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Preparation of Achiral and Chiral (*E*)-Enaminopyran-2,4-diones and Their Phytotoxic Activity

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A short and efficient approach to a range of new chiral and achiral functionalized (*E*)-enaminopyran-2,4-diones starting with commercially available dehydroacetic acid is described. The phytotoxic properties of these (*E*)-enaminopyran-2,4-diones were evaluated by their ability to interfere with the growth of *Sorghum bicolor* and *Cucumis sativus* seedlings. A different sensitivity of the two crops was evident with the (*E*)-enaminopyran-2,4-diones. The most active compounds were also tested against two weeds, *Ipomoea grandifolia* and *Brachiaria decumbens*. To the best of our knowledge, this is the first report describing enaminopyran-2,4-diones as potential plant growth regulators.

KEYWORDS: Pyran-2,4-diones; dehydroacetic acid; phytotoxic; herbicides; weeds

INTRODUCTION

In modern agriculture, organic synthetic pesticides are largely used to reduce crop loss, as they are cost-effective and generally increase productivity. Concerns related to environmental problems and human health associated with the use of hazardous chemicals have stimulated agrochemical companies to search for ecofriendly alternatives (*1*). One of the major problems associated with crop production is the decrease in productivity due to the presence of weeds. Since the 1940s, the use of organic herbicides has become the most reliable and least expensive tool for weed control throughout the world. During recent decades, important advances have been achieved in the chemical control of weeds, but the identification of novel herbicides is still highly desirable, especially to overcome weed resistance, rapidly raised as a result of severe selective pressure imposed by continuous application of products with the same mechanism of action (*2*). In this context, the development of herbicides with new modes of action is a constant challenge. Among several strategies used by chemical companies to search for compounds with new modes of action is the use of phytotoxic natural products as herbicides or to lead to the discovery of new herbicides (*3, 4*).

Biologically active natural products are incredibly diverse in terms of structural formulas. Among such compounds, many presenting the pyran-2,4-dione ring as a structural unit have pharmacological (*5, 6*) or phytotoxic activities (*7*). Several approaches have been described for the synthesis of functionalized pyran-2,4-diones (*8*−*10*), resulting in production of a wide variety of nitrogen-containing heterocycles with important pharmacological activities (*11*). In addition, several enaminones have been prepared for pharmacological uses (*12*−*15*). Derivatives of dehydroacetic acid **1** are very important due to the wide spectrum of their chemical properties and biological activities (*16*−*20*). Dehydroacetic acid is known to react with amines, yielding the corresponding enamino derivatives at the acetyl carbonyl group (*20*−*25*).

As part of our continuous efforts to develop new compounds with potential use as herbicides (*26*−*31*), we decided to investigate the potential phytotoxicity of new pyran-2,4-dione derivatives. In this context, we describe in this paper the synthesis of a series of chiral and achiral functionalized (*E*)-enaminopyran-2,4-diones, some of them synthesized for the first time, starting with commercially available dehydroacetic acid (*32*), and their inhibitory potential against either crops (*Sorghum bicolor* and *Cucumis sativus*) or weeds (*Brachiaria decumbens* and *Ipomoea grandifolia*).

MATERIALS AND METHODS

General Experimental Procedures. Ethyl acetate, hexane, 1,4-dioxane, and amines were purified as described by Armarego and Chai

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(*33*). The ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AVANCE DPX 250 spectrometer at 250 and 62.5 MHz using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. Mass spectra were recorded using high-resolution hybrid quadrupole (Q) and orthogonal time-of-flight (TOF) instruments. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrophotometer, with the samples prepared as a thin film on a NaCl plate, scanning from 635 to 4000 cm^{-1}. Optical rotation (α) was obtained using cubets of 1 cm at 20 °C. Analytical thin layer chromatography analyses were conducted on aluminum-packed precoated silica gel plates. Flash chromatography was performed over silica gel (0.035−0.070 mm).

General Procedure for the Synthesis of (*E*)-Enaminopyran-2,4-dione Derivatives (2a−k, 3a−b, and 4a−c). These compounds were prepared by stirring a mixture of **1** (84 mg, 0.5 mmol), alkylamine or arylamine or amino acid methyl ester hydrochloride (0.6 mmol), triethylamine (2 mL), and 1,4-dioxane (8 mL) under reflux for 16 h. The solvent was removed under reduced pressure, and the products were purified by silica gel flash column chromatography, eluting with a mixture of hexane and ethyl acetate.

*(E)-3-(1-(benzylamino)ethylidene)-6-methyl-3H-pyran-2,4-dione (**2a**).* Yellow solid; yield, 87%; mp 79−81 °C; IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3686, 3621, 3454, 3018, 1695, 1643, 1577, 1481, 1394, 1328, 1215, 1062, 1000, 930, 771, 669; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.04 (d, 3H, J = 0.5 Hz, CH_3), 2.60 (s, 3H, CH_3), 4.77 (d, 2H, J = 5.2 Hz, CH_2), 5.67 (br s, 1H, H5), 7.30−7.44 (m, 5H, Ph), 14.10 (br s, 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 18.4 (C7), 19.6 (C9), 47.6 (C10), 96.2 (C3), 107.4 (C5), 128.0 (C2′ and C6′), 128.3 (C4′), 129.4 (C3′ and C5′), 136.5 (C1′), 162.8 (C6), 163.3 (C2), 176.2 (C4), 183.8 (C8).

