SYNTHESIS AND ANTIOXIDANT EVALUATION OF NEW TRIAZOLES

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Abstract: This study describes the synthesis and antioxidant activity of new 1,4-disubstituted 1,2,3-triazoles. These compounds were generated semi-synthetically using the Cu(I)-catalysed azide-alkyne cycloaddition (CuAAC) reaction between ethyl 2-azidoacetate and terminal acetylenes derived from the natural products carvacrol, eugenol, isovanillin, thymol and vanillin. The products were obtained at 50 to 80% yield and characterised through several spectrographic techniques. Antioxidant activity was assayed using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2’-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS). The products exhibited moderate antioxidant activity, with ethyl 2-(4-((4-formyl-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl) acetate showing the highest antioxidant capacity (EC50 = 75.5 µg/mL) among the generated 1,4-disubstituted 1,2,3-triazoles. In conclusion, the generation of these compounds opens new possibilities for the development of new antioxidant agents.

Key words: Antioxidant activity, Free radicals, 1,2,3-Triazole, CuAAC Reaction.

INTRODUCTION

Oxidative stress plays a crucial role in the development of age-related diseases as well as diabetes, dementia, cancer, atherosclerosis, vascular disease, obesity, osteoporosis, and metabolic syndrome (Tan et al. 2018). Accordingly, the discovery and development of protective agents against oxidative stress are of great interest. One possible approach for the development of new antioxidant agents involves the use of virtual screening through molecular docking with the enzyme superoxide dismutase (SOD) (Gurunanjappa et al. 2016, Kumar et al. 2016, Hatai & Banerjee 2019). SOD acts as an endogenous antioxidant defence system, converting hydrogen peroxide-derived superoxide radicals to water and oxygen to neutralise these species and thus prevent their harmful effects on cellular components (Moloney & Cotter 2017, Rahal et al. 2014).

Among the classes of organic compounds that enhance SOD activity, 1,2,3-triazoles stand out (Biagi et al. 1990, Satapute et al. 2019, Zhang et al. 2016). 1,2,3-triazoles are heterocyclic compounds that are easily prepared through a Cu(I)-catalysed azide-alkyne cycloaddition (CuAAC) reaction. These compounds serve as analogues of various biological functional groups acting as hydrogen bond donors and acceptors (Dheer et al. 2017, Agalave et al. 2011, Santos et al. 2020). The objective of this work was to synthesise new molecules containing...
the 1,2,3-triazole scaffold and evaluate their antioxidant potential.

MATERIALS AND METHODS

Chemicals and materials

In the synthesis of compounds 4a-e: carvacrol (CAS number 499-75-2, Sigma-Aldrich, 99%), eugenol (CAS number 97-53-0, ReagentPlus®, 99%), isovanillin (CAS number 621-59-0, Sigma-Aldrich, 99%), propargyl bromide solution (CAS number 106-96-7, purum, ~80% in toluene), potassium carbonate anhydrous (CAS number 584-08-7, ACS reagent, ≥99%), thymol (CAS number 499-75-2, Sigma-Aldrich, 98%) and vanillin (CAS number 121-33-5, ReagentPlus®, 99%), were used to prepare terminal alkynes. Ethyl bromoacetate (CAS number 105-36-2, Sigma-Aldrich, 98%), Copper(II) sulfate pentahydrate (CuSO₄·5H₂O, CAS number 7758-99-8, ACS reagent, ≥98.0%), Sodium azide (NaN₃, CAS number 26628-22-8, ReagentPlus®, ≥99.5%), (+)-Sodium L-ascorbate (CAS number 134-03-2, Sigma-Aldrich, ≥99.0%), were used to prepare compounds 2 and 5a-e. The reactions were monitored by thin-layer chromatography (TLC) using silica gel plates (with fluorescent indicator F₂₅₄). TLC plates were visualized using UV light. The purification step was performed by liquid chromatography on a glass column using silica gel 60 (70-230 mesh) as the stationary phase, and the hexane and ethyl acetate solvents in different proportions as mobile phase. Spectral analyzes of the synthesized compounds were obtained using the Fourier transform infrared spectrophotometer (Spectrum 400 FT-IR / FT-NIR Spectrometer model PerkinElmer), the ¹H NMR and ¹³C NMR spectra were obtained on a Varian Unity Plus spectrometer 300 and 400 MHz with the chloroform-d (CAS number 865-49-6, Sigma-Aldrich, 99.96 atom % D) solvent and tetramethylsilane was used as an internal standard. The carbon, hydrogen and nitrogen contents of the compounds were determined by the Dynamic Flash Combustion technique, in a CHNS-O elementary analyzer, CE Instruments, model EA 1110. The melting points (mp) were obtained using a Electrothermal 9100 melting point apparatus and are not corrected.

