Phytogrowth Activity of 3-(3-Chlorobenzyl)-5-arylidenefuran-2(*5H*)-ones

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Nine new 3-(3-chlorobenzyl)-5-arylidenefuran-2(*5H*)-ones were prepared in 20 – 87 % yields by reaction of 3-(3-chlorobenzyl)furan-2(*5H*)-one with pertinent aldehydes. All compounds were fully characterized by IR and NMR spectroscopy as well as MS spectrometry. The phytotoxic properties of the synthesized lactones were evaluated as the ability to interfere with the growth of *Sorghum bicolor* and *Cucumis sativus* seedlings at 10 ppm and 100 ppm. Lactone **12**, at 10 ppm, was the most active and selective, inhibiting the *S. bicolor* and *C. sativus* root growth by 70.7 % and 10.7 %, respectively. At 10 ppm, lactone **14** caused the larger effect on the inhibition (41.9 %) of *C. sativus*. In general, the results indicate the influence of the benzylidene ring substitution on the phytotoxic activity.

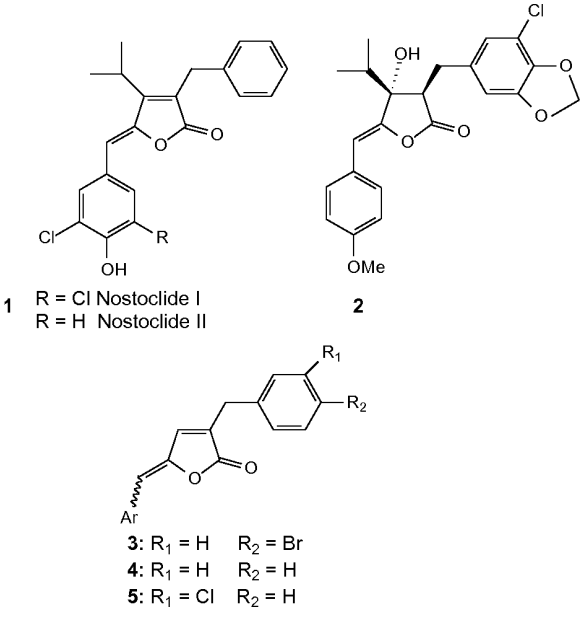
Key words: Nostoclides, Herbicides, Natural Products, Cyanobacterin, Phytotoxicity

Introduction

Over the years agrochemical companies have developed and brought to the market a myriad of chemical agents that have assisted farmers to control a variety of pests and diseases, including weeds [1]. Herbicide application has become the most reliable and least expensive tool of weed control [2, 3]. However, repeated use of the same active ingredients has led to herbicide resistance [4, 5]. Starting from the 1960s, hundreds of weed biotypes were reported to survive herbicide application [6]. As a consequence, there is a constant need for the development of new herbicides to overcome weed resistance. Moreover, modern herbicides should have a favorable combination of properties such as high levels of herbicidal activity, low application rates, crop tolerance, and low toxicity to mammals.

In the last few years, the great variety of compounds available from nature has been explored in the search for new agents to control weeds [7, 8]. This approach has afforded compounds that have been used directly as herbicides [9]. Moreover, natural products may provide novel lead compounds that may be optimized using well-established strategies [10, 11].

Within the frame of a long-established research, we have been using natural products as prototypes for the preparation of new active principles to control weeds [12 – 19], insects [20 – 22] and nematodes [23, 24]. In this context, we have been utilizing the nostoclides **1** as lead structures for the search of new herbicides [17 – 19]. Originally isolated from the culture of a symbiotic cyanobacterium, *Nostoc sp.*, in *Peltigera canina* [25], the nostoclides are structurally similar to the potent phytotoxin cyanobacterin (**2**) (Fig. 1). Synthetic efforts led to the preparation



