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Synthesis of Photosynthesis-Inhibiting Nostoclide Analogues

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A series of 34 3-benzyl-5-(arylmethylene)furan-2(5*H*)-ones, designed using the naturally occurring toxins nostoclides as a lead structure, was synthesized as potential inhibitors of the photosynthetic electron transport. All compounds were fully characterized by IR, NMR (^{1}H and ^{13}C), and MS spectrometry. HMBC and HSQC bidimensional experiments allowed ^{13}C and ^{1}H assignments. Their biological activities were evaluated in vitro as the ability to interfere with light-driven reduction of ferricyanide by isolated spinach chloroplasts. About two-thirds of the compounds exhibited inhibitory properties in the micromolar range against the basal electron flow from water to $K_3[Fe(CN)_6]$. The inhibitory potential of these 3-benzyl-5-(arylmethylene)furan-2(5*H*)-one lactones is higher than that of other nostoclide analogues previously synthesized in the same laboratories.

KEYWORDS: Herbicides; nostoclide analogues; photosynthetic electron transport inhibitors

INTRODUCTION

In modern agriculture, farmers continually face a battle to achieve high yields and quality products to feed an ever-increasing world population. The optimization of agriculture efficiency demands, along with other requirements, the application of crop protection agents to control a variety of diseases and pests, among which are weeds (*1*). The use of herbicides has become the most reliable and least expensive tool for weed control throughout the world. Since the introduction of 2,4-dichlorophenoxyacetic acid in 1946 by a British research team at the Rothamsted Experimental Station, agrochemical companies have developed and commercialized a plethora of herbicides (*2, 3*). Although important advances have been achieved in the chemical control of weeds, the identification of novel herbicides is highly desirable to overcome weed resistance, rapidly raised as a consequence of the severe selective pressure imposed by the continuous application of products with the same biochemical mechanism of action (*4–6*). Moreover, increasing public concern with regard to environmental pollution deriving from agricultural practice strictly requires that phytochemicals would be endowed with low recalcitrance, and thus may be rapidly mineralized by the soil microflora. Low toxicity to mammals, high specificity, low application rates, and fast soilborne microorganism degradation are thus important characteristics in the development of new herbicides.

Nowadays, strategies utilized to identify new chemical agents for weed control can no longer be distinguished from pharmaceutical research and development (*7*). Three different approaches are employed. The first one refers to the systematic screening of large numbers of synthetic compounds. Subsequently, lead compounds are optimized. This has been the most widely used strategy by agrochemical companies (*8*). The second one is the rational design of specific inhibitors of key metabolic processes (*9*). However, to date such an approach has not been fully successful. A third strategy is associated with the exploitation of natural products as herbicides or as leads for new herbicides (*10–14*). Even though the enormous variety of natural products has been relatively little explored, several active principles were discovered in this way (**Figure 1**). Bialaphos, originally isolated from various *Streptomyces* strains, is currently commercialized in Japan with the name Herbiace (*15*). Leptospermone, a major component of the essential oil of *Leptospermum scoparium* (*16*), was chemically modified to make mesotrione (*17*). Mesotrione is the active ingredient of the commercial herbicide Callisto, which is commercialized by Syngenta and suitable for use in corn fields. Another example is sulcotrione, a herbicide marketed in Europe by Bayer CropScience under the tradename Mikado (*18*). Sulcotrione is utilized to control a broad range of annual and perennial broadleaf weeds in maize and sugar cane. The commercial

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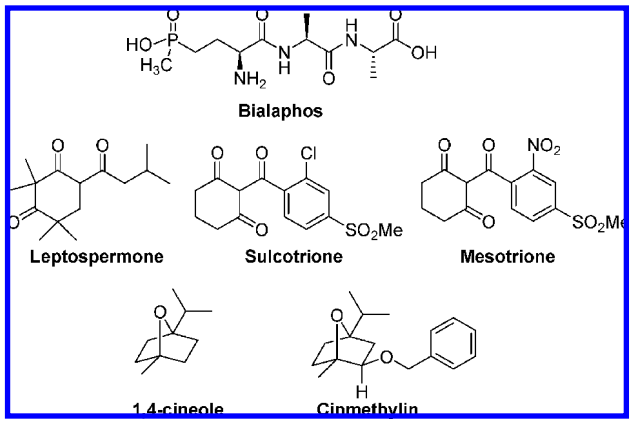

Figure 1. Examples of commercial herbicides developed from natural templates.

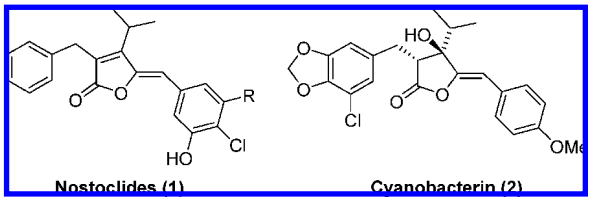

Figure 2. Structures of nostoclides (R = Cl, nostoclide I; R = H, nostoclide II) and cyanobacterin.

herbicide cinmethylin (*19, 20*) is a 2-benzyl ether derivative of the natural product 1,4-cineole that was developed to control annual grasses.

On the other hand, an increasing number of other natural products have been described in the literature as potential leads for the development of chemical agents for weed control, among which are coumarins, benzoquinones, flavonoids, terpenoids, and lactones, which might be involved in allelopathic effects with a low efficiency, in contrast with commercial herbicides (*21–23*). One example of naturally occurring lactones that could be considered attractive as model compounds are the nostoclides (**1**) (**Figure 2**). They are produced by a cyanobacterium (*Nostoc* sp.), which can live free or in symbiosis, for instance, in the lichen *Peltigera canina* (*24*), and belong to a family of compounds known as γ-alkylidenebutenolides (*25–27*). The nostoclides resemble cyanobacterin (**2**), a lactone isolated from the blue-green alga *Scytonema hofmanni* (*28*). Compound **2** is toxic to most cyanobacteria at a concentration as low as 5 μM and also inhibits the growth of several eukaryotic algae and mono- and dicotyledonous angiosperms (*29, 30*). Cyanobacterin acts by inhibiting the photosynthetic electron transport, leading to a series of events that result in the disruption of the thylakoid membrane (*31, 32*). On the contrary, the biological activity of nostoclides **1** has not been fully investigated, yet. Nostoclides I and II have shown moderate cytotoxicity against the mouse neuroblastoma cell lines Neuro-2a CCL and KB CCL 17. Owing to the structural similarity of **1** and **2** (both compounds present a 3-benzyl-5-arylmethylene-4-isopropyldihydrofuran-2-one ring) and the fact that *P. canina* cultures are usually not contaminated with microorganisms, it has been suggested that these chlorinated compounds may be allelopathic agents (*31*).

As part of our ongoing efforts to develop new herbicides (*33–36*), we decided to investigate the potential phytotoxicity of new nostoclide analogues (*37, 38*). In this paper, we describe the preparation of 34 3-benzyl-5-(arylmethylene)furan-2(5*H*)-ones. Their ability to inhibit the Hill reaction in isolated spinach chloroplasts was also assessed.

MATERIALS AND METHODS

General Experimental Procedures. All reactions were carried out under a protective atmosphere of dry nitrogen or utilizing a calcium chloride tube. Dichloromethane, tetrahydrofuran (THF), diethyl ether, and amines were purified as described by Perrin and Armarego (*39*). Commercially available *tert*-butyldimethylsilyltrifluoromethanesulfonate (TBDMSOTf), diisopropylethylamine (DIPEA), 8-diazabyciclo[5.4.0]undec-7-ene (DBU), and phosphoryl chloride ($POCl_3$) were purchased from Aldrich (Milwaukee, WI) and utilized without further purification. The compounds 3-bromobenzaldehyde, 4-methylbenzaldehyde, and 2,5-dimethoxybenzaldehyde were prepared from the corresponding commercially available (Aldrich) benzylic alcohols by Swern oxidation (*40*). The compound 3-(*N*,*N*-dimethylamino)benzaldehyde was prepared via reduction of the commercially available 3-(*N*,*N*-dimethylamino)benzoic acid with lithium aluminum hydride ($LiAlH_4$), followed by Swern oxidation of the produced 3-(*N*,*N*-dimethylamino)benzylic alcohol. Other aldehydes were purchased from Aldrich and utilized without further purification. The preparation of the silyl enol ethers from 2-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-hydroxybenzaldehyde, and 4-hydroxy-3-methoxybenzaldehyde was carried out by methodology previously described (*41*). Lactone **3** was synthesized in 43% yield, from furfural, by employing the methodology described by Näsman (*42*). Lactone **5** was prepared in 67% yield according to a procedure described in the literature (*43*). Commercially available *n*-butyllithium hexane solutions (1.4 mol L^{-1}) were titrated prior to use (*44*). The ^1H and ^{13}C NMR spectra were recorded on a Brucker AVANCE DRX 400 spectrometer at 400 and 100 MHz using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Mass spectra were recorded on a Shimadzu GCMS-QP5050A instrument by direct insertion, EI mode (70 eV). Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrophotometer, using potassium bromide (1% w/w) disks, scanning from 635 to 4000 cm^{-1}. Melting points are uncorrected and were obtained from an MQAPF-301 melting point apparatus (Microquimica, Brazil). Analytical thin layer chromatography analysis was conducted on aluminum-packed precoated silica gel plates. Column chromatography was performed over silica gel (60–230 mesh).

