JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Article

pubs.acs.org/JAFC

Synthesis of Rubrolide Analogues as New Inhibitors of the Photosynthetic Electron Transport Chain

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Supporting Information

ABSTRACT: Many natural products have been used as a model for the development of new drugs and agrochemicals. Following this strategy 11 rubrolide analogues, bearing electron-withdrawing and -donating groups at both benzene rings, were prepared starting from commercially available mucobromic acid. The ability of all compounds to inhibit the photosynthetic electron transport chain in the chloroplast was investigated. The rubrolide analogues were effective in interfering with the light-driven ferricyanide reduction by isolated chloroplasts. The IC_{50} values of the most active derivatives are in fact only 1 order of magnitude higher than those of commercial herbicides sharing the same mode of action, such as Diuron (0.27 μM). QSAR studies indicate that the most efficient compounds are those having higher ability to accept electrons, either by a reduction process or by an electrophilic reaction mechanism. The results obtained suggest that the rubrolide analogues represent promising candidates for the development of new active principles targeting photosynthesis to be used as herbicides.

KEYWORDS: *γ-alkylidenebutenolides, rubrolides, QSAR, Hill reaction inhibitors*

INTRODUCTION

During the past decades synthetic herbicides have been playing a very important role in controlling weeds in agriculture, contributing to the increase in crop productivity. Due to the development of herbicide resistance in weeds, the discovery of new active molecules continues to be an active area of research. In this endeavor old herbicides such as 2,4-dichlorophenoxyacetic acid have recently been modified to produce some new very active phosphorus derivatives that inhibit the pyruvate dehydrogenase complex.[1,2] The old class of diphenyl ether herbicides has also been the subject of recent investigation, and new compounds bearing an unsaturated carboxylate group have been discovered. This group of compounds constitutes the first commercial class of herbicides that inhibit the protoporphyrogen IX oxidase (PPO) enzyme.[3] In the search for new "green herbicides" the acetohydroxyacid synthase enzyme (AHAS) has been targeted, and novel disulfide-containing [1,2,4]triazole groups and isatin derivatives were produced. Such compounds constitute new candidates for the discovery of new herbicides for controlling weeds resistant to current commercial AHAS inhibitors.[4,5]

In line with the international community and within the framework of long-established research on substances with potential use as agrochemicals, especially for weed control, we have been using natural products isolated from microorganisms[6,7] and plants[8,9] as a model for the development of new biologically active compounds. This is a widely used strategy for the development of new agrochemicals.[10] In a previous study we prepared a series of compounds with general structure **3** using the naturally occurring nostoclides I and II (**1**, **2**) as models (Figure 1).

Several of them were found to inhibit the light-driven reduction of ferricyanide by isolated spinach chloroplasts, the so-called Hill reaction.[11] Further investigation led to the preparation of analogues of **3** bearing a chlorine at the 3-position of the benzyl ring. Most of these compounds were effective inhibitors of the growth of *Sorghum bicolor* and showed moderate activity against *Cucumis sativus*.[12] Introduction of a bromine on the benzyl ring at the para position resulted in a decrease of activity.[13] A QSAR analysis demonstrated that their effectiveness as Hill reaction inhibitors is in part associated with the presence of electron-withdrawing groups at the benzylidene unit.[14] The introduction of an isopropyl unit at position 4 of the lactone ring did not improve the inhibitory potential.[15] Although the synthetic analogues of nostoclides interfere with the photosynthetic apparatus at micromolar concentrations, their activity was limited by poor water solubility.

In view of the above promising results, we envisaged that rubrolides (Figure 1), due to their structural resemblance with nostoclides, could also represent a model for the development of new inhibitors targeting the photosynthetic electron transport chain. The rubrolides represent a large family of butenolides first isolated from the colonial tunicate *Ritterella*

Received: July 6, 2012
Revised: October 1, 2012
Accepted: October 2, 2012
Published: October 2, 2012

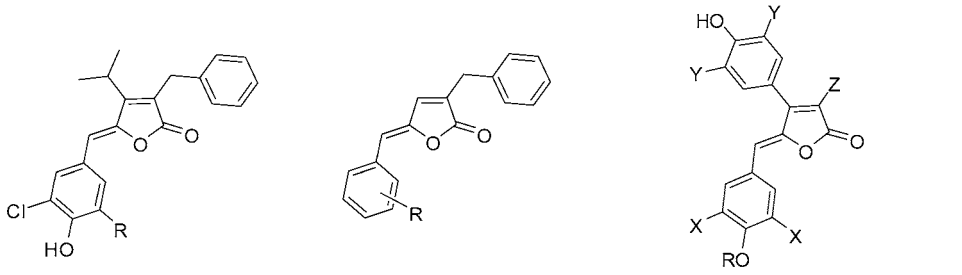


Figure 1. Naturally occurring lactones known as nostoclides I and II (**1**, **2**) and 3-benzyl-5-(arylmethylene)furan-2(5*H*)-ones designed on the basis of the nostoclides (**3**) and rubrolide A (**4**).[5]

rubra.[16] Further work resulted in the isolation of six other rubrolides from the ascidia *Synoicum blochmanni*.[17] Due to their properties, including anti-inflammatory activity,[18] cytotoxicity, and ability to inhibit human aldose reductase, these compounds caught the attention of many synthetic chemists, leading to several total syntheses.[19−22] Despite all of these efforts, to the best of our knowledge no one has to date investigated the ability of such compounds to inhibit photosynthesis in isolated chloroplasts. In this work we describe the preparation of several rubrolide analogues and their ability to act as inhibitors of the Hill reaction.[23] A QSAR study to correlate the inhibitory potential with theoretical molecular descriptors is also reported.

MATERIALS AND METHODS

General Experimental Procedures. All reactions were carried out under a protective atmosphere of dry nitrogen or utilizing a calcium chloride tube. Solvents were purified and dried as described by Perrin and Armarego.[24] All commercially available reagents were purchased from Aldrich (Milwaukee, WI, USA) and utilized without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 instrument (300 and 75 MHz, respectively), using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as internal standard ($\delta = 0$). IR spectra were obtained using a Perkin-Elmer Paragon 1000 FTIR spectrophotometer, using potassium bromide (1% v/v) disks, scanning from 600 to 4000 cm^{-1}. Low-resolution mass spectra were recorded on a Shimadzu GCMS-QP5050A instrument by direct insertion, EI mode (70 eV). Chemical ionization accurate mass spectra were recorded on an Apex III FT-ICR-MS spectrometer with high resolution (resolution = 10000 fwhm). Values quoted are reported as a ratio of mass to charge in daltons. 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-backed precoated silica gel plates. Column chromatography separations were performed over silica gel (60−230 mesh).

Synthetic Procedures. *3,4-Dibromofuran-2(5H)-one (**6**).* To a 250 mL round-bottom flask was added mucobromic acid (**5**) (7.17 g, 27.8 mmol) in anhydrous methanol (40 mL). After the system had cooled to 0 °C in an ice bath, $NaBH_4$ (1.58 g, 41.70 mmol) was added in small portions. The resulting mixture was stirred for 15 min at 0 °C before a solution of concentrated sulfuric acid (1.5 mL) in methanol (14 mL) previously cooled to 0 °C was added. After a further 15 min of stirring, diethyl ether (375 mL) was added. The organic phase was washed with brine (3 × 30 mL) and dried over magnesium sulfate. After evaporation of the solvent under reduced pressure, the crude product was obtained as a solid. This solid was recrystallized in a mixture of hexane/diethyl ether 1:1 (v/v), resulting in the required lactone **2** as white crystals (5.37 g, 22.4 mmol, 80% of yield): mp 89.9−90.5 °C (mp 90−91 °C);[25] IR (KBr) $\overline{\nu}_{max}$ (cm^{-1}) 1758, 1606, 1429, 1339, 1216, 1096, 1023, 992, 981; δ_H ($CDCl_3$) 4.87 (2H, s, H-5); δ_C ($CDCl_3$) 74.4 (C-5), 114.9 (C-3), 143.8 (C-4), 166.9 (C-2); EI-MS, *m*/*z* (%) 244 ([M + 4]$^{\bullet+}$, $C_4H_2Br_2O_2$, 12), 242 ([M + 2]$^{\bullet+}$, 24), 240 (M$^{\bullet+}$, 9), 215 (7), 213 (15), 211 (8), 163 (98), 161 (100), 133 (23), 131 (20), 119 (27), 117 (28), 107 (16), 105 (23), 81 (15), 79 (13), 53 (33).

