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Synthesis, Characterization and Cytotoxic Activity of Novel β-hydroxy-1,2,3-Triazoles Derived from Eugenol

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Abstract. Phenylpropanoids and their semisynthetic derivatives are an important class of compounds with diverse biological applications. Herein, a series of β-hydroxy-1,2,3-triazole derivatives of eugenol were synthetized via ring opening of eugenol epoxide and the subsequent copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC). The novel eugenol derivatives were characterized by 1D and 2D NMR spectroscopy and HR-MS. The cytotoxic activity of eugenol and 1,2,3-triazole derivatives against the human breast cancer cell line MCF-7 was investigated. Compounds **3a** and **3b** displayed a similar cytotoxic activity than eugenol, whereas derivatives **3c** and **3d** showed a slight lower cytotoxic than the natural phenylpropanoid.

J. Mex. Chem. Soc. **2026**, *70(1):e2541*
Regular Issue

ISSN-e 2594-0317

Resumen. Los fenilpropanoides y sus derivados semisintéticos son una importante clase de compuestos con diversas aplicaciones biológicas. En este trabajo, una serie de derivados β-hidroxi-1,2,3-triazoles de eugenol fueron sintetizados mediante la apertura del anillo del epóxido de eugenol y la subsecuente reacción de cicloadición de azida-alquino catalizada por cobre (CuAAC). Los nuevos derivados de eugenol fueron caracterizados por RMN en 1D y 2D y EM-AR. La actividad citotóxica del eugenol y de los derivados 1,2,3-triazoles fue investigada contra la línea celular de cáncer de mama humano MCF-7. Los compuestos **3a** y **3b** mostraron una actividad citotóxica similar al eugenol, mientras que los derivados **3c** y **3d** mostraron una citotoxicidad ligeramente menor que el fenilpropanoide de origen natural.

Introduction

Cancer is a serious public health problem, and approximately one in six deaths is due to this disease. In 2022, there were approximately 20 million new cases and 9.7 million deaths from cancer worldwide. In women, breast cancer was the most frequent cancer in both cases and deaths.[1] Historically, natural products and their semisynthetic derivatives have contributed to the treatment of this disease. From 1981 to 2019, 33 % of small molecules approved as anticancer drugs belong to these classes of compounds.[2] In this sense, natural phenylpropanoids and their derivatives have shown important pharmacological properties such as anticancer activity, among others.[3-6]

Eugenol (4-allyl-2-methoxyphenol) is a natural phenylpropanoid present as a main component of clove buds (*Syzygium aromaticum* L.) and cinnamon bark (*Cinnamomum verum*), containing 45–90 % and 20–50 % eugenol respectively.[7] This natural product has demonstrated multiple biological activities such as antioxidant, antimicrobial, anti-inflammatory, and anticancer, among others.[8-11] In addition, its chemical structure has been employed as scaffold in the construction of semisynthetic derivatives with potential pharmacologic applications.[12-14] Particularly, in recent years, 1,2,3-triazole derivatives of eugenol have shown significant biological activities, including antioxidant,[15] antimicrobial,[16-19] antiparasitic[20,21] and anticancer.[22-24] In these hybrids, the 1,2,3-triazole ring has been introduced into the eugenol structure at both the hydroxyl and the allylic groups, being the former the most common strategy. Despite the generation of β-hydroxy-1,2,3-triazole derivatives at the hydroxyl group of eugenol by epoxide ring opening reaction,[19,21] as well as the synthesis of β-amino and β-alkoxy alcohols by the ring opening of epoxide eugenol,[25,26] there are no reports in the literature on the synthesis of β-hydroxy-1,2,3-triazole derivatives of eugenol following this latter strategy (Fig. 1).

Herein, we describe the synthesis and characterization of a series of novel β-hydroxy-1,2,3-triazoles derived from eugenol. The 1,2,3-triazole derivatives were obtained by the ring opening of the eugenol epoxide and the subsequent copper-catalyzed azide-alkyne cycloaddition reaction. Furthermore, the cytotoxic activity of the compounds against the MCF-7 cell line (human breast adenocarcinoma) was evaluated.

