

Research Article

1-(2-Chlorobenzoyloxy)-3-[1,2,3]triazol-1-yl-propan-2-ol Derivatives: Synthesis, Characterization, and DFT-Based Descriptors Analysis

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A novel series of 1-(2-chlorobenzoyloxy)-3-[1,2,3]triazol-1-yl-propan-2-ol derivatives was designed and synthesized using copper catalyzed alkyne-azide cycloaddition in the key step. Theoretical investigation of molecular and electronic properties by means of global and local reactivity indexes of the synthesized compounds was carried out, using DFT (Density Functional Theory) at PBE/PBE/6-31++G** level.

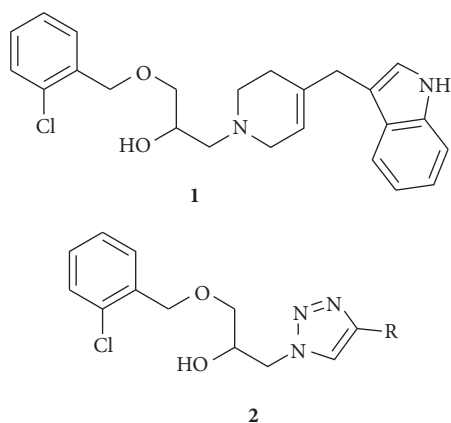
1. Introduction

Depression and similar psychological disorders affect about 350 million people worldwide and represent one of the leading causes of disability and a major contributor to the burden of suicide and ischemic heart diseases [1, 2]. This illness is associated with a decreased production of serotonin in conjunction with a decreased sensitivity of postsynaptic receptors to available serotonin [3]. Therefore, one of the most extended current therapies for this kind of diseases involve the use of commercially available drugs which work as selective serotonin reuptake inhibitors (SSRI) such as fluoxetine among other analogous compounds [4, 5]. Although all these compounds are effective as antidepressants, some side effects are observed during their use. This reason has motivated the design and development of diverse molecules, which display good reuptake inhibiting activity [6–8].

A particular molecule that has attracted us is a derivative from chlorobenzoyloxy-3,6-dihydropyridinyl propan-2-ol named DJLDU-3-79, **1** [9]. This compound was designed from a hybridization of two active reuptake inhibitory

molecules in order to improve the above-mentioned properties. However, a synthetic challenge in the preparation of this molecule is the tetrahydropyridine moiety prepared from 4-piperidone analogs, which in turn are obtained through several reaction steps [10, 11]. In this regard, we propose a synthesis of a novel family of compounds **2** analogs to molecule **1** based on a substitution of tetrahydropyridine ring by 1,2,3-triazole which is easily synthesized by copper catalyzed alkyne-azide cycloaddition (CuAAC), the most powerful click reaction (Scheme 1).

On the other hand, DFT-based methods have already proven to be useful in determining molecular structure of organic compounds, as well as in elucidating their electronic structure and reactivity [12]. There are two kinds of DFT-based reactivity indexes: global and local quantities. The global parameters measure the electronic features of the molecules as a whole and the local quantity reflects the reactivity of particular regions or atoms. The properties calculated in this study have been successfully applied in to explain the reactivity of organic and inorganic molecules, proteins, solids, and others [13].



SCHEME 1: Structure of DJLDU-3-79 (1) and general structure for molecules 2 proposed in this work.

Several studies have confirmed closed relationships between the biological performance of a family of compounds and their chemical reactivity. The pharmacokinetic and pharmacodynamic properties of SSRI molecules are strongly influenced by their interactions to the body proteins [9]. Therefore, the electron transfer properties in protein-ligand binding could be studied by using DFT reactivity indexes. To accomplish this goal, the use of global chemical reactivity parameters, chemical potential (I), electron affinity (A), chemical potential (μ), softness (S), and electrophilicity (ω), could aid the understanding of the interaction process between SSRI and biological molecules. Also, the local parameters could give some light about which molecular moieties are most involved in the binding structure

This report summarizes our most recent findings in the click chemistry area aiming to search and develop new molecules with high SSRI activity; also the theoretical characterization of the obtained molecules was carried out.

