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CHEMICAL SCIENCES

Synthesis of novel glycerol-fluorinated triazole derivatives and evaluation of their phytotoxic and cytogenotoxic activities

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Abstract: The control of weeds in agriculture is mainly conducted with the use of synthetic herbicides. However, environmental and human health concerns and increased resistance of weeds to existing herbicides have increased the pressure on researchers to find new active ingredients for weed control which present low toxicity to non-target organisms, are environmentally safe, and can be applied at low concentrations. It is herein described the synthesis of glycerol-fluorinated triazole derivatives and evaluation of their phytotoxic and cytogenotoxic activities. Starting from glycerol, ten fluorinated triazole derivatives were prepared in four steps. The assessment of them on *Lactuca sativa* revealed that they present effects on phytotoxic and cytogenotoxic parameters with different degrees of efficiency. The compounds 4a, 4b, 4d, 4e, 4i, and 4j have pre-emergent inhibition behavior, while all the investigated compounds showed post emergent effect. Mechanism of action as clastogenic, aneugenic, and epigenetic were observed in the lettuce root meristematic cells, with alterations as stick chromosome, bridge, delay, c-metaphase, and loss. It is believed that glycerol-fluorinated triazole derivatives possess a scaffold that can be explored towards the development of new chemicals for the control of weed species.

Key words: 1,2,3-triazole, cytotoxicity, fluorinated derivatives, glycerol, phytotoxicity.

INTRODUCTION

The use of herbicides for weed control is an important tool in modern agriculture because chemical control is fast, efficient, and cost effective. However, indiscriminate use of the same herbicide exerts high selection pressure on weed populations, which thus promotes the selection of biotypes resistant to these products (Han et al. 2021, Alves et al. 2021).

Based on the importance of herbicides, since the discovery of dichlorodiphenyltrichloroethane (DDT) in 1939, the agrochemical industry has been constantly developing successful new methodologies of organic synthesis with the objective of providing increasingly selective, efficient and environmentally safe compounds. Currently, more than 1.200 agrochemicals are known and many of them are regularly used by farmers to generate the food supply to support the expanding global population.

In the last two decades, fluorochemicals have been associated with significant advances in the agrochemical development process (Ogawa et al. 2020). Among the herbicides licensed worldwide, currently around 25% contain at least one fluorine atom and several

contain multiple fluorines in the form of difluoro and trifluoromethyl groups. Over the years, the use of halogens in the design of new agrochemicals has substantially increased as well as the presence of these atoms in the active ingredients of new commercial products. Jeschke stated "the introduction of halogens into active ingredients has become an important concept in the quest for a modern agrochemical with optimal efficacy, environmental safety, user friendliness, and economic viability" (Jeschke 2010). Taking fluorine into consideration, its van der Waals radius is similar to hydrogen. It can mimic hydrogen atoms or hydroxyl groups in bioactive compounds. Such modifications (substitution of an H or OH by a fluorine) can result, for example, in improved selectivity. Moreover, because of the high electronegativity associated with fluorine, the introduction of this atom in a molecule creates a high dipole moment and can alter the acidity of functional groups. Lipophilicity of compounds is another property that can be altered by the introduction of fluorine atoms. These features (among others) (Jeschke 2004) related to the introduction of fluorine atoms in compounds can result in changes in the physicochemical properties of the molecules which, in turn, can result in improved biological responses (Andrade-Vieira et al. 2012).

Fluorine-containing compounds have made a significant contribution to the development of products for the agrochemicals industry and many organofluorine entities have found stable market positions (Fujiwara & Hagan 2014).

Another class of organic compounds widely employed as pharmaceuticals and agrochemicals is the nitrogen containing heterocyclic compounds. Considering the heterocyclic systems, 1,2,3-triazoles hold great importance due to their broad spectrum of applications in pharmaceuticals, biochemical, medicinal, material sciences, and agrochemical (Avulaa et al. 2019). Their chemistry underwent a substantial growth over the past decades. 1*H*-1,2,3-triazole containing compounds were reported to exhibit a large range of biological activities such as fungicide, phytotoxic and cytogenotoxic (Costa et al. 2017, 2020).

Considering the importance of heterocyclic compounds containing nitrogen and fluoro-chemicals in the development of new agrochemicals and as well as our interest in the chemistry of triazoles and in the preparation of bioactive compounds that can be used as new active ingredients to control weeds, it is herein described the synthesis of novel 1,2,3-triazoles bearing fluorinated aryl moieties and evaluation of their phytotoxic and cytogenotoxic activities.

MATERIALS AND METHODS

Generalities

The solvents and reagents with high purity were purchased from Vetec (Rio de Janeiro, Brazil), except the terminal alkynes that were procured from Sigma-Aldrich (St. Louis, MO, USA), and used as received from the commercial suppliers. The reaction progress was monitored by thin layer chromatography (TLC). Analytical thin layer chromatography analysis was conducted on aluminum backed precoated silica gel plates using different solvent systems. TLC plates were visualized using potassium permanganate solution, phosphomolybdic acid solution, and/or UV light. Column chromatography was performed using silica gel 60 (60-230 mesh). The IR spectra were acquired using a Tensor 27 device and the attenuated total reflection technique (Bruker, Karlsruhe, Germany) scanning from 500 to 4000 cm^{-1}. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 instrument (Varian, Palo Alto, CA, USA), at 400 MHz for ^{1}H and 100 MHz for ^{13}C, using $CDCl_3$ as deuterated

solvent and TMS as internal standard. Mass spectra were recorded on a GCMS-QPPlus 2010 device (Shimadzu, Kyoto, Japan) under electron impact (70 eV) conditions of positive ion mode. Melting points were determined with MA 381 equipment (Marconi, São Paulo, Brazil) and are uncorrected.

The ^{1}H NMR data are presented as follows: chemical shift (δ) in ppm, multiplicity, the number of hydrogens, and *J* values in Hertz (Hz). Multiplicities are indicated by the following abbreviations: s (singlet), d (doublet), d_{ap} (apparent doublet), dd (doublet of doublets), td (triplet of doublets), tdd (triplet of doublet of doublets), t (triplet), t_{ap} (apparent triplet), tt (triplet of triplets), quartet, and m (multiplet).