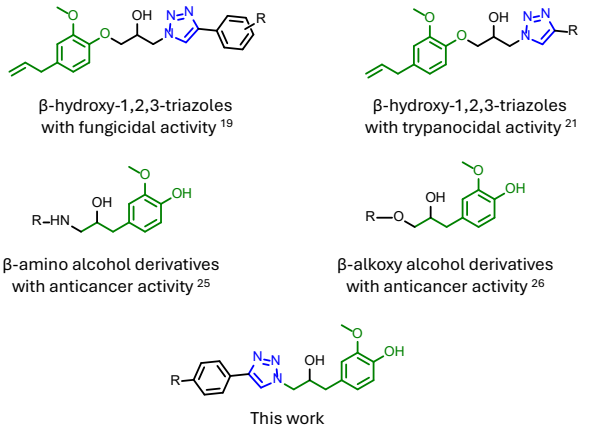

Fig. 1. Bioactive derivatives of eugenol obtained by epoxide ring opening reactions.[19,21,25,26]

J. Mex. Chem. Soc. **2026**, *70(1):e2541*
Regular Issue

ISSN-e 2594-0317

Experimental

Materials and methods

Chemicals such as eugenol, *meta*-chloroperbenzoic acid (mCPBA), sodium azide, ammonium chloride, sodium ascorbate, copper (II) sulfate pentahydrate, phenylacetylene, 4-ethynyltoluene, 1-ethynyl-4-fluorobenzene, 4-ethynylanisole, thiazolyl blue tetrazolium bromide (MTT), phosphate buffered saline, HRMPI-1640 medium, streptomycin-penicillin, trypsin 0.25 % with EDTA, Fetal Bovine Serum (FBS) and solvents from commercial sources were used as received without further purification. High-resolution mass spectrometry (HR-MS) analyses were performed on a JEOL GC-Mate II Mass-spectrometer using the electron impact ionization (EI) method. The ^{1}H, ^{13}C and 2D NMR spectra were obtained on a Bruker Avance III 400 spectrometer. Spectral data are reported in ppm using the residual solvent signal (DMSO-d_6) as internal reference. Melting point was measured on Electrothermal IA9100 apparatus and uncorrected.

Chemistry

Synthesis of β-azido alcohol derivative of eugenol (2)

Initially, eugenol epoxide was obtained using a modification of the method previously published.[25] A solution of eugenol **1** (10 mmol in 25 mL of dichloromethane) was added dropwise to a suspension of 70 % 3-chloroperbenzoic acid (mCPBA) (20 mmol in 25 mL of dichloromethane) at 0 °C. The mixture was stirred for 2 hours. Afterwards, it was filtered, and 25 mL of 10 % aqueous solution of sodium sulfate was added. The organic phase was washed with 10% $NaHCO_3$ solution (2 x 25 mL), dried with sodium sulfate anhydrous and evaporated under reduced pressure. Subsequently, the crude product, without further purification, NH_4Cl (15 mmol) and NaN_3 (25 mmol) were dissolved in 25 mL of ethanol.[27] The mixture was stirred and heated under reflux for four hours. The solvent was then removed, and 25 mL of water was added. The aqueous phase was extracted with ethyl acetate (2 x 25 mL). The organic phase was washed with brine (2 x 25 mL), dried with sodium sulfate anhydrous and evaporated under reduced pressure. The product was purified by column chromatography using silica gel as the stationary phase, and hexane/ethyl acetate mixtures as the mobile phase. Compound **2** was obtained as a yellow oil (0.9 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) 6.84 (d, J = 8.0 Hz, 1H, H5), 6.70 (d, J = 1.9 Hz, 1H, H3), 6.68 (dd, J = 8.0, 1.9 Hz, 1H, H6), 3.94 (dddd, J = 7.4, 6.7, 5.9, 3.7 Hz, 1H, H8), 3.85 (s, 3H, H10), 3.35 (dd, J = 12.5, 3.7 Hz, 1H, H9a), 3.27 (dd, J = 12.5, 6.7 Hz, 1H, H9b), 2.77 – 2.65 (m, 2H, H7). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7 (C2), 144.5 (C1), 128.9 (C4), 122.0 (C6), 114.7 (C5), 111.9 (C3), 71.9 (C8), 56.0 (C10), 55.9 (C9), 40.5 (C7). HRMS (EI): $(M)^+$ calcd for $C_{10}H_{13}N_3O_3$: 223.0957, found: 223.1000.