2. Experimental Section

2.1. Synthesis. The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. Solvents were distilled before use. Silica plates of 0.20 mm thickness were used for thin layer chromatography. Melting points were determined with a Krüss Optronic melting point apparatus and they are uncorrected. ^1H and ^{13}C NMR spectra were recorded using a Bruker AVANCE 300; the chemical shifts (δ) are given in ppm relative to TMS as internal standard (0.00). For analytical purposes the mass spectra were recorded on a Shimadzu GCMS-QP2010 Plus in the EI mode, 70 eV, 200°C via direct inlet probe. Only the molecular and parent ions (m/z) are reported. IR spectra were recorded on a Bruker TENSOR 27 FT instrument.

2.1.1. 2-Chlorophenyl-methanol (4). A solution of 2-chlorobenzaldehyde (1.125 mL, 1.40 g, 10.03 mmol) in ethanol (15 mL) was added to a suspension of sodium borohydride (0.189 g, 4.97 mmol) in absolute ethanol (6 mL) maintaining the

temperature below 25°C. The resulting mixture was heated at 50°C during 1.5 h. The solvent was removed in vacuo, and water (20 mL) was added; the mixture was acidified with diluted HCl (10%) to pH = 5. The product was extracted with CH_2Cl_2 (3×15 mL), the organic phases were joined and dried over Na_2SO_4 , and the solvent was removed in vacuo to yield a white solid (1.27 g, 90%), which was used without additional purification, m.p. 50°C; ^1H NMR (300 MHz, CDCl_3) δ 7.49 (dd, $J = 7.3, 2.0$ Hz, 1H), 7.37 (dd, $J = 7.5, 1.8$ Hz, 1H), 7.32–7.20 (m, 2H), 4.79 (d, $J = 6.0$ Hz, 1H), 1.69 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.1, 131.6, 128.2, 127.7, 127.6, 125.9, 61.7; IR (ATR, cm^{-1}): 3302, 3216, 2912, 2859, 1439; MS [EI+] m/z (%): 142 [M] $^+$ (1), 107 [$\text{C}_7\text{H}_7\text{O}$] $^+$ (35), 77 [C_6H_5] $^+$ (100), 51 [C_4H_3] $^+$ (91).

2.1.2. 2-(2-Chloro-benzyloxymethyl)-oxirane (5). A mixture of 40% aqueous solution of NaOH (6.5 mL) (2-chlorophenyl)-methanol 4 (0.71 g, 5 mmol) and tetrabutylammonium iodide (0.09 g, 0.25 mmol) was vigorously stirred at room temperature for 24 h. The mixture was cooled to 0°C and epichlorohydrin (1.55 mL, 1.83 g, and 19.9 mmol) was added dropwise. After completion, the reaction mixture was stirred at 0°C for 30 minutes and at room temperature overnight. The mixture was poured into ice cold water (20 mL). The product was extracted with CH_2Cl_2 (3×15 mL), the organic phases were joined and dried over Na_2SO_4 , and the solvent was removed in vacuo to yield a pale yellow oil (1.27 g, 90%), which was used without additional purification; ^1H NMR (300 MHz, CDCl_3) δ 7.50 (dd, $J = 7.4, 2.1$ Hz, 1H), 7.35 (dd, $J = 7.4, 1.8$ Hz, 1H), 7.31–7.19 (m, 2H), 4.68 (d, $J = 3.9$ Hz, 2H), 3.49–3.87 (dd, $J = 11.4, 5.8$ Hz, 2H), 3.27–3.18 (m, 1H), 2.65–2.82 (dd, $J = 5.0, 2.7$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 135.4, 132.6, 129.0, 128.7, 128.5, 126.5, 71.1, 69.9, 50.5, 43.9; IR (ATR, cm^{-1}): 3061, 2998, 2923, 2864, 1250, 1096; MS [EI+] m/z (%): 198 [M] $^+$ (5), 56 [$\text{C}_3\text{H}_5\text{O}$] $^+$ (100). HRMS (EI): calcd. For $\text{C}_{10}\text{H}_{11}\text{ClO}_2$: 198.0448; found: 198.0442.

