Geiparvarin Analogues: Synthesis and Anticancer Evaluation of α-Methylidene-γ-butyrolactone-Bearing Coumarins

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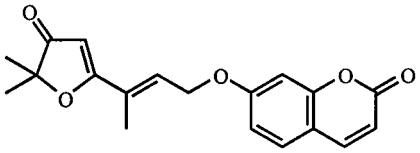
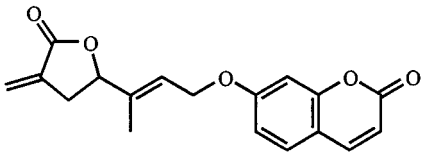
To determine some of the structural features of geiparvarin that account for its cytostatic activity *in vitro*, certain geiparvarin analogues modified in the furan-3(2*H*)-one moiety and the alkenyloxy substituent were synthesized and tested against the growth of 60 human cancer cell lines derived from nine cancer-cell types. These compounds demonstrated a strong growth-inhibitory activity against leukemia cell lines but were relatively inactive against non-small-cell lung cancers and CNS cancers. Comparison of the mean log GI_{50} values of γ-[(*E*)-1-methylprop-1-enyl]-α-methylidene-γ-butyrolactones **7**–**9** revealed that 7-[(*E*)-3-(2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl)but-2-enyloxy]-2*H*-1-benzopyran-2-one (**8**; −5.47) was more active than its 6-substituted counterpart **7** (−5.21) and its 3-chloro-4-methyl derivative **9** (−5.31) and had a potency similar to that of geiparvarin (log GI_{50} = −5.41). These results indicated that the furan-3(2*H*)-one moiety of geiparvarin could be replaced by an α-methylidene-γ-butyrolactone unit without losing the anticancer potency, and that the best substitution site at the coumarin moiety was C(7). The alkenyloxy substituent of **8** was also replaced by a methoxy substituent. Among these α-methylidene-γ-butyrolactones, 7-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one (**11**) was the most potent with a mean log GI_{50} value of −5.83 and a range value of 132 ($10^{2.12}$).

Introduction. – Geiparvarin, a naturally occurring product isolated from the leaves of *Geijera parviflora* LINDL in 1967 [1], has been shown to possess a significant inhibitory activity against a variety of cell lines including sarcoma 180, *Lewis* lung carcinoma, P-388 lymphocytic leukemia, and *Walker* 256 carcinosarcoma [2][3a]. Geiparvarin is constituted of three moieties, namely, the furan-3(2*H*)-one part, an unsaturated alkenyloxy substituent, and the coumarin moiety. The structural requirement for the cytotoxicity is the furan-3(2*H*)-one moiety, which acts as an alkylating agent by a *Michael*-type reaction (1,6-conjugate addition) with bionucleophiles. Due to its unique structural features, as well as its interesting anticancer activity, geiparvarin became a challenging target of synthesis [3]. Its analogues have also been prepared and evaluated for anticancer activity [4]. For the past few years, we were particularly interested in synthesizing α-methylidene-γ-butyrolactones bearing heterocycles and exploring their cardiovascular activities [5–13]. The present report describes the preparation and anticancer evaluation of new geiparvarin analogues in which the furan-3(2*H*)-one moiety was replaced by the α-methylidene-γ-butyrolactone moiety (see, e.g., **8**). The reason for this modification is to interrupt the conjugation between the *Michael* acceptor and the alkenyl C=C bond, because the introduction of an extra olefinic C=C bond, which increases the ability of the substrate to afford *Michael*-type

adducts, usually gives compounds which are much less active than geiparvarin [4b]. α-Methylidene-γ-butyrolactone is a functional unit in a wide range of natural products and exerts its biological activities by a *Michael*-type reaction with bionucleophiles, a mode of action in resemblance to the furan-3(2*H*)-one unit [14][15]. Furthermore, the modification of the alkenyloxy substituent to a simple methoxy substituent was also undertaken (see **10** and **11**). A number of possible drug candidates derived from the combination of the α-methylidene-γ-butyrolactone moiety, the methoxy substituent, and a carrier moiety were synthesized in view of the development of effective clinical anticancer drugs [16–23].