1 R = Cl Nostoclide I
R = H Nostoclide II

2

3: R_1 = H R_2 = Br
4: R_1 = H R_2 = H
5: R_1 = Cl R_2 = H

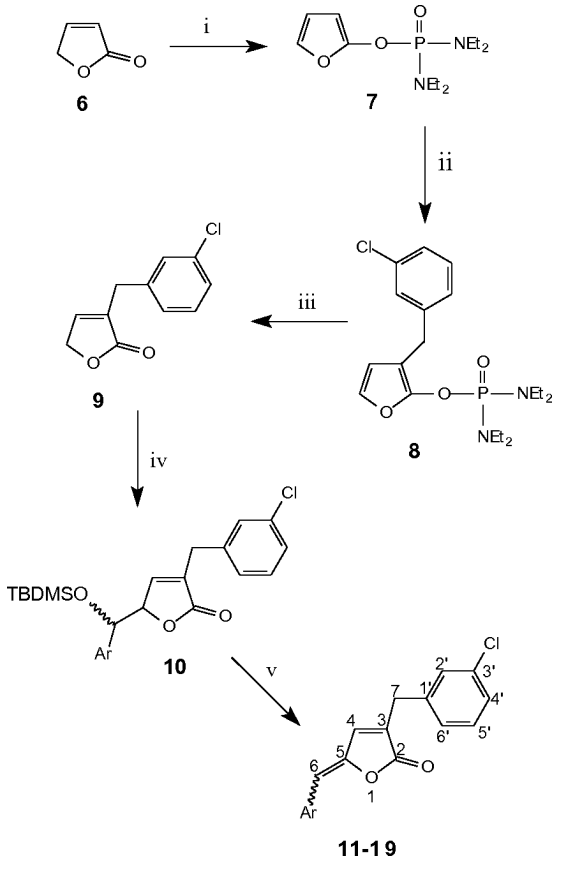
Fig. 1. Structures of nostoclides (**1**), cyanobacterin (**2**), and nostoclide analogs (**3**, **4** and **5**).

of a variety of nostoclide analogs possessing the general structures **3** and **4** [18, 19]. It was demonstrated that several analogs were able to significantly inhibit the electron flow in isolated chloroplasts from water to $K_3[Fe(CN)_6]$. As a general trend, it was found that the inhibitory potential of lactones of the type **4** is higher than that of other nostoclide analogs.

A basic structure-activity relationship study performed by Gleason's group [26] with cyanobacterin (**2**) showed that the halogen on the benzyl aromatic ring and the hydroxyl group at the C-3 position are essential for the phytotoxic activity associated with this compound [27 – 30]. In view of the structural similarity between the nostoclides **1** and the cyanobacterin (**2**), and also considering our interest in using the former as lead structures for the development of novel herbicides, we decided to investigate if lactone analogs of nostoclides **1** possessing a chlorine atom attached to the benzyl aromatic ring (Fig. 1, general structure **5**) would display phytotoxic activity. In this investigation, we describe the synthesis and structural characterization of a series of 3-(3-chlorobenzyl)-5-arylidenefuran-2(*5H*)-one analogs of nostoclides **1**. The results of the investigation of the phytogrowth activity of these derivatives on *Sorghum bicolor* and *Cucumis sativus*, at two different concentrations, are also discussed.

Results and Discussion

The new 3-(3-chlorobenzyl)-5-arylidenefuran-2(*5H*)-one derivatives were prepared as depicted in Scheme 1. Treatment of furan-2-yl *N,N,N′,N′*-tetraethyldiamidophosphate (**7**), a compound readily available from lactone **6** [20] with *n*-butyllithium promoted a regioselective lithiation at the C-3 position of the furan ring. The *in situ* generated organolithium reagent was captured with 3-chlorobenzyl bromide affording compound **8** which was not isolated. The alkylated product was treated with formic acid yielding lactone **9** in 50 % overall yield (from compound **7**). In the next step, substance **9** was converted to a variety of adducts (general structure **10**) *via* reaction with different aldehydes in the presence of diisopropylethylamine (DIPEA) and *tert*-butyldimethylsilyltrifluoromethanesulfonate (TBDMSOTf). The adducts were not isolated, and the elimination of the TBDMSO group from them was achieved by addition of 8-diazabicyclo[5.4.0]undec-7-ene (DBU) to the crude reaction mixture, resulting in the formation of the nostoclide derivatives **11 – 19** in yields ranging from 20 % to 87 % (Scheme 1).



Compound	Arylidene group	Yield (%)
11	benzylidene	87(*Z*)
12	1,3-dioxalenebenzylidene	40(*Z*)
13	4-fluorobenzylidene	20(*Z*)
14	4-bromobenzylidene	26(*Z*)
15	2-bromobenzylidene	33(*Z*)
16	4-trifluoromethylbenzylidene	45(*Z*)
17	2,5-dimethoxybenzylidene	46(*Z*)
18	3-nitrobenzylidene	67(*Z*)
19	2,4,6-trimethoxybenzylidene	25(*E*)

Scheme 1. Reagents and conditions: i) $POCl_3$, Et_3N, CH_2Cl_2, r. t.; Et_2N, Et_2O; ii) *n*-BuLi, THF, −78 °C, *m*-$ClC_6H_4CH_2Br$; iii) HCOOH; iv) ArCHO, TBDMSOTf, DIPEA, CH_2Cl_2, r. t.; v) DBU, reflux.