Synthesis of β-hydroxy-1,2,3-triazole derivatives of eugenol (3a–3d)

A solution of sodium ascorbate (0.5 mmol in 20 mL of water) was added to a solution of compound **2** (2 mmol in 15 mL of dichloromethane). Afterwards, the corresponding phenylacetylene (2.2 mmol) and copper (II) sulfate pentahydrate (0.2 mmol) were added to the mixture. The resulting mixture was stirred at room temperature for two hours. The organic phase was washed with brine (2 x 25 mL), dried with sodium sulfate anhydrous and evaporated under reduced pressure. The product was purified by column chromatography using silica gel as the stationary phase, and hexane/acetone mixtures as the mobile phase.

Compound **3a**: white powder (0.2 g, 31 %): mp 136-137°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H, C1–OH), 8.49 (s, 1H, H10), 7.86 (dd, J = 8.3, 1.2 Hz, 2H, H13 and H17), 7.44 (t, J = 7.6 Hz, 2H, H14 and H16), 7.32 (t, J = 7.4 Hz, 1H, H15), 6.84 (d, J = 1.8 Hz, 1H, H3), 6.71 (d, J = 8.0 Hz, 1H, H6), 6.66 (dd, J = 8.0, 1.8 Hz, 1H, H5), 5.22 (d, J = 5.6 Hz, 1H, C8–OH), 4.41 (dd, J = 13.8, 3.4 Hz, 1H, H9a), 4.25 (dd, J = 13.8, 7.9 Hz, 1H, H9b), 4.09 (bs, 1H, H8), 3.76 (s, 3H, H18), 2.65 (dd, J = 6.3, 2.7 Hz, 2H, H7). ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.3 (C2), 146.0 (C11), 144.9 (C1), 131.0 (C12), 128.9 (3C, C4, C14 and C16), 127.7 (C15), 125.1 (2C, C13 and C17), 122.3 (C10), 121.7 (C5), 115.3 (C6), 113.6 (C3), 70.5 (C8), 55.5 (C18), 55.1 (C9), 40.5 (C7). HRMS (EI): $(M)^+$ calcd for $C_{18}H_{19}N_3O_3$: 325.1426, found: 325.1440.

Compound **3b**: colorless oil (0.23 g, 34 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H, C1–OH), 8.43 (s, 1H, H10), 7.74 (d, J = 8.1 Hz, 2H, H13 and H17), 7.24 (d, J = 8.0 Hz, 2H, H14 and H16), 6.84 (d, J = 1.6 Hz, 1H, H3), 6.70 (d, J = 8.0 Hz, 1H, H6), 6.66 (dd, J = 8.0, 1.7 Hz, 1H, H5), 5.21 (d, J = 4.7 Hz, 1H, C8–OH), 4.39 (dd, J = 13.8, 3.4 Hz, 1H, H9a), 4.23 (dd, J = 13.8, 7.9 Hz, 1H, H9b), 4.08 (bs, 1H, H8), 3.76 (s, 3H, H18), 2.64 (dd, J = 6.3, 2.2 Hz, 2H, H7), 2.32 (s, 3H, H19).^{13}C NMR (100 MHz, DMSO-d_6) δ 147.3 (C2), 146.0