Syntheses. *(5Z)-3-Benzyl-5-benzylidenefuran-2(5H)-one (**6**).* To a two-neck round-bottom flask under nitrogen atmosphere were added 3-benzylfuran-2(5*H*)-one **5** (106 mg, 0.61 mmol), dichloromethane (3 mL), TBDMSOTf (170 μL, 0.74 mmol), DIPEA (310 μL, 1.2 mmol), and benzaldehyde (75 μL, 1.2 mmol). The resulting mixture was stirred at room temperature over 1 h. After DBU (120 μL, 1.22 mmol) was added, the reaction mixture was refluxed for an additional 3 h before the addition of dichloromethane (70 mL). The resulting organic layer was washed with 3 mol L^{-1} HCl aqueous solution (2 × 25 mL) and brine (25 mL). After separation, the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting material was purified by column chromatography on silica gel eluted with hexane/diethyl ether (10:1 v/v). The procedure described afforded compound **6** in 62% yield (99 mg, 0.38 mmol).

Compounds **7**−**35** were prepared by employing a procedure similar to that described for compound **6**, and yields are presented in **Table 1**. The synthesized compounds were fully characterized by IR, NMR (^1H and ^{13}C), and MS spectrometry. HMBC and HSQC bidimensional experiments allowed the ^{13}C and ^1H assignments. Structural characterization of compounds **6**−**8**, **11**, **13**, **21**, and **36**–**38** was already described (*37, 38, 45, 46*). The preparation of compounds **36**–**39** was carried out as previously reported (*46*). Structures for the remaining compounds are supported by the following spectroscopic data.

*Data for (5Z)-3-Benzyl-5-[4-(N,N-dimethylamino)benzylidene]furan-2(5H)-one (**9**)*: yellow solid; mp 136.8–137.3 °C; purified by column chromatography, eluent dichloromethane/hexane (2:1 v/v); IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 3094, 3026, 2915, 2884, 1732, 1642, 1607, 1588, 1524, 1365, 1186, 1037, 813, 699, 641, 523; ^1H NMR (400 MHz, $CDCl_3$), δ 3.01 (s, 6H, $N(C\underline{H}_3)_2$), 3.70 (s, 2H, H7), 5.80 (s, 1H, H6), 6.79 (br d, 2H, H3″/H5″), 6.91 (s, 1H, H4), 7.25–7.35 (m, 5H, Ph), 7.65 (d, 2H, H2″/H6″, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.61 (C7); 40.29 ($N(\underline{C}H_3)_2$), 112.24 (C6), 113.80 (C3″/C5″), 121.67 (C1″), 126.75 (C4′), 128.76 (C3′/C5′), 128.92 (C2′/C6′), 129.46 (C3), 132.15 (C2″/

Table 1. Yields Obtained in the Preparation of Compounds **6–39**

compd	arylidene group	yield[a] (%)
6	benzylidene	62 (*Z*)
7	1,3-dioxalenebenzylidene	83 (*Z*)
8	2,4,6-trimethoxybenzylidene	86 (*E*)
9	4-dimethylaminobenzylidene	43 (*Z*)
10	2-chloro-4-dimethylaminobenzylidene	16 (*Z*)
11	2,5-dimethoxybenzylidene	68 (*Z*)
12	4-nitrobenzylidene	33 (*Z*)
13	3-bromobenzylidene	33 (*Z*)
14	4-methylbenzylidene	32 (*Z*)
15	3-nitrobenzylidene	55 (*Z*)
16	3-methylbenzylidene	66 (*Z*)
17	4-chlorobenzylidene	68 (*Z*)
18	3-chlorobenzylidene	44 (*Z*)
19	4-methoxybenzylidene	63 (*Z*)
20	4-fluorobenzylidene	67 (*Z*)
21	4-bromobenzylidene	75 (*Z*)
22	3-fluorobenzylidene	32 (*Z*)
23	2-fluorobenzylidene	55 (*Z*)
24	2-chlorobenzylidene	41 (*Z*)
25	2-methylbenzylidene	82 (*Z*)
26	4-ethylbenzylidene	38 (*Z*)
27	2-bromobenzylidene	33 (*Z*)
28	pentafluorobenzylidene	21 (*Z*)
29	4-cyanobenzylidene	41 (*Z*)
30	4-trifluoromethylbenzylidene	33 (*Z*)
31	3-trifluoromethylbenzylidene	56 (*Z*)
32	2-trifluoromethylbenzylidene	25 (*Z*)
33	3-cyanobenzylidene	39 (*Z*)
34	3-dimethylaminobenzylidene	12 (*Z*)
35	4-phenylbenzylidene	47 (*Z*)
36	2-hydroxybenzylidene	74 (*Z*)
37	3-hydroxybenzylidene	78 (*Z*)
38	4-hydroxybenzylidene	91 (*Z*)
39	3-hydroxy-4-methoxybenzylidene	12 (*Z*)

[a] Yields based on compound **5**.

C6″), 137.84 (C1′), 139.65 (C4), 144.97 (C5), 150.34 (C4″), 171.05 (C2); MS, *m/z* (%) 305 (M^+, $C_{20}H_{19}NO_2$, 100), 161 (17), 133 (16), 132 (18), 115 (9), 91 (10), 77 (5), 69 (7), 65 (6), 57 (9), 51 (4).

*Data for (5Z)-3-Benzyl-5-(2-chloro-4-[N,N-dimethylamino)benzylidene]furan-2(5H)-one (**10**)*: yellow solid; mp 121.1–122.1 °C; purified by column chromatography, eluent dichloromethane/hexane (1:1 v/v); IR (film, dichloromethane, cm^{-1}). $\bar{\nu}_{max}$ 3087, 3059, 3028, 2905, 2859, 2814, 1747, 1643, 1591, 1514, 1444, 1371, 1290, 1179, 1028, 937, 831, 766, 749, 703, 630, 556; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.00 (s, 6H, $N(C\underline{H}_3)_2$), 3.71 (br s, 2H, H7), 6.30 (s, 1H, H6), 6.61 (dd, 1H, J = 9.0 Hz and J = 2.7 Hz, H3″), 6.66 (d, 1H, J = 2.7 Hz, H5″), 6.97 (t, 1H, J = 1.36 Hz, H4), 7.24–7.36 (m, 5H, Ph), 8.16 (d, 1H, J = 9.0 Hz, H2″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.64 (C7), 40.10 ($N(\underline{C}H_3)_2$), 108.93 (C6), 111.13 (C3″), 112.17 (C5″), 118.75 (C1″), 126.83 (C4′), 128.80 (C3′/C5′), 128.93 (C2′/C6′);, 130.23 (C3), 132.70 (C2″), 135.93 (C1′), 137.60 (C6″), 140.01 (C4), 145.76 (C5), 150.79 (C4″), 170.82 (C2); MS, *m/z* (%) 341 (M + 2, 45), 339 (M^+, $C_{20}H_{18}ClNO_2$, 100), 325 (4), 275 (5), 247 (8), 202 (10), 197 (6), 195 (20), 167 (40), 151 (15), 139 (9), 130 (46), 115 (18), 100 (9), 91 (9), 89 (15), 76 (9), 65 (6), 51 (3).

*Data for (5Z)-3-Benzyl-5-(4-nitrobenzylidene)furan-2(5H)-one (**12**):* yellow solid; mp 117.0–117.7 °C; purified by column chromatography, eluent hexane/dichloromethane (3:2 v/v); IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 3108, 3062, 3030, 2928, 1768, 1590, 1509, 1453, 1339, 1110, 1014, 877, 691, 637; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.75 (br s, 2H, H7), 5.91 (s, 1H, H6), 6.98 (s, 1H, J = 1.5 Hz, H4), 7.25–7.38 (m, 5H, Ph), 7.86 (d, 2H, J = 8.9 Hz, H2″/H6″), 8.21 (d, 2H, J = 8.9 Hz, H3″/H5″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.86 (C7), 109.55 (C6), 123.97 (C3″/C5″), 127.20 (C4′), 128.93 (C3′/C5′), 128.99 (C2′/C6′), 130.73 (C2″/C6″), 134.87 (C3), 136.60 (C1′), 139.19 (C4), 139.44 (C1″), 147.09 (C5), 149.85 (C4″), 169.47 (C2); MS, *m/z* (%) 307, (M^+, $C_{18}H_{13}NO_4$, 81), 262 (13), 231 (13), 215 (60), 202 (37), 165 (9), 143 (18), 133 (16), 115 (100), 91 (26), 89 (46), 76 (22), 65 (12), 63 (28), 51 (14).

