Prenylated Benzophenones and Xanthones from *Hypericum scabrum*

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Received January 30, 2004

Two new polyprenylated benzophenones, a new polyprenylated phloroglucinol, and six new xanthone derivatives were isolated from the aerial parts of the Uzbekistan medicinal plant *Hypericum scabrum*. Their structures were elucidated on the basis of spectroscopic evidence. The isolated compounds showed moderate cytotoxicity for human tumor cells.

The recent widespread interest in the antidepressant activity of *Hypericum perforatum* (St. John's wort) has encouraged the investigation of secondary metabolites from other *Hypericum* species.[1] The genus *Hypericum* occurs widely in temperate regions of the world and has been used as traditional medicinal plants in various parts of the world. It produces various types of secondary metabolites, including flavonoids, biflavonoids, xanthones, naphthodianthorones, and prenylated phloroglucinols.[2] These compounds show diverse biological activity.[3−8,11−13] *H. scabrum* is one of the most popular medicinal herbs in Uzbekistan and is used in the treatment of bladder, intestinal, and heart diseases, rheumatism, and cystitis.[12,13] The volatile oil constituents of *H. scabrum* have been studied,[14,15] and we previously reported nine novel polyprenylated benzoylphloroglucinol derivatives named hyperibones **A**−**I**.[16] As part of our continuing study of the chemical constituents of medicinal plants in Uzbekistan, we have examined the aerial parts of *H. scabrum* and isolated nine new compounds [hyperibones J−L (**1**−**3**), hyperxanthones A−F (**4**−**9**)] and 16 known compounds (**10**−**25**). In this paper, we describe the isolation, structure elucidation, and cytotoxicity of the isolated compounds for human tumor cells.

Results and Discussion

The methanol extract of air-dried aerial parts of *H. scabrum* was partitioned between H_2O and EtOAc. The EtOAc layer was separated by column chromatography (CC) to afford nine new (**1**−**9**) and 16 known (**10**−**25**) compounds.

Hyperibone J (**1**)[17] was assigned a molecular formula of $C_{31}H_{46}O_5$ on the basis of the positive-ion HRFABMS, and its IR spectrum showed a hydroxyl band (3323 cm^{-1}) and three carbonyl bands (1777, 1742, and 1678 cm^{-1}). The ^1H NMR spectrum of **1** indicated the presence of a hydroxyl proton [δ_H 7.70 (1H, brs)], three protons attached to double bonds [δ_H 5.02 (1H, t, J = 7.3 Hz), 4.96 (1H, t, J = 5.3 Hz), and 4.90 (1H, t, J = 6.8 Hz)], one isopropyl group [δ_H 3.18 (1H, sept, J = 6.6 Hz), 1.08, 0.91 (each 3H, d, J = 6.6 Hz)], five methylenes, and eight methyl singlets. The ^{13}C NMR spectrum of **1** showed three carbonyl carbons [δ_C 217.9, 209.9, and 207.0], three double-bond carbons [δ_C 136.1, 133.6, 131.9, 124.2, 122.1, and 115.9], two oxygenated quaternary carbons [δ_C 107.9 and 97.3], and three other quaternary carbons, two methine carbons, five methylene carbons, and 10 methyl carbons. On the basis of these data, **1** was assumed to be a prenylated phloroglucinol derivative. The ^{13}C NMR spectrum of **1** was very similar to that of 9-hydroxyhyperforin-9,3-hemiacetal[18] except for the chemical shifts of C-5 and C-19−C-23. The structure of **1** was presumed to be a C-5-substituted compound of 9-hydroxyhyperforin-9,3-hemiacetal. In the HMBC spectrum of **1**, the signal of H_3-19 (δ_H 1.12) was correlated with the carbon signals of C-4 (δ_C 209.9), C-5 (δ_C 51.5), C-6 (δ_C 34.3), and C-9 (δ_C 107.9). This indicated that a methyl group is located at C-5 of **1** in place of the isopentenyl group in 9-hydroxyhyperforin-9,3-hemiacetal. The relative configuration of C-7 and C-8 was determined on the basis of the following NOESY results: OH-9 [δ_H 7.70 (1H, s)] with H_3-25 [δ_H 0.98 (3H, s)], H_3-25 with H-6ax [δ_H 1.28 (1H, m)]; H-6eq [δ_H 1.86 (1H, dd, J = 14.3, 3.4)] with H-7 [δ_H 1.04 (1H, m)]. Thus, the structure of **1** (hyperibone J) was assigned as shown in Figure 1.

Hyperibone K (**2**) has a molecular formula of $C_{33}H_{40}O_4$ on the basis of negative-ion HRFABMS and showed a carbonyl absorption at 1701 cm^{-1} in its IR spectrum, and its UV spectrum showed the presence of an aromatic moiety (246 nm). The ^1H NMR spectrum revealed the presence of a benzene ring [δ_H 7.44 (1H, t, J = 7.3 Hz), 7.29 (2H, dd, J = 7.5, 7.3 Hz), and 7.22 (2H, d, J = 7.5 Hz)], three vinyl protons [δ_H 5.20 (1H, t, J = 7.3 Hz), 5.01 (1H, d, J = 8.1), and 4.93 (1H, t, J = 6.3 Hz)], two methines [δ_H 4.20 (1H, brd, J = 8.1 Hz) and 1.72 (1H, m)], three methylenes [δ_H 2.53 (2H, d, J = 7.3 Hz), 2.47 (2H, m), 2.48 and 2.42 (each 1H, m)], and eight methyls [δ_H 1.77, 1.75, 1.70, 1.68, 1.66, 1.63, 1.24, and 1.16 (each 3H, s)]. The ^{13}C NMR spectrum indicated that the presence of three carbonyl carbons [δ_C 203.6, 201.6, and 201.1], a benzoyl group [δ_C 193.4, 135.1, 132.6, 129.3 × 2, and 128.1 × 2], three double bonds [δ_C 135.0, 134.8, 134.5, 120.7, 119.5, and 118.8], four quaternary carbons [δ_C 79.5, 77.2, 69.2, and 53.6], two methines, three methylenes, and eight methyls. On the basis of these data, **2** was assumed to be a prenylated benzophenone derivative that has three 3-methyl-2-butenyl units. In the