Synthetic procedures

Preparation of compounds 1, 2, and 3

The intermediate compounds (2,2-dimethyl-1,3-dioxolan-4-yl) methanol (1), (2,2-dimethyl-1,3-dioxolan-4-yl)methyl-4-methyl benzenesulfonate (2), and 4-(azidomethyl)-2,2-dimethyl-1,3-dioxolane (3) were synthesized as previously reported in the literature (Costa et al. 2017, 2020).

General procedure for the synthesis of glycerol-fluorinated triazole derivatives 4a-4k

The azide 3 (1.50 equivalent), terminal alkyne (1.00 equivalent), aqueous solution of $CuSO_4$ $5H_2O$ (0.100 mol L^{-1}, 1.00 mL, 0.0960 mmol), sodium ascorbate (0.0600 g, 0.288 mmol) and aqueous solution of *tert*-butyl alcohol (1:1 v v^{-1}, 12.0 mL) were added to a round-bottomed flask. The resulting reaction mixture was stirred at 50 °C for 8 h. After the completion of the reaction, as verified by TLC analysis, distilled water (10.0 mL) was added and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The organic extracts were combined, and the resulting organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography eluting with ethyl acetate-methanol (9:1 v v^{-1}). The structures of compounds 4a-4k are supported by the following data.

Synthesis of 1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-4-phenyl-1*H*-1,2,3-triazole (4a)

White solid, prepared in 83% yield from the reaction between phenylacetylene (1.50 g, 14.7 mmol) and azide 3 (1.50 g, 9.60 mmol), m.p.120-123 °C. TLC: R_f = 0.57 (ether-dichloromethane, 10:1 v v^{-1}). IR (ATR) ν /cm^{-1}: 3145, 2992, 2923, 2853, 1607, 1484, 1461, 1438, 1373, 1262, 1224, 1202, 1166, 1115, 1063, 1041, 970, 883, 833, 767, 699. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (s, 3H), 1.36 (s, 3H), 3.74 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.0 Hz), 4.09 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.4 Hz), 4.40-4.50 (m, 2H), 4.55 (dd, 1H, J_1 = 12.8 Hz and J_2 = 2.8), 7.29 (tt, 1H, J_1 = 8.0 Hz and J_2 = 1.2 Hz), 7.37-7.41 (m, 2H), 7.80 (dd, 2H, J_1 = 8.0 Hz and J_2 = 1.2 Hz), 7.87 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 26.6, 52.2, 66.3, 74.0, 110.2, 120.9, 125.6, 128.0, 128.8, 130.5, 147.7. MS (*m*/*z*, %): 259 ($[M]^+$, 19), 244 ($[M-15]^+$, 16), 144 (18), 127 (18), 116 (25), 99 (33), 85 (56), 71 (70), 57 (100), 43 (79), 41 (29), 32 (11).

Synthesis of 1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-4-(3-fluorophenyl)-*1H*-1,2,3-triazole (4b)

White solid, prepared in 70% yield, from the reaction between 1-ethynyl-3-fluorobenzene (1.70 g, 14.2 mmol) and azide 3 (1.50 g, 9.60 mmol), m.p. 88-91 °C. TLC: R_f = 0.60 (ether-dichloromethane, 10:1 v v^{-1}); IR (ATR) ν /cm^{-1}: 3099, 2992, 1620, 1590, 1484, 1465, 1444, 1372, 1293, 1225, 1202, 1149, 1115, 1055, 1026, 969, 865, 835, 755, 687. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (s, 3H), 1.38 (s, 3H), 3.75 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.0 Hz), 4.12 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.4 Hz), 4.42-4.51 (m,

2H), 4.58 (dd, 1H, J_1 = 12.6 Hz and J_2 = 2.6), 6.99 (tdd, 1H, J_1 = 8.5 Hz, J_2 = 2.5 Hz and J_3 = 0.8 Hz), 7.33-7.38 (m, 1H), 7.51-7.59 (m, 2H), 7.90 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 26.6, 52.3, 66.3, 74.0, 110.2, 112.6 (d, J_{C-F} = 22.0 Hz), 114.9 (d, J_{C-F} = 21.0 Hz), 121.2 (d, J_{C-F} = 3.0 Hz), 121.3, 130.3 (d, J_{C-F} = 8.0 Hz), 132.6 (d, J_{C-F} = 9.0 Hz), 146.6 (d, J_{C-F} = 3.0 Hz), 163.1 (d, J_{C-F} = 253.0 Hz). MS (*m/z*, %): 277 ([M]$^+$, 34), 262 ([M-15]$^+$, 32), 248 (10), 219 (21), 206 (11), 190 (10), 177 (9), 162 (37), 148 (28), 134 (40), 120 (24), 101 (33), 83 (10), 73 (20), 57 (44), 43 (100), 41 (48), 31 (10).

Synthesis of 1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-4-(4-fluorophenyl)-1*H*-1,2,3-triazole (4c)

White solid, prepared in 81% yield from the reaction between 1-ethynyl-4-fluorobenzene (2.00 g, 16.7 mmol) and azide 3 (1.75 g, 11.1 mmol), m.p. 100-103 °C. TLC: R_f = 0.57 (ether-dichloromethane, 10:1 v v^{-1}); IR (ATR) ν /cm^{-1}: 3295, 2986, 2886, 1706, 1590, 1568, 1470, 1431, 1372, 1256, 1226, 1147, 1051, 1034, 971, 879, 831, 755, 676. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (s, 3H), 1.37 (s, 3H), 3.75 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.0 Hz), 4.11 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.4 Hz), 4.41-4.50 (m, 2H), 4.57 (dd, 1H, J_1 = 13.2 Hz and J_2 = 3.2), 7.08 (t, 2H, J_1 = 8.6 Hz), 7.76-7.79 (dd, 2H), 7.84 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0, 26.6, 52.2, 66.2, 73.9, 110.1, 115.7 (d, J_{C-F} = 21.0 Hz), 120.6, 126.7 (d, J_{C-F} = 3.0 Hz), 127.4 (d, J_{C-F} = 9.0 Hz), 146.7, 162.6 (d, J_{C-F} = 253.0 Hz). MS (*m/z*, %): 277 ([M]$^+$, 35), 262 ([M-15]$^+$, 35), 248 (16), 206 (12), 190 (7), 176 (9), 162 (25), 148 (29), 134 (47), 120 (29), 101 (29), 83 (9), 73 (21), 68 (32), 59 (33), 57 (46), 43 (100), 41 (44), 31 (10).