*Data for (5Z)-3-Benzyl-5-(4-methylbenzylidene)furan-2(5H)-one (**14**)*: white solid; mp 111.8–112.3 °C; purified by column chromatography, eluent hexane/dicloromethane (2:1 v/v); IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 3088, 3072, 3028, 2918, 1763, 1650, 1608, 1595, 1455, 1436, 812, 698, 651, 520; ^{1}H NMR (400 MHz, $CDCl_3$), δ 2.36 (s, 3H, $C\underline{H}_3$), 3.72 (s, 2H, H7), 5.84 (s, 1H, H6), 6.94 (s, 1H, H4), 7.16 (d, 2H, J = 8.0 Hz, H3″/H5″), 7.25–7.36 (m, 5H, Ph), 7.63 (d, 2H, J = 8.0 Hz, H2″/H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 21.45 ($\underline{C}H_3$), 31.68 (C7), 112.84 (C6), 126.92 (C4′), 128.84 (C3′/C5′), 128.93 (C2′/C6′), 129.56, 130.39, and 130.44 (C1″, C2″/C6″, C3″/C5″), 131.98 (C3), 137.32 (C1′), 139.28 (C4″), 139.69 (C4), 146.92 (C5), 170.54 (C2); MS, *m/z* (%) 276 (M^+, $C_{19}H_{16}O_2$, 100), 258 (7), 243 (9), 230 (23), 215 (32), 202 (6), 181 (7), 156 (5), 143 (20), 132 (27), 115 (39), 103 (56), 91 (16), 77 (42), 65 (8), 63 (8), 51 (13).

*Data for (5Z)-3-Benzyl-5-(3-nitrobenzylidene)furan-2(5H)-one (**15**)*: pale yellow solid; mp 131.0–131.5 °C; purified by column chromatography, eluent hexane/dichloromethane (3:2 v/v); IR (film, dichloromethane, cm^{-1}), $\bar{\nu}_{max}$ 3094, 3068, 3028, 1764, 1654, 1608, 1528, 1493, 1453, 1347, 951, 816, 701; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.75 (s, 2H, H7), 5.91 (s, 1H, H6), 6.99 (s, 1H, H4), 7.26–7.38 (m, 5H, Ph), 7.55 (t, 1H, J = 8.0 Hz, H3″), 8.13 (dd, 1H, J = 8.0 Hz and J = 1.2 Hz, H4″), 8.17 (br d, 1H, J = 8.0 Hz, H2″), 8.41 (br s, 1H, H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.83 (C7), 109.45 (C6), 123.05 (C4″), 124.68 (C6″), 127.16 (C4′), 128.94 (C3′/C5′), 128.97 (C2′/C6′), 129.79 (C3″), 134.41 (C1″), 134.77 (C3), 135.59 (C2″), 136.71 (C1′), 139.12 (C4), 148.57 (C5), 149.15 (C5″), 169.52 (C2); MS, *m/z* (%) 307, (M^+, $C_{18}H_{13}NO_4$, 67), 290 (46), 272 (8), 260 (7), 244 (7), 231 (13), 215 (52), 202 (35), 189 (11), 177 (9), 143 (20), 127 (11), 115 (100), 101 (16), 91 (26), 89 (49), 76 (18), 63 (27), 51 (12).

*Data for (5Z)-3-Benzyl-5-(3-methylbenzylidene)furan-2(5H)-one (**16**)*: white solid; mp 102.1–102.5 °C; purified by column chromatography, eluent hexane/dichloromethane (2:1 v/v); IR (film, dichloromethane, cm^{-1}), $\bar{\nu}_{max}$ 3108, 3062, 3032, 3018, 2922, 2860, 1765, 1645, 1608, 1495, 1454, 1027, 696; ^{1}H NMR (400 MHz, $CDCl_3$), δ 2.36 (s, 3H, $C\underline{H}_3$), 3.72 (br s, 2H, H7), 5.83 (s, 1H, H6), 6.93 (t, 1H, J = 1.4 Hz, H4), 7.12 (br d, 1H, J = 7.6 Hz, H4″), 7.24–7.29 (m, 4H, H3″, H2′/H6′, and H4′), 7.33–7.37 (m, 2H, H3′/H5′), 7.53 (br d, 1H, J = 8.9 Hz, H2″), 7.54 (br s, 1H, H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 21.83 ($\underline{C}H_3$), 31.66 (C7), 112.87 (C6), 126.91 (C4′), 127.68 (C2″), 128.64 (C3″), 128.82 (C3′/C5′), 128.90 (C2′/C6′), 129.80 (C4″), 130.92 (C6″), 132.30 (C3), 133.02 (C1″), 137.21 (C1′), 138.40 (C5″), 139.68 (C4), 147.30 (C5), 170.46 (C2); MS, *m/z* (%) 276 (M^+, $C_{19}H_{16}O_2$, 100), 258 (9), 243 (9), 231 (26), 215 (21), 202 (9), 184 (8), 144 (15), 132 (25), 115 (46), 104 (35), 91 (38), 78 (43), 77 (33), 65 (20), 51 (28).

*Data for (5Z)-3-Benzyl-5-(4-chlorobenzylidene)furan-2(5H)-one (**17**)*: white solid; mp 138.5–139 °C; purified by column chromatography, eluent hexane/dichloromethane (2:1 v/v)' IR (film, dichloromethane, cm^{-1}), $\bar{\nu}_{max}$ 3102, 3086, 3060, 3030, 2930, 1765, 1645, 1584, 1492, 857, 814, 696; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.72 (br s, 2H, H7), 5.81 (s, 1H, H6), 6.94 (t, 1H, J = 1.44 Hz, H5), 7.25–7.37 (m, 7H, Ph and H3″/H5″), 7.66 (d, 2H, J = 8.6 Hz, H2″/H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.74 (C7), 111.19 (C6), 127.03 (C4′), 128.86, 128.93, and 129.04 (C2′/C6′, C3′/C5′, C3″/C5″), 131.53 (C2″/C6″), 131.64 (C1″), 132.97 (C3), 134.79 (C4″), 137.05 (C1′), 139.45 (C4), 147.72 (C5), 170.10 (C2); MS, *m/z* (%) 298 (M + 2, 22), 296 ($C_{18}H_{13}ClO_2$, M^+, 68), 243 (27), 215 (33), 202 (13), 152 (25), 144 (20), 115 (47), 107 (17), 91 (32), 89 (100), 77 (7), 65 (19), 63 (35), 51 (16).

*Data for (5Z)-3-Benzyl-5-(3-chlorobenzylidene)furan-2(5H)-one (**18**)*: white solid; mp 126–126.4 °C; purified by column chromatography, eluent dichloromethane/hexane (3:2 v/v); IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 3099, 3060, 3027, 2926, 1769, 1651, 1612, 1586, 1561, 1027, 793, 700, 685; ^{1}H NMR (400 MHZ, $CDCl_3$), δ 3.72 (br s, 2H, H7), 5.78 (s, 1H, H6), 6.94 (t, 1H, J = 1.4 Hz, H4), 7.25–7.37 (m, 7H, H4″, H5″, and Ph), 7.61 (br d, 1H, J = 7.2 Hz, H6″), 7.70 (br s, 1H, H2″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.71 (C7), 110.87 (C6), 127.03 (C4′), 128.38 and 128.76 (C3″ and C4″)*, 128.89 (C3′/C5′), 128.91 (C2′/C6′), 129.31 (C2″/C6″), 133.40 (C3), 134.69 and 134.81 (C1″ and C5″)*, 136.94 (C1″), 139.37 (C4), 169.96 (C2); MS, *m/z* (%) 298 (M + 2, 19), 296 (M^+, $C_{18}H_{13}ClO_2$, 59), 243 (21), 215 (35), 202 (13), 152

(18), 144 (15), 115 (52), 107 (15), 91 (41), 89 (100), 77 (7), 65 (17), 63 (32), 51 (13). *, these assignments could be reversed.