2.1.3. 1-Azido-3-(2-chloro-benzyloxy)-propan-2-ol (6). 2-(2-Chloro-benzyloxymethyl)-oxirane 5 (0.965 g, 4.86 mmol), NH_4Cl (0.529 g, 9.89 mmol), and NaN_3 (2.652 g, 40.8 mmol) were added successively to a mixture of MeOH (8 mL) and H_2O (1 mL) and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed in vacuo and the product was extracted with AcOEt (3×15 mL); the organic phases were joined and dried over Na_2SO_4 and the solvent was removed in vacuo to yield a pale yellow oil (1.2981 g, 74.12%), which was used without additional purification; ^1H NMR (300 MHz, CDCl_3) δ 7.40 (dd, $J = 7.2, 2.2$ Hz, 1H), 7.35–7.30 (m, 1H), 7.29–7.16 (m, 2H), 4.60 (s, 2H), 3.94 (ddd, $J = 10.8, 5.9, 4.9$ Hz, 2H), 3.54 (s, broad, 1H), 3.52–3.34 (ddd, $J = 5.4, 2.3, 1.3$ Hz, 2H), 3.22 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 135.3, 133.2, 129.4, 129.4, 129.1, 126.9, 71.85, 70.6, 69.6, 53.5; IR (ATR, cm^{-1}): 3426, 2097, 1092, 751; MS [EI+] m/z (%): 241 [M] $^+$ (5), 149 [$\text{M}-\text{C}_7\text{H}_6\text{ClO}$] $^+$ (100), 125 [$\text{M}-\text{C}_7\text{H}_6\text{Cl}$] $^+$ (90), 107 [$\text{M}-\text{C}_3\text{H}_6\text{N}_3\text{O}$] $^+$ (90), 89 [$\text{M}-\text{C}_2\text{H}_4\text{N}_3\text{O}$] $^+$ (60), 43 [$\text{M}-\text{N}_3$] $^+$ (65). HRMS (EI): calcd. For $\text{C}_{10}\text{H}_{12}\text{ClN}_3\text{O}_2$: 241.0618; found: 241.0622.

2.2. General Procedure for the Synthesis of 1-(2-Chlorobenzoyloxy)-3-[1,2,3]triazol-1-yl-propan-2-oles. The appropriate alkyne (1 mol) was added in one portion to a solution of 1-azido-3-(2-chloro-benzoyloxy)-propan-2-ol **6** (0.241 g, 1 mmol), CuI (0.009 g, 0.05 mmol), and DIPEA (0.17 mL, 0.129 g, 1 mmol) in CH₂Cl₂ (15 mL). The resulting mixture was stirred at room temperature for 24 h. An aqueous solution of 2% EDTA (30 mL) was added and the stirring was continued for additional 24 h. The product was extracted with CH₂Cl₂ (3 × 15 mL), the organic phases were joined and dried over Na₂SO₄, the solvent was removed in vacuo, and the final product was purified by crystallization.

