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Artigo

SYNTHESIS OF GLYCEROL-FLUORINATED TRIAZOLE DERIVATIVES AND EVALUATION OF THEIR FUNGICIDAL ACTIVITY

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The control of fungal species in agriculture is mainly conducted with the use of contact or systemic fungicides. However, environmental and human health concerns and increased resistance of fungal species to existing fungicides have increased the pressure on researchers to find new active ingredients for fungal control which present low toxicity to non-target organisms, are environmentally safe, and can be applied at very low concentrations. It is herein described the synthesis of eleven glycerol triazole containing compounds (ten of them fluorinated derivatives) and evaluation of their fungicidal activity. Eight out of eleven synthesized compounds are novel and all of the glycerol derivatives were characterized using infrared (IR), nuclear magnetic ressonance (NMR), and mass spectrometry (MS) techniques. Theoretical calculations were also carried out and the results are discussed. Starting from glycerol, the triazole derivatives were prepared in four steps. Evaluation of them against *Colletrotricum gloesporioides* showed that compound 1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-4-(2-fluorophenyl)-1*H*-1,2,3-triazole (**4d**) (ED_{50} = 59.14 μg mL^{-1}) was slightly more active than commercial fungicide tebuconazole (61.35 μg mL^{-1}). Compound **4d** presented attractive physicochemical features for agrochemical purposes as revealed by the calculated physicochemical parameters. It is believed that glycerol-fluorinated triazole derivatives can be explored towards the development of new chemicals for the control of fungal species.

Keywords: glycerol; 1,2,3-triazole; fluorinated derivatives; fungicidal activity.

INTRODUCTION

The continuous population growth has resulted in several challenges to be faced by human beings, such as the increased demand for food, both in terms of quantity and quality.[1] Over the years, tremendous advances in agriculture have increased crop quality and productivity.[2,3] Within this context, pesticides have played important role in the management of a variety of pests,[4,5] which significantly decreases crop productivity as well as food quality.[6-8]

Fungal species represent an important problem in agriculture. They are widespread in nature and are vital for the recycling of nutrients present in organic matter. However, among the 120,000 described fungal species, around 20,000 causes one or more pathogenesis to crops leading to losses worldwide.[9,10] It is estimated that fungi are responsible for approximately 65% of all infectious diseases in plants.[11,12]

The most common method used for controlling fungal species is the employment of fungicides either contact or systemic.[4,5] From the historical standpoint, up to 1940, the fungicides used in agriculture were inorganic in nature, such as arsenic, copper sulfate, sulfur dust, lime sulfur, Bordeaux mixture, mercury chloride, among others. Typically, these early fungicides presented low selectivity and high toxicity, being mainly utilized in the control of fungi at horticultural crops (fruit and vegetable).[13] There were no concerns about the impact of these compounds on the environment as well as on the users.

From 1940 to 1970, systematic research resulted in the development of several classes of organic fungicides, for instance, dithiocarbamates and phtalimides. These new fungicides represented a major improvement compared to the inorganic fungicides since they were more active and easier to prepare by the users.[13]

The following decades witnessed a rapid growth in the development of new classes of fungicides, namely benzimidazole, morpholine, piperazine, imidazole, pyrimidine, triazole, and anilide.[14,15] Nature has been used as the source of inspiration for the development of new fungicides, resulting in the discovery of strobirulins.[16]

Although nowadays there several available fungicides for the control of a broad spectrum of infectious plant diseases,[17] environmental and human health concerns, as well as the increased resistance of fungal species to the existing fungicides[18] has pressured researchers to find new active ingredients to fungal control which present low toxicity to non-target organisms, are environmental safety, and can be applied at very low concentrations. Therefore, the development of new fungicides is an important demand.[19,20]

We have been involved in the search for new active molecular entities to control fungi. In this regard, our research group has explored the hybrid derivatives resulted from the combination of glycerol and 1,2,3-triazole functionalities. It has been found that

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some derivatives are equipotent or more active than commercial fungicides.[21,22]

Considering the premises and in continuation of our efforts to find new agents for the control of pathogenic fungi,[21,22] in the present investigation, we describe the synthesis and antifungal activity evaluation of eleven glycerol 1,2,3-triazole derivatives bearing fluorinated aromatic groups. All of the prepared glycerol derivatives was characterized by means of IR, NMR, and MS techniques. The rational for the preparation of the fluorinated derivatives described in this investigation resides on the importance of halogens in the search and development of new agrochemicals.[23] 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 that "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".[23] 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)[24] 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.

Theoretical calculations of physicochemical parameters of the compounds were carried out and the results are also discussed.

MATERIALS AND METHODS

Generalities

The solvents, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, sodium azide, *p*-toluene sulphonic acid, and pyridine were purchased from Vetec (Rio de Janeiro, Brazil) and used as received. The terminal alkynes and *p*-toluenesulfonyl chloride were procured from Sigma-Aldrich (St. Louis, MO, USA) and used as received from the commercial supplier. 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 (Bruker, Karlsruhe, Germany) and the attenuated total reflection (ATR) technique scanning from 500 to 4000 cm^{-1}. The ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 instrument (Varian, Palo Alto, CA, USA), at 400 MHz for ^1H 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) condition of positive ion mode. Melting points were determined with MA 381 equipment (Marconi, São Paulo, Brazil) and are uncorrected.

The ^1H 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 (double of doublets), td (triplet of doublets), tdd (triplet of double 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 by our research group.[21,22]

*General procedure for the synthesis of compounds **4a-4k***

The following general procedure was utilized in the preparation of derivatives **4a-4k**.