J. Mex. Chem. Soc. **2026**, *70(1):e2541*
Regular Issue

ISSN-e 2594-0317

(C11), 144.9 (C1), 137.0 (C15), 129.4 (2C, C14 and C16), 128.9 (C4), 128.2 (C12), 125.1 (2C, C13 and C17), 121.8 (C10), 121.6 (C5), 115.3 (C6), 113.6 (C3), 70.5 (C8), 55.5 (C18), 55.0 (C9), 40.5 (C7), 20.8 (C19). HRMS (EI): $(M)^+$ calcd for $C_{19}H_{21}N_3O_3$: 339.1583, found: 339.1576.
Compound **3c**: white powder (0.22 g, 32 %): mp 126-127°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H, C1–OH), 8.49 (s, 1H, H10), 7.89 (dd, *J* = 8.8, 5.5 Hz, 2H, H13 and H17), 7.28 (t, *J* = 8.9 Hz, 2H, H14 and H16), 6.83 (d, *J* = 1.7 Hz, 1H, H3), 6.70 (d, *J* = 8.0 Hz, 1H, H6), 6.65 (dd, *J* = 8.0, 1.7 Hz, 1H, H5), 5.21 (d, *J* = 5.6 Hz, 1H, C8–OH), 4.40 (dd, *J* = 13.8, 3.4 Hz, 1H, H9a), 4.24 (dd, *J* = 13.8, 7.9 Hz, 1H, H9b), 4.07 (bs, 1H, H8), 3.75 (s, 3H, H18), 2.64 (dd, *J* = 6.3, 2.3 Hz, 2H, H7). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7 (d, *J* = 244.2 Hz, C15), 147.3 (C2), 145.1 (C11), 144.9 (C1), 128.9 (C4), 127.6 (d, *J* = 3.1 Hz, C12), 127.1 (d, *J* = 8.1 Hz, 2C, C13 and C17), 122.2 (C10), 121.7 (C5), 115.8 (d, *J* = 21.5 Hz, 2C, C14 and C16), 115.3 (C6), 113.6 (C3), 70.5 (C8), 55.5 (C18), 55.1 (C9), 40.5 (C7). HRMS (EI): $(M)^+$ calcd for $C_{18}H_{18}N_3O_3F$: 343.1332, found: 343.1320.
Compound **3d**: white powder (0.25 g, 35 %): mp 133-134°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H, C1–OH), 8.38 (s, 1H, H10), 7.77 (d, *J* = 8.8 Hz, 2H, H13 and H17), 7.00 (d, *J* = 8.9 Hz, 2H, H14 and H16), 6.83 (d, *J* = 1.6 Hz, 1H, H3), 6.70 (d, *J* = 8.0 Hz, 1H, H6), 6.65 (dd, *J* = 8.0, 1.7 Hz, 1H, H5), 5.20 (d, *J* = 5.6 Hz, 1H, C8–OH), 4.38 (dd, *J* = 13.8, 3.4 Hz, 1H, H9a), 4.22 (dd, *J* = 13.8, 7.9 Hz, 1H, H9b), 4.07 (bs, 1H, H8), 3.78 (s, 3H, H19), 3.75 (s, 3H, H18), 2.63 (dd, *J* = 6.2, 2.3 Hz, 2H, H7). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.9 (C15), 147.3 (C2), 145.9 (C11), 144.9 (C1), 128.9 (C4), 126.4 (2C, C13 and C17), 123.6 (C12), 121.6 (C5), 121.3 (C10), 115.3 (C6), 114.3 (2C, C14 and C16), 113.6 (C3), 70.5 (C8), 55.5 (C18), 55.1 (C19), 55.0 (C9), 40.5 (C7). HRMS (EI): $(M)^+$ calcd for $C_{19}H_{21}N_3O_4$: 355.1532, found: 355.1535.

Cell cytotoxicity assay

The human breast cancer cell line MCF-7 (ATCC HTB-22) was used in this study to determine the cytotoxicity. MCF-7 cells were cultured in RMPI-1640 medium supplemented with 10 % heat-inactivated FBS and 0.5 % streptomycin-penicillin. The cells were maintained in a humidified atmosphere of 5 % CO_2 at 37 °C. Once the cells reached approximately 80 % confluency, they were treated with trypsin for passing or were seeded in 96-well microtiter plates for the cytotoxicity assays.

Cell cytotoxicity was evaluated using a previously reported MTT assay,[28] with slight modifications. Initially, 1 x 10^4 cells were seeded into each well of a 96-well microtiter plate and incubated for 24 hours to allow for cell adhesion. After this incubation period, the medium was removed and replaced with 200 µL of the compound dissolved in the culture medium without FBS. To prepare the test concentrations, a stock solution of each compound at a concentration of 100 mg/mL was prepared in DMSO. From this stock solution, a working solution of 1 mg/mL was prepared in the culture medium without FBS. The final concentrations for evaluation were prepared from this working solution at 300 µM in the culture medium without FBS. The final DMSO concentrations in the assays were at 0.1 %. The treatments were exposed over 48 hours. Negative controls consisted of untreated cells using the same conditions as treated cells. Following this, 20 µL of MTT solution at a concentration of 5 mg/mL was added to each well, and the plates were returned to the incubation for 3.5 hours. Then, 150 µL of MTT solution was removed, and 150 µL of DMSO:isopropyl was added. The absorbance was measured at 570 nm and a reference of 690 nm using a Cytation 3 microplate reader (CYT3M, BioTek Instruments, Inc.).