Synthesis of 1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-4-(2-fluorophenyl)-1*H*-1,2,3-triazole (4d)

Yellow solid, prepared in 85% yield from the reaction between 1-ethynyl-2-fluorobenzene (2.00 g, 16.7 mmol) and azide 3 (1.75 g, 11.1 mmol), m.p. 69-72 °C. TLC: R_f = 0.72 (ether-dichloromethane, 10:1 v v^{-1}); IR (ATR) ν /cm^{-1}: 3172, 2994, 2976, 2958, 2926, 1579, 1553, 1485, 1466, 1437, 1370, 1260, 1233, 1217, 1164, 1142, 1107, 1044, 967, 944, 906, 841, 819, 757, 670. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (s, 3H), 1.37 (s, 3H), 3.75 (dd, 1H, J_1 = 8.8 Hz and J_2 = 5.2 Hz), 4.10 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.0 Hz), 4.47-4.52 (m, 2H), 4.58 (dd, 1H, J_1 = 15.8 Hz and J_2 = 6.2), 7.08-7.13 (m, 1H), 7.20-7.31 (m, 2H), 8.04 (d_{ap}, 1H, J = 3.6 Hz), 8.26 (1H, td, J_1 = 7.6 Hz and J_2 = 2.0). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 26.7, 51.9, 66.1, 73.9, 110.2, 115.6 (d, J_{C-F} = 21.0 Hz), 118.4 (d, J_{C-F} = 16.0 Hz), 124.0 (d, J_{C-F} = 12.0 Hz), 124.5 (d, J_{C-F} = 3.0 Hz), 127.7 (d, J_{C-F} = 3.0 Hz), 129.2 (d, J_{C-F} = 9.0 Hz), 141.1 (d, J_{C-F} = 3.0 Hz), 159.1 (d, J_{C-F} = 242.0 Hz). MS (*m/z*, %): 277 ([M]$^+$, 52), 262 ([M-15]$^+$, 52), 248 (7), 219 (21), 206 (14), 190 (12), 177 (14), 162 (50), 148 (36), 134 (46), 120 (27), 107 (24), 101 (36), 83 (9), 68 (20), 59 (35), 57 (48), 43 (100), 41 (47), 31 (12).

Synthesis of 4-(3,4-difluorophenyl)-1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-1,2,3-triazole (4e)

Brown solid, prepared in 78% yield from the reaction between 3,4-difluorophenylacetylene (2.00 g, 14.5 mmol) and azide 3 (1.50 g, 9.60 mmol), m.p. 73-75 °C. TLC: R_f = 0.53 (ether-dichloromethane 10:1 v v^{-1}); IR (ATR) ν /cm^{-1}: 3138, 3114, 2990, 2927, 1608, 1566, 1509, 1462, 1440, 1370, 1366, 1273, 1239, 1186, 1151, 1117, 1072, 1052, 1005, 968, 882, 822, 773, 718, 628, 603. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (s, 3H), 1.37 (s, 3H), 3.75 (dd, 1H, J_1 = 8.8 Hz and J_2 = 5.6 Hz), 4.12 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.4 Hz), 4.41-4.50 (m, 2H), 4.58 (dd, 1H, J_1 = 13.4 Hz and J_2 = 3.0), 7.17 (1H, td, J_1 = 10.0 Hz, J_2 = 7.8 Hz and J_3 = 1.6), 7.49-7.53 (m, 1H), 7.61-7.66 (m, 1H), 7.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0, 26.3, 52.3, 66.1, 74.0, 110.1, 114.7 (d, J_{C-F} = 19.0 Hz), 117.6 (d_{ap}, J_{C-F} = 17.0 Hz), 121.0, 121.7 (dd, J_{C-F} = 6.0 Hz and J_{C-F} = 4.0 Hz), 127.7 (dd, J_{C-F} = 6.5 Hz and J_{C-F} = 3.5 Hz), 145.9, 150.1 (dd, J_{C-F} = 247.5 Hz and J_{C-F} = 12.5 Hz), 150.6 (dd, J_{C-F} = 247.5 Hz and J_{C-F} = 11.5 Hz). MS

(*m/z*, %): 295 ([M]$^+$, 35), 280 ([M-15]$^+$, 37), 266 (12), 237 (17), 224 (12), 208 (9), 180 (28), 166 (22), 152 (36), 138 (23), 125 (18), 119 (10), 101 (21), 83 (7), 73 (20), 68 (19), 57 (32), 43 (100), 41 (47), 31 (10).