*(S,E)-3-(1-(sec-butylamino)ethylidene)-6-methyl-3H-pyran-2,4-dione (**2b**).* White solid; yield, 91%; mp 51−53 °C; $[\alpha]_D^{20}$ = +2 (c = 0.36 g/100 mL); IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3446, 3018, 2987, 1695, 1640, 1577, 1477, 1394, 1217, 1062, 999, 772, 669; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.87 (t, 3H, J = 7.3 Hz, CH_3), 1.19 (d, 3H, J = 6.5 Hz, CH_3), 1.58 (quint, 2H, J = 7.3 Hz, CH_2), 2.05 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.95 (sextet, 1H, J = 6.5 Hz, CH), 5.64 (s, 1H, H5), 11.92 (br s, 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 12.2 (C13), 18.3 (C7), 19.6 (C9), 20.5 (C10), 29.4 (C12), 51.2 (C11), 95.7 (C5), 107.4 (C3), 162.6 (C6), 163.3 (C2), 174.4 (C4), 183.9 (C8). HRMS (ESI TOF-MS): calcd for $C_{12}H_{18}NO_3$, 224.1287; found, 224.1338.

*(E)-6-Methyl-3-(1-(propylamino)ethylidene)-3H-pyran-2,4-dione (**2c**).* Yellow solid; yield, 90%; mp 74−75 °C; IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3448, 3013, 2964, 2956, 2882, 1699, 1640, 1579, 1473, 1392, 1338, 1216, 1058, 906, 831, 771; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.93 (t, 3H, J = 7.3 Hz, CH_3), 1.61 (sextet, 2H, J = 7.3 Hz, CH_2), 2.05 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.46 (q, 2H, J = 7.3 Hz, CH_2), 5.67 (d, 1H, J = 0.5 Hz, H5), 13.80 (br s, 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 11.5 (C12), 18.1 (C7), 19.6 (C9), 22.2 (C11), 45.5 (C10), 95.9 (C5), 107.4 (C3), 162.6 (C6), 163.4 (C2), 175.9 (C4), 183.8 (C8);. HRMS (ESI TOF-MS): calcd for $C_{11}H_{16}NO_3$, 210.1130; found, 210.1192.

*(E)-6-Methyl-3-(1-(phenylamino)ethylidene)-3H-pyran-2,4-dione (**2d**).* White solid; yield, 79%; mp 127−128 °C; IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3454, 3055, 2987, 1714, 1699, 1574, 1471, 1392, 1362, 1267, 1190, 1161, 1064, 999, 952, 839, 742; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.11 (d, 3H, J = 0.8 Hz, CH_3), 2.49 (s, 3H, CH_3), 5.82 (q, 1H, J = 0.8 Hz, H5), 7.30−7.56 (m, 5H, Ph), 15.66 (br s, 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 19.9 (C7), 20.4 (C9), 97.3 (C5), 107.2 (C3), 125.6 (C3′ and C5′), 128.3 (C4′), 129.6 (C2′ and C6′), 136.4 (C1′), 163.5 (C6), 163.8 (C2), 175.4 (C4), 184.6 (C8).

*(E)-3-(1-(2-Hydroxyphenylamino)ethylidene)-6-methyl-2H-pyran-2,4-dione (**2f**).* Yellow solid; yield, 74%; mp 171−172 °C; IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3478, 3055, 2988, 1685, 1655, 1574, 1473, 1364, 1267, 1066, 1001, 897, 748; 1H NMR (250 MHz, DMSO-d_6) δ 2.10 (br s, 3H, CH_3), 2.45 (s, 3H, CH_3), 5.67 (s, 1H, H5), 6.88 (dt, 1H, J = 7.7, 1.2 Hz, H3′), 7.01 (dd, 1H, J = 8.2, 1.2 Hz, H6′), 7.22 (dt, 2H, J = 8.2, 7.7, 1.2 Hz, H4′ and H5′), 10.27 (br s, 1H, OH), 15.36 (br s, 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 19.7 (C7), 20.3 (C9), 96.9 (C5), 108.1 (C3), 116.9 (C4′), 119.8 (C5′), 123.7 (C6′), 127.2 (C3′), 129.7 (C1′), 151.9 (C2′), 163.5 (C6) 168.5 (C2), 175.7 (C4), 183.0 (C8). HRMS (ESI TOF-MS): calcd for $C_{14}H_{14}NO_4$, 260.0923; found, 260.1182.

Table 1. Crystal Data and Structure Refinement for Compound **2c**

empirical formula	$C_{11}H_{15}NO_3$
formula weight	209.24
temperature (K)	150(2)
wavelength (Å)	0.71073
crystal system	monoclinic
space group	$P2_1/c$
unit cell dimensions	a = 4.6727(2) Å b = 20.8465(8) Å c = 10.8060(4) Å β = 94.325(2)°
volume (Å^3)	1049.61(7)
Z	4
density (calc) (Mg/m^3)	1.324
absorption coefficient (mm^{-1})	0.096
F (000)	448
crystal size (mm^3)	0.22 × 0.11 × 0.05
θ-range for data collection (deg)	3.8−27.4
index ranges	$-5 \le h \le 5$, $-26 \le k \le 26$, $-13 \le l' \le 13$
reflections collected	4497
independent reflections	2308 [R(int) = 0.0351]
completeness to θ = 27.4°	97.7%
refinement method	full-matrix least-squares on F^2
data/restraints/parameters	2308/0/143
goodness-of-fit on F^2	1.025
final R for $I > 2\sigma(I)$	$R1$ = 0.0504
R for all data	w$R2$ = 0.1393
largest diff peak and hole (e·Å^{-3})	0.235 and −0.212