A round-bottomed flask was charged with azide **3** (1.50 equivalent), terminal alkyne (1.00 equivalent), aqueous solution of $CuSO_4 \cdot 5H_2O$ (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). 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 × 20.0 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 eluted 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-1H-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 (diethyl ether-dichloromethane, 10:1 v v^{-1}). IR (ATR) $\bar{\nu}/cm^{-1}$: 3145, 2992, 2923, 2853, 1607, 1484, 1461, 1438, 1373, 1262, 1224, 1202, 1166, 1115, 1063, 1041, 970, 883, 833, 767, 699. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.32 (s, 3H, C$\underline{H}_3$'), 1.36 (s, 3H, C$\underline{H}_3$''), 3.74 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.0 Hz, H_a-11), 4.09 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.4 Hz, H_b-11), 4.40-4.50 (m, 2H, H_a-9/H-10), 4.55 (dd, 1H, J_1 = 12.8 Hz and J_2 = 2.8, H_b-9), 7.29 (tt, 1H, J_1 = 8.0 Hz and J_2 = 1.2 Hz, H-4), 7.37-7.41 (m, 2H, H-3/H-5), 7.80 (dd, 2H, J_1 = 8.0 Hz and J_2 = 1.2 Hz, H-2/H-6), 7.87 (s, 1H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1(C$\underline{H}_3$'), 26.6 (C$\underline{H}_3$''), 52.2 (C-9), 66.3 (C-11), 74.0 (C-10), 110.2 (C-12), 120.9 (C-8), 125.6 (C-2/C-6), 128.0 (C-4), 128.8 (C-3/C-5), 130.5 (C-1), 147.7 (C-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 (diethyl ether-dichloromethane, 10:1 v v^{-1}); IR (ATR) $\bar{\nu}/cm^{-1}$: 3099, 2992, 1620, 1590, 1484, 1465, 1444, 1372, 1293, 1225, 1202, 1149, 1115, 1055, 1026, 969, 865, 835, 755, 687. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.33 (s, 3H, C$\underline{H}_3$'), 1.38 (s, 3H, C$\underline{H}_3$''), 3.75 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.0 Hz, H_a-11), 4.12 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.4 Hz, H_b-11), 4.42-4.51 (m, 2H, H_a-9/H-10), 4.58 (dd, 1H, J_1 = 12.6 Hz and J_2 = 2.6, H_b-9), 6.99 (tdd, 1H, J_1 = 8.5 Hz, J_2 = 2.5 Hz and J_3 = 0.8 Hz, H-4), 7.33-7.38 (m, 1H, H-6), 7.51-7.59 (m, 2H, H-2/H-5), 7.90 (s, 1H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1 (C$\underline{H}_3$'), 26.6 (C$\underline{H}_3$''), 52.3 (C-9), 66.3 (C-11), 74.0 (C-10), 110.2 (C-12), 112.6 (d, J_{C-F} = 22.0 Hz, C-2), 114.9 (d, J_{C-F} = 21.0 Hz, C-4), 121.2 (d, J_{C-F} = 3.0 Hz, C-6), 121.3 (C-8), 130.3 (d, J_{C-F} = 8.0 Hz, C-5), 132.6 (d, J_{C-F} = 9.0 Hz, C-1), 146.6 (d, J_{C-F} = 3.0 Hz, C-7), 163.1 (d, J_{C-F} = 253.0 Hz, C-3).

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)-1H-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 (diethyl ether-dichloromethane, 10:1 v v^{-1}); IR (ATR) $\bar{\nu}$/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, C$\underline{H}_3$'), 1.37 (s, 3H, C$\underline{H}_3$''), 3.75 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.0 Hz, H_a-11), 4.11 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.4 Hz, H_b-11), 4.41-4.50 (m, 2H, H_a-9/H-10), 4.57 (dd, 1H, J_1 = 13.2 Hz and J_2 = 3.2, H_b-9), 7.08 (t, 2H, J_1 = 8.6 Hz, H-3/H-5), 7.76-7.79 (dd, 2H, H-2/H-6), 7.84 (s, 1H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0 (C$\underline{H}_3$'), 26.6 (C$\underline{H}_3$''), 52.2 (C-9), 66.2 (C-11), 73.9 (C-10), 110.1 (C-12), 115.7 (d, $J_{C\text{-}F}$ = 21.0 Hz, (C-3/C-5), 120.6 (C-8), 126.7 (d, $J_{C\text{-}F}$ = 3.0 Hz, C-1), 127.4 (d, $J_{C\text{-}F}$ = 9.0 Hz, C-2/C-6), 146.7 (C-7), 162.6 (d, $J_{C\text{-}F}$ = 253.0 Hz, C-4). 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)-1H-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 (diethyl ether-dichloromethane, 10:1 v v^{-1}); IR (ATR) $\bar{\nu}$/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, C$\underline{H}_3$'), 1.37 (s, 3H, C$\underline{H}_3$''), 3.75 (dd, 1H, J_1 = 8.8 Hz and J_2 = 5.2 Hz, H_a-11), 4.10 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.0 Hz, H_b-11), 4.47-4.52 (m, 2H, H_a-9/H-10), 4.58 (dd, 1H, J_1 = 15.8 Hz and J_2 = 6.2, H_b-9), 7.08-7.13 (m, 1H, H-4), 7.20-7.31 (m, 2H, H-3/H-5), 8.04 (s_{ap}, 1H, J = 3.6 Hz, H-8), 8.26 (td, 1H, J_1 = 7.6 Hz and J_2 = 2.0, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1 (C$\underline{H}_3$'), 26.7 (C$\underline{H}_3$''), 51.9 (C-9), 66.1 (C-11), 73.9 (C-10), 110.2 (C-12), 115.6 (d, $J_{C\text{-}F}$ = 21.0 Hz, C-3), 118.4 (d, $J_{C\text{-}F}$ = 16.0 Hz, C-8), 124.0 (d, $J_{C\text{-}F}$ = 12.0 Hz, C-1), 124.5 (d, $J_{C\text{-}F}$ = 3.0 Hz, C-5), 127.7 (d, $J_{C\text{-}F}$ = 3.0 Hz, C-4), 129.2 (d, $J_{C\text{-}F}$ = 9.0 Hz, C-6), 141.1 (d, $J_{C\text{-}F}$ = 3.0 Hz, C-7), 159.1 (d, $J_{C\text{-}F}$ = 242.0 Hz, C-2). 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)-1H-1,2,3-triazole (**4e**)*