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10.1021/np040024+ CCC: $27.50
Published on Web 11/09/2004

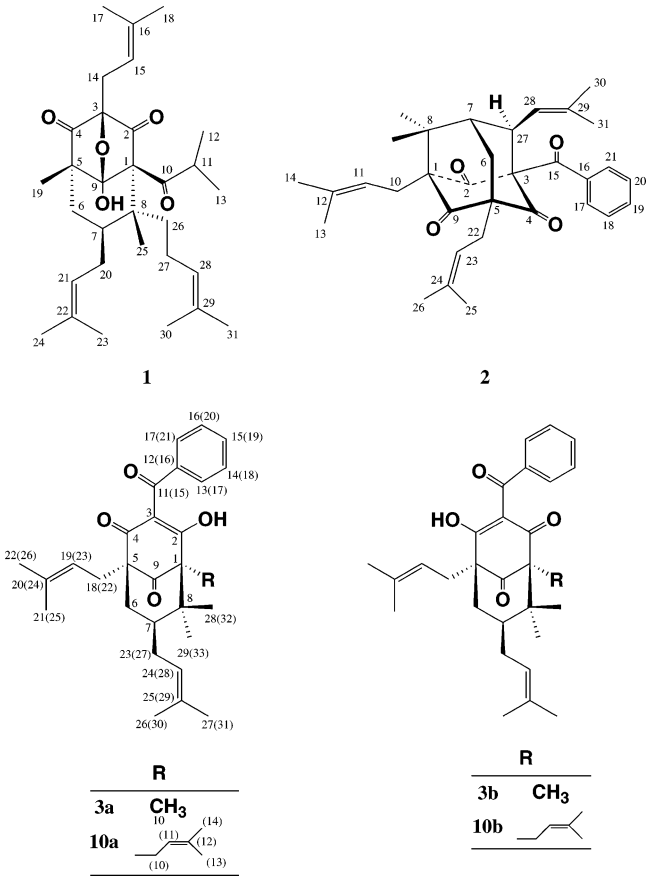

Figure 1.

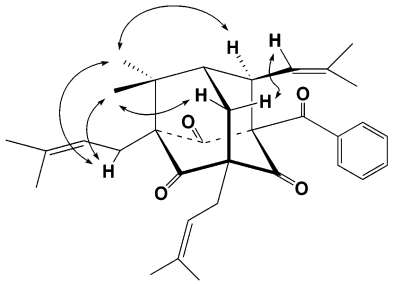

Figure 2. NOE correlations of compound **2**.

$^1H-^1H$ COSY spectrum, the signal of H-27 (δ_H 4.20) correlated with the signals of H-28 (δ_H 5.01) and H-7 (δ_H 1.72). Moreover, the long-range correlations of H-27 with C-3 (δ_C 79.5), C-4 (δ_C 201.6), C-6 (δ_C 41.2), and C-7 (δ_C 47.9) and H-7 with C-1 (δ_C 77.2), C-3, and C-5 (δ_C 69.2) were observed in the HMBC spectrum. These facts indicated that the methine carbon (C-27) was connected to three carbons (C-28, C-7, and C-3). The long-range correlations of H_2-10 (δ_H 2.47) with C-1 and H_2-22 (δ_H 2.53) with C-9 (δ_C 203.6), C-4, C-5, and C-6 (δ_C 41.2) showed that the two remaining 3-methyl-2-butenyl units were located at C-1 and C-5. Therefore, the benzoyl group must be located at C-3. The relative configuration of C-27 and C-8 was determined on the basis of the NOESY spectrum shown in Figure 2. Thus, the structure of **2** (hyperibone K) was assigned as shown.

Compound **3** showed a hydroxyl absorption (3349 cm^{-1}) and two carbonyl absorptions (1732 and 1673 cm^{-1}) in its IR spectrum and displayed a molecular ion peak at *m/z* 448.2589 ($[M]^+$, calcd 448.2614) in the HREIMS. These data indicated the molecular formula as $C_{29}H_{36}O_4$. However, there were duplicate signals in its ^1H and ^{13}C NMR spectra (in $CDCl_3$) in the ratio of approximately 2:1, and two proton signals of the enolic OH group (δ_H 17.70 and 15.48) were observed. **3** was thus considered to be a mixture of the enol tautomers of **3a** and **3b** (ca 2:1). In comparison with compounds isolated from Guttiferae, the ^{13}C NMR data of **3** were very similar to that of 7-epiclusianone (**10**), which was observed as a mixture of two enolic tautomers (5:4, in $CDCl_3$) in the NMR spectrum,[19] except for the C-10 methyl signal of **3**. In the HMBC spectrum of **3**, H_3-10 (δ_H 1.42) was correlated with the carbon signals of C-2 (δ_C 197.8), C-1 (δ_C 62.0), C-8 (δ_C 48.5), and C-9 (δ_C 209.2) in the major tautomer **3a**, and H_3-10 (δ_H 1.29) was correlated with the carbon signals of C-2 (δ_C 194.7), C-1 (δ_C 65.3), C-8 (δ_C 47.6), and C-9 (δ_C 209.2) in the minor tautomer **3b**. These facts indicated that the methyl group (C-10) was located at C-1. The assignment of other carbons was done by comparison of the ^{13}C NMR data with those of **10**. Thus, the structures of **3a** (hyperibone L-a) and **3b** (hyperibone L-b) were determined as shown.