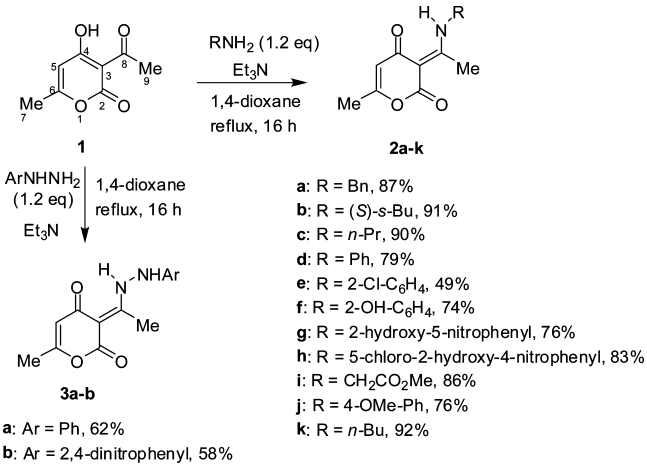
*(E)-3-(1-(2-Hydroxy-5-nitrophenylamino)ethylidene)-6-methyl-2H-pyran-2,4(3H)-dione (**2g**).* White solid; yield, 76%; mp 196−197 °C; IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3429, 2987, 2884, 1687, 1637, 1419, 1275, 897, 850; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.10 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 5.79 (s, 1H, H5), 6.87 (d, 1H, J = 8.2 Hz, H3′), 7.00 (dd, 1H, J = 8.2, 1.2 Hz, H4′), 7.22 (d, 1H, J = 1.2 Hz, H6′), 10.27 (br s, 1H, OH), 15.33 (br s, 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 20.4 (C7), 20.6 (C9), 97.4 (C3), 106.0 (C6), 107.4 (C5), 116.9 (C3′), 124.3 (C4′), 139.3 (C1′), 158.7 (C2), 145.4 (C2′), 148.6 (C5′) 163.4 (6), 172.1 (C8), 176.0 (C4). HRMS (ESI TOF-MS): calcd for $C_{14}H_{13}N_2O_6$, 305.0774; found, 305.0770.

*(E)-3-(1-(5-Chloro-2-hydroxy-4-nitrophenylamino)ethylidene)-6-methyl-2H-pyran-2,4(3H)-dione (**2h**).* Red solid; yield, 83%; mp 230−232 °C; IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3483, 3371, 3020, 1637, 1531, 1473, 1321, 1216, 873, 771, 669; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.24 (d, 3H, J = 0.8 Hz, CH_3), 2.53 (s, 3H, CH_3), 6.24 (br s, 1H, H5), 6.68 (s, 1H, PhH), 7.46 (s, 1H, PhH), 8.57 (br s, 1H, OH), 10.28 (br s, 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 14.9 (C7), 20.6 (C9), 99.9 (C3), 101.4 (C5), 113.7 (C3′), 120.8 (C6′), 121.6 (C5′), 133.2 (C4′), 142.1 (C2′), 145.4 (C1′), 148.6 (C2) 160.9 (6), 170.6 (C8), 180.9 (C4).

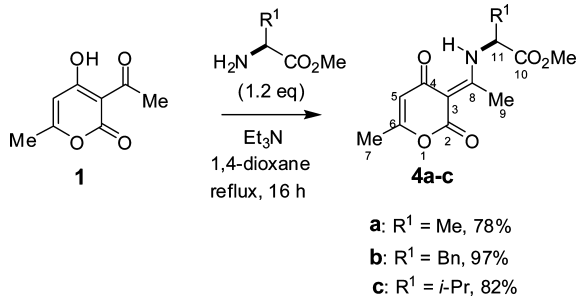
*Methyl 2(E)-(1-(6-Methyl-2,4-dioxopyridin-(2H)-pyran-3(4H)-ylidene)ethylamino)acetate (**2i**).* White solid; yield, 86%; mp 145−146 °C; IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3454, 3018, 1720, 1699, 1642, 1581, 1475, 1394, 1363, 1218, 1064, 1000, 929, 771, 669; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.06 (d, 3H, J = 0.5 Hz, CH_3), 2.51 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.54 (d, 2H, J = 5.0 Hz, CH_2), 5.72 (d, 1H, J = 0.5 Hz, H5), 14.02 (br s, 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 18.7 (C7), 19.6 (C9), 45.7 (C1′), 52.9 (OCH_3), 96.4 (C5), 107.2 (C3), 162.4 (C6), 169.1 (C2 and C2′), 175.6 (C4), 183.2 (C8). HRMS (ESI TOF-MS): calcd for $C_{11}H_{14}NO_5$, 240.0872; found, 240.0870.

*(E)-3-(1-(4-Methoxyphenylamino)ethylidene)-6-methyl-3H-pyran-2,4-dione (**2j**).* Yellow solid; yield, 66%; mp 180−182 °C; IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3055, 2987, 2941, 2887, 1699, 1645, 1627, 1573, 1530, 1475, 1321, 1265, 1031, 999, 897, 840, 746; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.14 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 5.74 (s, 1H, H5), 6.93 (d, 2H, J = 8.8 Hz, H2′ and H6′), 7.08 (d, 2H, J = 8.8 Hz, H3′ and H5′), 15.44 (br s, 1H, NH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 20.0 (C7), 20.5 (C9), 55.6 (OCH_3), 97.1 (C3), 107.0 (C5), 114.8 (C3′ and C5′), 126.7 (C2′ and C6′), 128.8 (C1′), 159.3 (C4′), 163.7 (C6), 163.9 (C2), 175.6 (C4), 184.3 (C8).