Brown solid, prepared in 78% yield from the reaction between 3,4-difluorophenylacetylene (2.0 g, 14.5 mmol) and azide **3** (1.5 g, 9.6 mmol), m.p. 73-75 °C. TLC: R_f = 0.53 (diethyl ether-dichloromethane 10:1 v v^{-1}); IR (ATR) $\bar{\nu}$/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, C$\underline{H}_3$'), 1.37 (s, 3H, C$\underline{H}_3$''), 3.75 (dd, 1H, J_1 = 8.8 Hz and J_2 = 5.6 Hz, H_a-11), 4.12 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.4 Hz, H_b-11), 4.41-4.50 (m, 2H, H_a-9/H-10), 4.58 (dd, 1H, J_1 = 13.4 Hz and J_2 = 3.0 Hz, H_b-9), 7.17 (td, 1H, J_1 = 10.0 Hz, J_2 = 7.8 Hz and J_3 = 1.6, H-5), 7.49-7.53 (m, 1H, H-6), 7.61-7.66 (m, 1H, H-2), 7.86 (s, 1H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0 (C$\underline{H}_3$'), 26.3 (C$\underline{H}_3$''), 52.3 (C-9), 66.1 (C-11), 74.0 (C-10), 110.1 (C-12), 114.7 (d, $J_{C\text{-}F}$ = 19.0 Hz, C-5), 117.6 (d_{ap}, $J_{C\text{-}F}$ = 17.0 Hz, C-2), 121.0 (C-8), 121.7 (dd, $J_{C\text{-}F}$ = 6.0 Hz and $J_{C\text{-}F}$ = 4.0 Hz, C-6), 127.7 (dd, $J_{C\text{-}F}$ = 6.5 Hz and $J_{C\text{-}F}$ = 3.5 Hz, C-1), 145.9 (C-7), 150.1 (dd, $J_{C\text{-}F}$ = 247.5 Hz and $J_{C\text{-}F}$ = 12.5 Hz, C-3), 150.6 (dd, $J_{C\text{-}F}$ = 247.5 Hz and $J_{C\text{-}F}$ = 11.5 Hz, C-4). 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)-1H-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 = 0.68 (diethyl ether-dichloromethane 10:1 v v^{-1}); IR (ATR) $\bar{\nu}$/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, C$\underline{H}_3$'), 1.36 (s, 3H, C$\underline{H}_3$''), 3.74 (dd, 1H, J_1 = 8.8 Hz and J_2 = 5.6 Hz, H_a-11), 4.10 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.0 Hz, H_b-11), 4.45-4.51 (m, 2H, H_a-9/H-10), 4.57 (dd, 1H, J_1 = 15.8 Hz and J_2 = 6.2, H_b-9), 6.83-6.89 (m, 1H, H-5), 6.93-6.98 (m, 1H, H-3), 7.99 (s_{ap}, 1H, J = 3.6 Hz, H-8), 8.20-8.26 (1H, m, H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1(C$\underline{H}_3$'), 26.3 (C$\underline{H}_3$''), 51.9 (C-9), 66.1 (C-11), 73.9 (C-10), 104.0 (t, $J_{C\text{-}F}$ = 25.5 Hz, C-3), 110.1 (C-12), 111.9 (dd, $J_{C\text{-}F}$ = 21.0 Hz and $J_{C\text{-}F}$ = 3.0 Hz, C-5), 114.9 (dd, $J_{C\text{-}F}$ = 13.0 Hz and $J_{C\text{-}F}$ = 4.0 Hz, C-1), 123.5 (d_{ap}, $J_{C\text{-}F}$ = 12.0 Hz, C-8), 128.7 (dd, $J_{C\text{-}F}$ = 9.5 Hz and $J_{C\text{-}F}$ = 6.5 Hz, C-6), 140.4 (d_{ap}, $J_{C\text{-}F}$ = 3.0 Hz, C-7), 159.1 (dd, $J_{C\text{-}F}$ = 249.0 Hz and $J_{C\text{-}F}$ = 12.0 Hz, C-2), 162.4 (dd, $J_{C\text{-}F}$ = 249.0 Hz and $J_{C\text{-}F}$ = 12.0 Hz, C-4). 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)-1H-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, 9.60 mmol), m.p. 100-102 °C. TLC: R_f = 0.60 (diethyl ether-dichloromethane 10:1 v v^{-1}); IR (ATR) $\bar{\nu}$/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, C$\underline{H}_3$'), 1.38 (s, 3H, C$\underline{H}_3$''), 3.75 (dd, 1H, J_1 = 8.8 Hz and J_2 = 5.8 Hz, H_a-11), 4.13 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.2 Hz, H_b-11), 4.41-4.50 (m, 2H, H_a-9/H-10), 4.59 (dd, 1H, J_1 = 13.0 Hz and J_2 = 2.6, H_b-9), 6.74 (tt, 1H, J_1 = 9.0 Hz and J_2 = 2.3 Hz, H-4), 7.32-7.35 (m, 2H, H-2/H-6), 7.91 (s, 1H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0 (C$\underline{H}_3$'), 26.7 (C$\underline{H}_3$''), 52.3 (C-9), 66.4 (C-11), 74.0 (C-10), 103.2 (t, $J_{C\text{-}F}$ = 25.5 Hz, C-4), 108.4 (dd, $J_{C\text{-}F}$ = 19.0 Hz and $J_{C\text{-}F}$ = 8.0 Hz, C-2/C-6), 110.2 (C-12), 121.5 (C-8), 133.6 (t, $J_{C\text{-}F}$ = 10.5 Hz, C-1), 145.8 (t, $J_{C\text{-}F}$ = 3.0 Hz, C-7), 163.3 (dd, $J_{C\text{-}F}$ = 247.0 Hz and $J_{C\text{-}F}$ = 13.0 Hz, C-3/C-5). 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)-1H-1,2,3-triazole (**4h**)*