Procedure for the synthesis of ethyl 2-azidoacetate (2)

The ethyl 2-azidoacetate (2) was prepared following the procedure of Liao et al. (2017). The ethyl 2-bromoacetate (1) (0.526 g, 3.15 mmol) was dissolved in 3 mL of acetone. The solution was cooled to 0 °C and a solution of sodium azide (0.683 g, 10.5 mmol) of water (3.0 mL) was slowly added under constant stirring. After the mixture was heated to 60 °C and stirred at that temperature for 12 h. The reaction mixture was diluted with dichloromethane (30 mL) and washed with water (4 × 30 mL). The combined organic layers were dried over Na₂SO₄, and concentrated in vacuum. The desired ethyl 2-azidoacetate (2) was obtained without further purification. The structure of compound (2) is supported by the following data. (Supplementary Material – Figures S1 to S2).

Ethyl 2-azidoacetate (2): Reaction time: 12 h; colorless oil; yield 98 %, ¹H NMR (300 MHz, CDCl₃) δ 1.32 (t, 2H, J = 7.0 Hz), 4.27 (q, 2H, J = 7.0 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 14.2, 50.4, 61.9, 168.3. This is in agreement with data previously reported (Liao et al. 2017).

General procedure for the synthesis of alkynes 4a-e

The alkynes (4a-e) were prepared following the procedure of Ferroni et al. (2017). Phenols (3a-e) (1.0 mmol) and anhydrous K₂CO₃ (0.276 g, 1.5 mmol) were added in a 25 mL two-necked flask and dissolved in 10 mL acetone. After 10 min, propargyl bromide (80% in toluene, 0.129
mL, 1.5 mmol) was slowly added and the reaction mixture was refluxed under N₂ atmosphere for 10 h. Then the mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried over Na₂SO₄ and the solvents were removed under reduced pressure followed by purification by flash column chromatography to yield the desired alkynes (4a-e). The structure of compound (4a-e) is supported by the following data (Figures S3 to S12).

4-isopropyl-1-methyl-2-(prop-2-yn-1-yloxy) benzene (4a): The crude product was purified by flash column chromatography, using ethyl acetate/hexane (08:92). Reaction time: 8 h; colorless oil; yield 90%; ¹H NMR (400 MHz, CDCl₃) δ 1.23 (d, 6H, J = 7.2 Hz), 2.20 (s, 3H), 2.48 (t, 1H, J = 2.4 Hz), 2.87 (q, 1H, J = 7.2 Hz), 4.69 (d, 2H, J = 2.4 Hz), 6.77 (d, 1H, J = 8.0 Hz), 6.81 (s, 1H), 7.05 (d, 1H, J = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 15.8, 24.04, 34.0, 55.9, 75.1, 79.1, 110.3, 119.1, 124.5, 130.6, 147.8, 155.7. This is in agreement with data previously reported (Aneja et al. 2018).

1-isopropyl-4-methyl-2-(prop-2-yn-1-yloxy) benzene (4b): The crude product was purified by flash column chromatography, using ethyl acetate/hexane (08:92). Reaction time: 10 h; colorless oil; yield 91%; ¹H NMR (400 MHz, CDCl₃) δ 1.14 (d, 6H, J = 7.2 Hz); 2.28 (s, 3H); 2.43 (t, 1H, J = 2.4 Hz); 3.25 (q, 1H, J = 7.2 Hz); 4.64 (d, 2H, J = 2.4 Hz); 6.72-6.75 (m, 2H); 7.06 (d, 1H, J = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.3, 22.8, 26.4, 56.1, 74.9, 79.1, 113.0, 122.2, 126.1, 134.7, 136.2, 154.7.