Scheme 1. Preparation of (*E*)-Enaminopyran-2,4-diones **2a**−**k** and **3a,b**



Scheme 2. Preparation of Chiral (*E*)-Enaminopyran-2,4-diones **4a**−**c**



*(E)-3-(1-(Butylamino)ethylidene)-6-methyl-3H-pyran-2,4-dione (**2k**).* Yellow oil; yield, 92%; IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3479, 3055, 2961, 2924, 2869, 1695, 1655, 1581, 1479, 1392, 1361, 1338, 1257, 1163, 1061, 999, 926, 837, 735; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.3 Hz, H4′), 1.44 (sextet, 2H, J = 7.3 Hz, H3′), 1.68 (m, 2H, H2′), 2.10 (d, 3H, J = 0.5 Hz, CH_3), 2.52 (s, 3H, CH_3), 3.46 (m, 2H, H1′), 5.68 (br d, 1H, J = 0.5 Hz, H5), 13.98 (br s, 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 13.6 (C4′), 18.1 (C3′), 19.7 (C9), 20.0 (C2′), 30.9 (C1′), 43.9 (C7), 96.4 (C5), 107.0 (C4), 162.0 (C2), 175.0 (C4), 182.0 (C8).

*(E)-6-Methyl-3-(1-(2-phenylhydrazinyl)ethylidene)-2H-pyran-2,4(3H)-dione (**3a**).* Red oil; yield, 62%; IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3460, 3055, 2987, 1743, 1610, 1552, 1421, 1265, 1103, 897, 750; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.25 (d, 3H, J = 0.8 Hz, CH_3), 2.42 (s, 3H, CH_3), 5.90 (br s, 1H, H5), 7.37 (t, 1H, J = 7.8 Hz, H4′), 7.56 (m, 2H, H3′ and H5′), 7.73 (d, 2H, J = 7.8 Hz, H2′ and H6′); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 14.7 (C9), 19.6 (C7), 102.4 (C3), 104.9 (C5), 120.9 (C2′ and C6′, 127.6 (C4′), 129.9 (C3′ and C5′), 136.9 (C1′), 144.9 (C2), 150.3 (C8), 154.5 (C4), 159.3 (C6). HRMS (ESI TOF-MS): calcd for $C_{14}H_{15}N_2O_3$, 259.1083; found, 259.1101.

*(E)-3-(1-(2-(2,4-Dinitrophenyl)hydrazinyl)ethylidene)-6-methyl-2H-pyran-2,4(3H)-dione (**3b**).* Red oil; yield, 58%; IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3445, 3055, 2987, 1740, 1700, 1645, 1625, 1549, 1421, 1344, 1261, 1039, 897, 748; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.24 (d, 3H, J = 0.8 Hz, CH_3), 2.45 (s, 1H, NH), 2.54 (s, 3H, CH_3), 6.27 (br s, 1H, H5), 8.18 (dd, 1H, J = 9.0, 0.3 Hz, H6′), 8.72 (dd, 1H, J = 9.0, 2.5 Hz, H5′), 8.88 (dd, 1H, J = 2.5, 0.3 Hz, H3′); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 14.7 (C9), 20.6 (C7), 99.9 (C3), 101.5 (C5), 105.8 (C6′), 122.0 (C3′), 132.9 (C5′), 146.8 (C2′), 147.8 (C4′), 151.5 (C1′), 154.7 (C6), 161.0 (C2), 170.7 (C8), 180.9 (C4). HRMS (ESI TOF-MS): calcd for $C_{14}H_{13}N_4O_7$, 349.0784; found, 349.0781.

*(S,E)-Methyl-3-methyl-2-(1-(6-methyl-2,4-dioxo-2H-pyran-3(4H)-ylidene)ethylamino)propanoate (**4a**).* White solid; yield, 78%; mp 121−122 °C; $[\alpha]_D^{20} = -7$ (c = 0.29 g/100 mL); IR (NaCl, cm^{-1}) $\bar{\nu}_{max}$ 3456, 3057, 2986, 2957, 1725, 1699, 1670, 1583, 1477, 1361, 1251, 1223, 1151, 1059, 1000, 895, 737; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.47 (d, 3H, J = 7.3 Hz, CH_3), 2.06 (d, 3H, J = 0.8 Hz, CH_3), 2.52 (s, CH_3), 3.72 (s, 3H, OCH_3), 4.88 (quintet, 1H, J = 7.3 Hz, CH), 5.71 (br s, 1H, H5), 14.23 (br s, 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 18.6 (C7), 18.8 (C9), 19.6 (C12), 52.2 (C11), 53.3 (OCH_3), 96.4 (C5), 107.4 (C3), 163.0 (C2 and C6), 171.5 (C10), 175.9 (C4), 184.0 (C8). HRMS (ESI TOF-MS): calcd for $C_{12}H_{16}NO_5$, 254.1028; found, 254.1186.

*(S,E)-Methyl-2-(1-(6-methyl-2,4-dioxo-2H-pyran-3(4H)-ylidene)ethylamino)-3-phenylpropanoate (**4b**).* White solid; yield, 97%; mp 91−92 °C; $[\alpha]_D^{20} = -202$ (c = 0.21 g/100 mL); IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3454, 3055, 2988, 2956, 1730, 1701, 1670, 1578, 1477, 1362, 1265, 1065, 999, 896, 746; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.05 (d, 3H, J = 0.5 Hz, CH_3), 2.34 (s, 3H, CH_3), 3.11 (dd, 1H, J = 14.0, 7.7 Hz, CH_2), 3.26 (dd, 1H, J = 14.0, 7.7 Hz, CH_2), 3.71 (s, 3H, OCH_3), 5.15 (t, 1H, J = 7.7 Hz, CH), 5.70 (br s, 1H, H5), 7.10−7.32 (m, 5H, Ph), 14.40 (br s, 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 18.4 (C7), 19.6 (C9), 35.7 (C12), 53.2 (OCH_3), 57.9 (C11), 96.4 (C5), 107.8 (C3), 127.6 (C4′), 128.9 (C2′ and C6′), 129.9 (C3′ and C5′), 135.7 (C1′), 163.8 (C2), 170.2 (C10), 176.3 (C4), 185.2 (C8). HRMS (ESI TOF-MS): calcd for $C_{18}H_{20}NO_5$, 330.1341; found, 330.1362.