White solid, prepared in 73% yield from the reaction between 1-ethynyl-4-(trifluoromethyl)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 (diethyl ether-dichloromethane 10:1 v v^{-1}); IR (ATR) $\bar{\nu}$/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, C$\underline{H}_3$'), 1.38 (s, 3H, C$\underline{H}_3$''), 3.76 (dd, 1H, J_1 = 8.8 Hz and J_2 = 5.6 Hz, H_a-11), 4.13 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.4 Hz, H_b-11), 4.43-4.52 (m, 2H, H_a-9/H-10), 4.60 (dd, 1H, J_1 = 12.6 Hz and J_2 = 2.6, H_b-9), 7.65 (d, 2H, J = 8.6 Hz, C-2/C-6), 7.92 (d, 2H, J = 8.6 Hz, C-3/C-5), 7.97 (s, 1H, H-8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0 (C$\underline{H}_3$'), 26.7 (C$\underline{H}_3$''), 52.3 (C-9), 66.4 (C-11), 73.9 (C-10), 110.1 (C-12), 121.8 (C-10), 124.0 (q, $J_{C\text{-}F}$ = 270.3, $\underline{C}F_3$), 125.8 (q, $J_{C\text{-}F}$ = 3.6, C-2/C-3/C-5/C-6), 129.97 (q, $J_{C\text{-}F}$ = 32.6, C-4), 134.0 (C-1), 146.3 (C-7). 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)-1H-1,2,3-triazole (**4i**)*

White solid, prepared in 61% yield from the reaction between 1-ethynyl-3-(trifluoromethyl)benzene (2.50 g, 14.7 mmol) and azide **3** (1.50 g, 9.60 mmol), m.p. 63-65 °C. TLC: R_f = 0.51 (diethyl ether-dichloromethane 10:1 v v^{-1}); IR (ATR) $\bar{\nu}$/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, C$\underline{H}_3$'), 1.39 (s, 3H, C$\underline{H}_3$''), 3.77 (dd, 1H, J_1 = 8.7 Hz and J_2 = 5.8 Hz, H_a-11), 4.12 (dd, 1H, J_1 = 8.7 Hz and J_2 = 6.0 Hz, H_b-11), 4.43-4.52 (m, 2H, H_a-9/H-10), 4.61 (dd, 1H, J_1 = 12.8 Hz and J_2 = 2.8, H_b-9), 7.52 (t, 1H, J = 7.6 Hz, H-5), 7.56 (d, 1H, J = 8.0 Hz, H-6), 7.96 (s, 1H, H-8), 8.01 (d, 1H, J = 7.2 Hz, H-4), 8.06 (s_{ap}, 1H, H-2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0 (C$\underline{H}_3$'), 26.6 (C$\underline{H}_3$''), 52.3 (C-9), 66.3 (C-11), 74.0 (C-10), 110.3 (C-12), 121.2 (C-8), 122.4 (q, $J_{C\text{-}F}$ = 4.0, C-5), 123.9 (q, $J_{C\text{-}F}$ = 269.6, $\underline{C}F_3$), 124.6 (q, $J_{C\text{-}F}$ = 3.6, C-6), 128.8 (C-1), 129.4 (C-2/C-4), 131.2 (q, $J_{C\text{-}F}$ = 32.0, C-3), 146.2 (C-7). 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)-1H-1,2,3-triazole (**4j**)*

Red solid, prepared in 58% yield from the reaction between 1-ethynyl-2-(trifluoromethyl)benzene (2.5 g, 14.7 mmol) and azide **3** (1.5 g, 9.6 mmol), m.p. 51-53 °C. TLC: R_f = 0.73 (diethyl ether-dichloromethane 10:1 v v^{-1}); IR (ATR) $\bar{\nu}$/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, C$\underline{H}_3$'), 1.36 (s, 3H, C$\underline{H}_3$''), 3.76 (dd, 1H, J_1 = 8.9 Hz and J_2 = 5.4 Hz, H_a-11), 4.12 (dd, 1H, J_1 = 8.9 Hz and J_2 = 5.8 Hz, H_b-11), 4.46-4.52 (m, 2H, H_a-9/H-10), 4.60 (dd, 1H, J_1 = 16.0 Hz and J_2 = 6.4, H_b-9), 7.46 (t, 1H, J = 7.0 Hz, H-4), 7.61 (t, 1H, J = 7.6 Hz, H-5), 7.73 (d, 1H, J = 8.0 Hz, H-6), 7.89 (s, 1H, H-8), 7.96 (d, 1H, J = 8.4 Hz, H-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.0 (C$\underline{H}_3$'), 26.3 (C$\underline{H}_3$''), 51.9 (C-9), 66.1 (C-11), 73.9 (C-10), 110.2 (C-12), 124.1 (q, $J_{C\text{-}F}$ = 256.0, $\underline{C}F_3$), 124.2 (q, $J_{C\text{-}F}$ = 5.6, C-3), 126.0 (q, $J_{C\text{-}F}$ = 5.6, C-1), 127.2 (q, $J_{C\text{-}F}$ = 28.0, C-2), 128.1 (C-8), 129.4 (q, $J_{C\text{-}F}$ = 2.0, C-4), 131.6 (C-5), 131.9 (C-6), 144.0 (C-7). 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)-1H-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) $\bar{\nu}$/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, C$\underline{H}_3$'), 1.40 (s, 3H, C$\underline{H}_3$''), 3.78 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.0 Hz, H_a-11), 4.16 (dd, 1H, J_1 = 8.8 Hz and J_2 = 6.4 Hz, H_b-11), 4.44-4.53 (m, 2H, H_a-9/H-10), 4.64 (dd, 1H, J_1 = 13.0 Hz and J_2 = 2.6, H_b-9), 7.80 (s, 1H, H-8), 8.05 (s, 1H, H-4), 8.26 (s, 2H, H-2/H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.1 (C$\underline{H}_3$'), 26.6 (C$\underline{H}_3$''), 52.7 (C-9), 66.2 (C-11), 73.8 (C-10), 110.2 (C-12), 121.5 (dq_{ap}, $J_{C\text{-}F}$ = 3.7, C-4), 121.9 (C-8), 123.1 (q, $J_{C\text{-}F}$ = 271.3, $\underline{C}F_3$), 125.5 (q, $J_{C\text{-}F}$ = 2.6, C-1), 132.2 (q, $J_{C\text{-}F}$ = 33.3, C-3/C-5), 132.7 (C-2/C-6), 144.9 (C-7). 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 assay