*3-Bromo-4-(2-methoxyphenyl)furan-2(5H)-one (**7a**).* To a two-necked round-bottom flask (150 mL) under nitrogen atmosphere and connected to a condenser was added a solution of 3,4-dibromofuran-2(5*H*)-one (**6**) (1.21 g, 5.0 mmol) in anhydrous THF (40 mL). To this solution were added 4-fluoro-2-methoxyphenylboronic acid (0.94 g, 5.50 mmol), Ag_2O (3.48 g, 14.98 mmol), $AsPh_3$ (0.31 g, 1.00 mmol), and $PdCl_2$ $(CH_3CN)_2$ (0.07 g, 0.25 mmol). The reaction mixture was stirred at 65 °C for 24 h, when TLC analysis revealed that all boronic acid had been consumed. The mixture was cooled to room temperature, diluted with ethyl acetate (250 mL), and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to yield a dark residue. The purification of this residue by silica gel column chromatography, eluting with a mixture of DCM/hexane of increasing polarity, produced the required compound **7a** with 76% yield (1.02 g, 3.8 mmol) and a small amount of 2,2′-dimethoxybiphenyl **8a** (1.07 mmol), resulting from the homocoupling of boronic acid: white solid; mp 106.9−107.9 °C; IR (KBr) $\overline{\nu}_{max}$ (cm^{-1}) 3070, 2986, 2958, 2930, 2849, 1775, 1617, 1601, 1457, 1439, 1341, 1312, 1266, 1250, 1122, 1067, 1043, 983, 935, 881, 749; δ_H ($CDCl_3$) 3.87 (s, 3H, 2′-OC$\underline{H}_3$), 5.26 (s, 2H, H-5), 6.99 (dd, 1H, $J_{3',4'}$ = 8.4 Hz, $J_{3',5'}$ = 1.2 Hz, H-3′), 7.08 (dt, 1H, $J_{5',4'} = J_{5',6'}$ = 7.5 Hz, $J_{5',3'}$ = 1.2 Hz, H-5′), 7.47 (ddd, 1H, $J_{4',3'}$ = 8.4 Hz, $J_{4',5'}$ = 7.5 Hz, $J_{4',6'}$ = 1.8 Hz, H-4′), 7.80 (dd, 1H, $J_{6',5'}$ = 7.5 Hz, $J_{6',4'}$ = 1.8 Hz, H-6′); δ_C ($CDCl_3$) 55.8 (2′-O$\underline{C}H_3$), 73.8 (C-5), 108.1 (C-3), 111.6 (C-3′), 118.8 (C-1′), 121.1 (C-5′), 130.3 (C-6′), 132.9 (C-4′), 157.4/157.8 (C-4/C-2′, 170.1 (C-2); EI-MS, *m*/*z* (%) 270 ([M + 2]$^{\bullet+}$, $C_{11}H_9BrO_3$, 34), 268 ([M]$^{\bullet+}$, 35), 241 (30), 239 (32), 226 (11), 224 (12), 189 (100), 161 (17), 145 (23), 133 (36), 131 (51), 115 (22), 105 (75), 102 (33), 89 (38), 77 (46).

*3-Bromo-4-(2-methoxy-4-fluorophenyl)furan-2(5H)-one (**7b**).* Compound **7b** was prepared using the same procedure described for **7a**. It was obtained as a white solid in 76% yield, along with a small amount of **8b** (1.36 mmol), resulting from the homocoupling of the starting boronic acid. Data for **7b**: mp 150.0−151.0 °C; IR (KBr) $\overline{\nu}_{max}$ (cm^{-1}) 3089, 3015, 2995, 2985, 2941, 1757, 1607, 1586, 1495, 1467, 1458, 1349, 1307, 1281, 1158, 1114, 1059, 1031, 987, 955, 835, 752; δ_H ($CDCl_3$) 3.87 (s, 3H, 2′-OC$\underline{H}_3$), 5.24 (s, 2H, H-5), 6.71 (dd, 1H, $J_{3',F}$ = 10.5 Hz, $J_{3',5'}$ = 2.4 Hz, H-3′), 6.80 (ddd, 1H, $J_{5',6'}$ = 8.7 Hz, $J_{5',F}$ = 7.8 Hz, $J_{5',3'}$ = 2.4 Hz, H-5′), 7.85 (dd, 1H, $J_{6',5'}$ = 8.7 Hz, $J_{6',F}$ = 6.3 Hz, H-6′); δ_C ($CDCl_3$) 56.2 (2′-O$\underline{C}H_3$), 73.6 (C-5), 100.1 (d, $J_{C,F}$ = 25.7 Hz, C-3′), 108.1 (C-3), 108.2 (d, $J_{C,F}$ = 21.8 Hz, C-5′), 115.0 (d, $J_{C,F}$ = 3.4 Hz, C-1′), 131.8 (d, $J_{C,F}$ = 10.9 Hz, C-6′), 156.6 (C-4), 159.2 (d, $J_{C,F}$ = 9.8 Hz, C-2′), 165.5 (d, $J_{C,F}$ = 251.3 Hz, C-4′), 169.9 (C-2); EI-MS, *m*/*z* (%) 288 ([M + 2]$^{\bullet+}$, $C_{11}H_8BrFO_3$, 40), 286 ([M]$^{\bullet+}$, 41), 259 (37), 257 (37), 244 (15), 242 (16), 207 (100), 179 (29), 163 (14), 149 (64), 123 (38), 107 (35), 101 (41), 84 (32), 75 (25).

*(Z)-5-(Benzo[d][1,3]dioxol-5-ylmethylene)-3-bromo-4-(2-methoxyphenyl)furan-2(5H)-one (**10d**).* To a two-necked round-bottom flask (25 mL), under nitrogen atmosphere, were added 3-bromo-4-(2-methoxyphenyl)furan-2(5*H*)-one (**3**) (100 mg, 0.37

mmol), dichloromethane (3 mL), TBDMSOTf (101 μL, 0.44 mmol), DIPEA (130 μL, 0.74 mmol), and benzo[*d*][1,3]dioxole-5-carbaldehyde (**9d**) (70 mg, 0.44 mmol). The resulting mixture was stirred at room temperature for 1 h. After this period, DBU (110 μL, 0.74 mmol) was added, and the resultant mixture was refluxed for 1 h before the addition of dichloromethane (70 mL). The resulting organic phase was washed with 3 mol L^{-1} HCl (2 × 25 mL) and brine (2 × 25 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel eluted with dichloromethane/hexane (3:2 v/v) to afford the required product **10d** (81 mg, 0.2 mmol) as a pale yellow solid in 55% yield. This solid was recrystallized from a mixture of dichloromethane/hexane (~1:1 v/v). Data for **10d**: mp 175.6−176.6 °C; IR (KBr) $\overline{\nu}_{max}$ (cm^{-1}) 3054, 3006, 2962, 2938, 2902, 2836, 2782, 1767, 1644, 1603, 1503, 1489, 1447, 1258, 1109, 1039, 802, 754; δ_H ($CDCl_3$) 3.85 (s, 3H, 2′-OC$\underline{H}_3$), 5.86 (s, 1H, H-6), 6.00 (s, 2H, −O−C$\underline{H}_2$−O−), 6.78 (d, 1H, $J_{5″,6″}$ = 8.1 Hz, H-5″), 7.05−7.11 (m, 2H, H-3′, H-6″), 7.10 (dt, 1H, $J_{5′,4′}$ = $J_{5′,6′}$ = 7.5 Hz, $J_{5′,3′}$ = 0.9 Hz, H-5′), 7.25 (dd, 1H, $J_{6′,5′}$ = 7.5 Hz, $J_{6′,4′}$ = 1.8 Hz, H-6′), 7.47 (d, 1H, $J_{2″,6″}$ = 1.8 Hz, H-2″), 7.52 (ddd, 1H, $J_{4′,3′}$ = 8.4 Hz, $J_{4′,5′}$ = 7.5 Hz, $J_{4′,6′}$ = 1.8 Hz, H-4′); δ_C($CDCl_3$) 55.9 (2′-O$\underline{C}H_3$), 101.8 (−O−$\underline{C}H_2$−O−), 108.8 (C-5″), 109.8 (C-3), 110.3 (C-2″), 111.9 (C-3′), 114.0 (C-6), 118.1 (C-1′), 120.9 (C-5′), 126.8 (C-6″), 127.3 (C-1″), 130.6 (C-6′), 132.1 (C-4′), 146.6 (C-4″), 148.6 (C-3″), 149.1 (C-5), 152.6 (C-4), 156.9 (C-2′), 165.6 (C-2); HRMS *m*/*z* (M + Na^+) calcd for $C_{19}H_{13}BrNaO_5^+$ 422.9839, found 422.9842; EI-MS, *m*/*z* (%) 402 ([M + 2]$^{•+}$, $C_{19}H_{13}BrO_5$, 80), 400 ([M]$^{•+}$, 79), 321(10), 293 (18), 275 (8), 265 (20), 235 (13), 207 (18), 175 (13), 162 (86), 149 (10), 134 (91), 104 (37), 88 (42), 86 (37), 84 (59), 77 (55), 76 (100), 51 (53), 50 (41).