Synthesis of 4-(2,4-difluorophenyl)-1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-1,2,3-triazole (4f)

White solid, prepared in 68% yield from the reaction between 1-ethynyl-2,4-difluorobenzene (2.00 g, 14.5 mmol) and azide 3 (1.50 g, 9.60 mmol), m.p. 95-97 °C. TLC: R_f = 0.58 (ether-dichloromethane 10:1 v v^{-1}); IR (ATR) ν /cm^{-1}: 3178, 3072, 2998, 2960, 1628, 1602, 1559, 1493, 1462, 1416, 1382, 1358, 1266, 1244, 1211, 1165, 1142, 1117, 1068, 1045, 980, 905, 869, 841, 804, 732, 662, 611. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (s, 3H), 1.36 (s, 3H), 3.74 (dd, 1H, J_1 = 8.8 Hz and J_2 = 5.6 Hz), 4.10 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.0 Hz), 4.45-4.51 (m, 2H), 4.57 (dd, 1H, J_1 = 15.8 Hz and J_2 = 6.2), 6.83-6.89 (m, 1H), 6.93-6.98 (m, 1H), 7.99 (d_{ap}, 1H, J = 3.6 Hz), 8.20-8.26 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 26.3, 51.9, 66.1, 73.9, 104.0 (t, J_{C-F} = 25.5 Hz), 110.1, 111.9 (dd, J_{C-F} = 21.0 Hz and J_{C-F} = 3.0 Hz), 114.9 (dd, J_{C-F} = 13.0 Hz and J_{C-F} = 4.0 Hz), 123.5 (d_{ap}, J_{C-F} = 12.0 Hz), 128.7 (dd, J_{C-F} = 9.5 Hz and J_{C-F} = 6.5 Hz), 140.4 (d_{ap}, J_{C-F} = 3.0 Hz), 159.1 (dd, J_{C-F} = 249.0 Hz and J_{C-F} = 12.0 Hz), 162.4 (dd, J_{C-F} = 249.0 Hz and J_{C-F} = 12.0 Hz). MS (*m/z*, %): 295 ([M]$^+$, 30), 280 ([M-15]$^+$, 37), 237 (15), 220 (11), 208 (8), 195 (8), 180 (29), 166 (21), 152 (36), 138 (24), 125 (19), 119 (11), 101 (18), 83 (7), 73 (19), 68 (21), 57 (33), 43 (100), 41 (44), 31 (9).

Synthesis of 4-(3,5-difluorophenyl)-1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-1,2,3-triazole (4g)

White solid, prepared in 65% yield from the reaction between 1-ethynyl-3,5-difluorobenzene (2.00 g, 14.5 mmol) and azide 3 (1.50 g, 9.6 mmol), m.p. 100-102 °C. TLC: R_f = 0.60 (ether-dichloromethane 10:1 v v^{-1}); IR (ATR) ν /cm^{-1}: 3081, 2992, 1626, 1594, 1470, 1434, 1373, 1265, 1227, 1203, 1150, 1117, 1056, 1027, 984, 923, 881, 858, 834, 749, 680, 664. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (s, 3H), 1.38 (s, 3H), 3.75 (dd, 1H, J_1 = 8.8 Hz and J_2 = 5.8 Hz), 4.13 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.2 Hz), 4.41-4.50 (m, 2H), 4.59 (dd, 1H, J_1 = 13.0 Hz and J_2 = 2.6), 6.74 (tt, 1H, J_1 = 9.0 Hz and J_2 = 2.3 Hz), 7.32-7.35 (m, 2H), 7.91 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0, 26.7, 52.3, 66.4, 74.0, 103.2 (t, J_{C-F} = 25.5 Hz), 108.4 (dd, J_{C-F} = 19.0 Hz and J_{C-F} = 8.0 Hz), 110.2, 121.5, 133.6 (t, J_{C-F} = 10.5 Hz), 145.8 (t, J_{C-F} = 3.0 Hz), 163.3 (dd, J_{C-F} = 247.0 Hz and J_{C-F} = 13.0 Hz). MS (*m/z*, %): 295 ([M]$^+$, 18), 280 ([M-15]$^+$, 31), 237 (8), 220 (11), 208 (8), 180 (24), 166 (16), 152 (28), 138 (16), 125 (16), 119 (9), 101 (23), 83 (7), 73 (18), 57 (28), 43 (100), 41 (50), 31 (9).

Synthesis of 1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (4h)

White solid, prepared in 73% yield from the reaction between 1-ethynyl-4-(trifluorometyl) benzene (2.50 g, 14.7 mmol) and azide 3 (1.50 g, 9.60 mmol), m.p. 125-127 °C. TLC: R_f = 0.80 (ether-dichloromethane 10:1 v v^{-1}); IR (ATR) ν /cm^{-1}: 3096, 2990, 1621, 1457, 1414, 1384, 1325, 1261, 1230, 1203, 1161, 1115, 1063, 1041, 1015, 970, 913, 881, 833, 782, 687, 658. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (s, 3H), 1.38 (s, 3H), 3.76 (dd, 1H, J_1 = 8.8 Hz and J_2 = 5.6 Hz), 4.13 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.4 Hz), 4.43-4.52 (m, 2H), 4.60 (dd, 1H, J_1 = 12.6 Hz and J_2 = 2.6), 7.65 (d, 2H, J = 8.6 Hz), 7.92 (d, 2H, J = 8.6 Hz), 7.97 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0, 26.7, 52.3, 66.4, 73.9, 110.1, 121.8, 124.0 (q, J_{C-F} = 270.3), 125.8 (q, J_{C-F} = 3.6), 129.97 (q, J_{C-F} = 32.6), 134.0, 146.3. MS (*m/z*, %): 327 ([M]$^+$, 21), 312 ([M-15]$^+$, 37), 298 (7), 269 (34), 256 (13), 240 (12), 227 (7), 212 (33), 198 (17), 185 (24), 170 (7), 151 (11), 134 (11), 116 (7), 101 (25), 83 (7), 73 (20), 68 (13), 59 (29), 57 (36), 43 (100), 41 (52), 31 (10).