4-allyl-2-methoxy-1-(prop-2-yn-1-yloxy) benzene (4c): The crude product was purified by flash column chromatography, using ethyl acetate/hexane (10:90). Reaction time: 6 h; yellow oil; yield 86%; ¹H NMR (400 MHz, CDCl₃) δ 2.49 (t, 1H, J = 2.4 Hz), 3.34 (d, 2H, J = 6.8 Hz), 3.86 (s, 3H), 4.73 (d, 2H, J = 2.4 Hz), 5.06-5.11 (m, 2H), 5.91-6.01 (m, 1H), 6.72-6.74 (m, 2H), 6.96 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 39.8, 55.7, 56.8, 75.5, 78.7, 112.3, 114.6, 115.7, 120.2, 134.2, 137.4, 145.0, 149.6. This is in agreement with data previously reported (Teixeira et al. 2018).

4-methoxy-3-(prop-2-yn-1-yloxy) benzaldehyde (4d): The crude product was purified by flash column chromatography, using ethyl acetate/hexane (30:70). Reaction time: 8 h; solid, mp 71-72 ºC, yield 88%; ¹H NMR (400 MHz, CDCl₃) δ 2.53 (t, 1H, J = 2.4 Hz), 3.95 (s, 3H), 4.81 (d, 2H, J = 2.4 Hz), 6.98 (d, 1H, J = 8.0 Hz), 7.49-7.53 (m, 2H), 9.85 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 56.1, 5.6, 76.4, 77.7, 110.9, 112.0, 127.2, 129.9, 147.3, 154.9, 190.6. This is in agreement with data previously reported (Hussaini et al. 2016).

3-methoxy-4-(prop-2-yn-1-yloxy) benzaldehyde (4e): The crude product was purified by flash column chromatography, using ethyl acetate/hexane (30:70). Reaction time: 8 h; solid, mp 84-85 ºC, yield 90%; ¹H NMR (400 MHz, CDCl₃) δ 2.58 (t, 1H, J = 2.4 Hz), 3.94 (s, 3H), 4.86 (d, 2H, J = 2.4 Hz), 7.14 (d, 1H, J = 8.0 Hz), 7.44 (d, 1H, J = 1.6 Hz), 7.47 (dd, 1H, J = 1.6 and 7.6 Hz), 9.88 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 55.9, 56.5, 76.6, 77.4, 109.5, 112.6, 126.2, 130.9, 149.9, 152.1, 190.8. This is in agreement with data previously reported (Fong et al. 2019).

General procedure for the synthesis of triazoles 5a-e

The triazoles (5a-e) were prepared following the procedure described by Rostovtsev et al. (2002). The alkyne (4a-e) (1.0 mmol) and ethyl 2-azidoacetate (2) (0.14 g, 1.1 mmol) were added to a 1:1 mixture of water and tert-buty alcohol (4 mL). Sodium ascorbate (0.1 mmol, in 300 µL of water) was added, followed by copper(II) sulfate pentahydrate (0.01 mmol, in 100 µL of water). The reaction mixture was stirred vigorously at room temperature (25±3 ºC) and monitored by TLC until the reagents were completely consumed. The reaction the mixture was extracted with 50 mL of dichloromethane and washed with.
water (3 × 30 mL). The combined organic phases were dried over Na₂SO₄ and the solvents were removed under reduced pressure followed by purification by flash column chromatography to yield the desired triazoles (5a-e). The structure of compound 5a-e is supported by the following data (Figures S13 to S22).

**Ethyl 2-(4-((5-isopropyl-2-methylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetate (5a):** The crude product was purified by flash column chromatography, using ethyl acetate/hexane (40:60). Reaction time: 2 h; white solid; mp 86-87 ºC; yield 70%; IR (KBr pellet) νₘₐₓ 3137, 2961, 1755, 1611, 1211 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.24 (d, 6H, J = 6.8 Hz), 1.30 (t, 3H, J = 7.6 Hz), 2.19 (s, 3H), 2.83-2.90 (m, 1H), 4.27 (q, 2H, J = 7.2 Hz), 5.16 (s, 2H), 5.26 (s, 2H), 6.77 (d, 1H, J = 7.2 Hz), 6.83 (s, 1H), 7.06 (d, 1H, J = 7.2 Hz), 7.73 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.9, 15.7, 24.0, 34.0, 50.8, 62.3, 62.3, 110.0, 118.6, 123.6, 124.1, 130.5, 145.3, 147.9, 156.2, 166.1; Anal. C, 64.21%; H, 7.37 %; N, 13.01%. calcd C₁₇H₂₃N₃O₃: C, 64.33%; H, 7.30%; N, 13.24%.