*(S,E)-Methyl-3-methyl-2-(1-(6-methyl-2,4-dioxo-2H-pyran-3(4H)-ylidene)ethylamino)butanoate (**4c**).* Yellow oil; yield, 82%; $[\alpha]_D^{20}$ = +4 (c = 1.18 g/100 mL); IR (NaCl, cm^{-1}), $\bar{\nu}_{max}$ 3448, 3020, 2971, 1705, 1697, 1650, 1577, 1479, 1394, 1363, 1216, 927, 777, 669; ^{1}H NMR (250 MHz, DMSO-d_6) δ 0.92 (d, 3H, J = 6.5 Hz, CH_3), 0.94 (d, 3H, J = 6.5 Hz, CH_3), 2.07 (d, 3H, J = 0.5 Hz, CH_3), 2.28 (m, 1H, H3′), 2.50 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.77 (dd, 1H, J = 8.2, 6.5 Hz, H2′), 5.73 (br s, 1H, H5), 14.30 (br s, 1H, NH); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 17.7 (C7), 18.6 (C4′), 18.8 (C5′), 19.6 (C3′), 31.4 (C9), 53.1 (OCH_3), 61.7 (C2′), 96.6 (C5), 108.0 (C3), 163.2 (C2 and C6), 170.3 (C1′), 176.8 (C4), 198.0 (C8); HRMS (ESI TOF-MS): calcd for $C_{14}H_{20}NO_5$, 282.1342; found, 282.1308.

X-ray Analysis. A well-shaped single crystal of (*E*)-3-(1-(propylamino)ethylidene)-6-methyl-3*H*-pyran-2,4-dione (**2c**) was selected for the X-ray diffraction experiment. This crystal was mounted on a glass fiber and afterward positioned on the goniometer head. Intensity data were collected at low temperature (150(2) K) provided by a cryogenic device (Oxford Cryosystem) and with graphite monochromated Mo Kα radiation (λ = 0.71073 Å), using a Enraf-Nonius Kappa-CCD diffractometer. The cell refinements were performed using the software Collect (*34*) and Scalepack (*35*), and the final cell parameters were obtained on all reflections. Data for compound **2c** were measured up to 27.4° in θ, totaling 4497 Bragg reflections. Data reduction was carried out using the software Denzo-SMN and Scalepack (*35*) with XdisplayF for visual representation of data. An absorption coefficient of 0.096 mm^{-1} was observed. Thus, absorption correction was not done.

The structure was solved using the software SHELXS-97 (*36*) and refined using the software SHELXL-97 (*37*), where the C, N, and O atoms were clearly solved and full-matrix least-squares refinement of these atoms with anisotropic thermal parameters was carried out. The amine hydrogen atom was located by difference Fourier analysis and was set as isotropic. On the other hand, the C−H hydrogens were positioned stereochemically and were refined with fixed individual displacement parameters [$U_{iso}(H) = 1.2U_{eq}(C_{sp^2})$ or $1.5U_{eq}(C_{sp^3})$] using a riding model with C−H bond lengths ranging between 0.93 Å and 0.97 Å. **Table 1** was prepared using WinGX (version 1.70.01) (*38*) and presents a summary of the X-ray diffraction experiment. ORTEP-3 (*39*) and MERCURY (*40*) were also used in order to publish the crystal

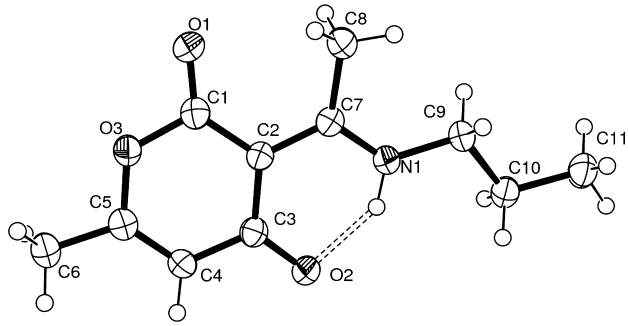


Figure 1. ORTEP-3 representation of compound **2c**.

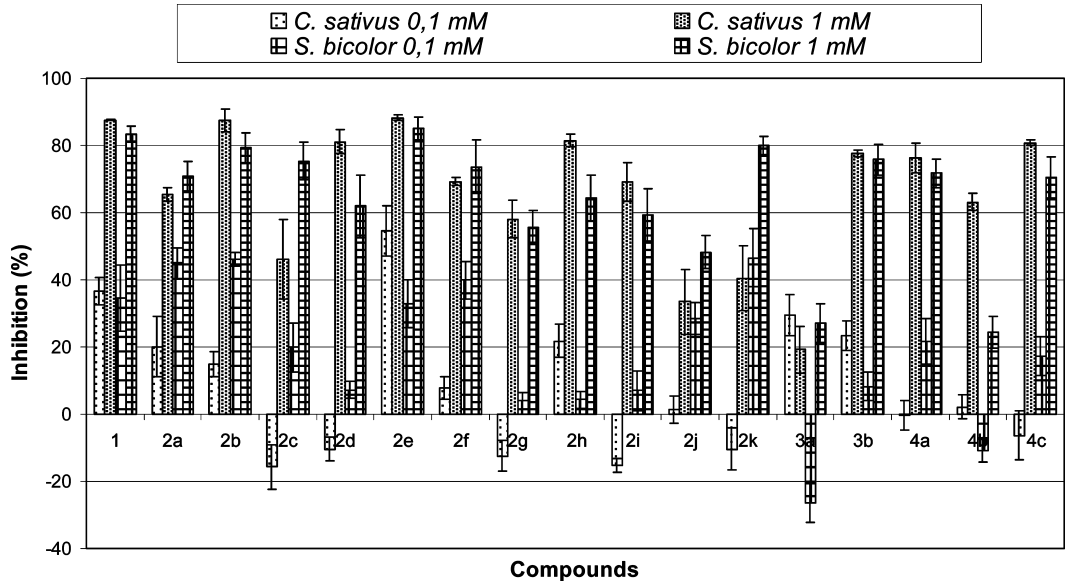


Figure 2. Effect of the compounds, at 10^{-4} mol L^{-1} (0.1 mM) and 10^{-3} mol L^{-1} (1 mM), on the radicle development of *C. sativus* and *S. bicolor*.