Hyperxanthone A (**4**) showed hydroxy and conjugated carbonyl bands at 3423 and 1650 cm^{-1} in its IR spectrum. The HREIMS of **4** gave a molecular ion at *m/z* 344.0913 ($[M]^+$, calcd 344.0896), suggesting the molecular formula of $C_{18}H_{16}O_7$. The ^1H NMR spectrum of **4** showed the presence of a hydrogen-bonded hydroxyl proton [δ_H 13.19 (1H, s)], one singlet aromatic proton [δ_H 6.75 (1H, s)], two *meta*-coupled aromatic protons [δ_H 6.25 (1H, d, J = 1.6 Hz) and 6.19 (1H, d, J = 1.6 Hz)], an oxygenated methine proton [δ_H 4.80 (1H, t, J = 9.2 Hz)], one methylene group attached to the aromatic ring [δ_H 3.72 (2H, d, J = 9.2 Hz)], and two methyl protons [δ_H 1.30 and 1.26 (each 3H, s)]. Its ^{13}C NMR spectrum (Table 3) revealed the presence of 18 carbons including one conjugated carbonyl carbon (δ_C 182.1), 12 aromatic carbons, one oxygenated quaternary carbon, one oxygenated methine carbon, one methylene carbon, and two methyl carbons. These data suggested that **4** is a xanthone derivative having a 2,3-dihydroxy-3-methylbutyl side chain. In the HMBC spectrum, the following key long-range correlations were observed: OH-1 with C-1, C-2, and C-9a; H-2 with C-1, C-3, C-4, and C-9a; H-4 with C-2, C-3, C-4a, and C-9a; H-5 with C-8a, C-4b, C-6, and C-7. These correlations indicated that four hydroxyl functions were located at C-1, C-3, C-6, and C-7. The long-range correlations of H_2-1′ with C-7 and C-8 revealed that the 2,3-dihydroxy-3-methylbutyl side chain is located at C-8. Furthermore, the downfield shifted carbon signal of C-2′ (δ_C 91.5) pointed out the existence of a five-membered ring located at C-7 and C-8.

Hyperxanthone B (**5**) had a molecular formula of $C_{18}H_{16}O_8$ on the basis of HREIMS (*m/z* 360.0852 $[M]^+$). The ^1H and ^{13}C NMR data of **5** were similar to those of **4**, except for H-1′ [**5**: δ_H 5.89 (1H, d, J = 5.5 Hz), **4**: δ_H 3.72 (2H, d, J = 9.2 Hz)], H-2′ [**5**: δ_H 4.47 (1H, d, J = 5.5 Hz), **4**: δ_H 4.80 (1H, d, J = 9.2 Hz)], C-1′ [**5**: δ_C 73.9, **4**: δ_C 32.9], and C-2′ [**5**: δ_C 97.1, **4**: δ_C 91.5]. In the HMBC spectrum, H_3-4′ and H_3-5′ were correlated with C-2′ (δ_C 97.1) and C-3′ (δ_C 70.7), and H-2′ was correlated with C-1′. These findings indicated the presence of a hydroxymethine at C-1′ in **5** instead of methylene in **4**. Thus, the structure of **5** was determined as shown.

Hyperxanthone C (**6**), $C_{18}H_{16}O_7$, exhibited a hydrogen-bonded hydroxyl proton [δ_H 13.45 (1H, s)], aromatic protons [δ_H 6.81 (1H, s), 6.31 and 6.19 (each 1H, brs)], and a 2-hydroxy-3-methyl-3-butenyl side chain [δ_H 5.14, 4.88 (each 1H, s), 4.53 (1H, dd, J = 10.2, 1.8 Hz), 4.20 (1H, dd, J = 13.2, 1.8 Hz), 3.10 (1H, dd, J = 13.2, 10.2 Hz), and 1.96 (3H, s)] in its ^1H NMR spectrum. Its ^{13}C NMR data were very similar to that of **4**, except for the chemical shifts

Table 1. ^{13}C NMR Data for **1** and 9-Hydroxyhyperforin-9,3-hemiacetal

1[a]		9-hydroxyhyperforin-9,3-hemiacetal[b]		**1**[a]		9-hydroxyhyperforin-9,3-hemiacetal[b]	
position	δ_C	position	δ_C	position	δ_C	position	δ_C
1	71.1	1	71.9			20	119.9
2	207.0	2	207.6			21	133.5
3	97.3	3	97.7			22	17.7
4	209.9	4	209.1			23	26.1
5	51.5	5	55.2	20	28.6	24	28.9
6	34.3	6	33.5	21	122.1	25	122.6
7	41.8	7	41.7	22	133.6	26	133.4
8	47.3	8	47.1	23	18.0	27	17.9
9	107.9	9	108.8	24	25.9	28	25.7
10	217.9	10	218.3	25	15.5	29	15.8
11	39.4	11	39.5	26	37.0	30	37.4
12	17.7	12	17.5	27	23.8	31	24.3
13	19.2	13	19.1	28	124.2	32	124.8
14	24.0	14	24.4	29	131.9	33	131.7
15	115.9	15	116.9	30	17.9	34	17.8
16	136.1	16	135.7	31	25.9	35	25.8
17	18.1	17	17.9				
18	25.8	18	25.9				
19	16.8	19	31.7				

[a] Measured in $CDCl_3$. [b] Measured in C_6D_6.

Table 2. NMR Data for **2**[a]

position	^1H (δ_H)	HMBC (^{13}C No.)	^{13}C (δ_C)
1			77.2
2			201.1
3			79.5
4			201.6
5			69.2
6	2.48 [1H, m]	4, 5, 8, 9	41.2
	2.42 [1H, m]		
7	1.72 [1H, m]	1, 3, 5	47.9
8			53.6
9			203.6
10	2.47 [2H, m]	1, 9, 11, 12	23.5
11	4.93 [1H, t (6.3)]	13, 14	119.5
12			134.5
13	1.63 [3H, s]	11, 12, 14	18.2
14	1.66 [3H, s]	11, 12, 13	26.1
15			193.4
16			135.1
17	7.22 [1H, d (7.5)]	15, 16, 18, 19, 21	129.3
18	7.29 [1H, dd (7.5, 7.3)]	16, 17, 19, 20	128.1
19	7.44 [1H, t (7.3)]	17, 18, 20, 21	132.6
20	7.29 [1H, dd (7.5, 7.3)]	16, 18, 19, 21	128.1
21	7.22 [1H, d (7.5)]	16, 17, 19, 20	129.3
22	2.53 [2H, d (7.3)]	4, 5, 6, 9, 23, 24	27.6
23	5.20 [1H, t (7.3)]	25, 26	118.8
24			135.0
25	1.68 [3H, s]	23, 24, 26	18.2
26	1.70 [3H, s]	23, 24, 25	26.1
27	4.20 [1H, brd (8.1)]	3, 4, 6, 7, 28, 29	51.4
28	5.01 [1H, d (8.1)]	3, 27, 30, 31	120.7
29			134.8
30	1.75 [3H, s]	28, 29, 31	18.5
31	1.77 [3H, s]	28, 29, 30	26.1
32	1.24 [3H, s]	1, 7, 8, 33	22.9
33	1.16 [3H, s]	1, 7, 8, 32	23.6

[a] Measured in $CDCl_3$. Coupling constants given (J in Hz) in parentheses.

