# Synthesis and Cytotoxicity Evaluation of Certain $\alpha$-Methylidene-$\gamma$-butyrolactones Bearing Coumarin, Flavone, Xanthone, Carbazole, and Dibenzofuran Moieties

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The cytotoxicities of $\alpha$-methylidene-$\gamma$-butyrolactones, which are linked to coumarins (see **15** and **16**) and to potential DNA-intercalating carriers such as flavones, xanthones, carbazole, and dibenzofuran (see **9a**–**e**, **10a**–**e**, **11**, and **12**), were studied. These compounds were synthesized *via* alkylation of their hydroxy precursors followed by a *Reformatsky*-type condensation (*Scheme*). These $\alpha$-methylidene-$\gamma$-butyralactones were evaluated *in vitro* against 60 human tumor cell lines derived from nine cancer cell types and demonstrated a strong growth-inhibitory activity against leukemia cancer cells (*Tables 1* and *2*). For flavone- and xanthone-containing $\alpha$-methylidene-$\gamma$-butyrolactones **9a**–**e** and **10a**–**e**, respectively, the overall potency (mean value) decreased on introduction of an electron-withdrawing substituent at the $\gamma$-phenyl substituent and increased with an electron-donating substituent. Comparing the different chromophores established the following order of decreasing potency (log $GI_{50}$): dibenzofuran (**12**, $-6.17$) > flavone (**9a**, $-5.96$) > carbazole (**11**, $-5.80$) and xanthone (**10a**, $-5.77$) > coumarin (**15**, $-5.60$; **16**, $-5.65$). Among them, the dibenzofuran derivative **12** showed not only strong inhibitory activities against leukemia cancer cell lines with an average log $GI_{50}$ value of $-7.22$, but also good inhibitory activities against colon, melanoma, and breast cancer cells with average log $GI_{50}$ values of $-6.23$, $-6.31$, and $-6.39$, respectively.

**Introduction.** – The $\alpha$-methylidene-$\gamma$-butyrolactone moiety is a characteristic component of a large number of natural products that possess wide-ranging biological activities, including antitumor, bactericidal, fungicidal, antibiotic, and anthelmintic properties [1]. The structural requirement for the cytotoxicity is the $O{=}C{-}C{=}CH_2$ moiety which acts as an alkylating agent by a *Michael*-type reaction with bionucleophiles [2]. Other representative clinically used alkylating antitumor drugs are chlorambucil, melphalan, cisplatin, and cyclophosphamide. Although these compounds are important antitumor agents, they have a serious drawback that is common to all alkylating agents, *i.e.*, they act by alkylating DNA, but have no particular affinity for it. This drawback could, in principle, be overcome by the incorporation of the alkylating pharmacophore onto a DNA-intercalating agent, which would result in specifically targetting the pharmacophore to the DNA.

In spite of this logical rationale, relatively little work has gone into the development of DNA-targeted $\alpha$-methylidene-$\gamma$-butyrolactones, compared to the efforts expended in attaching them to a great variety of other carriers, including steroidal hormones, purines, and pyrimidines [3]. *Creech et al.* have studied a series of mono- and difunctional alkyl mustards linked to various heterocyclic chromophores, particularly acridine [4]. They showed these compounds to be more potent than the corresponding

simple mustards against ascitic tumors *in vivo* and suggested that this was due to the high affinity of the chromophores for DNA [5]. Similar potential anticancer agents were prepared to study the structure-activity relationships for alterations in the chromophore or the bridging side chain [6].

Recently, we have synthesized certain $\alpha$-methylidene-$\gamma$-butyrolactones and explored their cardiovascular activities [7]. We have also studied the cytotoxicity of $\alpha$-methylidene-$\gamma$-butyrolactones bearing naphthaline and quinoline moieties [8]. The present report describes the cytotoxicity of a series of $\alpha$-methylidene-$\gamma$-butyrolactones linked to coumarins (=2*H*-1-benzopyran-2-one) or to potential DNA-intercalating carriers such as flavone (=2-phenyl-4*H*-1-benzopyran-4-one), xanthone (=9*H*-xanthen-9-one), carbazole, and dibenzofuran moieties. Although the flavone skeleton is not a system with three fused aromatic rings required for a minimal DNA-intercalating ligand, its third phenyl ring is appended at C(2), which can accommodate itself in a virtually coplanar fashion to the chromophore. A 2-phenyl derivative of quinoline-8-carboxamide had been shown to possess DNA-binding capability and a broad-spectrum activity in both leukemia and solid-tumor assays [9].