Results and discussion

The synthesis of the new β-hydroxy-1,2,3-triazoles derived from eugenol (**3a**–**3d**) was carried out following the synthetic route presented in Fig. 2. First, eugenol epoxide was obtained from the reaction of the commercially available phenylpropanoid **1** with mCPBA in dichloromethane, following a modification of the previously reported method.[25] The obtained product reacted with sodium azide and ammonium chloride in refluxing ethanol to give the desired β-azido alcohol **2** in moderate yield (40 %).[27] The characterization of the β-azido alcohol was carried out by HR-MS and NMR spectroscopy (figures S1–S5 and S22). The spectroscopic data were consistent with the proposed structure of compound **2**. Finally, the 1,2,3-triazole derivatives **3a**–**3d** were obtained by the copper-catalyzed azide-alkyne cycloaddition (CuAAC) between **2** and the corresponding phenylacetylene derivative. Following conventional chromatographic procedures, the compounds were obtained in moderate yields (31-35 %).

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J. Mex. Chem. Soc. **2026**, *70(1):e2541*
Regular Issue

ISSN-e 2594-0317

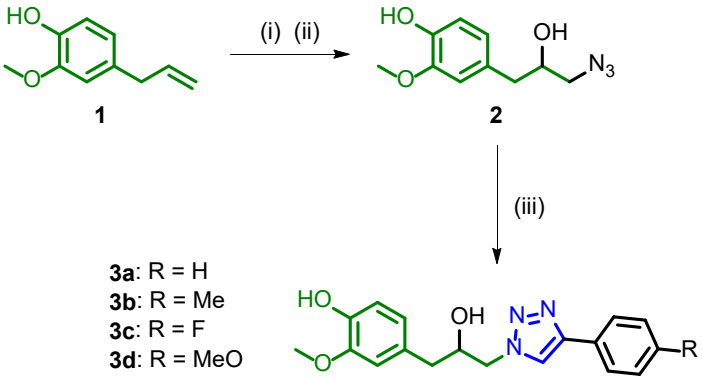

Fig. 2. Synthesis of β-hydroxy-1,2,3-triazoles derived from eugenol (**3a**–**3d**). Reagents and conditions: (i) mCPBA, dichloromethane, 0°C, 1.5 h; (ii) NH_4Cl, NaN_3, ethanol, reflux, 4 h; (iii) phenylacetylene derivative, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, dichloromethane/water, rt, 2h.

The β-hydroxy-1,2,3-triazoles **3a**–**3d** were characterized by 1D and 2D NMR spectroscopy. The ^1H and ^{13}C NMR signals were assigned by means of HSQC and HMBC experiments (figures S6–S21) and spectroscopic data are presented in Tables S1 and S2. In the ^1H NMR spectra, the aromatic protons of the phenol moiety were observed as two doublets and one doublet of doublets signals at approximately 6.83, 6.70 and 6.66 ppm, corresponding to protons 3, 6 and 5, respectively. The aromatic proton on the triazole ring was observed as a singlet signal at approximately 8.44 ppm. Furthermore, typical aromatic protons signals were observed for monosubstituted (**3a**) and 1,4-disubstituted (**3b**–**3d**) benzene rings at 7.9–7.0 ppm, corresponding to the aryl fragment attached to the triazole ring of the derivatives. In the allylic region of the spectra (for example see Fig. 3), the proton geminal to the hydroxyl group at position C-8 was observed as a broad signal at approximately 4.08 ppm. Methylene signals at C-9 were observed as two doublets of doublets at approximately 4.43–4.23 ppm, as part of an AM system. The signal of the methylene group at C-7 was observed as a doublet of doublets at approximately 2.64 ppm. The signal corresponding to the methoxy group at C-2 was observed as a singlet at approximately 3.76 ppm. Additionally, the protons of the hydroxyl groups at C-1 and C-8 were observed as singlet and doublet signals at approximately 8.75 and 5.22 ppm, respectively. The ^{13}C NMR spectra of the novel compounds showed the presence of signals corresponding to the three aromatic systems present in their structures in the region from 163.0 to 112.0 ppm. The signals corresponding to the carbons of the methine, methylene and methoxy groups at C8, C7, C9 and C18 were observed at approximately 70.5, 40.5, 55.0 and 55.5 ppm, respectively. The identity of the eugenol derivatives was also confirmed by HR-MS (figures S23-S26).