**Ethyl 2-(4-((2-isopropyl-5-methylphenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetate (5b):** The crude product was purified by flash column chromatography, using ethyl acetate/hexane (40:60). Reaction time: 2.3 h; white solid; mp 61-62 ºC; yield 60%; IR (KBr pellet) νₘₐₓ 3131, 2955, 1749, 1687, 1222 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.19 (d, 6H, J = 7.2 Hz), 1.30 (t, 3H, J = 6.8 Hz), 2.32 (s, 3H), 3.25-3.32 (m, 1H), 4.27 (q, 2H, J = 7.2 Hz), 5.17 (s, 2H), 5.24 (s, 2H), 6.77-6.79 (m, 2H), 7.11 (d, 1H, J = 7.6 Hz), 7.73 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.9, 15.7, 24.0, 34.0, 50.8, 62.3, 62.3, 110.0, 118.6, 123.6, 124.1, 130.5, 145.3, 147.9, 156.2, 166.1; Anal. C, 64.21%; H, 7.37 %; N, 13.01%. calcd C₁₇H₂₃N₃O₃: C, 64.33%; H, 7.30%; N, 13.24%.

**Ethyl 2-(4-((4-allyl-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetate (5c):** The crude product was purified by flash column chromatography, using ethyl acetate/hexane (45:55). Reaction time: 0.5 h; white solid; mp 93 ºC; yield 80%; IR (KBr pellet) νₘₐₓ 3138, 3079, 2996, 1753, 1638, 1518, 1209, 1038 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.27 (t, 3H, J = 7.3 Hz), 3.30 (d, 2H, J = 6.8 Hz), 3.83 (s, 3H), 4.21-4.26 (q, 2H, J = 7.3 Hz), 5.03-5.08 (m, 2H), 5.12 (s, 2H), 5.27 (s, 2H), 5.90-5.97 (m, 1H), 6.67-6.71 (m, 2H), 6.94 (d, 1H, J = 7.6 Hz), 7.76 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.9, 39.7, 50.8, 55.7, 62.3, 63.2, 112.2, 114.4, 115.6, 120.4, 124.2, 133.7, 137.4, 144.8, 145.8, 149.4, 166.0; Anal. C, 61.73%; H, 6.37 %; N, 12.80%. calcd for C₁₇H₂₁N₃O₄: C, 61.62%; H, 6.39%; N, 12.68%.

**Ethyl 2-(4-((5-formyl-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetate (5d):** The crude product was purified by flash column chromatography, using ethyl acetate/hexane (65:35). Reaction time: 0.5 h; white solid; mp 126-127 ºC; yield 50%; IR (KBr pellet) νₘₐₓ 3146, 2997, 1742, 1687, 1222 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.27 (t, 3H, J = 7.2 Hz), 3.91 (s, 3H), 4.25 (q, 2H, J = 7.2 Hz), 5.14 (s, 2H), 5.32 (s, 2H), 6.98 (d, 1H, J = 8.4 Hz), 7.49 (dd, 1H, J = 8.4, and 2.0 Hz), 7.54 (d, 1H, J = 1.6 Hz), 7.80 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.9, 50.8, 56.0, 62.4, 62.8, 110.9, 112.3, 124.4, 126.6, 129.9, 143.7, 148.1, 154.9, 166.0, 190.6; Anal. C, 56.21%; H, 5.33 %; N, 13.05%. calcd C₁₅H₁₇N₃O₅: C, 56.42%; H, 5.37%; N, 13.16%.