The structures of the synthesized derivatives were confirmed based on IR, NMR and MS techniques. The infrared spectra showed strong absorptions varying from 1735 to 1773 cm^{-1} corresponding to the C=O stretching. The molecular ion peaks were observed in all mass spectra confirming the molecular formulas of the final products. The number of ^{13}C NMR signals was consistent with the corresponding structures of the derivatives. Two-dimensional NMR techniques

Table 1. Effect of lactones **11** – **19** on radicle growth of *S. bicolor* and *C. sativus* seedlings.

	10 ppm		100 ppm	
	Radicle length (cm)[a]	% inhibition	Radicle length (cm)[a]	% inhibition
	S. bicolor			
11	5.19c	54.4	5.25b	53.9
12	3.33d	70.7	2.75d	75.8
13	6.95b	38.9	4.83c	57.4
14	5.38c	52.7	5.07c	55.4
15	6.20b	45.5	6.11b	46.3
16	5.67c	50.2	5.50b	51.6
17	7.12b	37.4	4.90c	56.9
18	6.34b	44.3	6.01b	47.2
19	6.70b	41.1	6.45b	43.3
Control	11.38a	–	11.38a	–
CV (%)	24.03		25.75	
	C. sativus			
11	4.81cd	28.3	4.78b	28.7
12	5.99b	10.7	7.38ab	−9.9
13	5.56c	17.1	5.53b	17.6
14	3.90d	41.9	3.95c	41.1
15	5.79c	13.7	4.56c	32.0
16	5.54c	17.4	5.63b	16.1
17	6.58b	1.9	7.46ab	−11.2
18	6.99b	−4.2	4.14c	38.3
19	8.88a	−32.3	9.20a	−37.1
Control	6.71b	–	6.71b	–
CV (%)	12.11		19.04	

[a] Means in the same column with the same letter are not significantly different at $P = 0.05$ % by Tukey's test.

(HMBC and HSQC) assisted in the ^{1}H and ^{13}C NMR assignments.

Under the reaction conditions specified in Scheme 1, it was found that the elimination of the *tert*-butyldimethylsilyloxy group (TBDMSO) of **10** led to the formation of the corresponding *Z* isomers except for compound **19** from which the *E* stereochemistry was obtained. In the case of the *Z* stereoisomers, the geometry of the double bound was confirmed by the observed correlation between the H-4 and H-6 signals in the NOESY contour plots. On the other hand, the absence of such correlation in the contour plot of compound **19** accounted for the *E* stereochemistry of the exocyclic double bond. The rational for these stereochemical outcomes has been discussed recently in the literature [31].

The effects of compounds **11** – **19** on radicle growth of the monocotyledonous test species *S. bicolor* are summarized in Table 1.

All compounds caused a significant inhibitory effect on the radicle growth of *S. bicolor*. None of the compounds exerted a significant effect on the germination rate. From a qualitative point of view, it is evident from Table 1 that the activity of the lactones varies with the substituent of the benzylidene ring. At the higher concentration, compound **12** was the most effective causing 75.8 % inhibition while derivative **19** displayed 43.3 % inhibition.

The phytotoxic activity of the lactones **11** – **19** was further investigated on *Cucumis sativus*, a dicotyledonous species (Table 1). As a general trend, the inhibitory effects on this species were less pronounced compared to *S. bicolor*. In fact, at the higher concentration stimulatory effects were observed for compounds **12**, **17**, and **19**. Considering inhibitory effects at 100 ppm, compounds **14** and **18** showed equipotent effects being the most actives against *C. sativus*. On the contrary, the fluorinated analogs **13** and **16** corresponded to the less active compounds inhibiting, respectively, by 17.6 % and 16.1 % at 100 ppm. It is worth to mention the variability in plant susceptibility, as observed for compounds **11** – **19** during the biological evaluation on *S. bicolor* and *C. sativus*, which is a promising feature toward the development of new selective herbicides.

Experimental Section

General procedures

All reactions were carried out under a protective atmosphere of dry nitrogen or dry conditions utilizing a calcium chloride tube adapted to the reaction flasks. Dichloromethane, tetrahydrofuran (THF), diethyl ether, and amines were purified as described in the literature [32]. Commercially available *tert*-butyldimethylsilyltrifluoromethanesulfonate (TBDMSOTf), diisopropylethylamine (DIPEA), 8-diazabicyclo[5.4.0]undec-7-ene (DBU), phosphoryl chloride ($POCl_3$), 3-chlorobenzylbromide, and aldehydes were purchased from Aldrich (Milwaukee, WI, USA) and utilized without further purification. Lactone **6** was synthesized in 43 % yield from furfural employing a published methodology [33]. Commercially available *n*-butyllithium hexane solutions (1.4 mol L^{-1}) were titrated prior to use [34]. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 instrument at 300 and 75 MHz using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP5050A instrument by direct insertion, in 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 analyses were conducted on aluminum-packed precoated silica gel plates.