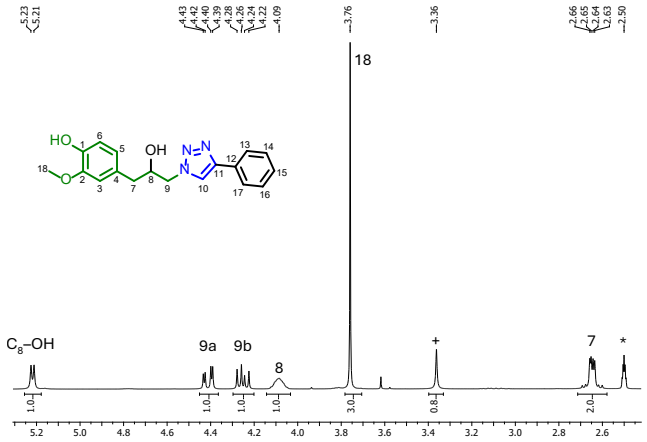

Fig. 3. Partial spectrum of ^1H NMR of compound **3a** (400 MHz, DMSO-d_6). *Residual solvent signal of DMSO-d_6, + residual water from the deuterated solvent.

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J. Mex. Chem. Soc. **2026**, *70(1):e2541*
Regular Issue

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The novel β-hydroxy-1,2,3-triazoles (**3a**–**3d**) as well as eugenol (**1**) were evaluated for *in vitro* cytotoxic activity against the human breast cancer cell line MCF-7 using the MTT assay. All compounds were tested at 300 µM and the results obtained are shown in Fig. 4 and Table S3. Derivatives **3a** and **3b** showed a similar cytotoxicity activity against MCF-7 cells (41.3 and 37.8 %, respectively) as the natural product **1** (38.4 %). Otherwise, compounds with –F (**3c**) or $–OCH_3$ (**3d**) substituents on the phenyl group attached to the triazole ring showed a reduction in the cytotoxic activity (30.1 and 28.0 %, respectively) compared to molecule **1**. These results indicate that the cytotoxic activity of new derivatives is sensitive to structural modifications in the phenyl fragment of their backbone. These novel hybrids of eugenol with 1,2,3-triazole ring tailored with phenyl moieties indicate that eugenol is an interesting scaffold to generate novel derivatives. Although results herein indicate that chemical modifications used did not impact significantly the cytotoxic effect of parent compound, this seminal approach provides hints of further modification directed to enhance activity. For instance, we envision that substituents attached to the 1,2,3-triazole ring of the derivatives, as well as the hydroxyl group at C-8, can be susceptible to further chemical modifications. Therefore, these structural modifications could lead to additional eugenol hybrids with potential cytotoxic activity.

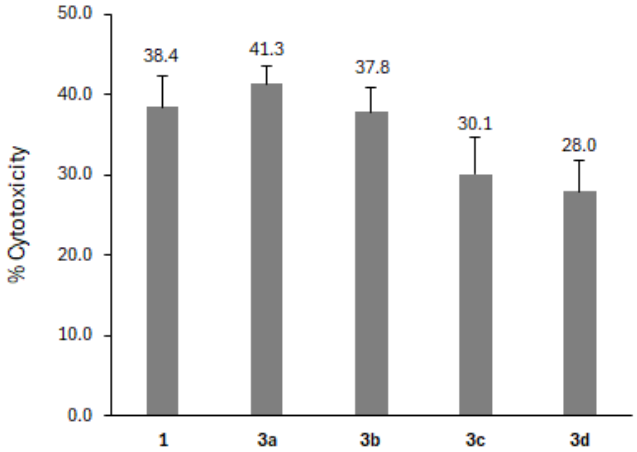

Fig. 4. Cytotoxic activity of eugenol (**1**) and 1,2,3-triazole derivatives of eugenol **3a**–**3d** at 300 µM against cancer cell line MCF-7.

Conclusions

In summary, a series of β-hydroxy-1,2,3-triazoles (**3a**–**3d**) derived from the natural product eugenol (**1**) were synthesized in moderate yields through the ring opening of the eugenol epoxide and the subsequent copper-catalyzed azide-alkyne cycloaddition. The new compounds were characterized by NMR and HR-MS and evaluated against the human breast cancer cell line MCF-7. Compounds **3a** and **3b** showed similar cytotoxic activity as eugenol; meanwhile, derivatives **3c** and **3d** showed a reduction in cytotoxic activity. The structure of the novel β-hydroxy-1,2,3-triazoles derived from eugenol is susceptible to further chemical modification that could lead to the generation of compounds with potential cytotoxic activity.

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J. Mex. Chem. Soc. **2026**, *70(1):e2541*
Regular Issue

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