Geiparvarin



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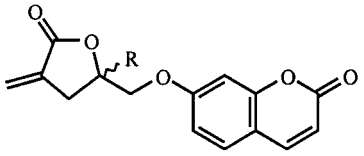
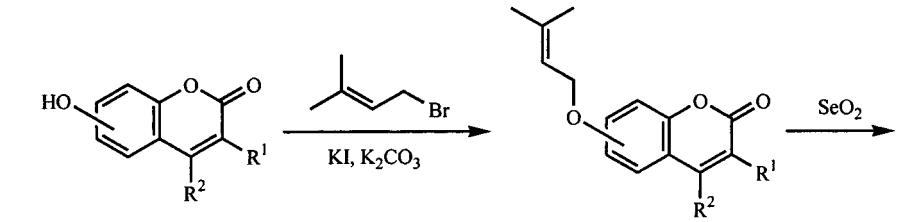


10 R = Me
11 R = Ph

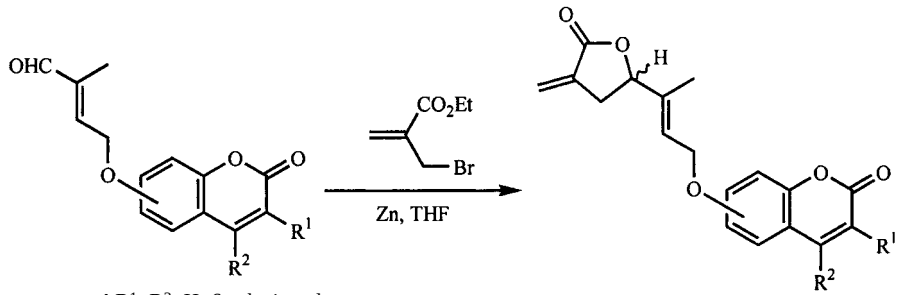
Results and Discussion. – The γ-[(*E*)-1-methylprop-1-enyl]-α-methylidene-γ-butyrolactones **7**–**9** were prepared from 6-hydroxycoumarin [24], 7-hydroxycoumarin [25], and 3-chloro-7-hydroxy-4-methylcoumarin [26], respectively, *via* **1**–**3** and **4**–**6** (*Scheme*). Thus, 6-hydroxycoumarin (from 2,5-dihydroxybenzaldehyde) was alkylated with 1-bromo-3-methylbut-2-ene to give 6-(3-methylbut-2-enyloxy)-2*H*-1-benzopyran-2-one (**1**). The latter was transformed into (*E*)-2-methyl-4-(2-oxo-2*H*-1-benzopyran-6-yloxy)but-2-enal (**4**) by chemo- and stereoselective allylic oxidation utilizing selenium dioxide. Reaction of the aldehyde **4** with ethyl 2-(bromomethyl)acrylate in dry THF (*Reformatsky*-type condensation) gave the target (butenyloxy)coumarin **7** in 33% overall yield. The methoxy-substituted analogues 7-[(2,3,4,5-tetrahydro-2-methyl-4-methylidene-5-oxofuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one (**10**) and its phenyl counterpart **11** were prepared from their respective 2-substituted 2-oxoethoxy precursors as described previously [6].

All compounds were evaluated *in vitro* against 60 human cancer cell lines derived from nine cancer-cell types (leukemia, non-small-cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer). For each compound, dose-response curves for each cell line were measured with five

Scheme



1 R^1=R^2=H; 6-substituted
2 R^1=R^2=H; 7-substituted
3 R^1=Cl, R^2=Me; 7-substituted



4 R^1=R^2=H; 6-substituted
5 R^1=R^2=H; 7-substituted
6 R^1=Cl, R^2=Me; 7-substituted

7 R^1=R^2=H; 6-substituted
8 R^1=R^2=H; 7-substituted
9 R^1=Cl, R^2=Me; 7-substituted

different drug concentrations, and the concentration causing 50% cell growth inhibition (GI_{50}) and 50% cell death (LC_{50}, −50% growth), compared with the control, was calculated. The *in vitro* inhibitory activity of α-methylidene-γ-butyrolactones **7**–**11** against selective cancer cells is outlined in *Table 1*. These compounds demonstrated a strong growth-inhibitory activity against leukemia cell lines but were relatively inactive against non-small-cell lung cancers and CNS cancers. Comparison of the mean log GI_{50} values of **7**–**9** revealed that 7-[(*E*)-3-(2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl)but-2-enyloxy]-2*H*-1-benzopyran-2-one (**8**; −5.47) was more active than its 6-substituted counterpart **7** (−5.21) and its 3-chloro-4-methyl derivative **9** (−5.31) and had a potency similar to that of geiparvarin (log GI_{50} = −5.41)[1]). These results indicated that the furan-3(2*H*)-one moiety of geiparvarin could be replaced by the α-methylidene-γ-butyrolactone moiety without losing the anticancer potency, and that the best substitution site at coumarin was C(7).