*Data for (5Z)-3-Benzyl-5-(4-methoxybenzylidene)furan-2(5H)-one (**19**)*: yellow solid; mp 107.2–108.0 °C; purified by column chromatography, eluent dichloromethane/hexane (3:2 v/v); IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 3101, 3058, 3023, 2968, 2930, 2888, 2837, 1743, 1652, 1599, 1510, 1300, 1259, 1028, 936, 825, 750, 699; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.71 (s, 2H, H7), 3.82 (s, 3H, $-OCH_3$), 5.82 (s, 1H, H6), 6.89 (d, 2H, J = 8.8 Hz, H3″/ H5″), 6.92 (s, 1H, H4), 7.25–7.36 (m, 5H, Ph), 7.69 (d, 2H, J = 8.8 Hz, H2″/H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.61 (C7), 55.31 ($-OCH_3$), 125.95 (C6), 126.84 (C3″/C5″), 128.78 and 128.88 (C2′/C6′ and C3′/C5′), 131.18 (C3), 132.08 (C2″/C6″), 137.39 (C1′), 139.64 (C4), 160.17 (C5), 170.62 (C2); MS, *m/z* (%) 292 (M^+, $C_{19}H_{16}O_3$, 100), 247 (10), 215 (9), 148 (34), 133 (21), 120 (28), 115 (23), 105 (11), 91 (49), 77 (34), 65 (10), 63 (11), 51 (31).

*Data for (5Z)-3-Benzyl-5-(4-fluorobenzylidene)furan-2(5H)-one (**20**)*: white solid; mp 108.6–108.9 °C; purified by column chromatography, eluent dichloromethane/hexane (2:1 v/v); IR (film, dichloromethane, cm^{-1}), $\bar{\nu}_{max}$ 3111, 3060, 3030, 2906, 2836, 1744, 1654, 1598, 1506, 1041, 748, 718; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.72 (br s, 2H, H7), 5.83 (s, 1H, H6), 6.94 (t, 1H, J = 1.5 Hz, H4), 7.05 (t, 2H, J = 8.7 Hz, H3″/H5″), 7.24–7.37 (m, 5H, Ph), 7.72 (dd, 2H, J = 8.7 Hz and J = 5.4 Hz, H2″/H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.70 (s, C7), 111.34 (s, C6), 115.93 (d, $J_{C\text{-}F}$ = 21.7 Hz, C3″/C5″), 126.99 (s, C4′), 128.88 (s, C3′/C5′), 128.93 (s, C2′/C6′), 129.43 (d, $J_{C\text{-}F}$ = 3.5 Hz, C1″), 132.29 (d, $J_{C\text{-}F}$ = 8.1 Hz, C2″/C6″), 132.51 (s, C3), 137.15 (s, C1′), 139.54 (s, C4), 147.09 (s, C5), 162.83 (d, $J_{C\text{-}F}$ = 249.5 Hz, C4″), 170.28 (s, C2); MS, *m/z* (%) 280 (M^+, $C_{18}H_{13}FO_2$, 100), 262 (17), 235 (39), 220 (13), 215 (11), 185 (10), 144 (19), 116 (33), 115 (44), 108 (69), 107 (43), 91 (31), 77 (6), 65 (18), 51 (15).

*Data for (5Z)-3-Benzyl-5-(3-fluorobenzylidene)furan-2(5H)-one (**22**)*: white solid; mp 89.2–89.8 °C; purified by column chromatography, eluent dichloromethane/hexane (2:1 v/v); IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 3099, 3034, 2922, 2826, 1763, 1649, 1603, 1576, 1445, 1017, 933, 878, 784, 758; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.73 (br s, 2H, H7), 5.83 (s, 1H, H6), 6.94 (t, 1H, J = 1.5 Hz, H4), 6.99 (ddd, 1H, J = 8.3 Hz, J = 2.6 Hz and J = 0.9 Hz, H4″), 7.25–7.37 (m, 6H, H2′/H6′, H3′/H5′, H4′, and H3″), 7.45 (br d, 1H, J = 7.8 Hz, H2″), 7.49 (m, 1H, H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.78 (s, C7), 111.20 (s, C6), 115.82 (d, $J_{C\text{-}F}$ = 21.4 Hz, C4″), 116.77 (d, $J_{C\text{-}F}$ = 22.7 Hz, C6″), 126.17 (d, $J_{C\text{-}F}$ = 2.8 Hz, C2″), 127.07 (s, C4′), 128.93 (s, C3′/C5′), 128.96 (s, C2′/C6′), 130.17 (d, $J_{C\text{-}F}$ = 8.3 Hz, C3″), 133.40 (s, C3), 135.15 (d, $J_{C\text{-}F}$ = 8.2 Hz, C1″), 139.42 (s, C4), 148.17 (s, C5), 162.92 (d, $J_{C\text{-}F}$ = 244.3 Hz, C5″), 170.00 (s, C2); MS, *m/z* (%) 280 (M^+, $C_{18}H_{13}FO_2$, 100), 262 (17), 235 (39), 220 (13), 215 (11), 185 (10), 144 (19), 116 (33), 115 (44), 108 (69), 107 (43), 91 (31), 77 (6), 65 (18), 51 (15).

*Data for (5Z)-3-Benzyl-5-(2-fluorobenzylidene)furan-2(5H)-one (**23**):* white solid; mp 124.7–125.1 °C; purified by column chromatography, eluent dichloromethane/hexane (2:1 v/v); IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 3104, 3062, 3024, 2932, 2848, 1758, 1655, 1614, 1605, 1485, 1457, 1229, 1029, 755, 699, 645; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.73 (br s, 1H, H7), 6.18 (t, 1H J = 1.2 Hz, H6), 7.02–7.07 (m, 1H, H3″), 7.18 (t, 1H, J = 7.6 Hz, H5″), 7.26–7.37 (m, 6H, Ph and H4″), 8.20 (dt, 1H, J = 9.3 Hz, J = 7.8 Hz, and J = 1.5 Hz, H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.73 (s, C7), 103.48 (d, $J_{C\text{-}F}$ = 7.9 Hz, C6), 115.25 (d, $J_{C\text{-}F}$ = 21.9, C3″), 121.23 (d, $J_{C\text{-}F}$ = 11.1 Hz, C1″), 124.60 (d, $J_{C\text{-}F}$ = 3.7 Hz, C5″), 127.04 (s, C4′), 128.85 (s, C3′/C5′), 128.90 (s, C2′/C6′), 130.42 (d, $J_{C\text{-}F}$ = 8.6 Hz, C4″), 131.44 (d, $J_{C\text{-}F}$ = 1.2 Hz, C6″), 133.19 (s, C3), 136.98 (s, C1′), 139.65 (s, C4), 148.31 (d, $J_{C\text{-}F}$ = 2.2 Hz, C5), 160.56 (d, $J_{C\text{-}F}$ = 250.6 Hz, C2″), 170.17 (s, C2); MS, *m/z* (%) 280 (M^+, $C_{18}H_{13}FO_2$, 100), 262 (19), 235 (44), 215 (17), 198 (8), 185 (14), 144 (19), 136 (28), 116 (41), 115 (60), 108 (68), 107 (52), 91 (37), 77 (8), 65 (20), 51 (18).

*Data for (5Z)-3-Benzyl-5-(2-chlorobenzylidene)furan-2(5H)-one (**24**)*: white solid; mp 68.3–69.5 °C; purified by column chromatography, eluent hexane/dichloromethane (2:1 v/v); IR (film, dichloromethane, cm^{-1}), $\bar{\nu}_{max}$ 3090, 3063, 3029, 2918, 1769, 1646, 1609, 1470, 1023, 941, 736, 698; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.74 (s, 2H, H7), 6.36 (s, 1H, H6), 7.01 (s, 1H, H4), 7.2 (td, 1H, J = 7.6 Hz, J = 1.7 Hz, H4″), 7.26–7.36 (m, 6H, Ph and H5″), 7.38 (dd, 1H, J = 7.6 Hz and 1.2 Hz, H3″), 8.20 (dd, 1H, J = 7.9 and 1.6 Hz, H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.74 (C7), 107.76 (C6), 127.05 (C4′), 127.20 (C5″), 128.91 and 128.95 (C2′/C6′ and C3′/C5′), 129,64 (C3″), 129,73 (C4″), 130.94 (C1″), 131.86 (C6″), 133.33 (C3), 134.18 (C2″), 136.92 (C1′), 139,81 (C4), 148.46 (C5), 170.14 (C2); MS, *m/z* (%) 298, (M + 2, 20), 296 (M^+, $C_{18}H_{13}ClO_2$, 58), 243 (21), 233 (16), 215 (34), 202 (15), 152 (18), 144 (16), 115 (51), 107 (14), 91 (33), 89 (100), 77 (8), 65 (15), 63 (25), 51 (12).