Fungicidal activity evaluation

The *in vitro* experiment to evaluate the fungicidal effect was conducted using a completely randomized design, with eleven treatments (compounds **4a**-**4k**) and five concentrations (65, 125, 250, 500, 750 μg mL^{-1}) with four replicates. The solutions were prepared dissolving the compounds with 0.32 mL of dimethyl sulfoxide (DMSO) and 0.32 mL of Tween 80, being the volume of the solution completed to 32 mL with distilled water. The solutions were homogenized. Then, to four Petri Dishes (60 x 15 mm each) were transferred to each one 8 mL of the solution and homogenized in BDA medium. The negative controls corresponded to distilled water, DMSO solution (1% v v^{-1}) and Tween 80 (1%v v^{-1}), while tebuconazole (Folicur EC 200) was used as a positive control. The *Colletotrichum gloeosporioides* isolate was obtained from wounded papaya fruit tissues. The Petri dishes were then kept in the dark at 25 °C with a mycelial disc of the fungus placed in the center. Mycelial growth assessments were carried out every 24 hours until the control filled the full diameter of the dish.[25,26] The whole experiment took 120 h.

Statistical Analysis

For fungicidal activity evaluation, an analysis of variance was performed on the data and logistic regression model was used to calculate the ED_{50} and ED_{90} values (the concentrations of the active ingredient necessary to inhibit mycelial growth of the pathogen by 50% and 90%, respectively).[16] The means were analyzed using the Dunnett's test. Statistical analyses were carried out using the DRC and Asbio packages of the R software environment (R Core Team 2020).[27,28]

Physico-chemical calculation properties of compounds 4a-4k

DFT Computational Details

Initially, it was carried out a conformational search for compounds **4a-4k** using semi-empirical AM1 method Monte Carlo search algorithm available in the SPARTAN software.[29] This procedure selected, for each compound, the best conformer suitable for optimization. Then, the lowest-energy conformers were taken for further DFT calculations.

The structures of compounds **4a-4k** were optimized with B3LYP density functional model, using the basis set 6-31G(d).[30] All structure optimizations of the compounds were carried out using the Gaussian 09 software.[31] The energy of HOMO and LUMO frontier orbitals, as well as the energy gap between them, were calculated from the optimized structures. Besides, the total energies, molecular

electrostatic potential (MEP) maps, electronic chemical potential (μ), chemical hardness (η), electrophilicity index (ω), electronegativity (χ), and dipole moments of the molecules were calculated with B3LYP (DFT)/6-31G(d) level.

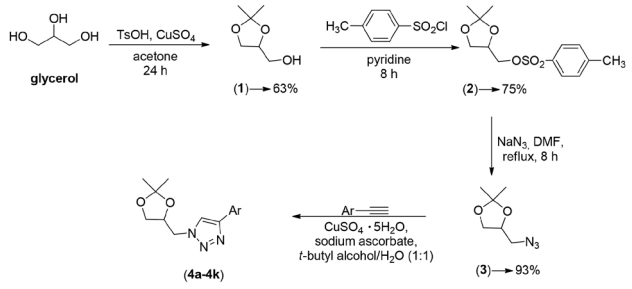
In addition to the physical-chemical properties previously mentioned, LogP, molecular weight, and total polar surface area (TPSA) were also determined using the Molinspiration package.[32,33]

RESULTS AND DISCUSSION

Preparation of compounds 4a-4k

The preparation of compounds **4a-4k** (Figure 1) involved a sequence similar to that previously reported by our research group.[21,22] The key step involved was the Cu(I)-catalyzed alkyne-azide cycloaddition reaction (CuAAC reaction)[21,22,34-36] between azide **3** and different commercially available aromatic terminal alkynes. Considering the last step, the derivatives **4a-4k** were prepared in good yields ranging from 58% to 85% (Figure 1).

The identities of the compounds **4a-4k** were confirmed base on IR and ^{1}H and ^{13}C NMR spectroscopies as well as MS analyses. Considering the IR spectra, two important bands are the =C-H stretching (observed within the 3081-3178 cm^{-1} range) and the N=N stretching (noted within the interval 1626-1579 cm^{-1}). The signals for the hydrogens of the triazole rings and the acetonide methyl groups were observed within 7.80-7.97 and 1.32-1.40 ppm, respectively. In ^{13}C NMR spectra, signals for methyl groups of acetonide fragment 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. The derivatives **4b, 4d-4g**,**4i-4k** has not been described in the literature. It should be mentioned that the acetonide fragment is the integrant part of the structures of commercial fungicides such as azaxonazole, difeconazole, and propiconazole.[4,5]



Compound	Ar	Yield (%)
4a	Phenyl	83
4b	3-fluorophenyl	70
4c	4-fluorophenyl	81
4d	2-fluorophenyl	85
4e	3,4-difluorophenyl	78
4f	2,4-difluorophenyl	68
4g	3,5-difluorophenyl	65
4h	4-trifluromethylphenyl	73
4i	3-trifluoromethylphenyl	61
4j	2-trifluoromethylphenyl	58
4k	3,5-bis(trifluoromethyl)phenyl	74

Figure 1. *Synthetic steps involved in the preparation of glycerol derivatives* ***4a-4k***

Once synthesized, the compounds **4a-4k** were submitted to evaluation of their fungicide activity.