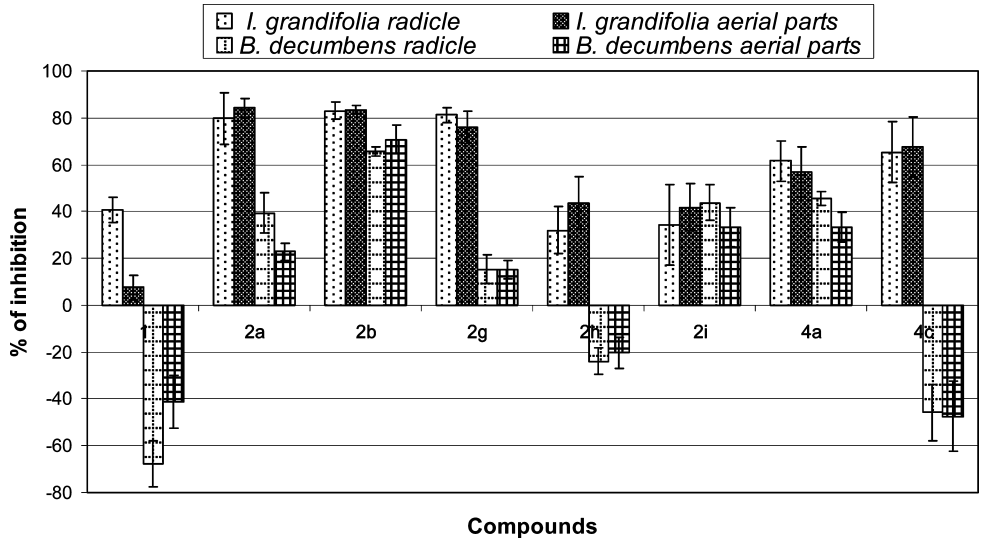


Figure 3. Effect of the compounds, at 5×10^{-4} mol L^{-1}, on the development of radicle and aerial parts of *I. grandifolia* and *B. decumbens*.

data, as well as MOGUL (*41*), a useful program to evaluate the molecular conformation and geometry by matching the values of bond distances and torsional and valence angles for a query compound with the corresponding ones of similar structures that are deposited at the Cambridge Structure Database (CSD) (*42*) (**Table 1**).

The crystallographic information file leading to the data sets (except the structure factors) for compound **2c** has been deposited with the Cambridge Structural Data Base under deposit code CCDC 694825 (copies of these data may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K.; fax, +44123-336-033; e-mail, deposit@ccdc.cam.ac.uk; or http:www.ccdc.ac.uk).

Plant Growth Inhibition Assays. In order to evaluate the growth regulatory potential of the synthesized (*E*)-enaminopyran-2,4-diones (**1**, **2a**−**k**, **3a**−**b**, and **4a**−**c**), three different bioassays were carried out.

Radicle Elongation Assay on Filter Paper. The solutions of (*E*)-enaminopyran-2,4-diones were prepared by dissolving a proper amount in xylene (48 μL) and pentan-3-one (24 μL) (*31*). After addition of the surfactant Tween 80 (72 μL), the resulting suspension was transferred to a volumetric flask and diluted with water to 50 mL, so as to obtain final concentrations of 1×10^{-3} mol L^{-1} and 1×10^{-4} mol L^{-1}. These suspensions were sonicated for 5 min, and then 4 mL aliquots were used to imbibe two sheets of filter paper (Whatman no. 1) placed in 100 mm × 15 mm glass Petri dishes. To each dish were added 20 seeds of *Sorghum bicolor* L. Moench (Geneze Company, Paracatu, Minas Gerais State, Brazil) or *Cucumis sativus* L. (purchased from a local market). The plates were incubated at 25 °C under fluorescent light (8 × 40 W) for 72 h. Radicle length was then measured, and total germination was recorded. Seeds were considered to have germinated if a radicle protruded at least 1 mm. Treatments were carried out in a completely randomized design with five replications. The data, expressed as percentage of radical growth inhibition with respect to untreated controls, were analyzed using Tukey's test at the 0.05 probability level.

Radicle Elongation Assay in Sand. Solutions of the most active compounds **1**, **2a**, **2b**, **2g**, **2h**, **2i**, **4a**, and **4c** were prepared by dissolving a proper amount in xylene (84 μL) and pentan-3-one (42 μL). After addition of the surfactant Tween 80 (127 μL), the resulting suspension was transferred to a volumetric flask and diluted in water to 88 mL, so as to obtain a final concentration of 5×10^{-4} mol L^{-1}. These suspensions were sonicated for 5 min and were used to imbibe acid-washed sand (165 g) in 90-mm Petri dishes. Seven pregerminated seeds of *Ipomoea grandifolia* or *Brachiaria decumbens* were transferred into each plate, and dishes were sealed with Parafilm and incubated at 28 °C. After 24 and 48 h, the radicle length was measured to the nearest millimeter. Treatments were carried out in a completely randomized design with four replications. The data were expressed and analyzed as above.