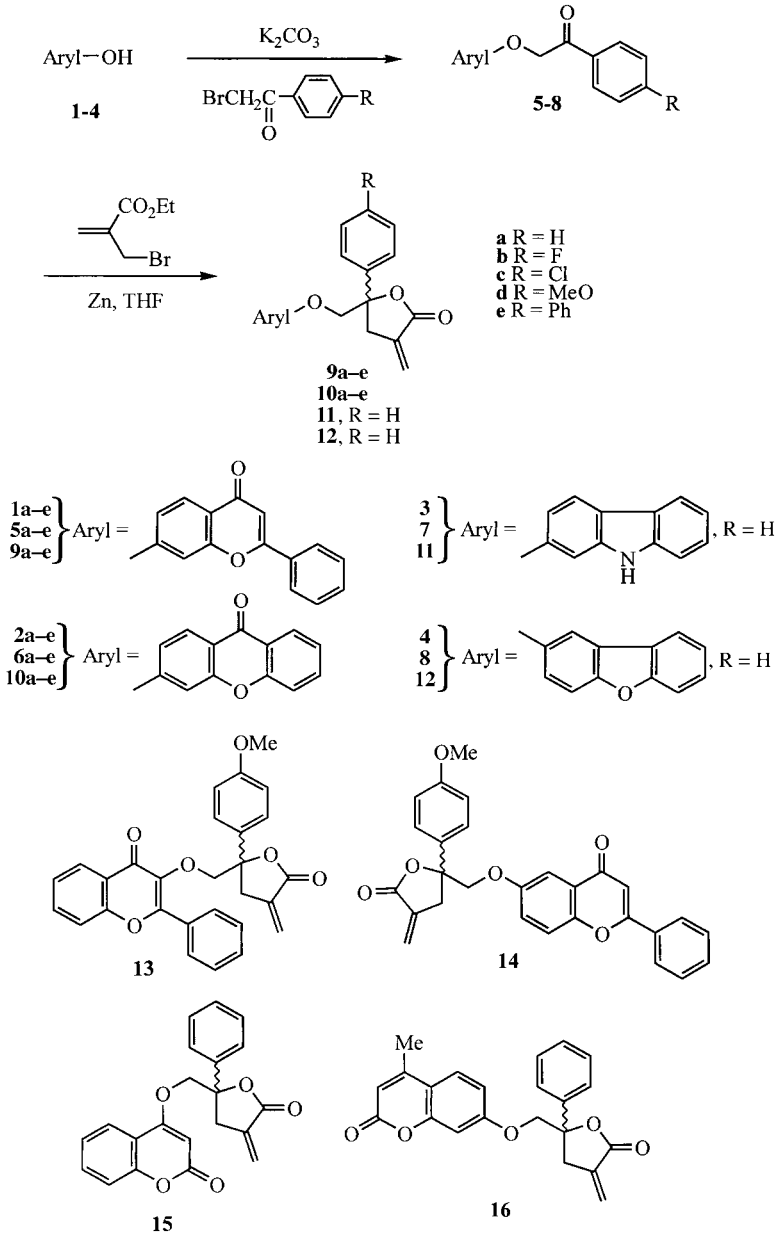
**Results and Discussion.** – The preparation of the $\alpha$-methylidene-$\gamma$-butyrolactones **9**–**12** from **1**–**4** *via* **5**–**8** is illustrated in the *Scheme*. Alkylation of 9*H*-carbazol-2-ol (**3**) with 2-bromoacetophenone (=2-bromo-1-phenylethan-1-one) under basic conditions provided 2-[(9*H*-carbazol-2-yl)oxy]-1-phenylethan-1-one (**7**), which was then treated with ethyl 2-(bromomethyl)acrylate and Zn powder in dry tetrahydrofuran (THF) (*Reformatsky*-type condensation) to afford 5-{[(9*H*-carbazol-2-yl)oxy]methyl}-4,5-dihydro-3-methylidene-5-phenylfuran-2-(3*H*)-one (**11**) in 62% overall yield. The same synthetic procedure was applied for the synthesis of **12**. Compounds **9a**–**e**, **10a**–**e**, **13**, and **14** were previously reported [7].

All compounds were evaluated *in vitro* against 60 human tumor 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 different drug concentrations, and the concentration causing 50% cell-growth inhibition ($GI_{50}$) relative to the control was calculated.