Fungicidal evaluation

The glycerol-derivatives **4a-4k** were investigated regarding their *in vitro* effectiveness in inhibiting the mycelial growth in *C. gloesporioides*. A sigmoidal logistic curve was fitted to study the inhibitory effect of each compound and Table 1 shows the inhibitory activities of compounds **4a**-**4k** for the growth of *C. gloeosporioides* mycelia. Inhibitory effects were demonstrated for the triazoles investigated, with inhibition levels growing as the concentration increases. However, the regression coefficients for compounds **4c** and **4h** were not statistically different from 0 by the F test at 5% probability and these compounds were not able to inhibit the fungus at the tested concentrations. The derivatives **4c** and **4h** present as a common feature the presence of a fluorine atom (in the case of **4c**) or a trifluoromethyl group (for **4h**) attached in the *para* position of benzene ring. Therefore, these structural features seem to do not contribute to the biological activity. The inhibition of mycelial of *C. gloeosporioides* isolate by the synthesized triazoles **4a**, **4b**, **4e**, **4f**, **4g**, **4i**, **4j**, and **4k** was weaker than that of the tebuconazole control. However, the ED_{50} value demonstrated that compound **4d** (59.14 **μg** mL^{-1}) is more active, on average, and showed excellent antifungal activities against *C. gloeosporioides*, with Dunnet's test indicating no significant difference between this compound and the tebuconazole control (61.35 μg mL^{-1}). On the other hand, the ED_{90} values of all compounds studied were significantly different when compared to the tebuconazole control (265.49 **μg** mL^{-1}). Considering the compounds bearing one fluorine atom, it can be noticed that the biological activity increases in the sequence **4c < 4b < 4d** (the symbol "<" denotes smaller than). As compared to the most active compound **4d**, the introduction of additional fluorine atom in the benzene ring (compounds **4h**, **4i**, and **4j**) did not improve the biological activity. Taking into account the compounds possessing one trifluoromethyl group (**4h**, **4i**, **4j**), while *para*-trifluoromethyl substituted derivative **4h** was not active, the derivatives **4i** (*meta* substituted) and **4j** (*ortho substituted*) are equipotent. The introduction of another CF_3 group in the aromatic ring (compound **4k**) did not improve the fungicidal activity as compared to compound **4d**. The regression models involved in the calculation of ED_{50} and ED_{90} are presented in Table S1 in the Supplementary material.

Table 1. ED_{50} and ED_{90} values of triazoles synthesized against *C. gloeosporioides*

Compounds	ED_{50} (μg mL^{-1})	ED_{90} (μg mL^{-1})
4a	280.26 d	607.39 e
4b	198.32 c	527.03 d
4c	n	n
4d	59.14 a	384.85 b
4e	228.84 c	499.11 c
4f	246.45 c	454.22 c
4g	134.49 b	612.35 e
4h	n	n
4i	192.82 c	491.94 c
4j	154.17 b	515.24 c
4k	230.45 c	735.43 e
Tubeconazole	61.35 a	265.49 a

Means followed by the same letter in the column do not differ at 5% probability by the Dunnett's test. n = not active.

Differences in the ED_{50} and ED_{90} values between treatments in this study can be related to aspects of the fungus physiology. Hydrophobic interactions between triazole compounds and the structural amino acids present at enzyme lanosterol 14α-demethylase (CYP51) sites, a possible target for the 1,2,3-triazoles, can affect sterol biosynthesis and the integrity of fungal membranes.[37] The stress resulting from these interactions can cause alterations in the target site, over-expression of the target with greater fungicide presence in the cytosol, efflux of fungicides from the target site, and even detoxification of the fungicide.[38]

The inhibitory activity of triazoles observed in this study suggests a rapid penetration and translocation of the molecules into the fungal hyphae. The effectiveness of 1,2,3-triazoles at reducing the mycelial growth of phytopathogenic fungi has been demonstrated by Huo and collaborators.[39] The authors synthesized 14 triazole compounds capable of inhibiting the mycelial growth of the fungi *Sclerotinia scleotiorium* and *Botrytis cinerea* by more than 50% at a dose of 50 μg mL^{-1}. In a similar study, Bassyouni and collaborators synthesized a series of aromatic triazoles capable of inhibiting the mycelial growth of *C. gloeosporioides* and obtained results consistent with those presented in the present investigation.[40]

The results of the present study indicate that compound **4d** reduces the mycelial growth of *C. gloeosporioides* at rates comparable to the commercial fungicide tebuconazole. Thus, of the synthesized triazoles, compound **4d** stands out as a potential candidate obtained from the glycerol bearing 1,2,3-triazole group scaffold and may represent a promising structure to be explored for the development of new agrochemicals for the control, for example, of anthracnose in papaya.

Even though fluorinated derivatives **4c** and **4h** were not effective against *C. gloesporiodes*, the remaining compounds were more active than compound **4a**, a no-fluorinated glycerol derivative. Therefore, in general, the introduction of fluorinated groups in the structures of the compounds herein evaluated improved the biological response of them as compared to the no-fluorinated counterpart.

Computational calculations

The knowledge of physico-chemical properties of compounds is an important aspect in the search and development of new pesticides or therapeutic agents. These properties are useful guiding the design and selection of the compounds. It should be taken into consideration that compounds must be absorbed by pests or humans, be transported to the target site, and then interact with the target receptors or enzymes; hydrophobicity is very important for absorption, transport, and interaction with receptors. Electronic and structural properties are also important factors for receptor-ligand interaction.[41,42] Considering these aspects, we carried out calculations to determine physico-chemical properties of the fluorinated-glycerol derivatives herein investigated.

The optimization of the compound structures was carried out by Gaussian 09 using B3LYP/6-31G(d). The energy levels of HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital), as well as the energy gap between those orbitals, were calculated from the optimized structure.

According to the frontier molecular orbital theory, the characteristics of the HOMO and LUMO are important factors that affect bioactivity.[43,44] While the HOMO serves as electron donor toward unoccupied orbitals of receptors, the LUMO acts as electron acceptor. HOMO energy (E_{HOMO}) of compound **4k** was the lowest reflecting its small ability to donate electrons. This compound also had the lowest LUMO energy (E_{LUMO}) (Table 2).