With this in mind, we then turned our attention to the modification of the 7-alkenyloxy substituent of **8**, *i.e.*, to the methoxy analogues **10** and **11** [6]. The substituted 7-methoxy-2*H*-1-benzopyran-2-one **11** exhibited not only a strong cancer cell inhibitory activity with a mean log GI_{50} value of −5.83 (*Table 1*), but also a good selectivity in

[1]) Data obtained from the *National Cancer Institute* (*NCI*), *U.S. National Institutes of Health.*

Table 1. *Inhibition of* in vitro *Cancer-Cell Lines by α-Methylidene-γ-butyrolactones* (log GI_{50} [M])[a])

Cell Line	**7**	**8**	**9**	**10**	**11**
Leukemia					
CCRF-CEM	– 5.63	– 5.47	– 5.67	– 6.39[b])	– 6.92[b])
RPMI-8226	– 5.76[b])	– 6.16[b])	– 5.78[b])	– 6.02	– 6.71
Non-small-cell lung cancer					
A549/ATCC	– 4.63[c])	– 5.01	– 4.73	– 4.81	– 5.10
HOP-62	– 4.84	– 5.10	– 4.94	– 4.76	– 4.88
Colon cancer					
COLO 205	– 5.36	– 5.75	– 5.30	– 5.79	– 6.46
SW-620	– 5.69	– 5.70	– 5.65	– 5.68	– 6.62
CNS cancer					
SF-295	– 4.82	– 4.94	– 4.78	– 4.86	– 5.36
SNB-19	– 4.77	– 4.94	– 4.86	– 4.59[c])	– 4.80[c])
Melanoma					
LOX IMVI	– 5.71	– 5.94	– 5.74	– 5.47	– 5.85
MALME-3M	– 5.72	– 5.81	– 5.69	– 5.64	– 5.76
Ovarian cancer					
IGROV1	– 5.60	– 5.55	– 5.68	– 5.45	– 5.84
SK-OV-3	– 4.71	– 4.92	– 4.69[c])	– 4.84	– 5.36
Renal cancer					
ACHN	– 5.54	– 5.65	– 5.55	– 4.98	– 5.56
TK-10	– 5.49	– 5.20	– 5.54	– 5.76	– 5.82
Prostate cancer					
PC-3	– 5.02	– 5.34	– 5.37	– 5.41	– 5.80
DU-145	– 5.10	– 5.19	– 5.39	– 5.62	– 5.82
Breast cancer					
HS-578T	– 5.21	– 5.24	– 4.99	– 4.80	– 5.07
MCF 7/ADR-RES	– 4.82	– 4.74[c])	– 4.89	– 5.68	– 5.60
Mean[d])	– 5.21	– 5.47	– 5.31	– 5.40	– 5.83
Range[e])	1.13	1.42	1.09	1.80	2.12

[a]) GI_{50}: Drug molar concentration causing 50% cell-growth inhibition. Data obtained from NCI's *in vitro* disease-oriented tumor-cells screen [27]. [b]) Most sensitive cell. [c]) Least sensitive cell. [d]) Mean values over all cell lines tested. Theses cell lines are: leukemia (CCRF-CEM, HL-60 (TB), K-562, MOLT-4, PRMI-8226, and SR); non-small-cell lung cancer (A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, and NCI-H522); colon cancer (COLC 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, and SW-620); CNS cancer (SF-268, SF-295, SF-539, SNB-19, SNB-75, and U251); melanoma (LOX IMVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-5, and UACC-257); ovarian cancer (IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OV-3); renal cancer (786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, and UO-31); prostate cancer (PC-3 and DU-145); breast cancer (MCF 7, MCF 7/ADR-RES, MDA-MB-231/ATCC, HS 578T, MDA-MB-435, MDA-N, and T-47D). [e]) Ratio of the least sensitive cell[c]) to the most sensitive cell[b]).

which the range value, *i.e.*, the ratio log GI_{50} for the CNS SNB-19 cancer cell (– 4.80, the least sensitive) and the CCRF-CEM leukemia cell (– 6.92, the most sensitive), is 132 ($10^{2.12}$). In comparison, geiparvarin has a range value of 13 ($10^{1.12}$)[1]) and the range value for **8** is 26 ($10^{1.42}$).