Synthesis of 1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (4i)

White solid, prepared in 61% yield from the reaction between 1-ethynyl-3-(trifluorometyl) benzene (2.50 g, 14.7 mmol) and azide 3 (1.50 g, 9.6 mmol), m.p. 63-65 °C. TLC: R_f = 0.51 (ether-dichloromethane 10:1 v v^{-1}); IR (ATR) ν /cm^{-1}: 3155, 2991, 2945, 1621, 1459, 1419, 1382, 1346, 1309, 1263, 1228, 1206, 1164, 1124, 1096, 1067, 1040, 1000, 985, 892, 831, 800, 717, 693, 649. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 3H), 1.39 (s, 3H), 3.77 (dd, 1H, J_1 = 8.7 Hz and J_2 = 5.8 Hz), 4.12 (dd, 1H, J_1 = 8.7 Hz and J_2 = 6.0 Hz), 4.43-4.52 (m, 2H), 4.61 (dd, 1H, J_1 = 12.8 Hz and J_2 = 2.8), 7.52 (t, 1H, J = 7.6 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.96 (s, 1H), 8.01 (d, 1H, J = 7.2 Hz), 8.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0, 26.6, 52.3, 66.3, 74.0, 110.3, 121.2, 122.4 (q, J_{C-F} = 4.0), 123.9 (q, J_{C-F} = 269.6), 124.6 (q, J_{C-F} = 3.6), 128.8, 129.4, 131.2 (q, J_{C-F} = 32.0), 131.3, 146.2. MS (*m/z*, %): 327 ([M]$^+$, 17), 312 ([M-15]$^+$, 31), 298 (6), 269 (29), 256 (11), 240 (10), 227 (7), 212 (30), 198 (15), 184 (24), 170 (7), 151 (10), 134 (8), 116 (5), 101 (22), 83 (7), 73 (19), 68 (13), 59 (23), 57 (33), 43 (100), 41 (51), 31 (8).

Synthesis of 1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-4-(2-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (4j)

Red solid, prepared in 58% yield from the reaction between 1-ethynyl-2-(trifluorometyl) benzene (2.50 g, 14.7 mmol) and azide 3 (1.50 g, 9.60 mmol), m.p. 51-53 °C. TLC: R_f = 0.73 (ether-dichloromethane 10:1 v v^{-1}); IR (ATR) ν /cm^{-1}: 2999, 2933, 1609, 1579, 1441, 1383, 1374, 1315, 1254, 1214, 1167, 1127, 1110, 1085, 1067, 1056, 1035, 995, 966, 879, 822, 773, 713, 683, 665, 645. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (s, 3H), 1.36 (s, 3H), 3.76 (dd, 1H, J_1 = 8.9 Hz and J_2 = 5.4 Hz), 4.12 (dd, 1H, J_1 = 8.9 Hz and J_2 = 5.8 Hz), 4.46-4.52 (m, 2H), 4.60 (dd, 1H, J_1 = 16.0 Hz and J_2 = 6.4), 7.46 (t, 1H, J = 7.0 Hz), 7.61 (t, 1H, J = 7.6 Hz), 7.73 (d, 1H, J = 8.0 Hz), 7.89 (s, 1H), 7.96 (d, 1H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0, 26.3, 51.9, 66.1, 73.9, 110.2, 124.1 (q, J_{C-F} = 256.0), 124.2 (q, J_{C-F} = 5.6), 126.0 (q, J_{C-F} = 5.6), 127.2 (q, J_{C-F} = 28.0), 128.1, 129.4 (q, J_{C-F} = 2.0), 131.6, 131.9, 144.0. MS (*m/z*, %): 327 ([M]$^+$, 11), 312 ([M-15]$^+$, 42), 269 (38), 256 (20), 240 (13), 212 (29), 198 (16), 184 (20), 165 (19), 151 (17), 134 (11), 115 (7), 101 (26), 83 (8), 73 (21), 59 (32), 57 (41), 43 (100), 41 (50), 31 (10).

Synthesis of 4-(3,5-bis(trifluoromethyl) phenyl)-1-((2,2-dimethyl-1,3-dioxolan-4-yl) methyl)-1*H*-1,2,3-triazole (4k)

White solid, prepared in 74% yield from the reaction between 1-ethynyl-3,5-bis(trifluoromethyl)benzene (3.50 g, 14.7 mmol) and azide 3 (1.50 g, 9.60 mmol), m.p. 60-63 °C. TLC: R_f = 0.17 (hexane-dichloromethane 1:1 v v^{-1}); IR (ATR) ν /cm^{-1}: 2933, 1465, 1383, 1321, 1276, 1234, 1210, 1173, 1130, 1107, 1079, 1045, 997, 966, 894, 828, 810, 749, 699, 680. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 3H), 1.40 (s, 3H), 3.78 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.0 Hz), 4.16 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.4 Hz), 4.44-4.53 (m, 2H), 4.64 (dd, 1H, J_1 = 13.0 Hz and J_2 = 2.6), 7.80 (s, 1H), 8.05 (s, 1H), 8.26 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1, 26.6, 52.7, 66.2, 73.8, 110.2, 121.5 (dq_{ap}, J_{C-F} = 3.7), 121.9, 123.1 (q, J_{C-F} = 271.3), 125.5 (q, J_{C-F} = 2.6), 132.2 (q, J_{C-F} = 33.3), 132.7, 144.9. MS (*m/z*, %): 395 ([M]$^+$, 11), 380 ([M-15]$^+$, 65), 376 (19), 337 (89), 320 (17), 308 (11), 280 (28), 266 (16), 252 (25), 240 (12), 219 (7), 169 (8), 101 (41), 83 (7), 73 (19), 57 (27), 43 (100), 41 (52), 31 (8).

Biological Assays

Plant Material

The evaluation of phytotoxicity and cytogenoxicity of compounds 4a-4k were performed using commercial seeds of the plant model *Lactuca sativa* L. "Crespa Grand Rapids - TBR" (ISLA).

Phytotoxicity evaluation

The phytotoxicity evaluation of the compounds 4a-4k were conducted using five different

concentrations (1000, 500, 250, 100, 50 μg mL^{-1}) of each compound. Twenty-five lettuce seeds were placed in each Petri dishes (9 cm in diameter) containing filter paper moistened with solution (2.5 mL) from each treatment. The experiments followed a completely randomized design (CRD), with four repetitions per treatment. The dishes were sealed with transparent plastic film to prevent evaporation and kept moist BOD (Biochemical Oxygen Demand) at 25 °C ± 2 ºC without light throughout the experiment period. As a negative control, distilled water and dichloromethane (99.5% v v^{-1}) were used. The commercial herbicide picloram 0.1% was utilized as a positive control. The germination process was evaluated from 8 to 48 h, at 8 h intervals. The macroscopic parameters evaluated were the germination speed index (GSI), the percentage of germinated seeds (GR), root length after 48 h (RL) and aerial growth (AG) after 120 h, as previously described (Pinheiro et al. 2015).