*Table 1* gives the log $GI_{50}$ values of flavone derivatives **9a**–**e**. All these compounds are more potent than cisplatin (log $GI_{50} = -5.35$) [10] and demonstrate a strong growth-inhibitory activity against leukemia cell lines. The overall potency (mean value) is decreased by the introduction of an electron-withdrawing substituent at the $\gamma$-phenyl substituent (see **9b** and **9c** with a mean log $GI_{50}$ value of $-5.67$ and $-5.81$, resp., compared to **9a** with log $GI_{50} = -5.96$) and increased by an electron-donating substituent (log $GI_{50}$ of **9d** $-5.97$ and log $GI_{50}$ of **9e** $-6.38$). Among the $\gamma$-(4-methoxyphenyl)butyrolactones, the 7-substituted flavone derivative **9d** is more potent than its 6-substituted isomer **14** ($-5.87$), while the 3-substituted counterpart **13** ($-5.74$) is relatively inactive. The steric hindrance exerted in **13** by the bulky lactone ring at C(3) of the flavone moiety may prevent the adjacent phenyl ring to lie coplanar with the bicyclic chromone which leads to decreased cytotoxicity.

The log $GI_{50}$ values of xanthones **10a**–**e**, its tricyclic analogues **11** and **12**, and the coumarin derivatives **15** and **16** are given in *Table 2*. All of them possess a strong

*Scheme*




inhibitory activity against leukemia cell lines. The overall potency is decreased by the introduction of an electron-withdrawing substituent at the $\gamma$-phenyl substituent (see **10a** and **10c** with a mean log $GI_{50}$ value of $-5.77$ and $-5.58$, resp.) and increased by an electron-donating substituent (log $GI_{50}$ of **10d** $-5.79$ and log $GI_{50}$ **10e** $-5.96$).

Table 1. *Inhibition of* in vitro *Cancer Cell Lines by Flavone Derivatives* **9a**–**e**, **13**, *and* **14**: *Average log* $GI_{50}$[a])

| Cell Line | **9a** | **9b** | **9c** | **9d** | **9e** | **13** | **14** |
|---|---|---|---|---|---|---|---|
| Leukemia | – 6.87 | – 6.60 | – 6.84 | – 6.64 | – 7.01 | – 5.84 | – 6.28 |
| Colon cancer | – 6.13 | – 5.61 | – 5.79 | – 5.95 | – 6.59 | – 5.75 | – 5.98 |
| CNS cancer | – 5.84 | – 5.55 | – 5.70 | – 5.76 | – 6.16 | – 5.59 | – 5.57 |
| Melanoma | – 5.91 | – 5.62 | – 5.70 | – 6.02 | – 6.18 | – 5.78 | – 5.76 |
| Ovarian cancer | – 5.84 | – 5.58 | – 5.66 | – 5.81 | – 6.15 | – 5.75 | – 5.76 |
| Renal cancer | – 5.79 | – 5.55 | – 5.62 | – 6.05 | – 6.56 | – 5.86 | – 5.91 |
| Prostate cancer | – 5.72 | – 5.48 | – 5.63 | – 5.79 | – 6.00 | – 5.84 | – 5.76 |
| Breast cancer | – 5.78 | – 5.58 | – 5.72 | – 5.87 | – 6.44 | – 5.85 | – 5.86 |
| Non-small-cell lung cancer | – 5.79 | – 5.46 | – 5.67 | – 5.78 | – 6.18 | – 5.70 | – 5.84 |
| Mean[b]) | – 5.96 | – 5.67 | – 5.81 | – 5.97 | – 6.38 | – 5.74 | – 5.87 |

[a]) $GI_{50}$: Drug concentration [M] causing 50% cell-growth inhibition. Data obtained from *NCI*'s *in vitro* disease-oriented tumor-cells screen [11]. [b]) 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); 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, HS578T, MDA-MB-435, MDA-N, and T-47D); non-small-cell lung cancer (A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, and NCI-H522).