Compounds **10a**−**c** and **10e**−**k** were prepared employing a procedure similar to that described for compound **10d**, and yields are presented in results. All compounds were fully characterized by IR, NMR (^1H, ^{13}C), and MS spectrometry. HMBC and HMQC bidimensional experiments helped in ^{13}C assignments. Structures of all compounds are supported by the following spectroscopic data.

*(Z)-5-(Benzo[d][1,3]dioxol-5-ylmethylene)-3-bromo-4-(4-fluoro-2-methoxy-phenyl)furan-2(5H)-one (**10a**).* Product **10a** (115 mg, 0.28 mmol) was obtained as a white solid in 79% yield after purification by column chromatography on silica gel eluted with dichloromethane/hexane (1:1 v/v). This solid was recrystallized from a mixture of dichloromethane/hexane (~1:1 v/v): mp 144.5−145.5 °C; IR (KBr) $\overline{\nu}_{max}$ (cm^{-1}) 3083, 3052, 3010, 2958, 2918, 2848, 2782, 1767, 1613, 1601, 1501, 1489, 1448, 1411, 1285, 1261, 1194, 1155, 1106, 1037, 990, 966, 954, 927, 873, 838, 811, 754; δ_H ($CDCl_3$) 3.84 (s, 3H, 2′-OC$\underline{H}_3$), 5.83 (s, 1H, H-6), 6.00 (s, 2H, −O−C$\underline{H}_2$−O−), 6.77−6.85 (m, 2H, H-3′, H-5′), 6.79 (d, 1H, $J_{5″,6″}$ = 8.4 Hz, H-5″), 7.10 (dd, 1H, $J_{6″,5″}$ = 8.4 Hz, $J_{6″,2″}$ = 1.8 Hz, H-6″), 7.22 (dd, 1H, $J_{6′,5′}$ = 8.1 Hz, $J_{6′,F}$ = 6.3 Hz, H-6′), 7.46 (d, 1H, $J_{2″,6″}$ = 1.8 Hz, H-2″); δ_C ($CDCl_3$) 56.2 (2′-O$\underline{C}H_3$), 100.4 (d, $J_{C,F}$ = 25.7 Hz, C-3′), 101.8 (−O−$\underline{C}H_2$−O−), 107.8 (d, $J_{C,F}$ = 21.8 Hz, C-5′), 108.9 (C-5″), 110.1 (C-3), 110.3 (C-2″), 113.9 (C-6), 114.1 (d, $J_{C,F}$ = 3.2 Hz, C-1′), 126.8 (C-6″), 127.2 (C-1″), 131.7 (d, $J_{C,F}$ = 10.4 Hz, C-6′), 146.6 (C-5), 148.6 (C-4″), 149.2 (C-3″), 151.6 (C-4), 158.4 (d, $J_{C,F}$ = 9.8 Hz, C-2′), 165.3 (d, $J_{C,F}$ = 249.0 Hz, C-4′), 165.4 (C-2); HRMS *m*/*z* (M + Na^+) calcd for $C_{19}H_{12}BrFNaO_5^+$ 440.9744, found 440.9800; EI-MS, *m*/*z* (%) 420 ([M + 2]$^{•+}$, $C_{19}H_{12}BrFO_5$, 59), 418 ([M]$^{•+}$, 57), 311 (15), 283 (24), 253 (11), 225 (15), 181 (11), 162 (74), 149 (22), 134 (87), 104 (32), 101 (34), 86 (31), 84 (50), 77 (15), 76 (100), 51 (48), 50 (46).

*(Z)-3-Bromo-4-(4-fluoro-2-methoxyphenyl)-5-(4-nitrobenzylidene)furan-2(5H)-one (**10b**).* Product **10b** (24 mg, 0.57 mmol) was obtained as a yellow solid in 16% yield after purification by column chromatography on silica gel eluted with dichloromethane/hexane (3:2 v/v). This solid was recrystallized from a mixture of dichloromethane/hexane (~1:1 v/v): mp 222.5−223.6 °C; IR (KBr) $\overline{\nu}_{max}$ (cm^{-1}) 3087, 3009, 2962, 2934, 2902, 2840, 2781, 1766, 1613, 1600, 1501, 1489, 1447, 1411, 1285, 1260, 1194, 1155, 1105, 1036, 989, 966, 953, 927, 873, 838, 809, 754; δ_H ($CDCl_3$) 3.86 (s, 3H, 2′-OCH_3), 5.95 (s, 1H, H-6), 6.82 (dd, 1H, $J_{3′,F}$ = 10.5 Hz, $J_{3′,5′}$ = 2.4 Hz, H-3′), 6.85 (dt, 1H, $J_{5′,6′}$ = $J_{5′,F}$ = 8.1 Hz, $J_{5′,3′}$ = 2.4 Hz, H-5′), 7.25 (dd, 1H, $J_{6′,5′}$ = 8.4 Hz, $J_{6′,F}$ = 6.3 Hz, H-6′), 7.88 (d, 2H, *J* = 8.7 Hz, H-2″/H-6″), 8.21 (d, 2H, *J* = 8.7 Hz, H-3″/H-5″); δ_C ($CDCl_3$) 56.2 (2′-OCH_3), 100.6 (d, $J_{C,F}$ = 25.8 Hz, C-3′), 108.1 (d, $J_{C,F}$ = 21.8 Hz, C-5′), 110.5 (C-6), 113.3 (d, $J_{C,F}$ = 3.2 Hz, C-1′), 113.4 (C-3), 124.2 (C-3″/C-5″), 131.3 (C-2″/C-6″), 131.6 (d, $J_{C,F}$ = 10.4 Hz, C-6′), 139.1 (C-1″), 147.6 (C-5), 150.3 (C-4″), 151.5 (C-4), 158.5 (d, $J_{C,F}$ = 10.8 Hz, C-2′), 164.5 (C-2), 165.5 (d, $J_{C,F}$ = 250.1 Hz, C-4′); HRMS *m*/*z* (M + Na^+) calcd for $C_{18}H_{11}BrFNNaO_5^+$ 441.9697, found 441.9700; EI-MS, *m*/*z* (%) 421 ([M + 2]$^{•+}$, $C_{18}H_{11}BrFNO_5$, 54), 419 ([M]$^{•+}$, 55), 340 (18), 312 (13), 297 (11), 284 (11), 266 (14), 249 (11), 237 (28), 181 (51), 149 (100), 137 (31), 133 (88), 106 (47), 101 (96), 89 (72), 86 (46), 84 (69), 77 (22), 75 (23), 63 (66), 51 (60), 50 (17).