Table 3. ^{13}C NMR Data (δ_C) for Enolic Tautomers of **3** (**3a/3b**) and **10** (**10a/10b**)[a]

position	**3a**	position	**10a**	position	**3b**	position	**10b**
1	62.0	1	66.1	1	65.3	1	69.0
2	197.8	2	197.8	2	194.7	2	193.5
3	114.8	3	116.5	3	114.8	3	116.5
4	194.4	4	193.2	4	198.3	4	198.3
5	62.7	5	63.4	5	58.3	5	58.9
6	40.4	6	40.6	6	38.7	6	39.4
7	46.5	7	46.9	7	46.1	7	46.7
8	48.5	8	48.9	8	47.6	8	48.3
9	209.2	9	207.9	9	209.2	9	207.9
10	12.9	10	27.2	10	13.4	10	26.6
		11	119.4			11	119.8
		12	135.0			12	135.0
		13	18.1			13	18.3
		14	26.1			14	26.0
11	197.0	15	196.8	11	196.7	15	197.9
12	137.0	16	137.3	12	136.8	16	137.3
13	129.0	17	129.5	13	128.9	17	126.6
14	128.0	18	127.9	14	128.1	18	127.7
15	132.8	19	132.5	15	132.8	19	132.9
16	128.0	20	127.9	16	128.1	20	127.7
17	129.0	21	129.5	17	128.9	21	126.6
18	31.6	22	31.9	18	32.1	22	31.2
19	119.9	23	120.6	19	119.0	23	120.9
20	134.9	24	134.8	20	135.1	24	134.8
21	18.3	25	18.3	21	18.3	25	18.4
22	26.2	26	26.3	22	26.2	26	26.2
23	29.2	27	29.2	23	29.3	27	29.4
24	123.8	28	124.2	24	124.1	28	124.8
25	133.0	29	132.7	25	133.1	29	132.7
26	17.9	30	17.8	26	18.0	30	17.8
27	25.9	31	25.8	27	26.0	31	25.9
28	27.2	32	27.0	28	27.0	32	26.9
29	23.1	33	23.0	29	22.5	33	22.5

[a] Measured in $CDCl_3$.

of C-6, C-7, and the side chain (Table 4). In the HMBC spectrum of **6**, H-5 was correlated to C-4b, C-6, C-7, and C-8a, and H_2-1′ was correlated with C-7 and C-8. These facts indicated that **6** is a 1,3,6,7-tetrahydroxyxanthone having a 2-hydroxyl-3-methyl-3-butenyl side chain at C-8.

The positive FABMS of hyperxanthone D (**7**) gave the quasi-molecular ion at *m/z* 329.0987 ($[M + H]^+$ calcd 329.1025), suggesting the molecular formula of $C_{18}H_{16}O_6$. The ^{13}C NMR data of **7** were similar to those of **6** except for the chemical shifts of C-4b−C-8a (Table 4). The ^1H NMR spectrum of **7** showed *ortho*-coupling protons at δ_H 7.32 and 7.26 (each 1H, d, J = 8.9 Hz). On consideration of the molecular formula of **6** and **7**, and the ^1H NMR differences, the structure of **7** was deduced to be a dehydroxy compound of **6**. The HMBC spectrum revealed the following correlations: H-5 (δ_H 7.26) with C-8a (δ_C 119.4) and C-7 (δ_C 153.5); H-6 (δ_H 7.32) with C-4b (δ_C 151.9) and C-8 (δ_C 126.8); H_2-1′ (δ_H 4.10, 3.11) with C-7, C-8, and C-8a. On the basis of these data, the structure of **7** was determined as shown.

Hyperxanthone E (**8**), $C_{18}H_{16}O_6$, showed hydroxyl (3421 cm^{-1}), conjugated carbonyl (1650 cm^{-1}), and aromatic (1613

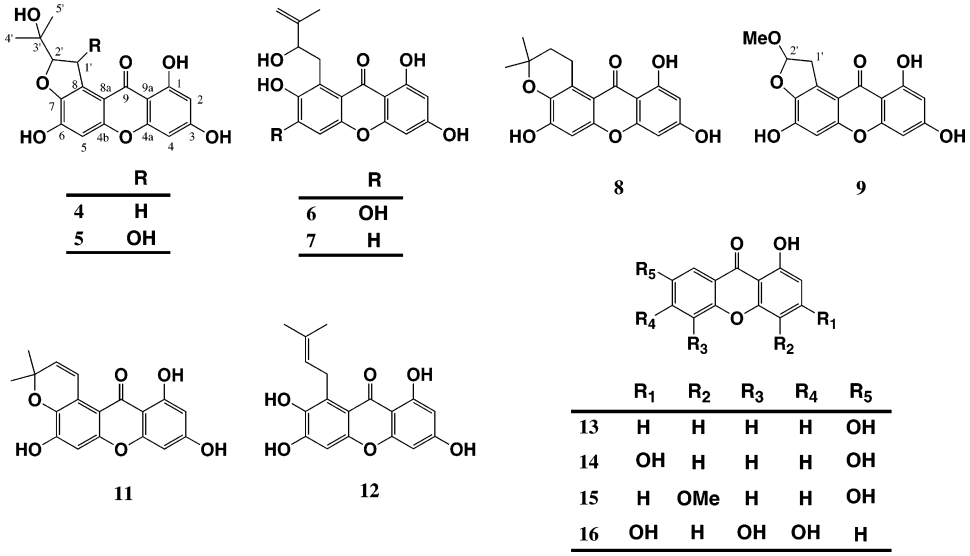

Figure 3.