Table 2. *Inhibition of* in vitro *Cancer Cell Lines by Xanthones* **10a**–**e**, *Carbazole Derivative* **11a**, *Dibenzofuran Derivative* **12**, *and Coumarin Derivatives* **15** *and* **16**: *Average log* $GI_{50}$[a])

| Cell Line | **10a** | **10c** | **10d** | **10e** | **11** | **12** | **15** | **16** |
|---|---|---|---|---|---|---|---|---|
| Leukemia | – 6.17 | – 6.24 | – 6.33 | – 6.71 | – 6.69 | – 7.22 | – 6.04 | – 6.35 |
| Colon cancer | – 5.76 | – 5.61 | – 5.78 | – 6.02 | – 5.75 | – 6.23 | – 5.78 | – 5.91 |
| CNS cancer | – 5.61 | – 5.44 | – 5.64 | – 5.90 | – 5.81 | – 6.12 | – 5.10 | – 5.18 |
| Melanoma | – 5.84 | – 5.61 | – 5.87 | – 6.04 | – 5.87 | – 6.31 | – 5.82 | – 5.83 |
| Ovarian cancer | – 5.64 | – 5.44 | – 5.70 | – 5.73 | – 5.63 | – 5.91 | – 5.53 | – 5.55 |
| Renal cancer | – 5.82 | – 5.55 | – 5.87 | – 5.84 | – 5.68 | – 5.98 | – 5.73 | – 5.65 |
| Prostate cancer | – 5.60 | – 5.32 | – 5.70 | – 5.68 | – 5.76 | – 5.93 | – 5.58 | – 5.55 |
| Breast cancer | – 5.79 | – 5.54 | – 5.76 | – 5.98 | – 5.74 | – 6.39 | – 5.59 | – 5.67 |
| Non-small-cell lung cancer | – 5.59 | – 5.40 | – 5.74 | – 5.70 | – 5.48 | – 5.52 | – 5.19 | – 5.07 |
| Mean[b]) | – 5.77 | – 5.58 | – 5.79 | – 5.96 | – 5.80 | – 6.17 | – 5.60 | – 5.65 |

[a])[b]) See corresponding footnotes in *Table 1*.

Comparing the different chromophores allows us to establish the following order of decreasing potency: dibenzofuran (**12**, – 6.17) > carbazole (**11**, – 5.80) and xanthone (**10a**, – 5.77) > coumarin (**15**, – 5.60; **16**, – 5.65). It is worth to mention that the dibenzofuran derivative **12** shows not only a strong inhibitory activity against leukemia cancer cell lines with an average log $GI_{50}$ value of – 7.22, but also good inhibitory activities against colon, melanoma, and breast cancer cells with average log $GI_{50}$ values of – 6.23, – 6.31, and – 6.39, respectively. Compounds **9a**, **10a**, and **12** were selected for preliminary *in vivo* hollow-fiber assay. Each compound was tested against a standard panel of 12 human tumor cell lines, including NCI-H23, NCI-H522, MDA-MB-231, MDA-MB-435, SW-620, COLO 205, LOX IMVI, UACC-62, OVCAR-3, OVCAR-5, U251, and SF-295. According to the *NCI*'s protocol, compounds with a combined intraperitoneal (IP) and subcutaneous (SC) score of 20, a SC score 8 or a net cell kill of

one or more cell lines in either implant site, are referred for xenograft testing. The results are: **9a**, IP = 10, SC = 6, and cell kill = 0; **10a**, IP = 8, SC = 0, and cell kill = 0; **12**, IP = 4, SC = 8, and cell kill = 1. Only dibenzofuran derivative **12** produced a reduction in the viable cell mass below the level present at the start of the implantation.

**Conclusion.** – The alkylating $\alpha$-methylidene-$\gamma$-butyrolactones were linked to coumarins or to potential DNA-intercalating carriers such as flavone, xanthone, carbazole, and dibenzofuran moieties with the aim to enhance the cytotoxicities and target specificity. The results of this study showed that the cytotoxicity decreased in the order of linked chromophore dibenzofuran > flavone > carbazole and xanthone > coumarin. Among them, the dibenzofuran-containing $\alpha$-methylidene-$\gamma$-butyrolactone **12** exhibited not only a strong inhibitory activity against leukemia cancer cell lines with an average log $GI_{50}$ value of − 7.22, but also good inhibitory activities against colon, melanoma, and breast cancer cells with average log $GI_{50}$ values of − 6.23, − 6.31, and − 6.39, respectively.