Column chromatography was performed over silica gel (60 – 230 mesh).

Synthesis

*3-(3-Chlorobenzyl)furan-2-5(H)-one (**9**)*

A 25 mL two-necked round-bottom flask was charged under nitrogen atmosphere with furan-2-yl-*N,N,N′,N′*-tetraethyldiamidophosphate (**7**) (252 mg; 0.90 mmol) and anhydrous THF (3.0 mL). The mixture was cooled to −78 °C under continuous stirring, and *n*-butyllithium (0.5 mol L^{-1} in hexane, 2.8 mL; 1.4 mmol) was then added dropwise over 8 min. The mixture was kept under continuous stirring at −78 °C for 30 min, 3-chloro benzyl bromide (0.2 mL, 1.68 mmol) dissolved in anhydrous THF (3.0 mL) was then added dropwise over 8 min, and stirring was continued at −78 °C for 30 min. The reaction mixture was allowed to warm up to r. t. under continuous stirring. Water (5.0 mL) and ethyl acetate (20 mL) were added, the phases were separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The organic extracts were combined, washed with brine (10 mL), dried (magnesium sulfate), filtered, and concentrated under reduced pressure. To the resulting oily residue, formic acid (1.0 mL) was added. The resulting mixture was stirred at r. t. for 45 min, benzene (3.0 mL) was then added, and the excess of formic acid was removed under reduced pressure. To the residue, ethyl acetate (10 mL) and a sodium chloride-sodium carbonate saturated aqueous solution (3.0 mL) were added. The organic phase was washed twice with the latter solution (2 × 10 mL). The combined aqueous phases were extracted with ethyl acetate (2 × 10 mL). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was purified by silica gel column chromatography (hexane/diethyl ether 2 : 1 v/v), and the lactone **9** was obtained in 50 % yield (440 mg; 2.53 mmol). – IR (KBr) ν = 3085, 2930, 2869, 1752 (C=O), 1654, 1598, 1574, 1475, 1447, 1069, 831, 626 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.60 (dd, J = 3.6, J = 2.1 Hz, 2 H, 6-H), 4.60 (dd, J = 2.1, J = 3.6 Hz, 2 H, 5-H), 6.95 (quint, J = 3.6, J = 3.6 Hz, 1 H, 4-H), 7.10 – 7.15 (m, 1 H, 6′-H), 7.20 – 7.30 (m, 3 H, 2′-H /5′-H /4′-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.70 (C-6), 70.53 (C-5), 127.34 (C-6′), 127.40 (C-4′), 129.20 (C-2′), 130.30 (C-5′), 133.80 (C-3′), 134.72 (C-3), 139.52 (C-1′), 146.15 (C-4), 173.93 (C-2). – MS (EI, 70 eV): *m/z* (%) = 208 (13) $[M]^+$ ($C_{11}H_9ClO_2$), 210 (4) $[M+2]^+$, 173 (30), 129 (100), 128 (82), 127 (69), 115 (47), 89 (18). – Anal.: calcd. C 63.32, Cl 16.99, H 4.35; found C 63.18, Cl 16.71, H 4.22.