To better understand how these α-methylidene-γ-butyrolactones inhibit the cancer cells, *i.e.*, by cytostatic or cytotoxic action, the GI_{50} and LC_{50} values for **8**, **10**, and **11**

against leukemia cell lines were compared (*Table 2*). For compound **8**, the GI_{50} values ranged from 0.68 to 3.41 μM demonstrating a strong cytostatic effect. On the contrary, its LC_{50} values of 100 μM for all the cell lines tested indicated a low cytotoxic potential. The same trend of a strong cytostatic effect (low GI_{50} value) and a low cytotoxic potency (high LC_{50} value) was observed for **10** and **11**.

Table 2. *Comparison of* GI_{50} *for* **8**, **10**, *and* **11** *against Leukemia Cell Lines*[a])

	GI_{50} (LC_{50}) [μM]		
	8	**10**	**11**
CCRF-CEM	3.41 (> 100)	0.40 (18.5)	0.12 (n.d.)[b])
HL-60 (TB)	1.70 (> 100)	0.51 (> 100)	0.10 (> 100)
K-562	2.12 (> 100)	0.98 (> 100)	0.17 (n.d.)
MOLT-4	2.74 (> 100)	n.d.	1.10 (> 100)
RPMI-8226	0.68 (> 100)	0.96 (> 100)	0.20 (> 100)
SR	1.29 (> 100)	2.93 (> 100)	0.60 (> 100)

[a]) GI_{50}: Drug molar concentration causing 50% cell-growth inhibition. LC_{50}: Drug molar concentration causing 50% cell death. [b]) Not determined.

In summary, we have synthesized the geiparvarin analogues **7**–**11** with α-methylidene-γ-butyrolactone moieties. These compounds demonstrated a strong cytostatic effect against the growth of leukemia cell lines. Among them, 7-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one (**11**) was the most potent with a mean log GI_{50} value of − 5.83 and a range value of 132 ($10^{2.12}$).

Experimental Part

General. TLC: precoated (0.2 mm) silica gel *60 F-254* plates from *EM Laboratories*, *Inc.*; detection by UV light (254 nm). M.p.: *Electrothermal IA9100* digital melting-point apparatus; uncorrected. IR Spectra (cm^{-1}): *Hitachi-260-30* IR spectrophotometer. ^{1}H- and ^{13}C-NMR Spectra: *Varian-Unity-400* spectrometer at 400 and 100 MHz or *Varian-Gemini-200* spectrometer at 200 and 50 MHz, chemical shifts δ in ppm with $SiMe_4$ as an internal standard (= 0 ppm), coupling constants *J* in Hz. Elemental analyses: *Heraeus-CHN-O-Rapid* elemental analyzer.

*6-(3-Methylbut-2-enyloxy)-2*H*-1-benzopyran-2-one* (**1**). To a soln. of 6-hydroxycoumarin (= 6-hydroxy-2*H*-1-benzopyran-2-one) [24] (2.43 g, 15 mmol) in acetone (80 ml), K_2CO_3 (2.07 g, 15 mmol), KI (0.50 g, 3 mmol), and 1-bromo-3-methylbut-2-ene (2.24 g, 15 mmol) were added. The resulting mixture was refluxed for 5 h (TLC monitoring). After cooling, the solvent was evaporated, the residue poured into H_2O (100 ml) and extracted with CH_2Cl_2 (3 × 100 ml), the combined extract washed with brine, dried (Na_2SO_4), and evaporated, and the solid residue crystallized from Et_2O: **1** (2.97 g, 86%). M.p. 129–130°. IR (KBr): 1707, 1566, 1441, 1281. ^{1}H-NMR ($CDCl_3$): 1.76 (*s*, Me); 1.81 (*s*, Me); 4.54 (*d*, *J* = 6.4, CH_2O); 5.49 (*m*, 1 H, CH=); 6.42 (*d*, *J* = 9.6, H–C(3)); 6.93 (*d*, *J* = 2.8, H–C(5)); 7.12 (*dd*, *J* = 9.2, 2.8, H–C(7)); 7.26 (*d*, *J* = 9.2, H–C(8)); 7.56 (*d*, *J* = 9.6, H–C(4)). ^{13}C-NMR ($CDCl_3$): 18.26, 25.82 (C(4′), C(5′)); 65.34 (C(1′)); 111.10 (C(5)); 117.04 (C(8)); 117.86 (C(3)); 119.14 (C(2′)); 119.18 (C(4a)); 120.15 (C(7)); 138.87 (C(3′)); 143.26 (C(4)); 148.46 (C(8a)); 155.37 (C(6)); 161.04 (C(2)). Anal. calc. for $C_{14}H_{14}O_3$: C 70.03, H 6.13; found: C 69.98, H 6.22.