## 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. UV Spectra ($\lambda_{max}$ (log $\varepsilon$) in nm): *Shimadzu-UV-160A* UV-VIS spectrophotometer. IR Spectra ($cm^{-1}$): *Hitachi-260-30* IR spectrophotometer. $^1$H- and $^{13}$C-NMR Spectra: *Varian-Unity-400* (400 and 100 MHz, resp.) or *Varian-Gemini-200* spectrometer (200 and 50 MHz resp.); chemical shifts $\delta$ in ppm with $SiMe_4$ as an internal standard (= 0 ppm), coupling constants $J$ in Hz. Elemental analyses were carried out on a *Heraeus-CHN-O-Rapid* elemental analyzer, and results were within ± 0.4% of calc. values.

*2-[(9*H*-Carbazol-2-yl)oxy]-1-phenylethan-1-one* (**7**). To a soln. of 9*H*-carbazol-2-ol (**3**; 1.83 g, 10 mmol) in acetone (20 ml), $K_2CO_3$ (3.46 g, 25 mmol) and phenacyl bromide (2.19 g, 11 mmol) were added. The resulting mixture was refluxed for 3 h (TLC monitoring). Evaporation gave a residue, which was poured into ice-water (50 ml). The resulting solid was collected and crystallized from EtOH: **7** (2.56 g, 85%). M.p. 142 – 143°. UV ($CH_2Cl_2$): 299 (4.05), 237 (4.46). IR (KBr): 1695, 1641, 1610, 1460, 1341, 1241, 1175. $^1$H-NMR ($CDCl_3$): 5.33 (*s*, $CH_2O$); 6.29 (*dd*, *J* = 8.8, 2.0, 1 H–C(3′)); 6.93 (*d*, *J* = 2.0, H–C(1′)); 7.19 (*m*, H–C(6′)); 7.30 – 7.36 (*m*, H–C(7′), H–C(8′)); 7.47 – 7.52 (*m*, 2 arom. H); 7.61 (*m*, 1 arom. H); 7.92 (*d*, *J* = 8.8, H–C(4′)); 7.95 (*d*, *J* = 8.0, H–C(5′)); 8.01 – 8.04 (*m*, 2 arom. H, NH). $^{13}$C-NMR ($CDCl_3$): 71.60 ($CH_2O$); 96.41 (C(1′)); 108.45 (C(3′)); 110.40 (C(8′)); 118.14 (C(4′a)); 119.55 (C(6′)); 119.57 (C(5′)); 121.10 (C(4′)); 123.29 (C(9′a); 124.80 (C(7′)); 128.22, 128.82, 133.85, 134.67 (arom. C); 139.68 (C(4′b)); 140.62 (C(8′a)); 157.35 (C(2′)); 195.01 (C=O). Anal. calc. for $C_{20}H_{15}NO_2$: C 79.72, H 5.02, N 4.65; found: C 79.69, H 5.15, N 4.57.

*2-[(Dibenzofuran-2-yl)oxy]-1-phenylethan-1-one* (**8**). As described for **7**: 90% yield. M.p. 136 – 137°. UV ($CH_2Cl_2$): 290 (4.20), 242 (4.37). IR (KBr): 1694, 1478, 1447, 1174. $^1$H-NMR ($CDCl_3$): 5.37 (*s*, $CH_2O$); 7.12 (*dd*, *J* = 9.0, 2.6, H–C(3′)); 7.27 – 7.66 (*m*, 8 arom. H); 7.88 (*m*, H–C(9′)); 8.01 – 8.07 (*m*, 2 arom. H). $^{13}$C-NMR ($CDCl_3$): 72.00 ($CH_2O$); 105.65 (C(1′)); 111.73 (C(6′)); 112.24 (C(4′)); 115.83 (C(3′)); 120.65 (C(9′)); 122.48 (C(8′)); 124.22, 124.79 (C(9′a), C(9′b)); 127.27 (C(7′)); 128.15, 128.84, 133.89, 134.59 (arom. C); 151.40 (C(4′a)); 154.29 (C(2′)); 156.93 (C(5′a)); 194.65 (C=O). Anal. calc. for $C_{20}H_{14}O_3$: C 79.46, H 4.67; found: C 79.38, H 4.75.