*(Z)-3-Bromo-4-(4-fluoro-2-methoxyphenyl)-5-(4-(trifluoromethyl)benzylidene)furan-2(5H)-one (**10c**).* Product **10c** (91 mg, 0.21 mmol) was obtained as a white solid in 30% yield after purification by column chromatography on silica gel eluted with dichloromethane/hexane (2:1 v/v). This solid was recrystallized from a mixture of dichloromethane/hexane (~1:1 v/v): mp 131.8−132.8 °C; IR (KBr) $\overline{\nu}_{max}$ (cm^{-1}) 3089, 3071, 3043, 3017, 2968, 2941, 2879, 2841, 1781, 1648, 1613, 1598, 1500, 1465, 1455, 1415, 1325, 1285, 1227, 1195, 1184, 1165, 1115, 1105, 1067, 1031, 1014, 985, 961, 873, 836, 752; δ_H($CDCl_3$) 3.85 (s, 3H, 2′-OC$\underline{H}_3$), 5.92 (s, 1H, H-6), 6.81 (dd, 1H, $J_{3′,F}$ = 10.8 Hz, $J_{3′,5′}$ = 2.4 Hz, H-3′), 6.85 (dt, 1H, $J_{5′,6′}$ = $J_{5′,F}$ = 8.4 Hz, $J_{5′,3′}$ = 2.4 Hz, H-5′), 7.25 (dd, 1H, $J_{6′,5′}$ = 8.4 Hz, $J_{6′,F}$ = 6.6 Hz, H-6′), 7.61 (d, 2H, $J_{3″,5″}$ = 8.4 Hz, H-3″/H-5″), 7.84 (d, 2H, $J_{2″,6″}$ = 8.4 Hz, H-2″/H-6″); δ_C ($CDCl_3$) 56.2 (2′-O$\underline{C}H_3$), 100.5 (d, $J_{C,F}$ = 25.8, C-3′), 108.0 (d, $J_{C,F}$ = 21.8 Hz, C-5′), 111.6 (C-6), 112.5 (C-3), 113.6 (d, $J_{C,F}$ = 2.9 Hz, C-1′), 124.1 (q, $J_{C,F}$ = 270.7 Hz, CF_3), 125.9 (q, $J_{C,F}$ = 4.1 Hz, C-3″/C-5″), 130.9 (q, $J_{C,F}$ = 32.1 Hz, C-4″), 130.9 (C-2″/C-6″), 131.7 (d, $J_{C,F}$ = 10.3 Hz, C-6′), 136.2 (C-1″), 149.3 (C-5), 151.6 (C-4), 158.5 (d, $J_{C,F}$ = 10.4 Hz, C-2′), 164.9 (C-2), 165.4 (d, $J_{C,F}$ = 249.5 Hz, C-4′); HRMS *m*/*z* (M + Na^+) calcd for $C_{19}H_{11}BrF_4NaO_3^+$ 464.9720, found 464.9707; EI-MS, *m*/*z* (%) 444 ([M + 2]$^{•+}$, $C_{19}H_{11}BrF_4O_3$, 87), 442 ([M]$^{•+}$, 100), 425 (10), 423 (9), 363 (28), 335 (31), 318 (17), 307 (21), 230 (23), 228 (24), 186 (24), 181 (58), 177 (25), 158 (61), 153 (22), 149 (97), 137 (32), 133 (26), 109 (21), 106 (28), 101 (68), 86 (39), 84 (62), 75 (15), 63 (17), 57 (31), 55 (25), 51 (77).

*(Z)-3-Bromo-4-(2-methoxyphenyl)-5-(4-nitrobenzylidene)furan-2(5H)-one (**10e**).* Product **10e** (123 mg, 0.31 mmol) was obtained as a yellow solid in 41% yield after purification by column chromatography on silica gel eluted with dichloromethane/hexane (3:2 v/v). This solid was recrystallized from a mixture of dichloromethane/hexane (~1:1 v/v): mp 181.1−182.0 °C; IR (KBr) $\overline{\nu}_{max}$ (cm^{-1}) 3100, 3070, 3046, 3015, 2961, 2944, 2839, 1781, 1643, 1611, 1592, 1510, 1486, 1462, 1432, 1342, 1301, 1275, 1249, 1181, 1162, 1109, 1044, 1019, 975, 957, 875, 827, 787, 751; δ_H ($CDCl_3$) 3.86 (s, 3H, 2′-OC$\underline{H}_3$), 5.98 (s, 1H, H-6), 7.09 (dl, 1H, $J_{3′,4′}$ = 8.4 Hz, H-3′), 7.13 (dt, 1H, $J_{5′,4′}$ = $J_{5′,6′}$ = 7.5 Hz, $J_{5′,3′}$ = 0.9 Hz, H-5′), 7.28 (dd, 1H, $J_{6′,5′}$ = 7.5 Hz, $J_{6′,4′}$ = 1.8 Hz, H-6′), 7.56 (ddd, 1H, $J_{4′,3′}$ = 8.4 Hz, $J_{4′,5′}$ = 7.5 Hz, $J_{4′,6′}$ = 1.8 Hz, H-4′), 7.89 (d, 2H, $J_{2″,6″}$ = 9.0 Hz, H-2″/H-6″), 8.21 (d, 2H, $J_{3″,5″}$ = 9.0 Hz, H-3″/H-5″); δ_C ($CDCl_3$) 55.9 (2′-O$\underline{C}H_3$), 110.5 (C-6), 112.0 (C-3′), 113.1 (C-3), 117.4 (C-1′), 121.0 (C-5′), 124.2 (C-3″/C-5″), 130.4 (C-6′), 131.3 (C-2″/C-6″), 132.5 (C-4′), 139.2 (C-1″), 147.5 (C-5), 150.3 (C-4″), 152.5 (C-4), 156.8 (C-2′), 164.7 (C-2); HRMS *m*/*z* (M + Na^+) calcd for $C_{18}H_{12}BrNaO_5^+$ 423.9791, found 423.9785; EI-MS, *m*/*z* (%) 403 ([M + 2]$^{•+}$, $C_{18}H_{12}BrNO_5$, 60), 401 ([M]$^{•+}$, 59), 322 (51), 294 (26), 281 (13), 266 (10), 248 (16), 231 (17), 219 (32), 205 (23), 189 (22), 176 (25), 163 (39), 131 (100), 119 (50), 115 (49), 103 (41), 102 (44), 89 (99), 88 (85), 77 (98), 63 (84).

*(Z)-3-Bromo-4-(2-methoxyphenyl)-5-(4-(trifluoromethyl)-benzylidene)furan-2(5H)-one (**10f**).* The product **10f** (131 mg, 0.31 mmol) was obtained as a white solid in 41% yield after purification by column chromatography on silica gel eluted with dichloromethane/hexane (2:1 v/v). This solid was recrystallized from a mixture of dichloromethane/hexane (~1:1 v/v): mp 152.0−152.5 °C; IR (KBr) $\overline{\nu}_{max}$ (cm^{-1}) 3065, 3005, 2985, 2953, 2843, 1785, 1647, 1609, 1578, 1493, 1467, 1453, 1437, 1415, 1325, 1284, 1250, 1226, 1197, 1185, 1166, 1129, 1115, 1068, 1022, 979, 954, 940, 873, 841, 827, 786, 772,