*3-Chloro-4-methyl-7-(3-methylbut-2-enyloxy)-2*H*-1-benzopyran-2-one* (**3**). Prepared as described for **1**: 82% yield. M.p. 121–123°. IR (KBr): 1718, 1613, 1256, 1207. ^{1}H-NMR ($CDCl_3$): 1.78 (*s*, Me); 1.82 (*s*, Me); 2.55 (*s*, Me–C(4)); 4.58 (*d*, *J* = 6.8, CH_2O); 5.47 (*m*, 1 H, CH=); 6.82 (*d*, *J* = 2.4, H–C(8)); 6.91 (*dd*, *J* = 8.8, 2.4, H–C(6)); 7.52 (*d*, *J* = 8.8, H–C(5)). ^{13}C-NMR ($CDCl_3$): 16.14 (*Me*–C(4)); 18.28, 25.80 (C(4′), C(5′)); 65.49 (C(1′)); 101.47 (C(8)); 113.14 (C(4a)); 113.58 (C(6)); 117.64 (C(3)); 118.53 (C(2′)); 125.78 (C(5)); 139.39 (C(3′)); 147.99 (C(4)); 153.08 (C(8a)); 157.49 (C(7)); 161.84 (C(2)). Anal. calc. for $C_{15}H_{15}ClO_3$: C 64.64, H 5.42; found: C 64.27, H 5.45.

*(*E*)-2-Methyl-4-(2-oxo-2*H*-1-benzopyran-6-yloxy)but-2-enal* (**4**). A suspension of SeO_2 (2.00 g, 18 mmol) and **1** (2.30 g, 10 mmol) in EtOH (80 ml) was refluxed for 24 h (TLC monitoring). After cooling, it was filtered though *Celite* and evaporated. The residual oil was dissolved in CH_2Cl_2 (150 ml), the soln. washed with H_2O (2×80 ml) and brine, dried (Na_2SO_4), and evaporated to give a solid residue which was crystallized from EtOH: **4** (1.27 g, 52%). M.p. 150–152°. IR (KBr): 1704, 1687, 1567, 1274. ^{1}H-NMR ($CDCl_3$): 1.86 (*d*, *J* = 1.2, Me–C(3′)); 4.91 (*dd*, *J* = 5.6, 1.2, CH_2O); 6.45 (*d*, *J* = 9.6, H–C(3)); 6.68 (*m*, 1 H, CH=); 6.94 (*d*, *J* = 2.8, H–C(5)); 7.14 (*dd*, *J* = 9.2, 2.8, H–C(7)); 7.30 (*d*, *J* = 9.2, H–C(8)); 7.66 (*d*, *J* = 9.6, H–C(4)); 9.51 (*s*, CHO). ^{13}C-NMR ($CDCl_3$): 9.77 (C(4′)); 65.42 (C(1′)); 111.13 (C(5)); 117.44 (C(8)); 118.20 (C(3)); 119.30 (C(4a)); 119.80 (C(7)); 140.26 (C(3′)); 142.89 (C(4)); 146.40 (C(2′)); 148.92 (C(8a)); 154.49 (C(6)); 160.70 (C(2)); 193.78 (CHO). Anal. calc. for $C_{14}H_{12}O_4$: C 68.85, H 4.95; found: C 68.59, H 5.02.