*(5Z)-3-(3-Chlorobenzyl)-5-(1,3-dioxalenebenzylidene) furan-2(5H)-one (**12**)*

A solution of compound **9** (208 mg; 1.0 mmol) and piperonal (180 mg; 1.2 mmol) in anhydrous dichloromethane (3.0 mL) was placed in a 25 mL two-necked round-bottom flask, and the system was kept under nitrogen atmosphere at r. t. To this solution, *tert*-butyldimethylsilyltrifluoromethanesulfonate (TBDMSOTf, 0.17 mL; 0.74 mmol) and diisopropylethylamine (DIPEA, 0.31 mL; 1.2 mmol) were added. The resulting reaction mixture was stirred at r. t. for 1 h, and then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.12 mL; 1.22 mmol) was added, followed by a 3 h reflux. The reaction mixture was diluted with dichoromethane (70 mL) and washed with hydrochloric acid (3 mol L^{-1}, 2 × 25 mL), followed by brine (2 × 25 mL). The organic phase was dried with magnesium sulfate, filtered, and concentrated under reduced pressure to produce a yellow solid. This residue was purified by silica gel column chromatography eluted with hexane/dichloromethane (1 : 1 v/v), affording the required product as a solid in 45 % yield (152 mg; 0.45 mmol). – M. p. 179.1 – 179.8 °C. – IR (KBr) ν = 3098, 2900, 1735 (C=O), 1654, 1602, 1489, 1446, 1379, 1341, 1262, 1036, 936 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.71 (s, 2 H, 7-H), 5.82 (s, 1 H, 6-H), 5.98 (s, 2 H, OCH_2O), 6.79 (d, J = 8.1 Hz, 1 H, 5″-H), 6.95 (t, J = 1.4 Hz, 1 H, 4-H), 7.10 (dd, J = 8.1, J = 1.8 Hz, 1 H, 6″-H), 7.15 – 7.36 (m, 4 H, 2′-H/4′-H/5′-H/6′-H), 7.42 (d, J = 1.8 Hz, 1 H, 2″-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.22 (C-7), 101.47 (OCH_2O), 108.54 (C-5″), 109.90 (C-2″), 113.16 (C-6), 125.86 (C-6″), 127.10 (C-4′), 127.14 (C-6′), 127.31 (C-1″), 128.92 (C-2′), 130.06 (C-5′), 130.44 (C-3), 134.53 (C-3′), 139.25 (C-1′), 139.82 (C-4), 145.98 (C-5), 148.22 (C-3″), 148.48 (C-4″), 170.21 (C-2). – MS (EI, 70 eV): *m/z* (%) = 340 (100) $[M]^+$ ($C_{19}H_{13}ClO_4$), 341 (20) $[M+1]^+$, 342 (33) $[M+2]^+$, 247 (6), 219 (6), 162 (40), 134 (42), 115 (20), 104 (23), 76 (70). – Anal.: calcd. C 66.97, Cl 10.40, H 3.85; found C 67.95, Cl 10.49, H 3.90.

Compounds **11**, **13** – **19** were prepared employing a procedure similar to that described for compound **12**, and yields are presented in Scheme 1. Structures of lactones **11**, **13** – **19** are supported by the following spectroscopic data:

*(5Z)-3-(3-Chlorobenzyl)-5-benzylidenefuran-2(5H)-one (**11**)*

M. p. 128.1 – 128.8 °C. – IR (KBr) ν = 3060, 3024, 2922, 1762 (C=O), 1647, 1606, 1495, 1451, 1426, 1022, 937, 870 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.67 (s, 1 H, 7-H), 5.90 (s, 1 H, 6-H), 6.94 (t, J = 1.2 Hz, 1 H, 4-H), 7.24 – 7.36 (m, 4 H, 2′-H/4′-H/5′-H/6′-H), 7.33 (t, J = 7.8 Hz, 1 H, 4″-H), 7.49 (d, J = 7.8 Hz, 2 H, 2″-H/6″-H), 7.97 (t, J = 7.8 Hz, 2 H, 3″-H/5″-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.17 (C-7), 109.83 (C-6), 126.97 (C-4′), 127.27 (C-6′), 128.85 (C-3″/C-5″), 129.87 (C-4″), 130.05 (C-2″/C-6″), 133.00 (C-2′), 134.03 (C-5′), 133.04 (C-1″), 134.54 (C-3′), 139.19 (C-1′), 139.95 (C-4), 147.47 (C-5), 170.30 (C-2). – MS (EI 70 eV): *m/z* (%) = 296 (42) $[M]^+$ ($C_{18}H_{13}ClO_2$), 298 (14) $[M+2]^+$, 268 (3), 261 (20), 243 (16), 217 (46), 216 (17), 215 (24), 206 (24), 202 (15), 125 (21), 124 (12), 115 (55),

101 (18), 91 (17), 90 (100), 77 (11), 63 (25), 51 (20). – Anal.: calcd. C 72.85, Cl 11.95, H 4.42; found C 72.77, Cl 11.89, H 4.15.