Table 4. ^{13}C NMR Data (δ_C) for Xanthone Derivatives (**4**–**9**, **11**)

position	**4**[a]	**5**[a]	**6**[a]	**7**[a]	**8**[b]	**9**[a]	**11**[c]
1	164.2	163.9	164.3	164.2	164.7	164.1	164.4
2	98.1	98.5	98.1	98.7	98.5	98.1	98.3
3	165.0	165.6	165.0	167.7	165.7	165.1	165.1
4	93.9	94.1	93.3	93.8	93.9	94.1	93.5
4a	158.4	158.4	157.6	157.9	158.5	158.3	157.8
4b	152.9	153.6	153.8	151.9	154.3	153.3	153.3
5	102.8	104.3	101.7	117.2	101.1	103.1	103.1
6	148.3	149.9	154.0	124.7	153.5	148.5	153.7
7	145.8	146.3	142.7	153.5	142.0	143.8	138.4
8	126.9	127.9	127.2	126.8	131.0	125.0	120.5
8a	110.7	110.6	111.5	119.4	112.1	110.6	108.0
9	182.1	181.1	182.7	183.3	183.5	181.0	182.7
9a	103.2	103.2	103.3	103.1	104.0	103.1	103.5
1′	32.9	73.9	33.9	33.9	44.3	38.7	121.1
2′	91.5	97.1	77.9	77.5	23.0	109.2	133.2
3′	71.2	70.7	148.7	148.9	72.1		76.4
4′	25.4	25.6	109.7	109.6	29.1		26.7
5′	25.1	25.0	18.1	18.1	29.1		26.7
OMe						55.4	

[a] Measured in acetone-d_6. [b] Measured in methanol-d_4. [c] Measured in DMSO-d_6.

cm^{-1}) absorption bands in its IR spectrum. The ^1H and ^{13}C NMR data of **8** were similar to those of toxyloxanthone B (**11**)[20−22] except for the side chain (Table 4). The side chain of **8** is a pyran ring fused between C-7 and C-8 [δ_H 3.45 (2H, t, J = 8.0 Hz) 1.81 (2H, t, J = 8.0 Hz), 1.35 (6H, s); δ_C 72.1 44.3, 29.1 × 2, 23.0]. On the basis of these data the structure of **8** was determined as shown.

The ^1H and ^{13}C NMR spectroscopic data of hyperxanthone F (**9**), $C_{16}H_{12}O_7$, were very similar to those of **4** except for the side chain. The ^1H NMR data of the side chain showed the presence of one oxygenated methine signal [δ_H 5.86 (1H, dd, J = 6.6, 2.2 Hz)], one methylene signal attached to the aromatic ring [δ_H 3.77 (1H, dd, J = 18.3, 6.6 Hz) and 3.58 (1H, dd, J = 18.3, 2.2 Hz)], one methoxy signal [δ_H 3.51 (3H, s)], and one acetal carbon signal (δ_C 109.2). In the HMBC spectrum, H_2-1′ (δ_H 3.77 and 3.58) was correlated with C-8, H-2′ (δ_H 5.86) was correlated with C-7 (δ_C 143.8), and H_3-OMe (δ_H 3.51) was correlated with C-2′ (δ_C 109.2). Thus, the structure of **9** was determined as shown.

The following known compounds were identified by comparison with literature data: 7-epiclusianone (**10**),[19] toxyloxanthone B (**11**),[20−22] 1,3,6,7-tetrahydroxy-8-(3-methyl-2-butenyl)-9*H*-xanthene-9-one (**12**),[23] 1,7-dihydroxyxanthone (**13**),[24] 1,3,7-trihydroxyxanthone (**14**),[25] 1,7-dihydroxy-4-methoxyxanthone (**15**),[26] 1,3,5,6-tetrahydroxyxanthone (**16**),[27] luteolin (**17**),[28] quercetine (**18**),[28] hyperin (**19**),[28] quercitrin (**20**),[29] avicularin (**21**),[28] quercetine-3-*O*-β-L-arabinoside (**22**),[28] myricetin (**23**),[30] myricetin-3-*O*-α-L-rhamnoside (**24**),[31] I3,II8-biapigenin (**25**).[32]

Table 5. Cytotoxicity Data for Compounds against Human Tumor Cells

	cell lines (IC_{50}, mcg/mL)[a]	
compound	A549[b]	MCF-7[b]
1	>20 (49)[c]	17.8
2	13.7	10.0
3	9.2	15.0
4	>20 (26)	>20 (27)
6	9.3	11.2
7	>20 (43)	>20 (34)
8	18.5	19.3
10	13.7	10.0
11	>20 (28)	>20 (17)
12	18.5	18.4
13	14.5	19.5
15	8.5	15.2
16	10.0	9.3
17	12.9	14.3
18	>20 (21)	19.5
19	NA[d]	NA
20	>20 (12)	>20 (18)
21	NA	NA
22	>20 (11)	>20 (17)
23	14.8	4.7
24	>20 (13)	11.2
25	>20 (27)	>20 (26)

[a] IC_{50} = concentration that causes a 50% reduction in absorbance at 562 nm relative to untreated cells using the SRB assay. [b] A549, lung; MCF-7, breast. [c] If inhibition is <50% at 20 mcg/mL, then percent inhibition observed is given as the value in parentheses. [d] NA: not active at 20 mcg/mL.

Compounds **1**−**4**, **6**−**8**, **10**−**13**, and **15**−**25** were assayed for cytotoxicity using a reported procedure.[33] Compounds **2**, **3**, **6**, **8**, **10**, **12**−**16**, and **23** showed moderate activity as inhibitors of human tumor cell replication (Table 5). Also, the same isolated compounds were assayed for anti-HIV activity,[34] but showed no effective results.