*(*E*)-4-(3-Chloro-4-methyl-2-oxo-2*H*-1-benzopyran-7-yloxy)-2-methylbut-2-enal* (**6**). Prepared as described for **4**: 48% yield. M.p. 190–191°. IR (KBr): 1726, 1685, 1617, 1258, 1214. ^{1}H-NMR ($CDCl_3$): 1.87 (*d*, *J* = 1.2, Me–C(3′)); 2.57 (*s*, Me–C(4)); 4.94 (*dd*, *J* = 5.6, 1.2, CH_2O); 6.66 (*m*, 1 H, CH=); 6.85 (*d*, *J* = 2.8, H–C(8)); 6.94 (*dd*, *J* = 8.8, 2.8, H–C(6)); 7.57 (*d*, *J* = 8.8, H–C(5)); 9.51 (*s*, CHO). ^{13}C-NMR ($CDCl_3$): 9.82 (C(4′)); 16.16 (*Me*–C(4)); 65.19 (C(1′)); 101.64 (C(8)); 113.14 (C(6)); 113.94 (C(4a)); 118.37 (C(3)); 126.15 (C(5)); 140.62 (C(3′)); 145.45 (C(2′)); 147.70 (C(4)); 153.04 (C(8a)); 157.16 (C(7)); 160.80 (C(2)); 193.63 (CHO). Anal. calc. for $C_{15}H_{13}ClO_4$: C 61.55, H 4.48; found: C 61.24, H 4.51.

*6-[(*E*)-3-(2,3,4,5-Tetrahydro-4-methylidene-5-oxofuran-2-yl)but-2-enyloxy]-2*H*-1-benzopyran-2-one* (**7**). To a soln. of **4** (0.73 g, 3 mmol) in dry THF (50 ml), activated Zn powder (0.28 g, 4.4 mmol), Cu powder (0.28 g, 4.4 mmol), hydroquinone (6 mg), and ethyl 2-(bromomethyl)acrylate (0.88 g, 4.5 mmol) were added. The mixture was refluxed under N_2 for 36 h (TLC monitoring). After cooling, it was poured into an ice-cold 5% HCl soln. (300 ml) and extracted with CH_2Cl_2 (3×80 ml). The CH_2Cl_2 extracts were combined and washed with H_2O, dried (Na_2SO_4), and then evaporated to give a residual solid which was purified by CC (silica gel, AcOEt/hexane 1 : 1) and crystallization from AcOEt: **7** (0.68 g, 73%). M.p. 118–119°. IR (KBr): 1744, 1706, 1570, 1437, 1377, 1273. ^{1}H-NMR ($CDCl_3$): 1.75 (*d*, *J* = 0.8, Me–C(3′)); 2.76 (*ddt*, *J* = 17.2, 6.4, 2.8, 1 H–C(3″)); 3.15 (*ddt*, *J* = 17.2, 8.0, 2.4, 1 H–C(3″)); 4.63 (*d*, *J* = 6.0, 2 H–C(1′)); 4.94 (*t*, *J* = 7.2, H–C(2″)); 5.68 (*t*, *J* = 2.4, 1 H, CH_2=C(4″)); 5.85 (*tt*, *J* = 6.0, 1.2, H–C(2′)); 6.28 (*t*, *J* = 2.8, 1 H, CH_2=C(4″)); 6.43 (*d*, *J* = 9.6, H–C(3)); 6.92 (*d*, *J* = 2.8, H–C(5)); 7.10 (*dd*, *J* = 8.8, 2.8, H–C(7)); 7.27 (*d*, *J* = 8.8, H–C(8)); 7.65 (*d*, *J* = 9.6, H–C(4)). ^{13}C-NMR ($CDCl_3$): 11.91 (*Me*–C(3′)); 32.44 (C(3″)); 64.83 (C(1′)); 79.92 (C(2″)); 111.13 (C(5)); 117.18 (C(8)); 117.95 (C(3)); 119.20 (C(4a)); 119.93 (C(7)); 122.56 (olef. C); 133.86 (C(4″)); 137.48 (C(3′)); 143.07 (C(4)); 148.63 (C(8a)); 154.91 (C(6)); 160.86 (C(2)); 169.91 (C(5″)). Anal. calc. for $C_{18}H_{16}O_5 \cdot 0.75\ H_2O$: C 66.35, H 5.41; found: C 66.14, H 5.38.