2.2.1. 1-(2-Chlorobenzoyloxy)-3-(4-phenyl-[1,2,3]triazol-1-yl)-propan-2-ol (**7**). White solid; yield: 85%; mp 58°C; ¹H NMR (300 MHz, CDCl₃) δ 7.86 (s, 1H), 7.78–7.65 (m, 2H), 7.47–7.30 (m, 5H), 7.32 (s, 1H), 7.30–7.20 (m, 2H), 4.65 (s, 2H), 4.64–4.57 (m), 4.49 (dd, *J* = 8.7, 7.0 Hz, 1H), 4.48–4.36 (m, 1H), 3.59–3.52 (m, 1H), 3.44–3.37 (m, 1H), 2.62 (s, broad, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 135.3, 133.2, 129.4, 129.4, 129.1, 126.9, 71.8, 70.6, 69.6, 53.5; IR (ATR, cm⁻¹): 3227, 3061, 2866, 1440, 750; MS [EI+] *m/z* (%): 343 [M]⁺ (5), 125 [C₇H₆Cl]⁺ (100). HRMS (EI): calcd. For C₁₈H₁₈ClN₃O₂: 343.1088; found: 343.1091.

2.2.2. 1-(2-Chlorobenzoyloxy)-3-(4-*p*-tolylmethyl-[1,2,3]triazol-1-yl)-propan-2-ol (**8**). White solid; yield: 99%; mp 25°C; ¹H NMR (300 MHz, CDCl₃) δ 7.70 (s, 1H), 7.46 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.41 (dd, *J* = 3.8, 1.7 Hz, 1H), 7.27 (dd, *J* = 12.2, 1.8 Hz, 1H), 7.20–7.13 (m, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 2.3 Hz, 1H), 6.83 (d, *J* = 2.1 Hz, 1H), 5.08 (s, 2H), 4.57 (s, 2H), 4.52–4.36 (dddd, *J* = 13.9, 14.0, 3.8, 7.1 Hz, 2H), 4.20 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.53–3.46 (ddd, *J* = 9.7, 5.4, 4.9 Hz, 2H), 2.49 (s, broad, 1H), 2.25 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 155.1, 143.0, 134.7, 134.2, 132.3, 129.5, 128.5, 127.9, 125.8, 123.4, 113.8, 70.6, 69.5, 68.1, 60.93, 52.1, 19.5; IR (ATR, cm⁻¹): 3312, 2925, 2860, 1269, 1120; MS [EI+] *m/z* (%): 387 [M]⁺ (5), 125 [C₇H₆Cl]⁺ (100). HRMS (EI): calcd. For C₂₀H₂₂ClN₃O₃: 387.1350; found: 387.1351.

2.2.3. 1-(2-Chlorobenzoyloxy)-3-[4-(4-methoxy-phenoxy)methyl-[1,2,3]triazol-1-yl]-propan-2-ol (**9**). White solid; yield: 46%; mp 76°C; ¹H NMR (300 MHz, CDCl₃) δ 7.78 (s, 1H), 7.75–7.68 (m, 2H), 7.39 (dd, *J* = 10.7, 4.2 Hz, 2H), 7.31–7.20 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 4.65 (s, 1H), 4.60–4.46 (dddd, *J* = 14.2, 3.6, 14.0, 6.8 Hz, 2H), 4.36–4.26 (m, 1H), 3.84 (s, 3H), 3.63–3.53 (ddd, *J* = 9.8, 4.9, 9.7, 5.7 Hz, 2H), 2.04 (s, broad, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 159.6, 147.5, 135.0, 133.5 de C3, 129.6, 129.6, 129.3, 126.9, 126.9, 126.9, 120.4, 114.2, 71.3, 70.8, 69.3, 55.3, 52.9; IR (ATR, cm⁻¹): 3256, 3141, 2958, 2924, 2854, 1360, 1249; MS [EI+] *m/z* (%): 403 [M]⁺ (28), 125 [C₇H₆Cl]⁺ (100).