*Data for (5Z)-3-Benzyl-5-(2-methylbenzylidene)furan-2(5H)-one (**25**)*: white solid; mp 103.3–103.9 °C; purified by column chromatography, eluent hexane/dichloromethane (2:1 v/v); IR (film, dichloromethane, cm^{-1}), $\bar{\nu}_{max}$ 3061, 3027, 2922, 1766, 1647, 1609, 1485, 1032, 937, 823, 756; ^{1}H NMR (400 MHz, $CDCl_3$), δ 2.36 (s, 3H, CH_3), 3.72 (s, 2H, H7), 6.07 (s, 1H, H6), 6.97 (s, 1H, H4), 7.16–7.29 (m, 6H, H2′/H6′, H4′, H3″, H4″, and H5″), 7.33–7.37 (m, 2H, H3′/H5′), 8.08 (d, 1H, J = 7.6 Hz, H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 20.09 (CH_3), 31.70 (C7), 109.66 (C6), 126.52 (C3″), 126.96 (C4′), 128.87, 128.97 (C2′/C6′, C3′/C5′, and C4″), 130.35 (C5″), 130.74 (C6″), 131.58 (C2″), 132.47 (C3), 137.07 (C1″), 137.23 (C1′), 139.80 (C4), 147.57 (C5), 170.54 (C2); MS, *m/z* (%) 276 (M^+, $C_{19}H_{16}O_2$, 100), 215 (15), 185 (24), 157 (26), 129 (23), 116 (26), 115 (56), 104 (34), 91 (35), 78 (38), 77 (32), 65 (20), 51 (22).

*Data for (5Z)-3-Benzyl-5-(4-ethylbenzylidene)furan-2(5H)-one (**26**)*: white amorphous solid; purified by column chromatography, eluent hexane/dichloromethane (2:1 v/v); IR (film, dichloromethane, cm^{-1}), $\bar{\nu}_{max}$ 3089, 3029, 2961, 2927, 2885, 1759, 1650, 1603, 1036, 937, 698; ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.24 (t, 3H, J = 7.6 Hz, $-CH_2CH_3$), 2.65 (q, 2H, J = 7.6 Hz, $-CH_2CH_3$), 3.72 (s, 2H, H7), 5.85 (s, 1H, H6), 6.93 (s, 1H, H4), 7.20 (d, 2H, J = 8.1 Hz, H3″/H5″), 7.25–7.36 (m, 5H, Ph), 7.66 (d, 2H, J = 8.1 Hz, H2″/H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 15.31 ($-CH_2CH_3$), 28.79 ($-CH_2CH_3$), 31.69 (C7), 112.85 (C6), 126.92 (C4′), 128.37 (C3″/C5″), 128.85 (C3′/C5′), 128.94 (C2′/C6′), 130.55 (C2″/C6″), 130.64 (C1″), 131.99 (C3), 137.33 (C1′), 139.68 (C4), 145.59 (C4″), 146.96 (C5), 170.54 (C2); MS, *m/z* (%) 290 (M^+, $C_{20}H_{18}O_2$, 100), 275 (18), 261 (8), 243 (18), 215 (20), 202 (10), 131 (72), 115 (75), 91 (41), 77 (43), 65 (22), 63 (19), 51 (19).

*Data for (5Z)-3-Benzyl-5-(2-bromobenzylidene)furan-2(5H)-one (**27**)*: yellow oil; purified by column chromatography, eluent hexane/dichloromethane (2:1 v/v); IR (film, NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3090, 3062, 3028, 2923, 2852, 1769, 1609, 1644, 1585, 1555, 1023, 940, 753, 699; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.73 (s, 2H, H7), 6.32 (s, 1H, H6), 7.01 (s, 1H, H4), 7.14 (t, 1H, J = 7.6 Hz, H4″), 7.19–7.38 (m, 6H, H5″ and Ph), 7.58 (d, 1H, J = 8 Hz, H3″), 8.19 (d, 1H, J = 8.0 Hz, H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.77 (C7), 110.51 (C6), 124.96 (C2″), 127.07 (C4′), 127.81 (C5″), 128.93 (C3′/C5′), 128.96 (C2′/C6′), 132.03 (C6″), 132.60 (C1″), 133.02 (C3″), 133.37 (C3), 136.93 (C1′), 139.78 (C4), 148.46 (C5), 170.12 (C2); MS, *m/z* (%) 342 (M + 2, 37), 340 (M^+, $C_{18}H_{13}BrO_2$ 36), 243 (13), 233 (13), 215 (38), 202 (20), 144 (12), 115 (52), 91 (32), 89 (100), 77 (10), 65 (15), 63 (53), 51 (19).

*Data for (5Z)-3-Benzyl-5-(pentafluorobenzylidene)furan-2(5H)-one (**28**)*: pale yellow solid; mp 137.2–137.6 °C; purified by column chromatography, eluent hexane/dichloromethane (2:1 v/v); IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 3098, 3075, 3026, 2926, 1766, 1671, 1619, 1523, 1495, 1041, 998, 981, 935, 885, 750; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.73 (s, 2H, H7), 5.75 (s, 1H, H6), 6.97 (s, 1H, H4), 7.25–7.38 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.95 (C7), 95.01 (C6), 127.26 (C4′), 128.99 (C3′/C5′), 129.02 (C2′/C6′), 136.38 (C1′), 136.77 (C3), 137.65 (C4), 151.14 (C5), 168.83 (C2); MS, *m/z* (%) 352 (M^+, $C_{18}H_9F_5O_2$, 50), 307 (18), 287 (32), 180 (24), 161 (13), 115 (100), 91 (24), 77 (9), 65 (26), 51 (21). Note: Signals for carbons of the benzylidene ring were not observed.

*Data for (5Z)-3-Benzyl-5-(4-cyanobenzylidene)furan-2(5H)-one (**29**)*: white solid; mp 140.1–140.9 °C; purified by column chromatography, eluent hexane/ethyl acetate (4:1 v/v); IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 3061, 3027, 2926, 2856, 2234, 1759, 1651, 1612, 1601, 1033, 938, 838, 750, 697, 555; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.74 (s, 2H, H7), 5.86 (s, 1H, H6), 6.97 (s, 1H, H4), 7.25–7.37 (m, 5H, Ph), 7.61 (d, 2H, J = 8.4 Hz, H3″/H5″), 7.79 (d, 2H, J = 8.4 Hz, H2″/H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.79 (C7), 110.03 (C6), 111.63 (C4″), 118.63 (CN), 127.14 (C4′), 128.91 (C3′/C5′), 128.95 (C2′/C6′), 130.51 (C2″/C6″), 132.35 (C3″/C5″), 134.45 (C3), 136.67 (C1′), 137.53 (C1″), 139.23 (C4),

149.48 (C5), 169.52 (C2); MS, *m/z* (%) 290 (M^+, $C_{19}H_{13}NO_2$, 100), 275 (18), 261 (8), 243 (18), 215 (20), 202 (10), 131 (72), 115 (75), 91 (41), 77 (43), 65 (22), 63 (19), 51 (19).

*Data for (5Z)-3-Benzyl-5-(4-trifluoromethylbenzylidene)furan-2(5H)-one (**30**)*: white solid; mp 92.7–93.3 °C; purified by column chromatography, eluent hexane/dichloromethane (2:1 v/v); IR (film, dichloromethane, cm^{-1}), $\bar{\nu}_{max}$ 3088, 3064, 3030, 1773, 1654, 1617, 1325, 1167, 1124, 940, 699; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.74 (s, 2H, H7), 5.87 (s, 1H, H6), 6.97 (s, 1H, H4), 7.26–7.38 (m, 5H, Ph), 7.60 (d, 2H, J = 8.2 Hz, H3″/H5″), 7.82 (d, 2H, J = 8.2 Hz, H2″/H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.78 (s, C7), 110.61 (s, C6), 123.93 (q, $J_{C\text{-}F}$ = 270.4 Hz, $\underline{C}F_3$), 125.62 (q, $J_{C\text{-}F}$ = 3.7 Hz, C3″/C5″), 128.93 (s, C2′/C6′ and C3′/C5′), 130.19 (q, $J_{C\text{-}F}$ = 32.3 Hz, C4″), 130.37 (s, C2″/C6″), 133.94 (s, C3), 136.46 (s, C1″), 136.81 (s, C1′), 139.56 (s, C4), 148.81 (s, C5), 169.87 (s, C2); MS, *m/z* (%) 330 (M^+, $C_{19}H_{13}F_3O_2$, 94), 312 (11), 285 (33), 248 (8), 233 (12), 215 (32), 202 (9), 158 (52), 144 (20), 116 (63), 115 (100), 91 (51), 89 (38), 77(11), 63 (26), 51 (27).