761, 753; δ_H ($CDCl_3$) 3.86 (s, 3H, 2′-OC<u>H</u>$_3$), 5.95 (s, 1H, H-6), 7.09 (dl, 1H, $J_{3',4'}$ = 8.1 Hz, H-3′), 7.13 (dt, 1H, $J_{5',4'} = J_{5',6'}$ = 7.5 Hz, $J_{5',3'}$ = 0.9 Hz, H-5′), 7.28 (ddd, 1H, $J_{6',5'}$ = 7.5 Hz, $J_{6',4'}$ = 1.8 Hz, $J_{6',3'}$ = 0.6 Hz, H-6′), 7.55 (ddd, 1H, $J_{4',3'}$ = 8.1 Hz, $J_{4',5'}$ = 7.5 Hz, $J_{4',6'}$ = 1.8 Hz, H-4′), 7.61 (d, 2H, J = 8.4 Hz, H-3″/H-5″), 7.84 (d, 2H, J = 8.4 Hz, H-2″/H-6″); δ_C ($CDCl_3$) 55.9 (2′-O<u>C</u>H$_3$), 111.7 (C-6), 111.9 (C-3′), 112.2 (C-3), 117.7 (C-1′), 121.0 (C-5′), 124.2 (q, $J_{C,F}$ = 282.6 Hz, CF_3), 125.9 (q, $J_{C,F}$ = 4.1 Hz, C-3″/C-5″), 130.5 (C-6′), 130.9 (q, $J_{C,F}$ = 31.7 Hz, C-4″), 130.9 (C-2″/C-6″), 132.4 (C-4′), 136.3 (C-1″), 149.3 (C-5), 152.5 (C-4), 156.9 (C-2′), 164.0 (C-2); HRMS m/z (M + Na^+) calcd for $C_{19}H_{12}BrF_3NaO_3^+$ 446.9814, found 446.9800; EI-MS, m/z (%) 424 ([M + 2]$^{\bullet+}$, $C_{19}H_{12}BrF_3O_3$, 98), 442 ([M]$^{\bullet+}$, 100), 407 (10), 405 (9), 345 (57), 317 (41), 300 (20), 289 (19), 167 (24), 163 (45), 159 (37), 158 (45), 135 (17), 131 (71), 119 (42), 115 (34), 103 (29), 102 (17), 91 (22), 89 (23), 88 (45), 86 (54), 84 (81), 77 (81), 63 (22), 51 (97).

*(Z)-5-Benzylidene-3-bromo-4-(2-methoxyphenyl)furan-2(5H)-one (**10g**).* Product **10g** (42 mg, 0.12 mmol) was obtained as a white solid in 32% yield after purification by column chromatography on silica gel eluted with dichloromethane/hexane (1:1 v/v). This solid was recrystallized from a mixture of dichloromethane/hexane (∼1:1 v/v): mp 147.2−148.2 °C; IR (KBr) $\bar{\nu}_{max}$ (cm^{-1}) 3092, 3067, 3047, 3026, 3008, 2955, 2930, 2836, 1777, 1637, 1609, 1489, 1458, 1434, 1345, 1281, 1253, 1228, 1181, 1111, 1046, 1027, 973, 957, 927, 864, 834, 765, 754; δ_H ($CDCl_3$) 3.86 (s, 3H, 2′-OC<u>H</u>$_3$), 5.95 (s, 1H, H-6), 7.08 (dl, 1H, $J_{3',4'}$ = 8.4 Hz, H-3′), 7.12 (dt, 1H, $J_{5',4'} = J_{5',6'}$ = 7.5 Hz, $J_{5',3'}$ = 0.9 Hz, H-5′), 7.28 (dd, 1H, $J_{6',5'}$ = 7.5 Hz, $J_{6',4'}$ = 1.8 Hz, H-6′), 7.33−7.40 (m, 3H, H-3″, H-4″, H-5″), 7.53 (ddd, 1H, $J_{4',3'}$ = 8.4 Hz, $J_{4',5'}$ = 7.5 Hz, $J_{4',6'}$ = 1.8 Hz, H-4′), 7.75 (dd, 2H, $J_{2''/6,3''/5''}$ = 8.4 Hz, $J_{2''/6'',4''}$= 1.8 Hz, H-2″/H-6″); δ_C ($CDCl_3$) 55.9 (2′-O<u>C</u>H$_3$), 110.9 (C-3), 111.9 (C-3′), 113.9 (C-6), 118.1 (C-1′), 120.9 (C-5′), 129.1 (C-3″/C-5″), 129.6 (C-4″), 130.6 (C-6′), 131.0 (C-2″/C-6″), 132.2 (C-4′), 133.0 (C-1″), 147.9 (C-5), 152.7 (C-4), 156.9 (C-2′), 165.5 (C-2); HRMS m/z (M + Na^+) calcd for $C_{18}H_{13}BrNaO_3^+$ 378.9940, found 378.9970; EI-MS, m/z (%) 358 ([M + 2]$^{\bullet+}$, $C_{18}H_{13}BrO_3$, 65), 356 ([M]$^{\bullet+}$, 62), 277 (30), 249 (23), 231 (15), 221 (18), 202 (13), 178 (20), 163 (27), 131 (56), 119 (32), 118 (80), 115 (52), 105 (17), 103 (23), 194 (19), 91 (46), 90 (100), 89 (74), 88 (54), 86 (42), 84 (63), 77 (77), 63 (27).

*(Z)-3-Bromo-5-(2-hydroxybenzylidene)-4-(2-methoxyphenyl)-furan-2(5H)-one (**10h**).* Product **10h** (127 mg, 0.34 mmol) was obtained as a white solid in 46% yield after purification by column chromatography on silica gel eluted with dichloromethane/hexane (2:1 v/v). This solid was recrystallized from a mixture of dichloromethane/hexane (∼1:1 v/v): mp 178.9−180.0 °C; IR (KBr) $\bar{\nu}_{max}$ (cm^{-1}) 3404, 3072, 3000, 2948, 2836, 1753, 1648, 1593, 1489, 1465, 1452, 1433, 1359, 1345, 1285, 1255, 1168, 1018, 986, 941, 897, 885, 792, 755; δ_H ($CDCl_3$) 3.77 (s, 3H, 2′-OC<u>H</u>$_3$), 5.86 (s, 1H, H-6), 6.76 (ddd, 1H, $J_{3'',4''}$ = 8.1 Hz, $J_{3'',5''}$ = 2.4 Hz, $J_{3'',6''}$ = 0.9 Hz, H-3″), 6.95−7.05 (m, 3H, H-3′/H5′/H5″), 7.00−7.15 (m, 1H, H-4″), 7.18 (dd, 1H, $J_{6',5'}$ = 7.5 Hz, $J_{6',4'}$ = 7.5 Hz, $J_{6',4'}$ = 1.8 Hz, H-6′), 7.29−7.34 (m, 1H, H6″), 7.45 (ddd, 1H, $J_{4',3'}$ = 8.6 Hz, $J_{4',5'}$ = 7.5 Hz, $J_{4',6'}$ = 1.8 Hz, H4′); δ_C ($CDCl_3$) 55.7 (2′-O<u>C</u>H$_3$), 110.2 (C-3), 111.8 (C-3′), 114.8 (C-6), 116.7 (C-6″), 117.5 (C-3″), 117.8 (C1′), 120.8 (C-5′), 123.2 (C-5″), 130.0 (C-4″), 130.4 (C-6′), 132.2 (C-4′), 133.8 (C-1″), 147.6 (C-5), 153.2 (C-4), 156.8 (C-2′), 157.4 (C2″), 166.3 (C-2); HRMS m/z (M + Na^+) calcd for$C_{18}H_{13}BrNaO_4^+$ 394.9889, found 394.9883; EI-MS, m/z (%) 374 ([M + 2]$^{\bullet+}$, $C_{18}H_{13}BrO_4$, 98), 372 ([M]$^{\bullet+}$, 97), 293 (27), 265 (32), 247 (20), 237 (24), 209 (17), 163 (24), 147 (27), 134 (78), 131 (49), 105 (49), 88 (32), 78 (39), 77 (100), 75 (15), 51 (37).