**Ethyl 2-(4-((4-formyl-2-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)acetate (5e):** The crude product was purified by flash column chromatography, using ethyl acetate/hexane (65:35). Reaction time: 0.7 h; white solid; mp 144-145 ºC; yield 70%; IR (KBr pellet) νₘₐₓ 3140, 2969, 1742, 1691, 1222 cm⁻¹; RMN ¹H (400 MHz, CDCl₃) δ 1.26 (t, 3H, J = 7.2 Hz), 3.89 (s, 3H), 4.24 (q, 2H, J = 7.2 Hz), 5.13 (s, 2H), 5.37 (s, 2H), 7.20 (d, 1H, J = 8.0 Hz), 7.40 (m, 2H), 7.81 (s, 1H), 9.82 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.9, 50.8, 55.9, 62.4, 62.7, 109.2, 112.5, 124.5, 126.6, 130.5, 143.6, 149.8, 152.9, 165.9, 190.8; Anal. C, 56.65%; H, 5.18 %; N, 13.11%. calcd C₁₅H₁₇N₃O₅: C, 56.42%; H, 5.37%; N, 13.16%.
Evaluation of the antioxidant activity of compounds 5a-e

The evaluation of antioxidant activity was performed according to two methodologies which are based on the capture of DPPH radicals (2,2-diphenyl-1-picrylhydrazyl) and 2,2’-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS). The DPPH free radical scavenging test was carried out according to the methodology described by Silva et al. (2006). In this assay, ascorbic acid was used as a positive control. In the second test performed, which was based on the capture the radical ABTS, the methodology described by Re et al. (1999) was used, in which (+)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox) as a positive control. Compounds 5a-e were tested in both methodologies at concentrations of 10 to 500 μg/mL and all tests were performed in triplicate. Antiradical efficiency was established using linear regression analysis in the 95% confidence interval (P < 0.05) obtained by the GraphPad Prism 5.0 statistical program. The results were expressed using the EC50 value, which represents the concentration of the sample necessary to sequester 50% of the DPPH radicals or the ABTS radical.

RESULTS AND DISCUSSION

Synthesis and characterisation of target compounds

1,4-Disubstituted 1,2,3-triazoles were obtained in three steps by incorporating the 1,2,3-triazole scaffold into the natural products carvacrol (3a), thymol (3b), eugenol (3c), vanillin (3d), and isovanillin (3e), as shown in Figure 1. First, ethyl 2-azidoacetate (2) was prepared by azidation of ethyl 2-bromoacetate (1). In parallel, the terminal alkynes 4a-e were prepared by the propargylation reaction of natural products 3a-e. Subsequently, the CuAAC reaction was performed to obtain the desired compounds 5a-e.

The first step provided compound 2 with 98% yield after 12 h. Spectroscopic data for compound 2 were consistent with those described by Liao et al. (2017). The propargylation reaction of compounds 3a-e provided terminal alkynes 4a-e. These propargylated derivatives were obtained in high yields after reaction times ranging from 6 to 10 h after chromatographic purification (Figure 2). Compounds 4a-e were obtained without significant differences in yield. Additionally, the structural characterisation of compounds 4a-e was consistent with reported
data (Liao et al. 2017, Aneja et al. 2018, Teixeira et al. 2018, Hussaini et al. 2016, Fong et al. 2019). The final step resulted in compounds 5a-e in yields ranging from 50 to 80% after chromatographic purification (Figure 3). In general, the CuAAC reaction time and yield varied significantly, depending on the substrate used. Studies have shown that deprotonation of the terminal alkyne to form the copper(I) acetylide is an important step in this reaction, and electron-withdrawing groups are expected to both increase the acidity of the terminal alkyne hydrogen and the reactivity of the corresponding alkyne (Iacobucci et al. 2015, Zhang et al. 2016). However, due to the presence of an sp<sup>3</sup>-hybridised carbon between the oxygen of the aromatic ring and the reaction site (C≡C–H) in compounds 4a-e, resonance does not occur, and the weak inductive effect caused by removing electrons has little influence on product formation 5a-e. Additionally, compound 5b required a longer reaction time than compound 5a, which was attributed to steric hindrance caused by the isopropyl group present in the ortho position in the aromatic ring of compound 4b. Compounds 5c, 5d, and 5e were obtained in shorter reaction times (Figure 3).