Cytogenotoxic evaluation

After 48 hours of exposure to treatments, the roots of *L. sativa* were collected and fixed in ethanol-acetic acid (3:1 v v^{-1}). Fixer changes were made within 10 min and 24 h after the first fixation, being stored at -20 °C during the entire process. After 24 h, slides from the root meristems were prepared using the crushing technique and stained with 2% acetic orcein (Andrade-Vieira et al. 2012). Approximately 4.000 meristematic cells were evaluated per treatment, observing, and quantifying the different phases of mitotic division, possible chromosomal, and nuclear changes. The mitotic index (MI) was obtained by dividing the number of cells in division (prophase, metaphase, anaphase, and telophase) by the total number of cells evaluated in each treatment. The frequencies of chromosomal and nuclear changes were obtained by dividing the number of changes, chromosomal, and nuclear, respectively, by the total number of cells evaluated (Andrade-Vieira et al. 2012). The frequency of changes, which represents the occurrence of each change individually, was assessed based on the ratio between the number of changes individually (c-metaphase, bridge, sticky, delay, brake and lost) and the number of cells per division (Andrade-Vieira et al. 2012). The analysis of the slides was performed using a Nikon eclipse 80i microscope. The interest images were captured on a Nikon Plan Fluor 100x/1.30 oil OFN25 DIC H/N2 objective, with a Nikon DS camera – Fi1c attached to the microscope.

Statistics Analysis

For phytotoxicity and cytogenotoxicity analyzes, the data obtained were subjected to analysis of variance and the means compared by Dunnett's test (p<0.05), as it is the most suitable for experiments that seek to compare treatments with controls (McHugh 2011). All analyses were performed using the statistical analysis program GENES VS 2015.5.0 (Cruz 2013).

RESULTS AND DISCUSSION

Preparation of compounds 4a-4k

The synthetic steps involved in the preparation of the compounds 4a-4k, herein investigated, are outlined in Figure 1. Glycerol was converted to acetonide 1 in 63% yield by treatment of the triol with acetone in the presence of TsOH and $CuSO_4$. Then, the reaction of acetonide 1 with *p*-toluene sulphonyl chloride gave the corresponding ester sulfonate 2 in 75% yield. The reaction between 2 and sodium azide resulted in the formation of 3 in 93%. Finally, the Cu(I)-catalyzed alkyne-azide cycloaddition reaction (CuAAC reaction, also known as the click reaction) (Costa et al. 2017, 2020, Aher et al. 2009, Agalave et al. 2011, Borgati et al. 2013) between

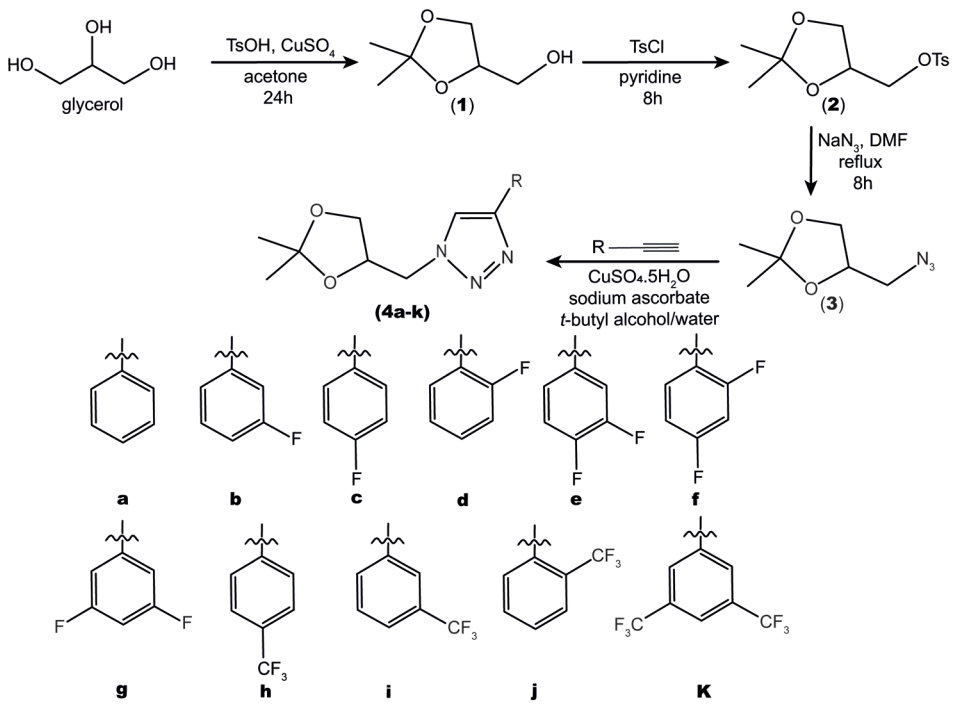

Figure 1. Synthetic route for the preparation of glycerol derivatives 4a-4k.

azide 3 and different commercially available aromatic terminal alkynes afforded the glycerol 1,2,3-triazoles derivatives 4a-4k in 58-85% yields. The structures of 4a-4k were confirmed by IR and ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometric analyses. In IR spectra, the band corresponding to the =C-H stretching was observed within the 3081-3178 cm^{-1} range, while the N=N stretching of the triazole ring was noted within the interval 1626-1579 cm^{-1}. In the ^{1}H NMR spectra, signals corresponding to the hydrogens of the triazole ring and methyl groups of acetonide were observed within 7.80-7.97 and 1.32-1.40 ppm, respectively. In ^{13}C NMR spectra, signals for methyl acetonide group were observed within 25.0-26.7 ppm range, while carbons from the triazole portion appeared at 120.6-147.7 ppm. Molecular formulas of the glycerol 1,2,3-triazole derivatives were confirmed based on mass spectrometry analyses.