*Data for (5Z)-3-Benzyl-5-(3-trifluoromethylbenzylidene)furan-2(5H)-one (**31**)*: white solid; mp 95.4–96.5 °C; purified by column chromatography, eluent hexane/dichloromethane (2:1 v/v); IR (film, dichloromethane, cm^{-1}), $\bar{\nu}_{max}$ 3088, 3062, 3030, 2918, 1770, 1653, 1607, 1330, 1167, 1126, 1025, 942, 907, 882, 800, 695; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.74 (br s, 2H, H7), 5.88 (s, 1H, H6), 6.97 (t, 1H, J = 1.2 Hz, H4), 7.26–7.38 (m, 5H, Ph), 7.48 – 7.56 (m, 2H, H3″ and H4″), 7.86 (br s, 1H, H6″), 7.99 (br d, 1H, J = 7.6 Hz, H2″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31,77 (s, C7), 110.64 (s, C6), 125.17 (q, $J_{C\text{-}F}$ = 270.9 Hz, $\underline{C}F_3$), 125.17 (q, $J_{C\text{-}F}$ = 3.6 Hz, C4″), 126.81 (q, $J_{C\text{-}F}$ = 3.8 Hz, C6″), 127.08 (s, C4″), 128.93 (s, C2′/C6′ and C3′/C5′), 129.31 (s, C3″), 131.20 (q, $J_{C\text{-}F}$ = 32 Hz, C5″), 133.21 (s, C2″), 133.77 (s, C3), 133.86 (s, C1″), 136.88 (s, C1′), 139.33 (s, C4), 148.46 (s, C5), 169.88 (s, C2); MS, *m/z* (%) 330, (M^+, $C_{19}H_{13}F_3O_2$, 91), 312 (11), 285 (40), 243 (15), 233 (13), 215 (33), 202 (12), 158 (52), 144 (19), 116 (60), 115 (100), 91 (52), 89 (43), 77(11), 63 (29), 51 (32).

*Data for (5Z)-3-Benzyl-5-(2-trifluoromethylbenzylidene)furan-2(5H)-one (**32**)*: white amorphous solid; purified by column chromatography, eluent hexane/dichloromethane (2:1 v/v); IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 3089, 3031, 2923, 1770, 1650, 1602, 1574, 1495, 1455, 1315, 1163, 1117, 1035, 943, 765, 699, 657; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.74 (s, 2H, H7), 6.21 (s, 1H, H6), 7.00 (s, 1H, H4), 7.16–7.43 (m, 6H, Ph and H4″), 7.58 (t, J = 8.0 Hz, H5″), 7.67 (d, 1H, J = 8.0 Hz, H3″), 8.25 (d, 1H, J = 8.0 Hz, H6); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.77 (s, C7), 106.96 (s, C6), 124.11 (q, $J_{C\text{-}F}$ = 272.3 Hz, $\underline{C}F_3$), 125.99 (q, $J_{C\text{-}F}$ = 5.8 Hz, C3″), 127.12 (s, C1′), 128.24 (s, C4′), 128.33 (q, $J_{C\text{-}F}$ = 29.6 Hz, C2″), 128.95 (s, C3′/C5′), 128.96 (s, C2′/C6′), 130.92 (br s, C1″), 132.03 (s, C5″), 132.24 (s, C6″), 133.93 (s, C3), 136.75 (s, C1′), 139.77 (s, C4), 148.77 (s, C5), 170.02 (s, C2); MS, *m/z* (%) (M^+, $C_{19}H_{13}F_3O_2$, 100), 285 (44), 215 (36), 158 (54), 144 (21), 115 (100), 91 (53), 89 (39), 77 (12), 65 (28), 63 (29), 51 (44).

*Data for (5Z)-3-Benzyl-5-(cyanobenzylidene)furan-2(5H)-one (**33**)*: white solid; mp 120.2–120.8 °C; purified by column chromatography, eluent hexane/dichloromethane/ethyl acetate (5:1:1 v/v); IR (film, dichloromethane, cm^{-1}), $\bar{\nu}_{max}$ 3086, 3060, 3030, 2231, 1769, 1655, 1610, 1495, 1479, 1454, 1429, 1027, 903, 700, 683; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.74 (s, 2H, H7), 5.82 (s, 1H, H6), 6.96 (s, 1H, H4), 7.25–7.34 (m, 5H, Ph), 7.48 (t, 1H, 8.0 Hz, H3″), 7.56 (br d, 1H, J = 8.0 Hz, H4″), 7.95 (br s, 1H, H6″), 7.98 (br d, 1H, J = 8.0 Hz, H2″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.81 (C7), 109.53 (C6), 113.19 (C5″), 118.37 ($\underline{C}N$), 127.14 (C4′), 128.94 (C3′/C5′), 128.94 (C2′/C6′), 129.62 (C3″), 131.69 (C4″), 133.37 (C6″), 134.06 (C2″), 134.24 (C3), 134.39 (C1″), 136.74 (C1′), 148.92 (C5), 169.57 (C2); MS, *m/z* (%) 287 (M^+, $C_{19}H_{13}NO_2$, 59), 269 (10), 242 (36), 215 (5), 144 (12), 116 (35), 115 (100), 91 (24), 77(6), 65 (15), 51 (13).

*Data for (5Z)-3-Benzyl-5-[3-(N,N-dimethylamino)benzylidene]furan-2(5H)-one (**34**)*: yellow solid; mp 85.1–85.4 °C; purified by column chromatography, eluent hexane/dichloromethane (1:1 v/v); IR (film, dichloromethane, cm^{-1}), $\bar{\nu}_{max}$ 3088, 3029, 2898, 2806, 1761, 1650, 1595, 1571, 1496, 1357, 1031, 935, 699; ^{1}H NMR (400 MHz, $CDCl_3$), δ 2.98 (s, 6H, $N(\underline{C}H_3)_2$), 3.72 (s, 2H, H7), 5.85 (s, 1H, H5), 6.77 (br d, 1H, J = 7.8 Hz, H4″), 6.94 (t, 1H, J = 1.4 Hz, H4), 7.25–7.38 (m, 8H, H2″, H3″, H6″, and Ph); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.64 (C7), 40.91 ($N(\underline{C}H_3)_2$), 113.56 (C6), 113.91 (C6″), 114.46 (C4″), 119.78 (C2″), 126.87 (C4′), 128.80 (C3′/C5′), 128.90 (C2′/C6′), 129.44 (C3″), 132.12 (C3), 133.74 (C1″), 137.21 (C1′), 139.77 (C4), 147.22 (C5), 150.32 (C5″), 170.47 (C2); MS, *m/z* (%) 305 (M^+, $C_{20}H_{19}NO_2$, 100), 276 (8), 215 (5), 160 (16), 129 (23), 115 (16), 91 (17), 77(6), 65 (7), 51 (7).

*Data for (5Z)-3-Benzyl-5-(4-phenylbenzylidene)furan-2(5H)-one (**35**)*: pale yellow solid; mp 156.6–156.8 °C; purified by column chromatography, eluent hexane/diethyl ether (6:1 v/v); IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 3102, 3058, 3026, 2922, 1759, 1646, 1600, 1943, 1454, 1035, 920, 763, 696; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.73 (br s, H7), 5.90 (s, H6), 6.96 (t, 1H, J = 1.4 Hz, H4), 7.25–7.30, 7.33–7.38, 7.42–7.46, 7.60–7.62 (m, 12H, H3″−H5″, and 2 × Ph), 7.80 (d, 2H, J = 8.4 Hz, H2″/H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.73 (C7), 112.31 (C6), 128.94 and 130.91 (C2″/C6″, C3″/C5″), 132.19 (C1″), 132.44 (C3), 139.60 (C4), 141.51 (C4″), 147.54 (C5), 170.39 (C2), 126.97, 127.02, 127.39, and 140.24 (signals for the phenyl ring attached to the benzylidene ring); 127.74, 128.88, 137.22 (signals for the benzyl ring)*; MS, *m/z* (%) 338 (M^+, $C_{24}H_{18}O_2$, 100), 215 (9), 194 (21), 165 (90), 115 (32), 91 (25), 77 (9), 65 (10), 51 (9). *, there was a signal coincidence for C-2′/C-6′and C-3′/C-5′.