Experimental Section

General Experimental Procedures. NMR experiments were run on a Bruker ARX-400 instrument (^1H NMR 400 MHz,

^{13}C NMR 100 MHz) using TMS as internal standard. Mass spectra were obtained on a JEOL JMSD-300 instrument. Chromatography column: silica gel 60 (Merck), Sephadex LH-20 (Pharmacia), and Toyopearl HW-40 (TOSOH). GPC: Shodex H-2001, 2002, $CHCl_3$; Asahipak, GS-310 2G, MeOH. Silica gel HPLC: YMC-Pack SIL-06 SH-043-5-06, 250 × 20 mm. IR spectra were recorded on a 1720 infrared Fourier transform spectrometer (Perkin-Elmer), and UV spectra were measured on a UV 2100 UV−vis recording spectrometer (Shimadzu) and a 330 spectrometer (Hitachi). Optical rotations were measured with a JASCO DIP-370 digital polarimeter.

Plant Material. The dried aerial parts of *Hypericum scabrum* (2.1 kg) were collected in June 1998 in Chimgan, Uzbekistan. Herbarium specimens (ESM-3910) were deposited in the Herbarium of the Academy of Science, Institute of Botany and Botanical Garden, Uzbekistan.

Extraction and Isolation. The dried aerial parts of *H. scabrum* (2.1 kg) were crushed and extracted three times with MeOH at 60 °C. The MeOH extracts were concentrated in vacuo to give a residue (520 g), which was partitioned between EtOAc and H_2O. The EtOAc layer was concentrated to give a residue (100 g), which was loaded on a silica gel column and eluted with different solvents of increasing polarity (*n*-hexane−EtOAc; EtOAc−MeOH) to give 41 fractions (1−41). Fraction 2 (5.8 g) was subjected to a silica gel column with *n*-hexane−acetone and a silica gel HPLC (*n*-hexane−EtOAc, 95:5) and purified by GPC ($CHCl_3$) to give **1** (271 mg). Fraction 3 (3.1 g) was subjected to a Toyopearl column with $CHCl_3$−MeOH (2:1) to give three fractions (3.1−3.3). Fraction 3.2 was chromatographed on a silica gel column with *n*-hexane−EtOAc to give six fractions (3.2.1−3.2.6) containing **10** (1.02 g). Fraction 3.2.2 was applied to a silica gel HPLC with *n*-hexane−EtOAc (9:1) and a GPC with $CHCl_3$ and purified by silica gel HPLC with *n*-hexane−$CHCl_3$ (3:2) to give **2** (12 mg). Fraction 4 (1.3 g) was chromatographed on a silica gel column with *n*-hexane−EtOAc and a Toyopearl column with $CHCl_3$−MeOH (2:1) to give **3** (27 mg). Fraction 9 (1.3 g) was recrystallized from MeOH to give **13** (250 mg). Fraction 15 (3.9 g) was subjected to a silica gel column eluted with $CHCl_3$−MeOH to give seven fractions (15.1−15.7). Fraction 15.2 was separated by a Sephadex LH-20 chromatography column with MeOH to give five fractions (15.2.1−15.2.5). Fraction 15.2.4 on a silica gel HPLC column with *n*-hexane−EtOAc (1:1) yielded **15** (19 mg). Fraction 15.3 was recrystallized from MeOH to give **11** (79 mg) and a residue. This residue was chromatographed on a GPC column with MeOH and an ODS column with MeOH−H_2O (9:1) and isolated by preparative TLC with $CHCl_3$−MeOH−H_2O (7:1:0.1) to yield **7** (12 mg). Fraction 17 (3.1 g) was subjected to a silica gel column with $CHCl_3$−MeOH and a Sephadex LH-20 chromatography column with MeOH and purified by a GPC column with MeOH to give **14** (7 mg). Fraction 19 (2.3 g) was separated by a Sephadex LH-20 chromatography column with MeOH and an ODS (MeOH−H_2O, 7:3) to give **6** (18 mg) and **12** (14 mg). Fraction 21 (1.0 g) was subjected to a silica gel column with $CHCl_3$−MeOH to give **18** (200 mg). Fraction 23 (9.9 g) was subjected to a Sephadex LX-20 chromatography column with MeOH to give five fractions (23.1−23.5). Fraction 23.2 was applied to a silica gel column with $CHCl_3$−MeOH and a GPC column with MeOH to give **5** (9 mg) and **8** (15 mg). Fraction 23.4 was subjected to a silica gel column with $CHCl_3$−MeOH to give nine fractions (23.4.1−23.4.9) including **23** (223 mg) and **25** (1.20 g). Fraction 23.4.2 on a GPC column with MeOH yielded **4** (17 mg), **9** (5 mg), and **17** (7 mg). Fraction 23.4.4 was applied to a Sephadex LH-20 chromatography column with acetone and purified by a GPC column with MeOH to give **16** (10 mg). Fraction 30 (7.9 g) was subjected to a Sephadex LH-20 chromatography column with MeOH to give four fractions (30.1−30.4). Fraction 30.3 was chromatographed on a silica gel column with $CHCl_3$−MeOH to give five fractions (30.3.1−30.3.5) including **20** (420 mg). Fraction 30.3.2 was subjected to a GPC column with MeOH to give **22** (67 mg) and **21** (27 mg). Fraction 30.3.5 was isolated by a GPC column with MeOH to give **24** (162 mg). Fraction 33 (3.0 g) was chromatographed on a Sephadex LH-20 chromatography column with MeOH and a GPC column with MeOH to yield **19** (19 mg).