*(5Z)-3-(3-Chlorobenzyl)-5-(4-fluorobenzylidene)furan-2(5H)-one (**13**)*

M. p. 135.7 – 136.3 °C. – IR (KBr) ν = 3069, 2953, 2928, 2886, 2856, 1746 (C=O), 1595, 1507, 1485, 1237, 1044, 822, 800 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 3.56 (s, 2 H, 7-H), 5.76 (s, 1 H, 6-H), 6.93 (t, J = 1.3 Hz, 1 H, 4-H), 7.06 (dd, J_{ortho} = 8.7, J_{orthoF} = 8.5 Hz, 2 H, 3″-H/5″-H), 7.25 – 7.38 (m, 4 H, 2′-H/6′-H/5′-H/4′-H), 7.72 (dd, J_{ortho} = 8.7, J_{orthoF} = 5.7 Hz, 2 H, 2″-H/6″-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.27 (C-7), 113.21 (C-6), 115.36 (d, $^2J_{C-F}$ = 21.7 Hz, C-3″/C-5″), 127.25 (C-4′), 128.87 (C-6′), 129.03 (C-2′), 129.27 (C-5′), 129.61 (C-3), 132,47 (d, $^3J_{C-F}$ = 8.6 Hz; C-2″/C-6″), 132.70 (C-3′), 136.25 (C-1′), 139.69 (C-4), 147.24 (C-5), 163.37 ($^1J_{C-F}$ = 250 Hz, C-4″), 170.12 (C-2). – MS (EI 70 eV): *m/z* (%) = 314 (100) $[M]^+$ ($C_{18}H_{12}ClFO_2$), 316 (33) $[M+2]^+$, 296 (4), 279 (20), 261 (26), 215 (24), 206 (22), 183 (10), 125 (10), 136 (30), 115 (50), 108 (60), 91 (43), 89 (30), 77 (56), 51 (29). – Anal.: calcd. C 68.69, Cl 11.26, H 3.84; found C 67.97, Cl 11.32, H 3.77.

*(5Z)-3-(3-Chlorobenzyl)-5-(4-bromobenzylidene)furan-2(5H)-one (**14**)*

M. p. 165.1 – 166.8 °C. – IR (KBr) ν = 3069, 2952, 2930, 2892, 2854, 1757 (C=O), 1643, 1577, 1487, 1405, 1311, 1279, 1144, 822, 800 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 2 H, 7-H), 5.80 (s, 1 H, 6-H), 6.94 (t, J = 1.3 Hz, 1 H, 4-H), 7.24 – 7.36 (m, 4H, 2′-H/4′-H/5′-H/6′-H), 7.48 (dd, J = 8.7, J = 1.8 Hz, 2 H, 3″-H/5″-H), 7.60 (d, J = 8.7 Hz, 2 H, 2″-H/6″-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.98 (C-7), 111.56 (C-6), 123.41 (C-4″), 127.27 (C-4′), 128.97 (C-6′), 129.14 (C-2′), 129.18 (C-5′), 132.00 (C-2″/C-6″), 132.23 (C-5″/C-3″), 133.17 (C-3), 133.26 (C-1″), 134.46 (C-3′), 137.21 (C-1′), 139.75 (C-4), 148.00 (C-5), 170.02 (C-2). – MS (EI 70 eV): *m/z* (%) = 374 (29) $[M]^+$ ($C_{18}H_{12}BrClO_2$), 376 (28) $[M+2]^+$, 378 (16) $[M+4]^+$, 295 (3), 277 (4), 260 (5), 232 (10), 215 (24), 203 (11), 196 (2), 149 (4), 115 (32), 101 (16), 89 (100), 63 (27), 39 (13). – Anal.: calcd. C 57.55, Br 21.27, Cl 9.44, H 3.22; found C 57.47, Br 21.36, Cl 9.50, H 3.15.

*(5Z)-3-(3-Chlorobenzyl)-5-(2-bromobenzylidene)furan-2(5H)-one (**15**)*

M. p. 162.1 – 163.4 °C. – IR (KBr) ν = 3069, 2930, 2892, 1757 (C=O), 1643, 1577, 1487, 1405, 1311, 1279, 1144, 822, 800 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 2 H, 7-H), 6.47 (s, 1 H, 6-H), 7.12 (s, 1 H, 4-H), 7.30 (ddd, J = 7.8, J = 1.8, J = 0.6 Hz, 1 H, 3″-H), 7.50 (dt, J = 7.8, J = 1.8 Hz, 1 H, 5″-H), 7.73 (dd, J = 7.8, J = 1.5 Hz, 1 H, 6″-H), 8.33 (dd, J = 7.8, J = 1.5 Hz, 1 H, 4″-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.52 (C-7), 113.26 (C-6), 119.23 (C-2″), 124.86 (C-4′), 127.10 (C-6′), 127.31 (C-5″), 128.94 (C-6″), 129.74 (C-2′), 130.06 (C-5′), 130.44 (C-4″), 131.47 (C-3″), 132.23 (C-3), 134.43 (C-3′), 138.25 (C-1′), 139.83 (C-4), 146.02 (C-5), 173.21 (C-2). – MS (EI 70 eV): *m/z* (%) = 374 (29) $[M]^+$ ($C_{18}H_{12}BrClO_2$), 376 (28) $[M+2]^+$, 378 (16) $[M+4]^+$, 295 (3), 277 (4), 260 (5), 232 (10), 215 (24), 203 (11), 196 (2), 149 (4), 115 (32), 101 (17), 89 (100), 63 (27), 39 (13). – Anal.: calcd. C 57.55, Br 21.27, Cl 9.44, H 3.22; found C 56.99, Br 21.42, Cl 9.72, H 3.11.