*Data for (5Z)-3-Benzyl-5-(4-hydroxy-3-methoxybenzylidene)furan-2(5H)-one (**39**)*: yellow solid; mp 142.9–143.3 °C; purified by column chromatography, eluent hexane/ethyl acetate (2:1 v/v); IR (KBr, cm^{-1}), $\bar{\nu}_{max}$ 3309 (broadband), 3602, 3028, 3002, 2955, 2912, 2836, 1732, 1602, 1651, 1581, 1517, 1293, 1048, 888, 751, 699; ^{1}H NMR (400 MHz, $CDCl_3$), δ 3.71 (s, 2H, H7), 3.94 (s, 3H, $OC\underline{H}_3$), 5.80 (s, 1H, H6), 5.86 (s, 1H, $O\underline{H}$), 6.89 (d, 1H, J = 8.3 Hz, H3″), 6.93 (s, 1H, H4), 7.12 (dd, 1H, J = 8.3 Hz and J = 1.9 Hz, H2″), 7.25–7.36 (m, 5H, Ph), 7.45 (d, 1H, J = 1.9 Hz, H6″); ^{13}C NMR (100 MHz, $CDCl_3$), δ 31.66 (C7), 56.11 ($O\underline{C}H_3$), 112.10 (C6″), 113.02 (C6), 114.59 (C3″), 125.20 (C2″), 125.87 (C1″), 126.88 (C4″), 128.82 (C3′/C5′), 128.91 (C2′/C6′), 131.15 (C3), 137.44 (C1′), 139.68 (C4), 145.94 (C4), 146.75 (C5″), 146.90 (C4″), 170.54 (C2); MS, *m/z* (%) 308 (M^+, $C_{19}H_{16}O_4$, 100), 164 (50), 149 (22), 136 (28), 115 (43), 101 (19), 91 (37), 77 (24), 65 (61), 51 (24).

Biological Tests. The ability of the synthesized compounds to interfere with the photosynthetic electron transport chain was evaluated in vitro by the Hill reaction, as previously described (*38*). Photosynthetically active thylakoid membranes were isolated from market spinach (*Spinacea oleracea* L.) leaves. Deveined plant material was resuspended in 5 mL g^{-1} of ice-cold 20 mM *N*-tris(hydroxymethyl) methylglycine (Tricine)−NaOH buffer (pH 8.0) containing 10 mM NaCl, 5 mM $MgCl_2$, and 0.4 M sucrose and homogenized for 30 s in a blender at maximal speed. The homogenate was filtered through surgical gauze, and the filtrate was centrifuged at 4 °C for 1 min at 500*g*; the supernatant was further centrifuged for 10 min at 1500*g*. Pelleted chloroplasts were osmotically swollen by resuspension in sucrose-lacking buffer. The suspension was immediately diluted 1:1 with sucrose-containing buffer, kept on ice in the dark, and used within a few hours from preparation. Following proper dilution with 80% (v/v) acetone, the absorbance of each sample was determined at 645 and 663 nm, and the chlorophyll content was calculated on the basis of Arnon's formula. The basal rate of photosynthetic electron transport was measured following light-driven ferricyanide reduction. Aliquots of membrane preparations corresponding to 20 μg of chlorophyll were incubated at 24 °C in 1- mL cuvettes containing 20 mM Tricine−NaOH buffer (pH 8.0), 10 mM NaCl, 5 mM $MgCl_2$, 0.2 M sucrose, and 1 mM $K_3Fe(CN)_6$. The assay was initiated by exposure to saturating light (800 μmol m^{-2} s^{-1}), and the rate of ferricyanide reduction was measured at 30 s intervals for 10 min against an exact blank at 420 nm. Activity was calculated over the linear portion of the curve from a molar extinction coefficient of 1000 M^{-1} cm^{-1}. The mean value for untreated controls was 59.3 ± 2.2 nmol s^{-1} (mg of chlorophyll)$^{-1}$ in 36 independent thylakoid membrane preparations. Nostoclide analogues were dissolved in DMSO so as to obtain 25 or 50 mM solutions that were then diluted with water, as appropriate. Their effect upon the Hill reaction was evaluated in parallel assays in which the compounds were added to the reaction mixture to concentrations of 5, 10, or 20 μM. Each dose was carried out at least in triplicate, and results were expressed as percentage of untreated controls.

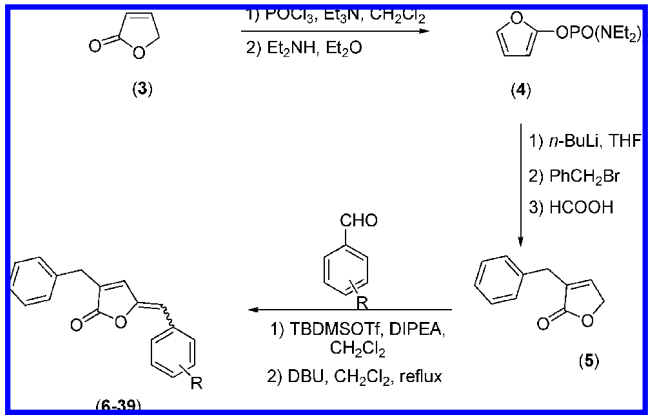

Figure 3. Synthetic steps involved in the preparation of nostoclide analogues **6–39**.

Molecular Modeling. Molecular modeling calculations were carried out with the AM1 semiempirical method (*47*) as implemented in the TITAN (*48*) molecular orbital package. Calculations were done for both *Z* and *E* stereoisomers. Determination of the most stable conformers for each *Z* or *E* stereoisomer was performed using the conformer distribution subroutine of the TITAN software. After identification of the three or four most relevant conformers in each case, these were further fully optimized with the AM1 method.

RESULTS AND DISCUSSION

Synthesis of Nostoclide Analogues. The synthesis of nostoclide analogues was accomplished as previously described (*37, 38, 45, 46*). Briefly, reaction of lactone (**5**), prepared as shown in **Figure 3**, with pertinent aldehydes in the presence of *tert*-butyldimethylsilyltrifluoromethanesulfonate and diisopropylethylamine followed by treatment of the silyl ether generated in situ with DBU (*43, 49–53*) afforded compounds **6–39** in yields ranging from 12 to 91% (**Table 1**). It is important to note that in the preparation of compounds **36**−**39**, *tert*-butyldimethylsilyloxy aldehydes were employed. After various attempts, the removal of the *tert*-butyldimethylsilyl protecting group was achieved with a mixture of MeCN/HF (1:1 v/v) (*46, 54*).

Although reaction conditions were not optimized, in general the reactions were complete 3 h after the addition of DBU under refluxing. For the preparation of the compounds **12**, **15**, **29**, and **30**−**33**, the reaction mixture was refluxed for 1 h, a procedure that afforded these compounds in moderate yields. It was observed that extended refluxing time led to the formation of a complex mixture. For reasons not well understood, some compounds were obtained with low yield (**Table 1**). The structures of lactones (**6**−**39**) were confirmed on the basis of NMR, IR, and MS analyses. In all cases, the presence of a molecular ion peak was observed in the MS spectra, which correlated with the expected molecular formulas. The IR spectra of these compounds revealed intense absorption bands for carbonyl groups ranging from 1721 to 1773 cm^{-1}. Interestingly, the frequency of the carbonyl stretching varies with the substitution pattern in the benzylidene ring. A combination of two-dimensional NMR analyses (HSQC and HMBC) of the lactones synthesized not only confirmed the presence of the five-membered ring α,β-unsaturated lactone moiety, substituted by both the benzyl and benzylidene functionalities, but also allowed complete hydrogen and carbon assignments. Some of the major long-range correlations (J^2 and J^3) observed in the HMBC contour plot of compound **14** are outlined in structure **A** (**Figure 4**).

The stereochemistry of the exocyclic double bond in lactones **6**−**39** was confirmed by bidimensional NOESY experiment.

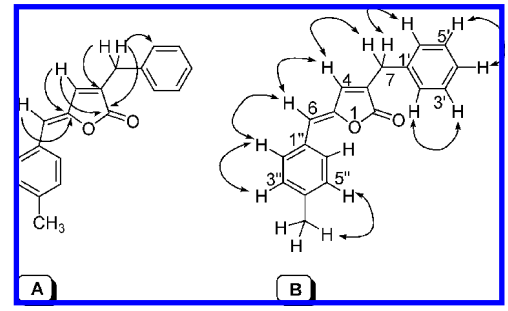

Figure 4. Selected long-range HMBC (structure **A**) and NOESY (structure **B**) correlations found in the corresponding contour plots of compound **14**.