Once synthesized, the compounds 4a-4k were submitted to the evaluation of their phytotoxic and cytotoxic activities.

Phytotoxicity Evaluation

The analysis of the phytotoxicity evaluation data (Figure 2) revealed that compounds 4a, 4b, 4d, and 4i were the ones that presented effects on seed germination. The derivative 4a at 1000 µg mL^{-1} inhibited approximately 25% of *L. sativa* seed germination, an effect that was similar to the positive control picloram. Compounds 4b and 4d (at 500 µg mL^{-1}) and 4i (at 1000 and 500 µg mL^{-1}) also inhibited germination when compared to the negative controls (Figure 2).

Compound 4a, at the highest concentration, presented an effect on GSI similar to picloram, inhibiting GSI by 65% as compared to negative controls. The derivatives 4a (at 500 µg mL^{-1}), 4b (at 1000, 500, and 250 µg mL^{-1}), 4d and 4e (at 1000, 500 µg mL^{-1}), 4i and 4j (at 1000, 500 µg mL^{-1}) promoted inhibition on the GSI when compared to the negative controls (Figure 2). Some compounds, 4b, 4d, 4e, 4i, and 4j, showed inhibitory effects only on this germination parameter, presenting no difference when compared to the percentage of final germination. This is a characteristic

Figure 2. Phytotoxicity evaluation of triazoles 4a-4k. The effects of the compounds were assessed on the plant model *Lactuca sativa* at five concentrations. Positive control was picloram and negative controls corresponded to dichloromethane and water. The G% = germination percentage; GSI = Germination Speed Index; RG = Root Growth; AG = Aerial Growth. The means followed by the letter *a* were equal to the negative control water, those followed by the letter *b* were equal to the negative control dichloromethane and those followed by the letter *c* were equal to the positive control picloram (0.1%) according to the Dunnett test (p <0.05).

found in compounds classified as biocides (Iganci et al. 2006).

Regarding root growth, the triazole 4i (at 1000 and 500 µg mL^{-1}) was equipotent to picloram, inhibiting approximately 80% of root lettuce development as compared to the negative controls (Figure 2). The compounds 4b and 4j (at 1000, 500, and 250 µg mL^{-1}), 4d and 4e (at 1000 and 500 µg mL^{-1}), 4a (at 1000 µg mL^{-1}), and 4i (at 250 and 100 µg mL^{-1}) inhibited root growth as compared to the negative controls (Figure 2). On the contrary, compound 4c (at 250, 100, and 50 µg mL^{-1}) stimulated growth. Root growth a parameter is considered the most sensitive among those analyzed in the phytotoxicity evaluation assays, being responsive even for compounds displaying mild/moderate toxicity (Aragão et al. 2017). Besides, when the germination process of the plant begins, there is the imbibition of liquid before germination and the greatest absorption of the compound occurs. For this reason, RG is one of the most affected parameters, since the roots are the first to have direct contact with the compound, being the largest consumers of nutrients and liquid retained in the seed (Aragão et al. 2017).

In terms of the aerial growth (AG) analyses, the compounds 4a, 4b, 4d, 4e, 4f, 4g, and 4h showed statistical difference at all concentrations when compared to the negative control, and the non-statistical difference was noticed regarding the positive control. The AG inhibition was higher than 80% when compared to the negative control (Figure 2). The triazole 4i (at 1000, 500, 250, and 100 μg mL^{-1}) and 4c and 4j (at 1000 and 500 μg mL^{-1}) also showed AG equal to the positive control (Figure 2). The based-triazole commercial herbicide Front® has a pre-emergent character, and it acts by inhibiting photosynthesis through photosystem II. These three new synthetic 1,2,3-triazoles (4c, 4i, and 4j) may be acting on the same metabolic pathway as the commercial herbicide. With the consumption of the energy retained in the seed by the root growth, the seed loses vigor to aerial growth, which in turn is prevented from performing photosynthesis to recover the plant, leading to a slower growth rate and subsequently causing the death of it (Toledo et al. 2010).

Although less effective than the commercial herbicide used as a positive control, the compound 4k at all tested concentrations, 4j (at 250 and 100 μg mL^{-1}), and 4i (at 50 μg mL^{-1}) inhibited the AG when compared to negative controls (Figure 2).

Still considering AG, it was possible to observe that the compound 4c (at 250, 100, and 50 μg mL^{-1}) induced growth, differing from controls (Figure 2). Some molecules have an inducer potential when used at low concentrations, behaving as a synthetic auxin. This increase may be related to the elongation of cells that occurs during the process of cell growth and derivation (Aragão et al. 2017).

The analysis of phytotoxic parameters, such as the percentage of germination and the germination speed index can indicate if a compound presents pre-emergent inhibition behavior, while the investigation of root and aerial growth can provide information regarding the post-emergent inhibition effect (Vargas & Roman 2006). Thus, the compounds 4a, 4b, 4d, 4e, 4i, and 4j have pre-emergent inhibition behavior, while all the investigated compounds showed post emergent effect (Figure 2). The knowledge of the action of compounds concerning the emergence of a plant is an important feature to be considered. A pre-emergent compound does not allow seed germination; directly related to plantations to be implanted, it can act on invasive plants before they start to compete with the culture of interest. On the other hand, a compound with post-emergent behavior can be used for cultures already installed (Vargas & Roman 2006).

Cytogenotoxic Evaluation

In the cytogenotoxic assessment, the compounds promoted both increase and decrease in the mitotic index. The increase was caused by 4k (at 500, 250, 100, and 50 μg mL^{-1}), 4a, 4b, 4g, 4h (at 250, 100, and 50 μg mL^{-1}), 4d, 4f (at 100 and 50 μg mL^{-1}), and 4c, 4e, and 4j (at 50 μg mL^{-1}). The decrease was observed in meristematic cells treated with 4i (1000, 500, and 250 μg mL^{-1}), and 4a, 4c, 4d, 4e, 4f, 4g, 4h, and 4i (1000 μg mL^{-1}) (Figure 3). The increase in MI can occur when a plant tries to develop to leave a stressed place, while the decrease can occur due to cell death (Iganci et al. 2006).