*5-{[(9*H*-Carbazol-2-yl)oxy]methyl}-4,5-dihydro-3-methylidene-5-phenylfuran-2(3*H*)-one* (**11**). To a soln. of **7** (0.90 g, 3 mmol) in dry THF (20 ml), activated Zn powder (85 mg, 1.3 mmol), hydroquinone (2 mg), and ethyl 2-(bromomethyl)acrylate (0.26 g, 1.3 mmol) were added. The mixture was refluxed under $N_2$ for 4 h (TLC monitoring). After cooling, it was poured into an ice-cold 5% HCl soln. (100 ml) and extracted with $CH_2Cl_2$ (3 × 50 ml). The $CH_2Cl_2$ extracts were combined and washed with brine, dried ($Na_2SO_4$), and evaporated to give a white solid, which was crystallized from AcOEt: **11** (0.81 g, 73%). M.p. 161 – 162°. UV ($CH_2Cl_2$): 299 (4.11), 238 (4.36). IR (KBr): 1758, 1610, 1462, 1448, 1309, 1286, 1231, 1176. $^1$H-NMR ($CDCl_3$): 3.19 (*dt*, *J* = 16.9, 2.9, 1 H–C(4)); 3.69 (*dt*, *J* = 16.9, 2.4, 1 H–C(4)); 4.17, 4.24 (*AB*, *J* = 10.0, 2 H, $CH_2O$); 5.68 (*t*, *J* = 2.4, 1 H, $CH_2$=C(3)); 6.31 (*t*, *J* = 2.9, 1 H, $CH_2$=C(3)); 6.75 (*dd*, *J* = 8.2, 2.1, H–C(3′)); 6.82 (*d*, *J* = 2.1, H–C(1′)); 7.19 (*m*, H–C(6′)); 7.28 – 7.53 (*m*, 5 arom. H, H–C(7′), H–C(8′)); 7.88 (*d*, *J* = 8.5, H–C(4′)); 7.95 (*d*, *J* = 7.7,

H–C(5′)); 8.14 (br. *s*, NH). $^{13}$C-NMR ($CDCl_3$): 37.37 (C(4)); 74.89 ($CH_2O$); 84.42 (C(5)); 96.16 (C(1′)); 108.36 (C(3′)); 110.44 (C(8′)); 117.97 (C(4′a)); 119.53, 119.56 (C(5′), C(6′)); 121.02 (C(4′)); 121.56 (*C*$H_2$=C); 123.28 (C(9′a); 124.78 (C(7′)); 125.12, 128.50, 128.77, 140.47 (arom. C); 135.09 (C(3)); 139.65 (C(4′b)); 140.60 (C(8′a)); 157.51 (C(2′)); 169.52 (C(2)). Anal. calc. for $C_{24}H_{19}NO_3$; C 78.03, H 5.18, N 3.79; found: C 77.86, H 5.28, N 3.72.

*5-{[(Dibenzofuran-2-yl)oxy]methyl}-4,5-dihydro-3-methylidene-5-phenylfuran-2(3*H*)-one* (**12**). As described for **11**: 68% yield. M.p. 104–105°. UV ($CH_2Cl_2$): 322 (3.77), 290 (4.26), 253 (4.21), 237 (4.24). IR (KBr): 1762, 1636, 1447, 1178. $^1$H-NMR ($CDCl_3$): 3.23 (*dt*, *J* = 16.9, 2.8, 1 H–C(4)); 3.73 (*dt*, *J* = 16.9, 2.5, 1 H–C(4)); 4.20, 4.28 (*AB*, *J* = 9.6, $CH_2O$); 5.71 (*t*, *J* = 2.5, 1 H, $CH_2$=C(3)); 6.33 (*t*, *J* = 2.8, 1 H, $CH_2$=C(3)); 6.98 (*dd*, *J* = 8.8, 2.6, H–C(3′)); 7.25–7.56 (*m*, 5 arom. H, H–C(1′), H–C(4′), H–C(6′), H–C(7′), H–C(8′)); 7.85 (*m*, H–C(9′)). $^{13}$C-NMR ($CDCl_3$): 37.38 (C(4)); 75.50 ($CH_2$); 84.36 (C(5)); 105.36 (C(1′)); 111.78 (C(6′)); 112.20 (C(4′)); 115.71 (C(3′)); 120.61 (C(9′)); 121.61 (C(8′)); 122.54 (*C*$H_2$=C); 124.25, 124.76 (C(9′a), C(9′b)); 125.14, 128.55, 128.81, 140.44 (arom. C); 127.30 (C(7′); 135.05 (C(3)); 151.34 (C(4′a)); 154.44 (C(2′)); 156.94 (C(5′a)); 169.42 (C(2)). Anal. calc. for $C_{24}H_{18}O_4$: C 77.82, H 5.90; found: C 77.61, H 5.99.

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