*7-[(*E*)-3-(2,3,4,5-Tetrahydro-4-methylidene-5-oxofuran-2-yl)but-2-enyloxy]-2*H*-1-benzopyran-2-one* (**8**). Prepared as described for **7**: 76% yield. M.p. 108–109°. IR (KBr): 1757, 1709, 1614, 1279, 1233. ^{1}H-NMR ($CDCl_3$): 1.76 (*d*, *J* = 0.8, Me–C(3′)); 2.77 (*ddt*, *J* = 17.2, 6.4, 2.8, 1 H–C(3″)); 3.16 (*ddt*, *J* = 17.2, 8.0, 2.4, 1 H–C(3″)); 4.66 (*d*, *J* = 6.2, 2 H–C(1′)); 4.95 (*t*, *J* = 7.2, H–C(2″)); 5.69 (*d*, *J* = 2.4, 1 H, CH_2=C(4″)); 5.84 (*tt*, *J* = 6.2, 1.2, H–C(2′)); 6.26 (*d*, *J* = 9.6, H–C(3)); 6.29 (*t*, *J* = 2.8, 1 H, CH_2=C(4″)); 6.79 (*d*, *J* = 2.8, H–C(8)); 6.84 (*dd*, *J* = 8.8, 2.8, H–C(6)); 7.38 (*d*, *J* = 8.8, H–C(5)); 7.65 (*d*, *J* = 9.6, H–C(4)). ^{13}C-NMR ($CDCl_3$): 11.98 (*Me*–C(3′)); 32.45 (C(3″)); 64.63 (C(1′)); 79.78 (C(2″)); 101.49 (C(8)); 112.70 (C(4a)); 113.01 (C(3)); 113.24 (C(6)); 121.93 (olef. C); 122.62 (C(2′)); 128.82 (C(5)); 133.78 (C(4″)); 137.82 (C(3′)); 143.34 (C(4)); 155.78 (C(8a)); 161.09, 161.59 (C(2), C(7)); 169.89 (C(5″)). Anal. calc. for $C_{18}H_{16}O_5 \cdot 0.25\ H_2O$: C 68.24, H 5.17; found: C 68.21, H 5.12.

*3-Chloro-4-methyl-7-[(*E*)-3-(2,3,4,5-tetrahydro-4-methylidene-5-oxofuran-2-yl)but-2-enyloxy]-2*H*-1-benzopyran-2-one* (**9**). Prepared as described for **7**: 68% yield. M.p. 108–110°. IR (KBr): 1760, 1720, 1619, 1598, 1379, 1282, 1255, 1207. ^{1}H-NMR ($CDCl_3$): 1.76 (*d*, *J* = 0.8, Me–C(3′)); 2.56 (*s*, Me–C(4)); 2.76 (*ddt*, *J* = 17.2, 6.4, 2.8, 1 H–C(3″)); 3.16 (*ddt*, *J* = 17.2, 8.0, 2.4, 1 H–C(3″)); 4.67 (*d*, *J* = 6.2, 2 H–C(1′)); 4.94 (*t*, *J* = 7.2, H–C(2″)); 5.69 (*t*, *J* = 2.4, 1 H, CH_2=C(4″)); 5.83 (*tt*, *J* = 6.2, 1.2, H–C(2′)); 6.28 (*t*, *J* = 2.8, 1 H, CH_2=C(4″)); 6.80 (*d*, *J* = 2.4, H–C(8)); 6.90 (*dd*, *J* = 8.8, 2.8, H–C(6)); 7.54 (*d*, *J* = 8.8, H–C(5)). ^{13}C-NMR ($CDCl_3$): 12.06 (*Me*–C(3′)); 16.18 (*Me*–C(4)); 32.51 (C(3″)); 64.74 (C(1)); 79.76 (C(2″)); 101.47 (C(8)); 113.44 (C(6)); 113.51 (C(4a)); 117.97 (C(3)); 121.82 (olef. C); 122.67 (C(2′)); 125.98 (C(5)); 133.79 (C(4″)); 137.99 (C(3′)); 147.92 (C(4)); 153.06 (C(8a)); 157.37 (C(7)); 161.37 (C(2)); 169.91 (C(5″)). Anal. calc. for $C_{19}H_{17}ClO_5 \cdot 0.25\ H_2O$: C 62.47, H 4.83; found: C 62.25, H 5.02.

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