The HOMO and LUMO energies of the most active antifungal compound (**4d**) were analyzed. The E_{HOMO} and E_{LUMO} energies were -6.13 eV and -0.75 eV, respectively. The distribution of charge density of the two frontier molecular orbitals for compound **4d** are presented in Figure 2. The molecular charge transfer from HOMO to LUMO is the most probable electronic transition within a molecular system. As seen from HOMO and LUMO plots (Figure 2), the HOMO is mostly localized on π molecular orbitals of the 1,2,3-triazole and aromatic benzene rings, whereas the LUMO is placed over π* molecular orbitals of the 1,2,3-triazole ring. This electron localization on HOMO and LUMO is a π/π* electronic transition. The HOMO-LUMO gap is an important parameter that measures the intramolecular charge transfer and the kinetic stability; it has been extensively used to explain biological activity results.[45] Generally, molecules with a large energy gap are associated with less chemical reactivity and high kinetic stability, while those with a small gap are more reactive and less stable. The $E_{HOMO-LUMO}$ gap presented the highest value (5.38 eV) for compound **4d**.

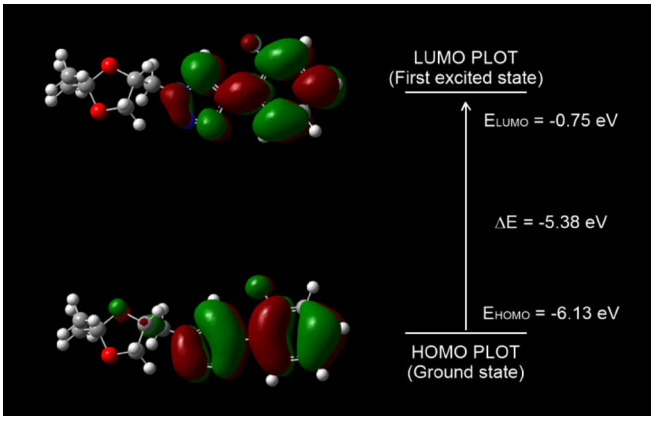


Figure 2. *The HOMO, LUMO and energy gap of compound* ***4d****, obtained by the DFT calculations*

The SCF (Self Consistent Field) of surface electron density traced with MEP of the compound **4d** is shown in Figure 3. The total electron density varies between two extreme limits: $-5.891.10^{-2}$ a.u. and $+5.891.10^{-2}$ a.u. As can be seen from the molecular electrostatic potential map of the compound, the negative region is mainly localized on the nitrogen atoms. The most electron deficient region is near to aromatic benzene group. The electron density reveals the polarity of the molecule.

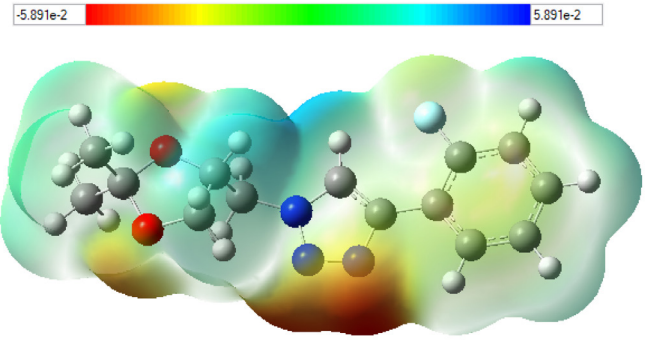


Figure 3. *The total electron density surface of compound* ***4d***

As described by Berredjem and co-workers,[46] the energy of HOMO and LUMO frontier orbitals are useful for the calculation of other physical chemical properties, namely, dipole moment, ionization energy (*I*), electron affinity (*A*), electronegativity (χ), electronic chemical potential (μ), chemical hardness (η), electrophilicity index,

and molecular softness (*S*).[47-50] Thus, based on the energy levels of the frontier orbital pairs of compounds **4a-4k**, the aforementioned properties were determined and the calculated values are depicted in Table 2.

Eletronegativity (χ) is a measure of the power of an atom to attract electrons (or electron density) towards itself when forming chemical bonds.[51] The chemical hardness (η) can be defined as the measure of the resistance to change in the electron distribution in a collection of nuclei and electrons.[47] Softness (*S*) is just the reciprocal of chemical hardness.[52] The electrophilicity index (ω) is considered to be a measure of electrophilic power.[53]

The compounds **4h** (presenting one CF_3 group at the *para* position of the aromatic benzene ring) and **4k** (with two CF_3 groups also attached to the aromatic benzene ring) displayed the highest dipole moments (6.63 for **4h** and 6.78 for **4k**).

The derivatives **4k** and **4a** exhibited the highest and the lowest χ values, respectively. The charge transfer resistance estimated from global hardness values (η) showed no great variation (2.61-2.71) among the compounds analyzed. The electronic acceptability of a molecule is ascribed to the global softness (*S*). Since the molecules do not significantly differ in terms of functional groups, there was no significant difference in this parameter (0.37-0.38). The energy reduction resulted from the electron flow from HOMO (donor) to LUMO (acceptor) is associated with the electrophilicity index (ω).[54] Electrophilicity is a fundamental property of organic compounds, which involves some adequate information regarding structure, reactivity, aromaticity, and toxicity, etc.[55] The compound **4k** showed the highest electrophilicity value (2.90).

Log P, previously employed to analyze the assimilation capacity of oral usage drugs,[56] can also be used to determine the bioavailability of a given organic compound for a plant, as described by Tice,[57] after the fitting of those parameters to the herbicidal and insecticidal activity requirements, and the addition of a new parameter (number of rotatable bonds). The optimal values of those parameters proposed by Tice are: H-bond donors ≤ 3; H-bond acceptors ≥ 2 and ≤ 12; molecular weight ≥ 150 and ≤ 500; cLogP ≤ 4; rotatable bonds ≤ 12. These studies have been greatly influential as they provide useful clues for agrochemical development based on physico-chemical parameters, which are easy to calculate. The parameters are summarized in Table 3 for all the obtained derivatives.