*(Z)-3-Bromo-4-(4-fluoro-2-methoxyphenyl)-5-(2-hydroxybenzylidene)furan-2(5H)-one (**10i**).* Product **10i** (68 mg, 0.17 mmol) was obtained as a white solid in 50% yield after purification by column chromatography on silica gel eluted with dichloromethane/hexane (2:1 v/v). This solid was recrystallized from a mixture of dichloromethane/hexane (∼1:1 v/v): mp 195−198.3 °C (decomp); IR (KBr) $\bar{\nu}_{max}$ (cm^{-1}) 3389, 3068, 2979, 2964, 2948, 2886, 1752, 1649, 1313, 1495, 1453, 1409, 1362, 1319, 1278, 1224, 1177, 1153, 1107, 1023, 987, 957, 883, 831, 754; δ_H ($CDCl_3$) 3.78 (s, 3H, 2′-OC<u>H</u>$_3$), 5.85 (s, 1H, H-6), 6.72−6.82 (m, 3H, H3′/H5′/H5″), 6.98 (dl, 1H, $J_{3'',4''=}$ 8.1 Hz, H3″), 7.10−7.21 (m, 2H, H6′/H4″), 7.34−7.36 (m, 1H, H6″), 9.85 (s, 1H, OH); δ_C ($CDCl_3$) 56.1 (2′-O<u>C</u>H$_3$), 100.4 (d, $J_{C,F}$ = 25.5 Hz, C-3′), 107.8 (d, $J_{C,F}$ = 21.75 Hz, C-5′), 110.5 (C-3), 114.7 (C-6), 115.8 (C1′), 116.7 (C-6″), 117.6 (C-5″), 123.3 (C-3″), 130.0 (C-4″), 131.6 (d, $J_{C,F}$ = 10.4 Hz, C-6′), 133.7 (C-1″), 147.5 (C-5), 152.2 (C-4), 157.5 (C-2′), 158.4 (C2″), 165.1 (C-2), 165.2 (d, $J_{C,F}$ = 249 Hz, C-4′); HRMS m/z (M + Na^+) calcd for$C_{18}H_{12}BrFNaO_4^+$ 412.9795, found 412.9789; EI-MS, m/z (%) 392 ([M + 2]$^{\bullet+}$, $C_{18}H_{12}BrFO_4$, 76), 390 ([M]$^{\bullet+}$, 76), 311 (21), 283 (26), 268 (10), 255 (19), 209 (10), 181 (21), 177 (22), 149 (29), 134 (100), 131 (10), 106 (33), 105 (43), 101 (33), 78 (26), 77 (31), 51 (21).

*(Z)-3-Bromo-5-(3-hydroxybenzylidene)-4-(2-methoxyphenyl)-furan-2(5H)-one (**10j**).* Product **10j** (81 mg, 0.22 mmol) was obtained as a white solid in 58% yield after purification by column chromatography on silica gel eluted with dichloromethane/hexane (2:1 v/v). This solid was recrystallized from a mixture of dichloromethane/hexane (∼1:1 v/v): mp 209.5−213.7 °C (decomp); IR (KBr) $\bar{\nu}_{max}$ (cm^{-1}) 3394, 3100, 3043, 3014, 2942, 1741, 1633, 1609, 1579, 1491, 1463, 1453, 1368, 1285, 1253, 1220, 1181, 1163, 1047, 1009, 954, 945, 884, 844, 789, 765; δ_H ($CDCl_3$) 3.79 (s, 3H, 2′-OC<u>H</u>$_3$), 6.51 (s, 1H, H-6), 6.72 (dd, 1H, $J_{4'',5''}$ = 8.4 Hz, $J_{4'',6''}$ = 1.5 Hz, H-4″), 6.81−6.89 (m, 1H, H5′), 6.97−7.07 (m, 2H, H3′/H2″), 7.07−7.15 (m, 1H, H5″), 7.24 (dd, 1H, $J_{6',5'}$ = 7.8 Hz, $J_{6',4'}$ = 1.5 Hz, H6′), 7.45 (ddd, 1H, $J_{4',3'}$ = 8.2 Hz, $J_{4',5'}$ = 7.5 Hz, $J_{4',6'}$ = 1.5 Hz, H4′), 8.11 (dd, 1H, $J_{6'',5''}$ = 7.8 Hz, $J_{6'',4''}$ = 1.5 Hz, H6″); δ_C ($CDCl_3$) 55.7 (2′-O<u>C</u>H$_3$), 109.1 (C-6), 109.5 (C-3), 111.8 (C-3′), 115.5 (C-4″), 118.3 (C-1″), 120.4 (C-5′), 120.8 (C-2″), 130.7 (C6′), 131.1 (C-5″), 131.7 (C-6″), 131.9 (C-4′/C1″), 147.1 (C-5), 156.2 (C-4), 156.7 (C-2′), 160.0 (C-3″), 166.0 (C-2); HRMS m/z (M + Na^+) calcd forC$_{18}$H$_{12}$BrFNaO$_4^+$ 412.9795, found 412.9790; EI-MS, m/z (%) 374 ([M + 2]$^{\bullet+}$, $C_{18}H_{13}BrO_4$, 88), 372 ([M]$^{\bullet+}$, 86), 293 (100), 278 (26), 247 (15), 234 (43), 221 (33), 161 (15), 159 (40), 133 (21), 131 (74), 115 (29), 106 (26), 105 (24), 78 (55), 77 (86), 51 (40).

*(Z)-3-Bromo-4-(4-fluoro-2-methoxyphenyl)-5-(3-hydroxybenzylidene)furan-2(5H)-one (**10k**).* Product **10k** (75 mg, 0.19 mmol) was obtained as a white solid in 55% yield after purification by column chromatography on silica gel eluted with dichloromethane/hexane (2:1 v/v). This solid was recrystallized from a mixture of dichloromethane/hexane (∼1:1 v/v): mp 151.1−153.2 °C; IR (KBr) $\bar{\nu}_{max}$ (cm^{-1}) 3415, 3070, 2924, 2852, 1739, 1637, 1615, 1582, 1499, 1456, 1409, 1367, 1287, 1255, 1195, 1157, 1103, 1027, 1010, 961, 890, 843, 763; δ_H ($CDCl_3$) 3.78 (s, 3H, 2′-OC<u>H</u>$_3$), 6.50 (s, 1H, H-6), 6.70−6.78 (m, 3H, H-3′/H5′/H2″), 6.81−6.87 (m, 1H, H-4″), 7.08−7.14 (m, 1H, H5″), 7.18−7.24 (m, 1H, H-6′), 8.08 (dd, 1H, $J_{6'',5''}$ = 8.0 Hz, $J_{6'',4''}$ = 1.5 Hz, H6″); δ_C ($CDCl_3$) 56.0 (2′-O<u>C</u>H$_3$), 100.3 (d, $J_{C,F}$ = 25.8 Hz, C-3′), 107.7 (d, $J_{C,F}$ = 21.8 Hz, C-5′), 109.1 (C-6), 109.7 (C-3), 114.2 (C-1′), 115.5 (C-2″), 120.4 (C-4″), 130.9 (C1″), 131.3 (C-5″), 131.6 (C-6″), 131.8 (d, $J_{C,F}$ = 10.3 Hz, C-6′), 147.1 (C-5), 152.2 (C-4), 156.3 (C-3″), 158.4 (C-2′), 165.1 (d, $J_{C,F}$ = 247.9 Hz, C-4′), 166.2 (C-2); HRMS m/z (M + Na^+) calcd for $C_{18}H_{12}BrFNaO_4^+$ 412.9795, found 412.9791; EI-MS, m/z (%) 392 ([M + 2]$^{\bullet+}$, $C_{18}H_{12}BrFO_4$, 88), 390 ([M]$^{\bullet+}$, 83), 311 (100), 296 (17), 268 (15), 252 (45), 239 (33), 196 (12), 177 (38), 161 (19), 149 (38), 134 (29), 133 (48), 131 (40), 106 (57), 105 (26), 101 (38), 78 (62), 77 (36), 61 (14), 51 (34).

Biological Assays. The ability to interfere with the photosynthetic electron transport chain was evaluated on photosynthetically active thylakoid membranes isolated from market spinach (*Spinacia oleracea* L.) leaves. The IC_{50} for each test compound was determined according to the procedure previously described by Barbosa et al.[13]

Computations. The conformational analysis of the 13 rubrolide analogues was done using the conformer distribution subroutine of the SPARTAN'06 software.[26] The geometry with the lowest energy was selected for further calculations with the MOPAC code,[27] again using the AM1[28,29] semiempirical method. After geometry reoptimization with MOPAC, all structures were confirmed as a local minimum by calculation of the Hessian matrix force constant (no negative eigenvector).

