indicated structure **4** for the new compound adenaflorin D.

Naphthopyrane compounds were first reported from *Aspergillus niger*<sup>7</sup> and later in a few higher plants.<sup>3-5</sup> This

**Table 3.** Cytotoxic Activity of Plant Extracts and Compounds 1–4

compound/extract	GI <sub>50</sub> (μg/mL)		
	MCF-7	H-460	SF-268
<i>A. floribunda</i> young leaves	12.0	12.0	9.4
total EtOAc/MeOH extract			
adenaflorine A (1)	0.24	0.16	0.13
adenaflorine B (2)	4.3	2.9	3.9
adenaflorine C (3)	1.2	1.1	1.4
adenaflorine D (4)	>10	9.3	>10
adriamycin	6.5 × 10 <sup>-7</sup>	7.2 × 10 <sup>-7</sup>	8.6 × 10 <sup>-7</sup>

is the first report of the occurrence of naphthopyrane compounds in the Lythraceae. It is of interest to indicate that the TLC profile of the mature leaves did not show any of the compounds isolated from the young leaves and, thus, could support the ecological-based selection of plant material in the Panamanian ICBG program.<sup>1</sup>

Table 3 shows GI<sub>50</sub> values of compounds 1–4. Compound 1 showed strong activity, and compounds 2 and 3 showed moderate activities, while compound 4 was inactive. However, naphthopyrane compounds have been shown to possess potent antibiotic, cytotoxic, and mutagenic activities.<sup>8</sup> Other compounds belonging to this class of natural metabolites also have demonstrated antitumor, antileukemic, and antiviral activities.<sup>9</sup>

## Experimental Section

**General Experimental Procedures.** Melting points were uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. NMR spectra were recorded using a Bruker Avance 300 spectrometer in CDCl<sub>3</sub> at 300 MHz for <sup>1</sup>H and 75 MHz for <sup>13</sup>C NMR. Mass spectra were obtained on a Kratos MS50TC mass spectrometer. Silica gel [Merck, Kieselgel 60 (0.063–0.200 mm) and (0.015–0.040 mm)] and LiChroprep RP-18 (Merck, 9303) were used for column chromatography. Silica gel plates (Merck, Kieselgel 60 F<sub>254s</sub>) were used for TLC.

**Cytotoxicity Bioassays.** The cytotoxic activity was determined against breast (MCF-7), lung (H-460), and central nervous system (SF-268) human cancer cell lines according to the method given by Monks et al.<sup>10</sup> During the isolation process, the activity of all fractions was monitored using all three cell lines.

**Plant Material.** Young leaves of *A. floribunda* were collected from Monumento Natural Barro Colorado, Península de Bohío, Panama (N 9°14'2", W 79°39'30") in May 2002. Voucher specimens are deposited in the Herbarium of the Smithsonian Tropical Research Institute, Panama.

**Extraction and Isolation.** Fresh, young leaves (505 g) were extracted and subjected to solvent partitioning as described before.<sup>11</sup> The activity was retained in hexane and MeOH fractions. The two fractions were combined according to the TLC profile (12.8 g). Flash chromatography of the combined fraction on a Si gel column using a gradient mixtures of hexane and EtOAc (0 to 100% EtOAc) yielded five fractions. Fraction 5 was chromatographed on a C<sub>18</sub>-RP Lobar column using 5% H<sub>2</sub>O in MeOH as eluent, to yield pure 3 (15 mg, 0.000029%). Si gel column chromatography of fractions 3 and 4 using 15% EtOAc in hexane yielded 1 (50 mg, 0.000099%). Fractions 1 and 2 were combined and chromatographed on Si gel using 5% of EtOAc in hexane to afford 2 (20 mg, 0.000039%) and 4 (10 mg, 0.000020%).

**Adenaflorin A:** orange crystals, mp 102–105 °C; [α]<sub>D</sub><sup>28</sup> –86.7° (c 0.09, CHCl<sub>3</sub>); IR (KBr) ν<sub>max</sub> 3310, 2910, 2860, 1595, 1545, 1410, 1385 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>), see Table 1; FABMS, positive, *m/z* 411 [M + 1]<sup>+</sup> (4), 410 (10), 355 (4), 307 (29), 289 (16), 219 (3) 154 (100), 136 (71); HRFABMS *m/z* 411.21761 [M + 1]<sup>+</sup> (calcd for C<sub>25</sub>H<sub>31</sub>O<sub>5</sub>, 411.21709).

**Adenaflorin B:** orange yellow crystals, mp 87–90 °C; IR (KBr) ν<sub>max</sub> 3250, 2860, 1616, 1580, 1548, 1410, 1385 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>), see Table 1; FABMS, positive, *m/z* 409 [M + 1]<sup>+</sup> (11), 408 (22), 391 (4), 353 (6), 307 (26), 289 (13), 220 (6), 205 (4), 154 (100), 136 (71); HRFABMS *m/z* 409.20324 [M + 1]<sup>+</sup> (calcd for C<sub>25</sub>H<sub>29</sub>O<sub>5</sub>, 409.20150).

**Adenaflorin C:** orange-yellow crystals, mp 114–115 °C; IR (KBr) ν<sub>max</sub> 3225, 2915, 1661, 2873, 1595, 1545, 1405, 1395 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>), see Table 2; FABMS, positive, *m/z* 437 [M + 1]<sup>+</sup> (27), 436 (50), 381 (8), 368 (12), 307 (22), 297 (13), 219 (5) 154 (100), 136 (71); HRFABMS *m/z* 437.23353 [M + 1]<sup>+</sup> (calcd for C<sub>27</sub>H<sub>32</sub>O<sub>5</sub>, 437.23264).

**Adenaflorin D:** orange crystals, mp 133–135 °C; IR (KBr) ν<sub>max</sub> 3150, 2910, 2860, 1570, 1410, 1375, 1350 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>), see Table 2; FABMS, positive, *m/z* 437 [M + 1]<sup>+</sup> (6), 436 (67), 391 (16), 368 (5), 307 (21), 289 (13), 259 (11), 154 (100), 136 (73); HRFABMS *m/z* 437.23146 [M + 1]<sup>+</sup> (calcd for C<sub>27</sub>H<sub>32</sub>O<sub>5</sub>, 437.23280).

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