All tested compounds did fit the rule, as they have cLog P values < 4 (2.14 - 3.86), which agrees with Tice requirements. Besides, none of the compounds exceeded the number of rotatable bonds (3-5), H-bond donors (0), or H-bond acceptors (5). It should be noticed that we did not find plain correlations between the calculated physico-chemical parameters herein described and the fungicidal activity. However, as previously mentioned, the knowledge of physico-chemical parameters of bioactive compounds is an important

Table 2. The calculated dipole moment, HOMO energy (E_H), LUMO energy (E_L), energy gap (E_{H-L}), electronegativity (χ), chemical hardness (η), molecular softness (S), electrophilicity index (ω), ionization energy (I), electron affinity (A), and electron chemical potential (μ)

Compound	Dipole moment	E_{HOMO}	E_{LUMO}	E_{H-L}	χ[a]	η[b]	*S*[c]	ω[d]	*I*[e]	*A*[f]	μ[g]
4a	3.45	-6.04	-0.63	5.41	3.33	2.71	0.37	2.05	6.04	0.63	-3.33
4b	2.68	-6.21	-0.86	5.35	3.53	2.67	0.37	2.33	6.21	0.86	-3.53
4c	3.92	-6.04	-0.66	5.38	3.35	2.69	0.37	2.09	6.04	0.66	-3.35
4d	2.70	-6.13	-0.75	5.38	3.44	2.69	0.37	2.19	6.13	0.75	-3.44
4e	5.21	-6.00	-0.71	5.29	3.35	2.64	0.38	2.12	6.00	0.71	-3.35
4f	2.76	-6.17	-0.77	5.40	3.47	2.70	0.37	2.23	6.17	0.77	-3.47
4g	5.71	-6.22	-0.85	5.37	3.53	2.69	0.37	2.32	6.22	0.85	-3.53
4h	6.63	-6.26	-1.04	5.22	3.65	2.61	0.38	2.56	6.26	1.04	-3.65
4i	4.24	-6.21	-0.87	5.34	3.54	2.67	0.37	2.35	6.21	0.87	-3.54
4j	1.66	-6.38	-1.08	5.30	3.73	2.65	0.38	2.63	6.38	1.08	-3.73
4k	6.78	-6.53	-1.28	5.25	3.91	2.63	0.38	2.90	6.53	1.28	-3.91

[a]Electronegativity (χ) = $-(E_{HOMO} + E_{LUMO})/2$; [b]Chemical Hardness (η) = $(E_{LUMO} - E_{HOMO})/2$; [c]molecular softness (*S*) = $1/2\eta$; [d]electrophilicity index (ω) = $\mu^2/2\eta$; [e]Ionization energy (*I*) = $-E_{HOMO}$; [f]electron Affinity (*A*) = $-E_{LUMO}$; [g]electronic chemical potential (μ) = $-\mu = (E_{HOMO} + E_{LUMO})/2$.

Table 3. Molecular parameter values found for compounds **4a-4k**

Compound	cLogP[a]	TPSA[b]	Molecular weight	H-bond acceptors[c]	H-bond donors[d]	Rotatable bonds
4a	2.14	49.19	259.31	5	0	3
4b	2.28	49.19	277.30	5	0	3
4c	2.30	49.19	277.30	5	0	3
4d	2.26	49.19	277.30	5	0	3
4e	2.40	49.19	295.29	5	0	3
4f	2.40	49.19	295.29	5	0	3
4g	2.40	49.19	295.29	5	0	3
4h	3.04	49.19	327.31	5	0	4
4i	3.01	49.19	327.31	5	0	4
4j	2.99	49.19	327.31	5	0	4
4k	3.86	49.19	395.30	5	0	5

[a]cLogP = calculated LogP; [b]TPSA = Total polar surface area; [c]H-bond acceptors = hydrogen bond acceptors; [d]H-bond donors = hydrogen bond donors.

knowledge in the research and development of agrochemicals and pharmaceuticals.

In a recent study, Ogaha and co-workers analyzed the contribution that organofluorine compounds make to the agrochemical industry.[58] They undertook the task of analyzing 424 fluorine-containg agrochemicals. Among several investigated features of the set of compounds is the distribution of these agrochemicals by molecular weight and LogP. It was found that 57% of herbicides and 55% of fungicides present molecular weight within the 300 to 400 Da range. The compounds **4h-4k** have molecular weights within this interval, while the compounds **4a-4g** have molecular weights < 300. In the investigation of Ogaha and co-workers, the compounds presenting molecular weight below 300 corresponded to 9% of herbicides. Concerning the calculated Log P and CLop, 52% of herbicides and 67% of fungicides displayed both LopP and CLogP values inside the 3 to 5 interval. In the present study, the most active compounds **4h**, **4i**, and **4k** has the CLogP within this range, while the remaining compounds have CLogP < 3. Still regarding Ogawa and collaborators' report, 32% of herbicides and 10% of fungicides have CLogP lower than 3.

CONCLUSIONS

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 fluorinated derivatives. The compounds were evaluated on *Colletotrichum gloeosporioides* which is the causative agent of anthracnose in papaya. Among the evaluated compounds, the derivative **4d** reduces the mycelial growth of *C. gloeosporioides* at rates comparable to the commercial fungicide tebuconazole used as the positive control. Theoretical calculations revealed that the synthesized derivatives present favorable physicochemical parameters for agrochemical purposes. Taking together, the results presented in this investigation point to the fact that the glycerol-fluorinated triazole derivatives may be a scaffold that can be explored towards the development of new agents for fungal control.

SUPPLEMENTARY MATERIAL

The regression equations used in the calculation of ED_{50} and ED_{90} values of triazoles synthesized against *C. gloeosporioides* and some selected IR, ^{1}H and ^{13}C NMR, and MS spectra are freely available at http://quimicanova.sbq.org.br, in pdf format.

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