With the exception of compound **8**, all lactones synthesized exhibited the *Z* configuration (**Table 1**). This configuration was supported by the observation of a NOE cross-peak between H4 and H6, as exemplified for compound **14** in **Figure 4** (structure **B**). Other correlations found in the NOESY contour plot of **14** are also shown. Regarding compound **8**, the exocyclic double bond presented an *E* configuration. Because the ortho positions are both substituted by methoxy groups, the compound attains the *E* configuration to alleviate the nonbonding destabilizing steric interaction between O-1 in the lactone ring and the methoxy groups. In fact, density functional theory calculations (B3LYP/6-31+G(d) level) using the Gaussian 03 program demonstrated that for substance **8** the *E* configuration is more stable than the *Z* configuration (*45*). The opposite situation is observed for the other nostoclide analogues synthesized. In these cases, AM1 calculations revealed that the *Z* isomer is more stable than the *E* isomer, on average by 0.8 kcal mol^{-1}. Although the energy differences between both isomers are indeed small, it is systematic, always giving the *Z* stereoisomer as the more stable. Therefore, experimental preference for the *Z* stereoisomer seems to indicate that the isomer selection forces drive the reaction to the thermodynamically more stable isomer. Preferential formation of *Z* stereoisomers was also recently reported for similar systems (*55*).

Inhibition of the Photosynthetic Electron Transfer in Thylakoids. Because of their structural similarity to cyanobacterin and to other nostoclide analogues, both of which had been previously found to inhibit the photosynthetic electron transport chain (*32, 37, 38*), the synthesized compounds were expected to potentially show biological activity against the photosynthetic process. To verify such a hypothesis, their ability to interfere with ferricyanide reduction by isolated spinach chloroplasts was evaluated. Results are summarized in **Table 2**. At 5×10^{-6} M, 21 of the 34 compounds were indeed able to significantly reduce the rate of the light-driven electron transport chain, whereas 13 analogues were substantially ineffective. Among the active compounds, at 10^{-5} M, 8 analogues (**8**, **11**, **12**, **23**, **26**, **30**−**32**) caused more than 40% inhibition. It should be noted that compounds **12** and **30**, which present a strong electron-withdrawing group at the para position, exhibited the highest percentage of inhibition. The effectiveness even of the most active derivatives was strikingly lower than that of the commercial herbicide diuron, taken as a comparison term. Notwithstanding this, the occurrence of a remarkable variability among the compounds suggests that the presence of various substituents in the benzylidene moiety, and their position as well, may strongly influence the ability to interfere with the photosynthetic apparatus. In particular, the presence of a trifluoromethyl group at any of the three positions, as in compounds **30**−**32**, was found to significantly enhance the effect against the Hill reaction.

Table 2. In Vitro Effects of Nostoclide Analogues on Ferricyanide Reduction by Functionally Intact Chloroplasts Isolated from *Spinacia oleracea* Leaves[a]

compd	arylidene group	5 μM	10 μM
6	benzylidene	12.7 ± 3.2	29.2 ± 1.4
7	1,3-dioxalenebenzylidene	N	N
8	2,4,6-trimethoxybenzylidene	25.2 ± 2.4	43.6 ± 2.1
9	4-dimethylaminobenzylidene	5.7 ± 2.7	7.1 ± 1.5
10	2-chloro-4-dimethylaminobenzylidene	13.8 ± 1.5	25.37 ± 4.2
11	2,5-dimethoxybenzylidene	30.3 ± 0.6	43.5 ± 2.7
12	4-nitrobenzylidene	49.8 ± 1.6	57.8 ± 1.0
13	3-bromobenzylidene	13.8 ± 3.6	22.6 ± 2.9
14	4-methylbenzylidene	N	8.0 ± 1.7
15	3-nitrobenzylidene	30.0 ± 1.0	39.5 ± 0.8
16	3-methylbenzylidene	8.0 ± 2.1	16.7 ± 2.6
17	4-chlorobenzylidene	N	5.8 ± 1.4
18	3-chlorobenzylidene	5.8 ± 0.7	20.3 ± 4.8
19	4-methoxybenzylidene	8.5 ± 0.7	15.0 ± 1.4
20	4-fluorobenzylidene	9.2 ± 1.1	25.6 ± 1.8
21	4-bromobenzylidene	N	N
22	3-fluorobenzylidene	9.5 ± 2.9	28.8 ± 1.2
23	2-fluorobenzylidene	24.5 ± 3.3	49.5 ± 1.9
24	2-chlorobenzylidene	19.4 ± 2.3	30.8 ± 3.7
25	2-methylbenzylidene	16.7 ± 0.4	26.0 ± 0.1
26	4-ethylbenzylidene	40.6 ± 1.5	50.7 ± 4.1
27	2-bromobenzylidene	N	21.8 ± 2.2
28	pentafluorobenzylidene	N	6.6 ± 2.8
29	4-cyanobenzylidene	N	N
30	4-trifluoromethylbenzylidene	34.6 ± 2.7	55.5 ± 1.7
31	3-trifluoromethylbenzylidene	27.3 ± 4.8	49.9 ± 1.7
32	2-trifluoromethylbenzylidene	23.5 ± 4.5	44.9 ± 2.6
33	3-cyanobenzylidene	N	N
34	3-dimethylaminobenzylidene	10.9 ± 3.2	38.6 ± 5.4
35	4-phenylbenzylidene	N	N
36	2-hydroxybenzylidene	N	N
37	3-hydroxybenzylidene	N	6.9 ± 0.8
38	4-hydroxybenzylidene	N	6.5 ± 2.3
39	3-hydroxy-4-methoxybenzylidene	N	N
diuron		93.2 ± 0.5	95.1 ± 0.7

[a] Basal activity was measured as described under Materials and Methods either in the absence or in the presence of nostoclide analogues at a concentration of 5 or 10 μM. Each treatment was carried out in triplicate, and values (±SD) were expressed as percent inhibition of the rate of ferricyanide reduction in untreated controls. N, no effect ($P < 0.05$).

As to the scaffold effect, the activity of 12 of the compounds was compared with that of a group of 3-(4-bromobenzyl)-5-arylmethylene-5*H*-furan-2-one lactones, previously synthesized and characterized (*38*), that differ only by a bromine substituent in the benzyl moiety. The effect of each pair on the rate of the light-driven electron transport chain at 20 μM is shown in **Figure 5**. A noteworthy correlation between the corresponding effects seems to account once more for a pivotal role of the substituents in the benzylidene moiety as the determinant of the biological activity. In the case of the active compounds, the distribution of all dots above the 1:1 line, with the only exception that of compound **16** versus its brominated counterpart, suggests a general, slightly higher effectiveness of non-brominated nostoclide analogues, mainly for compounds **8** and **10**. Preliminary data seem to relate such a higher efficacy to a different water solubility, thus facilitating the access of the inhibitors to the active site and/or their partition between water and the lipophilic thylakoid membranes. However, further data are required to elucidate this point.

A number of new analogues of the naturally occurring toxins nostoclides were synthesized, purified, and thoroughly characterized from a chemical point of view. Their potential as inhibitors of photosynthetic electron transfer was investigated. Several of them were able to various degrees to interfere with the light-driven ferricyanide reduction by isolated chloroplasts.

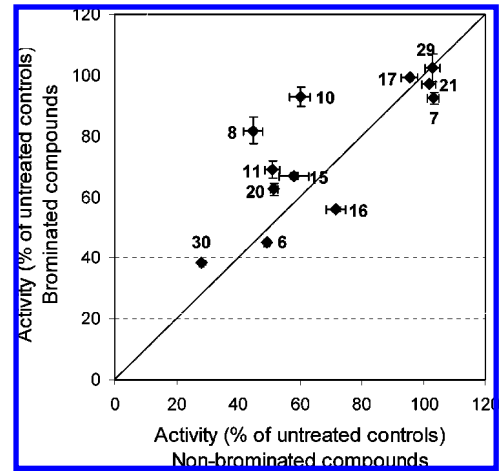

Figure 5. Comparison between the effectiveness of 3-benzyl-5-(arylmethylene)-furan-2(*5H*)-ones **6**−**8**, **10**, **11**, **15**−**17**, **20**, **21**, **29**, and **30**, and their (4-bromobenzyl)- counterparts (*38*). The photosynthetic electron transport rate was measured either in the absence or in the presence of each compound at 20 μM. Assays were carried out in triplicate, and values are expressed as percentage ± SD of untreated controls. The 1:1 line indicates equipotency. A point above the line shows that the brominated analogue is less effective than the corresponding nonbrominated compound, vice versa for a point below the line.

However, when added at micromolar concentrations none of the compounds was capable of completely suppressing the Hill reaction. Nevertheless, their inhibitory potential is higher than that of other nostoclide analogues previously characterized in our laboratories (*37, 38*). Moreover, the strong effect of the substituents in the benzylidene moiety in varying nostoclide effectiveness opens the way to the exploitation of their structure for the design of new substances endowed with biological activity. On the basis of a structure–activity relationship analysis of the present data, work is currently under way both to achieve the synthesis of new nostoclide analogues with better photosynthesis-inhibiting properties and to evaluate in vivo effects of the most active compounds.

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