*(5Z)-3-(3-Chlorobenzyl)-5-(4-trifluoromethylbenzylidene) furan-2(5H)-one (**16**)*

M. p. 109.2 – 109.6 °C. – IR (KBr) ν = 3090, 3064, 2929, 2854, 1773 (C=O), 1652, 1617, 1598, 1574, 1475, 1324, 1167, 1124, 1068, 1016, 940, 865 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 2 H, 7-H), 5.93 (s, 1 H, 6-H), 7.02 (t, J = 1.3 Hz, 1 H, 4-H), 7.15 – 7.20 (m, 1 H, 6′-H), 7.25-7.35 (m, 3 H, 2′-H/4′-H/5′-H), 7.61 (d, J = 8.1 Hz, 2 H, 3″-H/5″-H), 7.83 (d, J = 8.1 Hz, 2 H, 2″-H/6″-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.60 (C-7), 111.34 (C-6), 122.32 (C-4″), 125.86 (4″-CF_3), 127.40 (C-3″/C-5″), 127.60 (C-2′/C-6″), 129.21 (C-4′), 130.27 (C-6′), 130.46 (C-2′), 130.67 (C-5′), 133.13 (C-3), 134.90 (C-3′), 136.60 (C-1″), 139.01 (C-1′), 139.86 (C-4), 148.82 (C-5), 169.92 (C-2). – MS (EI 70 eV): *m/z* (%) = 364 (57) $[M]^+$ ($C_{19}H_{12}ClF_3O_2$), 366 (20) $[M+2]^+$, 318 (7), 329 (8), 311 (23), 283 (28), 249 (26), 158 (56), 143 (21), 125 (11), 115 (100), 91 (20), 89 (50), 63 (39), 49 (32), 39 (29). – Anal.: calcd. C 62.57, Cl 9.71, H 3.32; found C 62.51, Cl 9.69, H 3.24.

*(5Z)-3-(3-Chlorobenzyl)-5-(2,5-dimethoxybenzylidene) furan-2(5H)-one (**17**)*

M. p. 87.1 – 89.8 °C. – IR (KBr) ν = 3064, 2998, 2930, 2852, 2834, 1758 (C=O), 1681, 1598, 1494, 1464, 1237, 1046, 1026, 884, 777 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 2 H, 7-H), 3.82, (s, 6 H, 2″,5″-OCH_3), 6.43 (s, 1 H, 6-H), 6.77 (d, J = 7.6 Hz, 1 H, 3″-H), 6.83 (dd, J = 7.6, J = 2.7 Hz, 1 H, 4″-H), 7.01 (t, 1 H, J = 1.2 Hz, 4-H), 7.13 – 7.17 (m, 1 H, 4′-H), 7.23 – 7.30 (m, 3 H, 2′-H/4′-H/5′-H), 7.72 (d, J = 2.7 Hz, 1 H, 6″-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.74 (C-7), 56.05 (2″-OCH_3), 56.44 (5″-OCH_3), 107.15 (C-6), 111.94 (C-3″), 115.90 (C-6″), 116.88 (C-4″), 122.76 (C-1″), 127.35 (C-4′), 129.20 (C-6′), 130.29 (C-2′), 131.12 (C-5′), 134.80 (C-1″), 135.80 (C-3′), 139.51 (C-1′), 140.47 (C-4), 147.46 (C-5), 152.40 (C-2″), 153.94 (C-5″), 172.03 (C-2). – MS (EI 70 eV): *m/z* (%) = 356 (100) $[M]^+$ ($C_{20}H_{17}ClO_4$), 358 (33) $[M+2]^+$, 321 (15), 307 (6), 251 (14), 178 (10), 163 (40), 151 (3), 136 (40), 115 (42),

91 (51), 77 (24), 65 (19), 51 (15). – Anal.: calcd. C 67.32, Cl 9.94, H 4.80; found C 67.13, Cl 10.03, H 4.72.