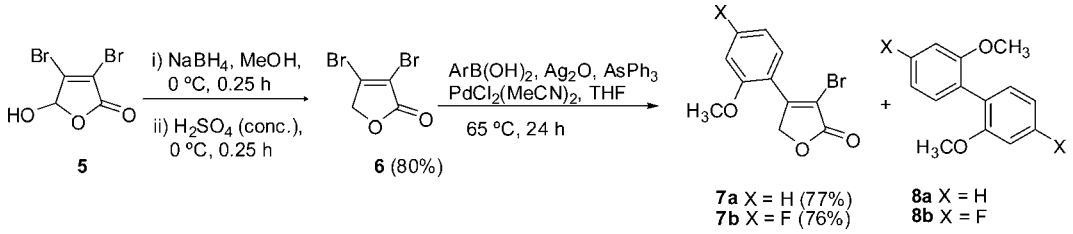
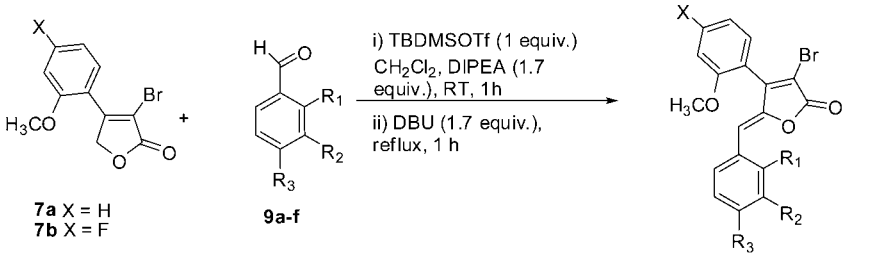


Figure 2. Preparation of 3-bromo-4-arylfuran-2(5*H*)-ones **7a** and **7b**.



10a X = F, R_1 = H, R_2-R_3 = -OCH_2O- (79%)
10b X = F, R_1 = H, R_2 = H, R_3 = NO_2 (16%)
10c X = F, R_1 = H, R_2 = H, R_3 = CF_3 (30%)
10d X = H, R_1 = H, R_2-R_3 = -OCH_2O- (54%)
10e X = H, R_1 = H, R_2 = H, R_3 = NO_2 (16%)
10f X = H, R_1 = H, R_2 = H, R_3 = CF_3 (41%)
10g X = H, R_1 = R_2 = R_3 = H (32%)
10h X = H, R_1 = OH, R_2 = R_3 = H (46%)
10i X = F, R_1 = OH, R_2 = R_3 = H (50%)
10j X = H, R_1 = R_3 = H, R_2 = OH (58%)
10k X = F, R_1 = R_3 = H, R_2 = OH (55%)

Figure 3. Preparation of (*Z*)-5-arylidene-3-bromo-4-arylfuran-2(5*H*)-ones **10a**–**k**.

For the QSAR analysis the outputs from the MOPAC calculations were used to generate a set of molecular descriptors, using the CODESSA software.[30] Two sets of outputs were obtained with the MOPAC code. In one of them the following keywords were used: AM1, PRECISE, XYZ, EF, ENPART, VECTORS, BONDS, PI, and POLAR. In the second one, which was used to calculate the thermodynamic properties, the following keywords were used: AM1, PRECISE, THERMO, ROT=1, and XYZ. Both outputs from MOPAC were used as input to CODESSA. In the statistical analysis using CODESSA the following parameters were employed: maximum number of descriptors per model, 1; criterion of significance of parameter, 0.01; level of high correlation, 0.99; level of intercorrelation significance, 0.8.

RESULTS AND DISCUSSION

Synthesis of Analogues. Our approach to the preparation of rubrolide analogues started with commercially available mucobromic acid (**5**), which is very cheap (US $273.00/100 g). This compound was converted into the more expensive 3,4-dibromofuran-2(5*H*)-one (**6**) (US $169.00/g) by means of a reduction with sodium boron hydride followed by dehydration with sulfuric acid (Figure 2). Compound **6** was obtained in good yield (80%) and on a multigram scale.[31] This compound is a useful template for the preparation of sulfur- and nitrogen-containing heterocycles including agrochemical precursors.[32,33]

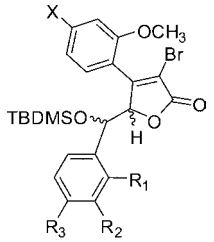
The introduction of the aryl group at position 4 in lactone **6** was achieved by a selective Suzuki reaction employing Ag_2O, $AsPh_3$, and $PdCl_2(MeCN)_2$ conditions as developed by Rossi et al.[34] The reaction was accomplished with 4-fluoro-2-methoxybenzaldehyde and 2-methoxybenzaldehyde and produced the required compounds **7a** and **7b**. In both cases small and variable amounts of the homocoupling products **8a** (1.07 mmol) and **8b** (1.36 mmol) were formed and isolated. At this early stage of our investigation we did not embark on a production of a large number of compounds with functionalities at this phenyl ring. Although the choice of the substituents was arbitrary, we prepared a compound with an electron-donating group (OMe) at position 2 (**7b**) and for comparison another compound containing an extra electron-withdrawing F atom at position 4 (**7a**).

These reactions occurred with high degree of regioselectivity, as described for similar cases,[32] and the structures of both products were confirmed by spectroscopic analysis.

The conversion of compounds **7a** and **7b** into the benzylidenes**10a**–**k** was accomplished using the same procedure employed for the synthesis of several nostoclide analogues reported previously.[10,11,35,36] Briefly, the two-step transformation consisted initially of an aldol condensation between the *tert*-butyldimethylsilyl derivative of **7a**/**7b** with the aldehydes **9a**–**f**, followed by elimination of TBDMSOH (Figure 3). For this, lactones **7a**/**7b** were treated with *tert*-butyldimethylsilyltrifluoromethanesulfonate and diisopropylethylamine to yield the corresponding silyl ethers that were not isolated (Figure 4), but immediately reacted with the aldehydes to produce the intermediates of type **11a**–**k**. The formation of such intermediates has been previously proved,[37] but in the present work they were not isolated but submitted to a reaction with DBU, to afford the required compounds **10a**–**k**.

The yields for this reaction varied from 16 to 79%, with the aldehydes containing electron-withdrawing groups such as NO_2 being less efficient.

The confirmation of the structures of **10a**–**k** was based on their spectroscopic data, including nuclear Overhauser effect difference spectroscopy (NOEdiff) that revealed a correlation



11a-k

Figure 4. Structure of the silyl ethers not isolated.

between H-6 and H-6′ in the aromatic ring, in agreement with the *Z* stereochemistry for the *exo* double bond.

Biological Assays and QSAR Studies. To evaluate whether the intermediates **7a** and **7b**, lacking the arylidene unit, and the final products **10a**−**k** are able to interfere with the photosynthetic electron transport chain, the rate of ferricyanide reduction by isolated spinach chloroplasts was evaluated in the presence of a given compound at levels ranging from 1 to 100 μM. Results were summarized as the concentrations able to inhibit by 50% the rate measured in untreated controls (Table 1).

Table 1. Concentrations of Rubrolides Able To Inhibit by 50% (IC_{50}) the Photosynthetic Electron Transport Chain in Isolated Spinach Chloroplasts

compd	IC_{50}[a] (μM)	log(1/IC_{50}) (M)	log*P*[b]
7a	ne[c]		1.92
7b	ne		1.77
10b	1.1 ± 0.2	5.96	3.39
10d	39.5 ± 8.6	4.40	2.97
10g	20.5 ± 5.2	4.69	3.19
10a	12.6 ± 0.9	4.90	3.13
10e	1.3 ± 0.3	5.89	3.23
10f	8.1 ± 2.1	5.09	4.11
10c	3.5 ± 0.4	5.46	4.27
10j	>100		2.80
10h	12.6 ± 1.2	4.90	2.80
10k	9.2 ± 4.7	5.04	2.96
10i	5.9 ± 0.9	5.54	2.96

[a]For Diuron IC_{50} = 0.27 μM. [b]The values were obtained with Spartan software.[38] [c]ne, not effective at the highest dose tested. Each treatment was carried out in triplicate, and the values are the mean ± SD.