Hyperibone J (1): colorless oil; $[\alpha]_D$ +16.9° (*c* 0.3 $CHCl_3$); IR (KBr) ν_{max} cm^{-1} 3323, 2970, 2930, 1777, 1742, 1678, 1451, 1385, 1331, 1301, 1119; HRFABMS *m/z* 499.3461, $[M + H]^+$ (calcd for $C_{31}H_{47}O_5$, 499.3423); ^{1}H NMR ($CDCl_3$) δ_H 7.70 (1H, brs, OH-9), 5.02 (1H, t, *J* = 7.3 Hz, H-15), 4.96 (1H, t, *J* = 5.3 Hz, H-28), 4.90 (1H, t, *J* = 6.8 Hz, H-21), 3.18 (1H, sept, *J* = 6.6 Hz, H-11), 2.72 (1H, dd, *J* = 15.2, 7.3 Hz, H-14a), 2.53 (1H, dd, *J* = 15.2, 7.3 Hz, H-14b), 2.25 (1H, m, H-27a), 2.08 (1H, m, H-20), 1.86 (1H, dd, *J* = 14.3, 3.4 Hz, H-6eq), 1.80 (1H, m, H-27), 1.71 (1H, m, H-26a), 1.67 (3H, s, H_3-24), 1.64 (3H, s, H_3-31), 1.62 (1H, m, H-20), 1.62 (6H, s, H_3-17 and H_3-18), 1.57 (1H, m, H-26b), 1.56 (3H, s, H_3-30), 1.53 (3H, s, H_3-23), 1.28 (1H, m, H-6ax), 1.12 (3H, s, H_3-19), 1.08 (3H, d, *J* = 6.6 Hz, H_3-12), 1.04 (1H, m, H-7), 0.98 (3H, s, H_3-25), 0.91 (3H, d, *J* = 6.6 Hz, H_3-13); ^{13}C NMR ($CDCl_3$) Table 1.

Hyperibone K (2): colorless gum; $[\alpha]_D$ +22.3° (*c* 0.3 $CHCl_3$); IR (KBr) ν_{max} cm^{-1} 2928, 1701, 1448, 1377, 1255, 1146; UV (MeOH) λ_{max} nm (log ϵ) 246 (4.0); HRFABMS *m/z* 499.2873, $[M - H]^-$ (calcd for $C_{33}H_{39}O_4$, 499.2848); ^{1}H NMR ($CDCl_3$) Table 2; ^{13}C NMR ($CDCl_3$) Table 2.

Hyperibone L (3): red gum; $[\alpha]_D$ +69.5° (*c* 0.2 $CHCl_3$); IR (KBr) ν_{max} cm^{-1} 3349, 2917, 2852, 1732, 1673, 1549, 1450, 1373, 1288; UV (MeOH): λ_{max} nm (log ϵ) 279 (3.9), 248 (3.9); HREIMS *m/z* 448.2589, $[M]^+$ (calcd for $C_{29}H_{36}O_4$, 448.2614).

Hyperibone L-a (3a): ^{1}H NMR ($CDCl_3$) 15.48 (1H, brs, OH-2), 7.54 (1H, t, *J* = 7.1 Hz, H-15), 7.49 (2H, d, *J* = 7.9 Hz, H-13 and H-17), 7.37 (2H, dd, *J* = 7.9, 7.13 Hz, H-14 and H-16), 5.24 (1H, t, *J* = 7.0 Hz, H-19), 4.87 (1H, t, *J* = 6.4 Hz, H-24), 2.55 (1H, dd, *J* = 13.9, 8.6 Hz, H-18a), 2.41 (1H, dd, *J* = 13.9, 5.7 Hz, H-18b), 2.26 (1H, m, H-23a), 2.16 (1H, dd, *J* = 14.2, 1.7 Hz, H-6eq), 2.04 (1H, dd, *J* = 14.2, 6.9 Hz, H-6ax), 1.92 (1H, m, H-23b), 1.77 (3H, s, H_3-22), 1.66 (3H, s, H_3-21), 1.62 (3H, s, H_3-27), 1.53 (1H, m, H-7), 1.43 (3H, s, H_3-26), 1.42 (3H, s, H_3-10), 1.28 (3H, s, H_3-29), 1.04 (3H, s, H_3-28); ^{13}C NMR ($CDCl_3$) Table 3.

Hyperibone L-b (3b): ^{1}H NMR ($CDCl_3$) 17.70 (1H, brs, OH-4), 7.54 (1H, m, H-15), 7.49 (2H, m, H-13 and H-17), 7.41 (2H, m, H-14 and H-16), 5.14 (1H, t, *J* = 6.6 Hz, H-19), 4.90 (1H, m, H-24), 2.61 (2H, m, H_2-18), 2.31 (2H, m, H_2-23), 2.10 (1H, m, H-23a), 1.91 (1H, m, H-23b), 1.72 (3H, s, H_3-22), 1.70 (3H, s, H_3-27), 1.68 (3H, s, H_3-21), 1.53 (3H, s, H_3-26), 1.50 (1H, m, H-7), 1.29 (3H, s, H_3-10), 1.09 (3H, s, H_3-29), 0.95 (3H, s, H_3-28); ^{13}C NMR ($CDCl_3$) Table 3.

Hyperxanthone A (4): yellow powder; $[\alpha]_D$ −15.6° (*c* 0.3 acetone); IR (KBr) ν_{max} cm^{-1} 3423, 1650, 1626, 1503, 1468, 1280, 1172, 1136, 993; UV (MeOH) λ_{MAX} nm (log ϵ) 370 (3.9), 314 (4.0), 257 (4.3), 239 (4.3); HREIMS *m/z* 344.0913, $[M]^+$ (calcd for $C_{18}H_{16}O_7$, 344.0896); ^{1}H NMR (acetone-d_6) δ_H 13.19 (1H, s, OH-1), 6.75 (1H, s, H-5), 6.25 (1H, d, *J* = 1.6 Hz, H-4), 6.19 (1H, d, *J* = 1.6 Hz, H-2), 4.80 (1H, t, *J* = 9.2, H-2′), 3.72 (2H, d, *J* = 9.2 Hz, H_2-1′), 1.30 (3H, s, H_3-4′), 1.26 (3H, s, H_3-5′); ^{13}C NMR (acetone-d_6) Table 4.