Greenhouse Trials. Plastic pots (0.13 L) were filled with acid-washed sand, which was saturated with the solution of the test compound (60

mL/450 g of sand, corresponding to 5.9×10^{-5} mmol a.i./g substrate). Four seeds of *I. grandifolia* or *B. decumbens* were placed in each pot. Seedlings were grown in a greenhouse and watered as required with tap water or, twice a week, with half-strength Hoagland solution, to maintain the humidity at 13.3% w/w. Twenty-one days after sowing, plants were harvested, and the roots and aerial parts were separated and weighed. Tissues were then dried at 60 °C until constant weight, and the corresponding dry mass was determined. The percentage of root and aerial part growth inhibition was calculated in relation to the mass of the respective control. Data were expressed and analyzed as previously indicated.

RESULTS AND DISCUSSION

Synthesis of (*E*)-Enaminopyran-2,4-diones. Treatment of dehydroacetic acid **1** with the corresponding primary alkyl or aryl amines proceeded smoothly in the presence of triethylamine in refluxing 1,4-dioxane to give the corresponding functionalized (*E*)-enaminopyran-2,4-diones **2a**−**k** in excellent yields (**Scheme 1**). The use of (*S*)-*sec*-butylamine gave chiral enamino-2,4-dione **2b** in 91% isolated yield. Usually, the reaction with alkyl amines led to better yields when compared with aryl amines.

The next step involved the reactions of dehydroacetic acid **1** with phenylhydrazines to give the (*E*)-enaminopyran-2,4-diones **3a** and **3b** in good yields (**Scheme 1**). We next moved to the reactions of dehydroacetic acid **1** with the corresponding chiral α-amino esters (**Scheme 2**). We were able to get excellent yields by reacting **1** with the α-amino esters derived from L-alanine, L-phenylalanine, and L-valine, affording the desired (*E*)-enaminopyran-2,4-diones **4a**−**c**.

X-ray Analysis. The structures of the products were confirmed by X-ray analysis of compounds **2a**−**2c** (**Figure 1**). Of the two possible isomers, the (*E*)-enaminone is formed preferentially as hydrogen bonding occurs with the more electron rich oxygen. In **Figure 1**, an ORTEP-3 representation (*38*) of compound **2c** is shown. This compound crystallizes in the centrosymmetric monoclinic space group $P2_1/c$ with one entire molecule in the asymmetric unit. In the solid state, the X-ray diffraction analyses have revealed that the major tautomer is the form presenting the nitrogen atom covalently hydrogen bonded, whereas the two exocyclic oxygen atoms are either carbonyl or carboxyl (**Figure 1**). An interesting intramolecular feature in the **2c** structure is the occurrence of a chelating six-membered system closed by the classical noncovalent hydrogen bond N1−H1···O2 in which the nitrogen atom of the propylamino moiety is the hydrogen donor and the carbonyl oxygen of the δ-lactone ring is the acceptor.

Phytotoxic Assay. Compounds **1**, **2a**−**k**, **3a**,**b**, and **4a**−**c** were then submitted to a plant growth bioassay to evaluate their effect on the radicle growth of *Cucumis sativus* and *Sorghum bicolor*. The experiments were carried out at two concentrations (10^{-4} and 10^{-3} mol L^{-1}) of each compound, and the results are shown in **Figure 2**.

None of the compounds caused a significant effect on the germination rate for *C. sativus* at the two concentrations tested. However, at 10^{-4} mol L^{-1}, several different effects were observed: stimulating effects (**2c** and **2i**, 15%), lesser inhibitory effects (**2a**, 20%; **2h**, 22%; **3b**, 23%), and moderate inhibitory effects (**3a**, 29%; **1**, 37%; **2e**, 54%). At 10^{-3} mol L^{-1}, all compounds showed inhibitory effects, ranging from 19% to 88%, on the radicle growth of *C. sativus*. The six most active compounds (**1**, **2b**, **2d**, **2e, 2h**, and **4c**) caused more than 80% inhibition of radicle growth. It is interesting to note that compound **2b**, which presents a (*S*)-*sec*-butyl group attached to the nitrogen, is much more active (88% inhibition) than compound **2k** (44% inhibition), bearing a butyl group. This result could in principle suggest that chirality could have some effect on the activity. This hypothesis was disproved, since it was observed that chiral (*E*)-enaminopyran-2,4-diones (**4a**−**c**) were as active as (63−81% of inhibition) the achiral compound (**2i**) (69%) in inhibiting the radicle development of *C. sativus*.

The aromatic enamine **2d** bearing an unsubstituted phenyl ring caused the best result of inhibition against *C. sativus*, compared with the aromatic enamines with substitutions in the ring. Despite a stimulating effect on radicle growth at 10^{-4} mol L^{-1}, at the higher concentration **2d** inhibits (81% inhibition) as much as **2e** (88%) and **2h** (81%). These data and others presented in **Figure 2** suggest that the presence of substitution on the aromatic ring of these enamines is not a requisite for herbicide activity against *C. sativus*.

For the hydrazines (**3a** and **3b**) it was observed that the presence of two nitro groups on the aromatic ring had a significant impact on the activity. Compound **3b** caused 78% inhibition of radicle growth, while **3a** was four times less active, causing only 19% inhibition.

For *S. bicolor*, none of the compounds caused a significant effect on the germination rate at 10^{-4} mol L^{-1}. However, at 10^{-3} mol L^{-1} were observed inhibitions with **2a** (16%), **2f** and **2k** (18%), **2d** (22%), **2h** (25%), **1** (73%), and **2e** (76%).