Compounds **7a** and **7b** were ineffective, clearly demonstrating that the benzylidene moiety is essential for the biological activity. This conclusion does not rule out the possibility that analogues of **7a**/**7b** bearing other substituents on the phenyl ring such as nitro and trifluoromethyl would present some activity. All other derivatives with a benzylidene unit, except **10j**, presented inhibitory activities with IC_{50} < 40 μM. The most active compounds, **10b** and **10e**, both bear a nitro group at the benzylidene ring. In this case the presence of fluorine at the phenyl ring does not seem to have a great influence on the inhibitory potential. Compounds **10f** and **10c**, both with an electron-withdrawing group CF_3 at the benzylidene ring, were also remarkably active. In the case of this pair, and of pair **10d** and **10a** as well, the presence of the fluorine atom seems to exert a small promoting effect on the biological activity. As observed from log*P* values (Table 1), compounds with nitro and trifluoromethyl groups are more polar. However, we found no correlation between polarity and the ability of rubrolide analogues to inhibit the photosynthetic electron transport chain in isolated chloroplasts.

Although the number of compounds tested is limited, the scaffold of rubrolide seems therefore a promising lead structure toward the development of new active compounds targeting the chloroplast electron transport chain. The IC_{50} values of the most active derivatives are in fact only 1 order of magnitude higher than those of commercial herbicides sharing the same mode of action, such as Diuron (0.27 μM) and Hexazinone (0.11 μM).[39]

To better understand the relationship between the molecular structure and the biological activity, QSAR studies were carried out. To determine the correlation between molecular descriptors and the efficiency of the set of rubrolides, we tested a set of models as discussed below.

At first, a structural analysis of the studied compounds was carried out. The geometries of the 13 rubrolide analogues were obtained from AM1 semiempirical calculations, after a conformational analysis using the conformer distribution subroutine of the SPARTAN'06 software. The geometry with the lowest energy for each derivative was then reoptimized with the MOPAC software, again using the AM1 method. The outputs from the MOPAC calculation were used to generate a set of molecular descriptors (see the Supporting Information), using the CODESSA software.

CODESSA may generate about 400 molecular descriptors associated with molecular constitution, geometry, and topology and with electrostatic, thermodynamic, and quantum chemical parameters. The molecular descriptors generated by CODESSA were correlated to the biological efficiency using the heuristic method.[40,41] After elimination of descriptors with low variance or high intercorrelation, the best correlations were found with the molecular descriptors HOMO, LUMO, LUMO+1, and FNSA3.[42,43] HOMO, LUMO, and LUMO+1 are the energies of the well-known frontier orbitals. FNSA3 is a molecular descriptor that reports the fractional negatively charged partial surface area and is associated with the polarity of the molecule. The values of this descriptor are obtained as a quotient of two other descriptors, PNSA3 (charge weighted partial negative surface area) at the numerator and TMSA (total molecular surface area) at the denominator, as described below:[44]

$$\mathrm{FNSA3} = \frac{\mathrm{PNSA3}}{\mathrm{TMSA}}$$

where

$$\mathrm{PNSA3} = \sum_A (q_A S_A) A \in \quad (q_A < 0)$$

and q_A = atomic charge in atom A, S_A = weighted partial negatively charged molecular surface area, and TMSA = total molecular surface area.

The best four models are given in Figures 5−8, with the corresponding calculated versus measured efficiency plots.

These models suggest a correlation between the energy of the frontier orbitals and the inhibitory potential. A lower energy of the frontier orbitals leads to compounds with higher efficiency, confirming that these compounds may interfere with the chloroplastic electron transport chain,[11] acting by an electron acceptor mechanism in the photosynthetic process. The FNSA3 descriptor indicates that the greater the fraction of negatively charged molecular surface, the greater the inhibitory efficiency of a compound. Therefore, the most effective

$$\text{Log } (1/IC_{50}) = -4.50e{+}01(\pm 7.24e{+}00)\textbf{(FNSA3)} + 1.81e{+}00(\ 5.48e{-}01)$$
$$n = 10;\ r^2 = 0.83;\ F = 38.65;\ s^2 = 0.05;\ R^2_{cv} = 0.75$$

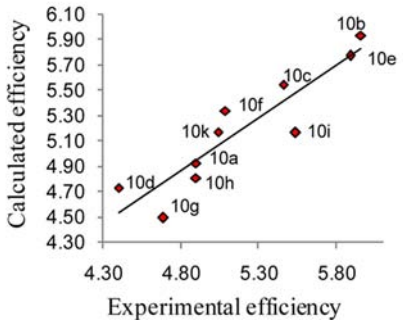


Figure 5. Experimental versus calculated efficiency with the FNSA3 descriptor.

$$\text{Log } (1/IC_{50}) = -1.58e{+}00(\pm 2.99e{-}01)\textbf{(LUMO+1)} + 4.28e{+}00(\ 1.90e{-}01)$$
$$n = 10;\ r^2 = 0.78;\ F = 28.07;\ s^2 = 0.07;\ R^2_{cv} = 0.66$$

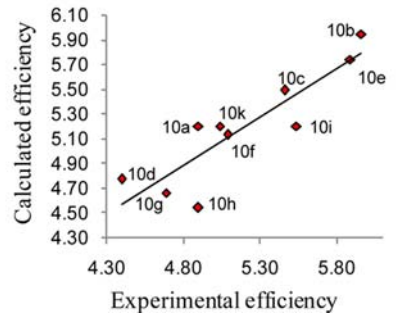


Figure 6. Experimental versus calculated efficiency with the LUMO+1 descriptor.

$$\text{Log } (1/IC_{50}) = -1.38e{+}00(\pm 2.75e{-}01)\textbf{(HOMO)} - 7.21e{+}00(\ 2.47e{+}00)$$
$$n = 10;\ r^2 = 0.76;\ F = 25.27;\ s^2 = 0.07;\ R^2_{cv} = 0.65$$

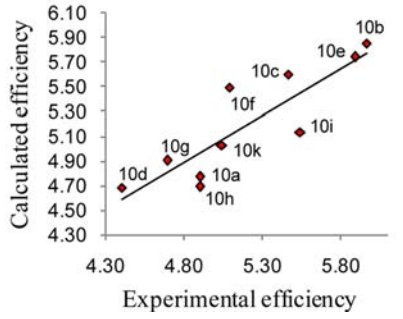


Figure 7. Experimental versus calculated efficiency with the HOMO descriptor.

compounds are those with the most electronegative groups in their structure, as seen for the derivatives with either the NO_2 or CF_3 moiety in the benzylidene ring.

In conclusion, we have demonstrated that rubrolide analogues are effective in interfering with the light-driven ferricyanide reduction by isolated chloroplasts. Because of a higher water solubility than the previously characterized nostoclides, they could represent promising candidates for the development of new active principles targeting photosynthesis. QSAR results indicate that the most efficient compounds are those having higher ability to accept electrons, for example, by an electrophilic reaction mechanism. This is justified by the models obtained with either the energies of the frontier orbitals or the molecular descriptor FNSA3, which is associated with the fraction of negatively charged molecular surface area.

$$\text{Log } (1/IC_{50}) = -1.78e{+}00(\pm 4.16e{-}01)\textbf{(LUMO)} + 2.37e{+}00(\ 6.65e{-}01)$$
$$n = 10;\ r^2 = 0.70;\ F = 18.35;\ s^2 = 0.09;\ R^2_{cv} = 0.56$$

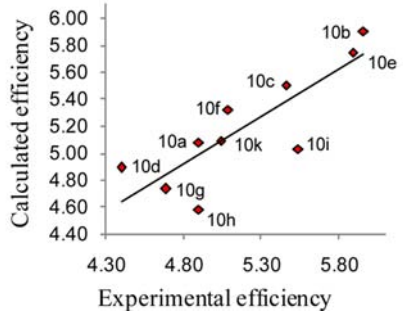


Figure 8. Experimental versus calculated efficiency with the LUMO descriptor.

■ ASSOCIATED CONTENT

Supporting Information

Table containing values of the descriptors selected in the different models (FNSA-3 in e^-; HOMO, LUMO, and LUMO +1 in eV). This material is available free of charge via the Internet at http://pubs.acs.org.

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Funding

We acknowledge the following Brazilian agencies: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for research fellowships (L.C.A.B., C.R.A.M., J.W.M.C.) and financial support; Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG), Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), and FINEP for financial support. We also acknowledge support from the University of Ferrara (Fondo di Ateneo per la Ricerca 2010).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Akshat Rathi from the University of Oxford (UK) for the high-resolution mass spectra data.

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