*(5Z)-3-(3-Chlorobenzyl)-5-(3-nitrobenzylidene)furan-2(5H)-one (**18**)*

M. p. 143.1 – 144.7 °C. – IR (KBr) ν = 3093, 3068, 3028, 1764 (C=O), 1654, 1607, 1528, 1453, 1348, 951, 816 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 2 H, 7-H), 5.91 (s, 1 H, 6-H), 6.98 (s, 1 H, 4-H), 7.25 – 7.34 (m, 4 H, 2′-H/4′ –H/5′-H/6′-H), 7.55 (dd, *J* = 8.4, *J* = 8.2 Hz, 1 H, 5″-H), 8.12 (dt, *J* = 8.4, *J* = 1.2 Hz, 1 H, 4″-H), 8.15 (dt, *J* = 8.2, *J* = 1.2 Hz, 1 H, 6″-H), 8.41 (t, *J*= 1.2 Hz, 1 H, 2″-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.83 (C-7), 111.45 (C-6), 123.05 (C-4″), 125.08 (C-2″), 127.36 (C-4′), 127.53 (C-6′), 129.11 (C-2′), 130.22 (C-5′), 134.52 (C-3′), 129.84 (C-5″), 134.41 (C-1″), 134.71 (C-3), 135.59 (C-6″), 136.71 (C-1′), 139.12 (C-4), 148.57 (C-5), 149.15 (C-3″), 170.52 (C-2). – MS (EI 70 eV): *m/z* (%) = 341 (45) $[M]^+$ ($C_{18}H_{12}ClNO_4$), 343 (15) $[M+2]^+$, 296 (57), 288 (11), 216 (46), 202 (20), 135 (22), 115 (100), 89 (89), 77 (25), 63 (55), 51 (18). – Anal.: calcd. C 63.26, Cl 10.37, H 3.54; found C 63.11, Cl 10.52, H 3.41.

*(5E)-3-(3-Chlorobenzyl)-5-(2,4,6-trimethoxybenzylidene) furan-2(5H)-one (**19**)*

M. p. 129.1 – 129.7 °C. – IR (KBr) ν = 3054, 2917, 2848, 1749 (C=O), 1600, 1583, 1467, 1456, 1333, 1205, 1156, 1119, 1035, 813 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 2 H, 7-H), 3.79 (s, 6 H, 2″,6″-OCH_3), 3.81 (s, 3 H, 4″-OCH_3), 6.08 (s, 2 H, 3″-H/5″-H), 6.44 (s, 1 H, 6-H), 7.08 (s, 1 H, 4-H), 7.16 – 7.25 (m, 4 H, 2′-H/4′-H/5′-H/6′-H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.74 (C-7), 55.47 (4″- OCH_3), 55.95 (2″/6″- OCH_3), 90.91 (C-3″/C5″), 101.98 (C-6), 127.32 (C-4′), 127.47 (C-6′), 128.97 (C-2′), 129.25 (C-5′), 133.17 (C-3), 133.89 (C-3′), 136.39 (C-1′), 140.50 (C-4), 148.23 (C-5), 151.51 (C-2″/6″), 161.52 (C-4″), 173.02 (C-2). – MS (EI 70 eV): *m/z* (%) = 386 (100) $[M]^+$ ($C_{21}H_{19}ClO_5$), 388 (34) $[M+2]^+$, 351 (11), 343 (3), 265 (4), 205 (10), 181 (31), 166 (59), 165 (21), 149 (21), 115 (37), 109 (13), 69 (20), 63 (18), 53 (13). – Anal.: calcd. C 65.20, Cl 19.17, H 4.95; found C 65.09, Cl 9.30, H 4.87.

Root elongation assays on Petri dishes with seeds of Sorghum bicolor and Cucumis sativus

The biological assay was carried out as previously described [35] with seeds of *S. bicolor* and *C. sativus* at 10 ppm and 100 ppm. Stock solutions at 100 ppm of each tested compound were prepared as follows: Each compound was dissolved in xylene (24 μL), with surfactant Tween 80 (36 μL) and pentan-3-one (12 μL). The resultant suspension was shaken for 1 min and then transferred to a volumetric flask and the volume supplemented with water to 50 mL. The resultant suspension was sonicated for 5 min. The 10 ppm solutions were prepared diluting the 100 ppm ones accordingly.

The biological assays were conducted in Petri dishes (i. d. = 9 cm) lined with two sheets of filter paper. Groups of twenty seeds along with 4 mL of the solution contaning the compound to be tested were placed in Petri dishes. The Petri dishes were sealed with Parafilm and incubated at 25 °C under fluorescent light (8 × 40 W) in an incubator for 3 d. Radicle length was measured and total germination recorded. Seeds were considered to have germinated if a radicle protruded at least 1 mm. Controls were included using xylene, pentan-3-one and surfactant Twen 80. Each bioassay was replicated five times in a completely randomized design. The percentage of radicle growth inhibition was calculated in relation to the root length of the control. The data were analyzed using Tukey's test at 0.05 probability level.

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