Hyperxanthone B (5): yellow powder; $[\alpha]_D$ −7.1° (*c* 0.2 acetone); IR (KBr) ν_{max} cm^{-1} 3737, 1639, 1500, 1362, 1281, 1161; UV (MeOH): λ_{MAX} nm (log ϵ) 375 (4.1), 320 (3.9), 258 (4.3), 238 (4.3); HREIMS: *m/z* 360.0852, $[M]^+$ (calcd for $C_{18}H_{16}O_8$, 360.0845); ^{1}H NMR (acetone-d_6) δ_H 12.78 (1H, s, OH-1), 6.90 (1H, s, H-5), 6.39 (1H, brs, H-4), 6.24 (1H, brs, H-2), 5.89 (1H, d, *J* = 5.5 Hz, H-1′), 4.47 (1H, d, *J* = 5.5 Hz, H-2′), 1.35 (3H, s, H_3-4′), 1.32 (3H, s, H_3-5′); ^{13}C NMR (acetone-d_6) Table 4.

Hyperxanthone C (6): yellow powder; $[\alpha]_D$ −9.7° (*c* 0.1 acetone); IR (KBr) ν_{max} cm^{-1} 3380, 1650, 1612, 1505, 1460, 1276, 1165, 830; UV (MeOH) λ_{max} nm (log ϵ) 370 (4.1), 317 (4.0), 257 (4.3), 239 (4.3); HRFABMS *m/z* 343.0818, $[M - H]^-$ (calcd for $C_{18}H_{15}O_7$, 343.0808); ^{1}H NMR (acetone-d_6) δ_H 13.45 (1H, s, OH-1), 6.81 (1H, s, H-5), 6.31 (1H, brs, H-4), 6.19 (1H, brs, H-2), 5.14 (1H, s, H-4′a), 4.88 (1H, s, H-4′b), 4.53 (1H, dd, *J* = 10.2, 1.8 Hz, H-2′), 4.20 (1H, dd, *J* = 13.2, 1.8 Hz, H-1′a), 3.10 (1H, dd, *J* = 13.2, 10.2 Hz, H-1′b), 1.96 (3H, s, H_3-5′); ^{13}C NMR (acetone-d_6) Table 4.

Hyperxanthone D (7): yellow powder; $[\alpha]_D$ −6.8° (*c* 0.2 acetone); IR (KBr) ν_{max} cm^{-1} 3273, 1646, 1608, 1585, 1469,

1270, 1167, 1087; UV (MeOH) λ_{max} nm (log ϵ) 374 (3.9), 313 (4.2), 254 (4.6), 240 (4.5); HRFABMS *m/z* 329.0987, $[M + H]^+$ (calcd for $C_{18}H_{17}O_6$, 329.1025); ^{1}H NMR (acetone-d_6) δ_H 13.25 (1H, s, OH-1), 7.32 (1H, d, J = 8.9 Hz, H-6), 7.26 (1H, d, J = 8.9 Hz, H-5), 6.32 (1H, d, J = 1.6 Hz, H-4), 6.19 (1H, d, J = 1.6 Hz, H-2), 5.12 (1H, s, H-4′a), 4.74 (1H, s, H-4′b), 4.51 (1H, dd, J = 10.1, 2.1 Hz, H-2′), 4.10 (1H, dd, J = 13.1, 2.1 Hz, H-1′a), 3.11 (1H, dd, J = 13.1, 10.1 Hz, H-1′b), 1.95 (3H, s, H_3-5′); ^{13}C NMR (acetone-d_6) Table 4.

Hyperxanthone E (8): yellow powder; IR (KBr) ν_{max} cm^{-1} 3421, 1650, 1613, 1505, 1460, 1281, 1164; UV (MeOH): λ_{max} nm (log ϵ) 363 (3.9), 313 (4.0), 248 (4.2), 238 (4.2); HREIMS *m/z* 328.0945, $[M]^+$ (calcd for $C_{18}H_{16}O_6$, 328.0947); ^{1}H NMR (CD_3OD) δ_H 6.71 (1H, s, H-5), 6.22 (1H, d, J = 1.8 Hz, H-4), 6.20 (1H, d, J = 1.8 Hz, H-2), 3.45 (2H, t, J = 8.0 Hz, H-1′), 1.81 (2H, t, J = 8.0 Hz, H-2′), 1.35 (6H, s, H_3-4′ and H_3-5′); ^{13}C NMR (CD_3OD) Table 4.

Hyperxanthone F (9): yellow powder; $[\alpha]_D$ −15.6° (*c* 0.1 acetone); IR (KBr) ν_{max} cm^{-1} 3402, 1649, 1604, 1473, 1304, 1172, 1065; UV (MeOH) λ_{max} nm (log ϵ) 370 (4.0), 314 (4.4), 254 (4.4), 240 (4.3); HREIMS *m/z* 316.0580, $[M]^+$ (calcd for $C_{16}H_{12}O_7$, 316.0583); ^{1}H NMR (acetone-d_6) δ_H 13.07 (1H, s, OH-1), 6.83 (1H, s, H-5), 6.34 (1H, d, J = 1.4 Hz, H-4), 6.20 (1H, d, J = 1.4 Hz), 5.86 (1H, dd, J = 6.6, 2.2 Hz, H-2′), 3.77 (1H, dd, J = 18.3, 6.6 Hz, H-1′a), 3.58 (1H, dd, J = 18.3, 2.2 Hz, H-1′b), 3.51 (3H, s, H_3-OMe); ^{13}C NMR (acetone-d_6) Table 4.

Cytotoxicity Assay. All stock cultures were grown in T-25 flasks (5 mL of RPMI-1640 medium supplemented with 25 mM HEPES, 0.25% sodium bicarbonate, 10% fetal bovine serum, and 100 μg/mL kanamycin). Freshly trypsinized cell suspensions were seeded in 96-well microtiter plates at densities of 1500−7500 cells per well with test compounds from DMSO-diluted stock. After 3 days in culture, cells attached to the plastic subtratum were fixed with cold 50% trichloroacetic acid and then stained with 0.4% sulforhodamine B (SRB). The absorbance at 562 nm was measured using a microplate reader after solubilizing the bound dye. The IC_{50} is the concentration of test compound that reduced cell growth by 50% over a 3-day assay period.

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NP040024+