Only **3a** and **4b** showed a stimulating effect at 10^{-4} mol L^{-1} (26% and 11%, respectively). A small inhibitory effect (less than 10%) was noted for compounds **2d**, **2g**, **2h**, **2i**, and **3b**, while approximately 46% inhibition was observed for compounds **2a**, **2b**, and **2k**. At 10^{-3} mol L^{-1}, compounds **3a** and **4b** showed lower inhibitory effects (27% and 24%, respectively), while moderate inhibitory effects (**2i**, 59% and **2j**, 48%) and high inhibitions were found for compounds **2c** and **3b** (76%), **2b** and **3k** (80%), **1** (83%), and **2e** (85%).

The chiral (**4a**−**c**) and achiral (**2i**) enamine methyl esters showed large differences over the radicle development of *S. bicolor*. The aromatic compound **4b** showed a small inhibitory effect (11% and 24%, at 10^{-4} and 10^{-3} mol L^{-1}, respectively) on radicle growth, while for the others high inhibitory activities (**2i**, 7% and 59%; **4c**, 17% and 70%; **4a**, 22% and 72%) were registered. Since the observed inhibitory activities for **2i**, **4c**, and **4a** are quite similar, it seems that for these compounds the chirality is not a requirement for inhibitory activity. Moreover, since the aromatic compound **4b** displayed a small inhibitory effect, it is apparent that the presence of an alkyl group attached to the chiral carbon may contribute to the activity of compounds (**4a**−**c**) against *S. bicolor*.

At 10^{-3} mol L^{-1} hydrazine **3b** caused higher inhibition (76%) on the radicle development of *S. bicolor* than **3a** (27% inhibition). These results are consistent with those reported for *C. sativus*, confirming the strong influence of the nitro groups on the activity of these compounds.

Compound **2e**, an aromatic enamine with a chorine in the ring, presented the best result of inhibition (85% at 10^{-3} mol L^{-1}) against *S. bicolor* compared with other aromatic enamines. The presence of a chlorine atom seems to have little effect on herbicide activity, since **2d** caused 62% of inhibition at the same concentration. On the other hand, compound **2h**, which differs from **2g** by the presence of chlorine in the ring and by the position of the nitro group, was 8% more active at 10^{-3} mol L^{-1}, while **2f** (with a hydroxyl in ring) was 11% less active than **2e** at 10^{-3} mol L^{-1}.

For the alkyl enamines **2b** (79% inhibition), **2c** (75%), and **2k** (80%), no significant differences for the herbicide activity at 10^{-3} mol L^{-1} were observed. At the same concentration, compound **2c** (20% inhibition) was much less active than the

others. These data suggest that the size of the alkyl chain could be associated with activity. Futher investigation should be carried out in order to evaluate this proposal.

After confirming the inhibitory activity of the pyran-2,4-diones on the development of *C. sativus* and *S. bicolor*, the effect of the most active compounds (**1**, **2a**, **2b**, **2g**−**i**, **4b**, and **4d**) on the growth of the important weeds *Ipomoea grandifolia* and *Brachiaria decumbens* was investigated. At 5×10^{-4} mol L^{-1}, all the compounds caused inhibition of the biomass of the roots (ranging from 32% to 83%) and on the aerial parts (from 8% to 84%) of *I. grandifolia*. Compounds **2a**, **2b**, and **2g** were the most active, causing around 81% (for the three compounds) inhibition on root biomass development, and 84%, 84%, and 76% on the aerial parts of *I. grandifolia*, respectively. These data suggest that the presence of *sec*-butyl, benzyl, or 2-hydroxy-5-nitrophenyl groups has similar contributions to the herbicide activity of these enamines. The same behavior was observed for **4a** and **4c**, where a methyl or isopropyl on the chiral carbon did not cause a significant change in herbicide activity (roots: **4a**, 62% inhibition; **4c**, 65%. aerial parts: **4a**, 57% inhibition; **4c**, 68%). When compared with **2i**, the presence of methyl or isopropyl groups (**4a** or **4c**) significantly increases herbicide activity (**2i**: roots, 34%; aerial parts, 42%) against *I. grandifolia*.

For *B. decumbens*, compound **2g** inhibited roots and aerial parts by 15%, while **2h** increased the development of roots by 24% and the aerial parts by 20%. Compound **4a** caused 46% and 33% inhibition on roots and aerial part development, respectively; for **4c** induction of the development of roots and aerial parts (around 46%) was observed. There was no significant difference between **4a** and **2i** (roots inhibition, 44%; aerial parts inhibition, 33%).

Compound **2b**, a chiral alkyl enamine, showed the highest inhibitory effect on the development of roots (66%) and aerial parts (71%) of *B. decumbens*.

The effect of the precursor dehydroacetic acid (*1*) was also investigated. Dehydroacetic acid inhibits the development of roots (41%) and aerial parts (8%) of *Ipomoea grandifolia* but increases the development of roots (68%) and aerial parts (41%) of Brachiaria *decumbens* at a concentration of 5×10^{-4} mol L^{-1}.

The highest activities presented by the tested compounds and the selective effect observed on the root growth of monocotyledons (*B. decumbens*) and dicotyledons (*I. grandifolia*) should be further investigated. These compounds also could be exploited for the design of new substances closely related to dehydroacetic acids endowed with herbicidal activity.

CONCLUSIONS

We have prepared a variety of new functionalized achiral and chiral (*E*)-enaminopyran-2,4-diones, starting with dehydroacetic acid. In addition, we have described their effect on radicle growth of *Sorghum bicolor* and *Cucumis sativus*. The most active compounds against *S. bicolor* and *C. sativus* were tested on the development on the radicle and aerial parts of the *I. grandifolia* and *B. decumbens*. Based upon a preliminary structure−activity relationship analysis discussed in this paper, work is currently underway to achieve the synthesis of new pyran-2,4-dione derivatives with better herbicide activity.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR of compounds **2a**, **2c**, and **4c**; experimental bond lengths and angles for **2c**; hydrogen-bonding geometry for **2c**; and hydrogen bond scheme for **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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