The formation of compounds 5a-e was confirmed by IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR spectroscopy. Upon analysis of the IR spectra, a vibration band with wavelengths ranging from 3131 to 3146 cm<sup>-1</sup> was observed. This is characteristic of the stretching of the C<sub>sp</sub><sup>2</sup>–H bond of the triazole ring, which is evidence for the formation of 1,2,3-triazoles, as described by Kaushik et al. (2016). In the <sup>1</sup>H NMR spectrum, a signal with a multiplicity of the singlet type and integral equal to 1 from 7.73 to 7.81 ppm was found in all compounds 5a-e, this signal can be attributed to the hydrogen of the triazole ring (Irfan et al. 2015, Santos et al. 2019). In the <sup>13</sup>C NMR spectra, the signals most characteristic of the formation of 1,4-disubstituted 1,2,3-triazoles were observed from 123.6 to 124.5 ppm and 143.6 to 145.3 ppm, which are ranges corresponding to the C<sub>sp</sub><sup>2</sup> carbons of the triazole rings (Creary et al. 2012). Taken together, these results indicate the formation of the desired products.

**Evaluation of antioxidant activity**

The evaluation of the antioxidant activity of compounds 5a-e was carried out through two assays based on the detection of DPPH and ABTS radicals. These assays are widely used because of their simplicity, speed, and sensitivity (Huang et al. 2005). Antioxidant activity was expressed as the effective concentration of the sample that led to a 50% reduction (EC<sub>50</sub>) in the initial concentration of DPPH (or ABTS) (Olugbami et al. 2015). The EC<sub>50</sub> values obtained for compounds 5a-e are listed in Table I.

It was observed that compounds 5a-e had EC<sub>50</sub> values ranging from 75.5 to 299.1 µg/mL in the DPPH assay and from 101.1 to 441.5 µg/
mL in the ABTS assay, indicating generally low antioxidant activities of 5a-e when compared to those of standards (ascorbic acid and TROLOX). Compound 5e, derived from vanillin, was more active than compounds 5a-d. This result corroborated with those of prior studies on antioxidant activity (Tai et al. 2011, Zhao et al. 2017). Studies have shown that vanillin can eliminate the free radical peroxyl, which simulates in vivo radical production in lipid peroxidation (Scipioni et al. 2018, Zhao et al. 2017), triggering antioxidative and anti-inflammatory neuroprotective activity (Gupta & Sharma 2014).

Lee et al. (2011) reported the synthesis of a series of vanillin-based dendrimers with enhanced antioxidant properties. Scipioni et al. (2018) reported the strong antioxidant activity (determined using the DPPH assay), ferric reducing ability of plasma, and oxygen radical absorbance capacity of derivatives obtained from the reductive amination between vanillin and various amines. Subsequently, Scipioni et al. (2019) reported the antioxidant activity of vanillin derivatives containing a tacrine or naphthalimido group.

Another important aspect in the search for new drug candidates is the prior evaluation of pharmacokinetic properties that makes investment in these molecules feasible; a significant number of compounds do not advance in clinical studies due to poor pharmacokinetic properties (Waterbeemd & Gifford 2003). Therefore, the SwissADME bioinformatics platform was used to calculate the theoretical LogP values of compounds 5a-e. Compounds 5a-e showed theoretical LogP values between 1.27 and 2.83. These values lie within the ideal range described by Barreiro & Fraga (2015) and do not violat Lipinski’s rule (Lipinski et al. 1997); thus, good oral absorption is expected for compounds 5a-e.

Figure 3. Derivatives of the new 1,4-disubstituted 1,2,3-triazoles semi-synthetic 5a-e.
CONCLUSION

This work describes, for the first time, the synthesis and biological assessment of new 1,4-disubstituted 1,2,3-triazoles 5a-e, which were obtained in yields ranging from 50% to 80%. Moderate antioxidant potential was observed for synthesised compounds with EC$_{50}$ values above 75.5 µg/mL. In addition, through in silico studies, it was found that compounds 5a-e present satisfactory LogP values. Thus, the results presented in this study are the first steps towards the targeted development of new antioxidant agents.

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SUPPLEMENTARY MATERIAL

Figures S1 to S22. Concerning the spectra of synthesized compounds.

How to cite
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LIMA JAC, SILVA JAC and SANTOS CS performed the synthesis, characterization of the compounds and the writing of the manuscript. CAIANA RRA, CAMARA CAG and MORAES MM conducted the experiments of antioxidant activity and data analysis. FREITAS JCR participated in the writing of the manuscript and project supervision.