All the studied compounds caused an increase in nuclear alterations at certain concentrations. Changes such as micronuclei or condensed nuclei were observed for 4a, 4b, and 4d (Figure 3). For the other derivatives, only a condensed nucleus was observed, which is the cytological evidence of the occurrence of cell death (Andrade-Vieira et al. 2012).

An increase in CA was observed for compounds 4d, 4e, 4f, 4g, 4h, 4j, and 4k, at

Figure 3. Cytogenotoxic variables evaluated in *Lactuca sativa* meristematic cells treated with five concentrations of triazoles 4a to 4k and positive control (picloram) and negative controls (water and dichloromethane) (I). Where: MI = Mitotic index; CA = Chromosome alterations; NA = Nuclear alterations; MNC = Micronucleus; CN = Condensed nucleus. The means followed by the letter *a* were equal to the negative control water, those followed by the letter *b* were equal to the negative control dichloromethane and those followed by the letter *c* were equal to the positive control picloram (0.1%) according to the Dunnett test (p <0.05).

all concentrations. In the case of 4a (at 250, 100, and 50 µg mL^{-1}), 4c (at 500, 250, 100, and 50 µg mL^{-1}), and 4i, (at 1000, 500, 100, and 50), an increase in CA was also noticed (Figure 3). Chromosomal alterations are determined by the number of chromosomes in abnormalities, whether structural or numerical. These changes can be classified according to the mechanism of action as clastogenic, aneugenic, and epigenetic (Bernardes et al. 2015, Freitas et al. 2016). One of the alterations found was Stick, which was observed for all compounds, except in the case of 4a and 4b (Figure 4). This alteration is classified as clastogenic, aneugenic, and epigenetic (Freitas et al. 2016, Silveira et al. 2017, Dos Santos et al. 2019). Another alteration observed for 4e, 4f, 4i, and 4k derivatives was Bridge (Figure 4), which is classified as clastogenic according to its mechanism of action (Dos Santos et al. 2019). The aneugenic observed changes corresponded to delay, c-metaphase, and loss (Figure 4). The delay was observed for most compounds, not being found only for 4a-4c (Figure 4). C-metaphase was observed for 4g, 4i, 4j, and 4k (Figure 4), resulting from the inactivation of the spindle (Fernandes et al. 2009). Another

Figure 4. Frequency of chromosomal alterations (Lost, sticky, c-metaphase, bridge, delay and break) observed in *Lactuca sativa* meristematic cells treated with five concentrations of triazoles 4a to 4k and positive control (picloram) and negative (water and dichloromethane) (l). The means followed by the letter *a* were equal to the negative control water, those followed by the letter *b* were equal to the negative control dichloromethane and those followed by the letter *c* were equal to the positive control picloram (0.1%) according to the Dunnett test ($p < 0.05$).

alteration observed only for 4k was lost (Figure 4), which occurs due to abnormal functioning of the microtubules, leading to the non-alignment of chromosomes during mitotic division (Dos Santos et al. 2019). Examples of the cell cycle alterations in meristematic cells of *L. sativa* can be seen in Figure 5.

In summary, using as starting material the readily available glycerol, a series of eleven 1,2,3-triazole derivatives were synthesized in four steps. Ten of these compounds were novel fluorinated derivatives. The evaluation of the compounds on *Lactuca sativa* revealed that they presented effects on phytotoxic and cytogenotoxic parameters with different degrees of efficiency. The compounds 4a, 4b, 4d, 4e, 4i, and 4j have pre-emergent inhibition behavior, while the compounds 4a, 4b, 4d, 4e, 4f, 4g, 4h, and 4i showed post emergent effect at all tested concentrations, evidencing the efficiency of low concentrations in inhibiting plant shoot growth. The cytogenotoxic parameters corroborate the phytotoxic data, with clastogenic, aneugenic and epigenetic action of the compounds in roots meristematic cells. It is believed that the glycerol-fluorinated triazole the scaffold can be

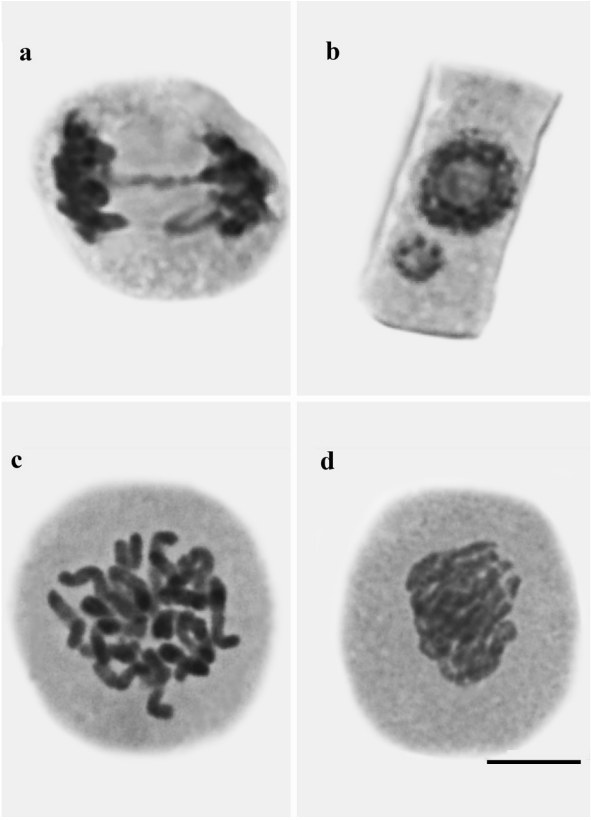

Figure 5. Cell cycle alterations observed in *Lactuca sativa* meristematic cells treated with five concentrations of triazoles 4a to 4k and positive control (picloram) and negative (water and dichloromethane). (a) bridge in anaphase, (b) interphase with micronuclei (c) C-metaphase (d) sticky chromosomes. Bar=10 µm.

explored toward the development of new active ingredients to control weeds.

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