2.2.4. 1-(2-Chlorobenzoyloxy)-3-(4-*p*-tolyl-[1,2,3]triazol-1-yl)-propan-2-ol (**10**). White solid; yield: 51%; mp 120°C; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (s, 1H), 7.64–7.55 (m, 2H), 7.42 (dd, *J* = 6.4, 2.9 Hz, 1H), 7.29–7.14 (m, 5H), 4.64 (s, 2H), 4.58–4.45 (dddd, *J* = 14.0, 7.2, 3.8, 4.8 Hz, 2H), 4.44–4.38 (m, 1H), 3.61–3.57 (m, 2H), 2.36 (s, 3H), 1.26 (s, broad, 1H); ¹³C

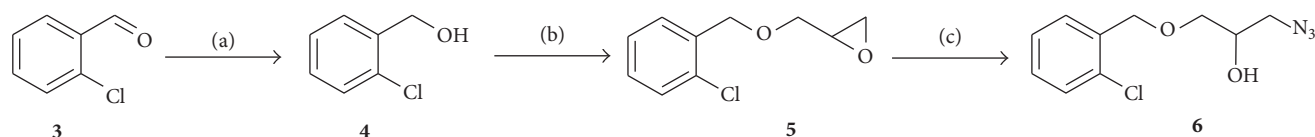
NMR (75 MHz, CDCl₃) δ 155.1, 143.0, 134.7, 134.22, 132.3, 129.5, 128.5, 128.8, 127.9, 125.8, 123.4, 113.8, 70.6, 69.5, 68.1, 60.9, 52.1, 19.5; IR (ATR, cm⁻¹): 3392, 2918, 2865, 1442, 1107; MS [EI+] *m/z* (%): 357 [M]⁺ (5), 125 [C₇H₆Cl]⁺ (100). HRMS (EI): calcd. For C₁₉H₂₀ClN₃O₂: 357.1244; found: 357.1247.

2.2.5. 2-[1-[3-(2-Chlorobenzoyloxy)-2-hydroxy-propyl]-1H-[1,2,3]triazol-4-ylmethyl]-2-methyl-cyclopentane-1,3-dione (**11**). Colorless oil; yield: 66%; ¹H NMR (300 MHz, CDCl₃) δ 7.44 (s, 1H), 7.48–7.41 (m, 1H), 7.36–7.31 (m, 1H), 7.26–7.19 (m, 2H), 4.60 (s, 2H), 4.46–4.29 (dddd, *J* = 14.0, 13.9, 7.3, 3.6 Hz, 2H), 4.14 (dq, *J* = 9.4, 5.3 Hz, 1H), 3.50 (d, *J* = 5.2 Hz, 2H), 3.05 (s, 2H), 2.80 (d, *J* = 3.2 Hz, 4H), 2.01 (s, broad, 1H), 1.17 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 212.2, 202.7, 137.5, 130.5, 128.0, 124.5, 124.4, 124.1, 122.02, 118.20, 66.9, 65.6, 64.1, 50.3, 48.1, 30.1, 26.0, 25.9, 25.3; IR (ATR, cm⁻¹): 3304, 2925, 2869, 1442, 1361, 1219; MS [EI+] *m/z* (%): 391 [M]⁺ (10), 125 [C₇H₆Cl]⁺ (100). HRMS (EI): calcd. For C₁₉H₂₂ClN₃O₄: 391.1299; found: 391.1303.

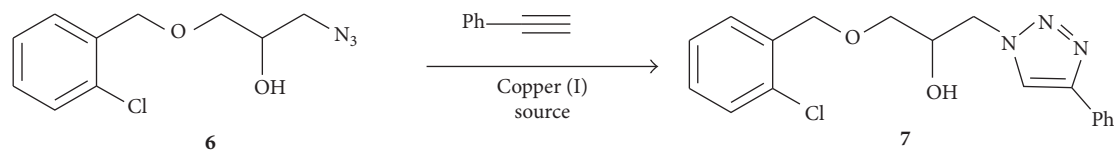
2.2.6. 3-[1-[3-(2-Chlorobenzoyloxy)-2-hydroxy-propyl]-[1,2,3]triazol-4-yl]-propan-1-ol (**12**). Colorless oil; yield: 84%; ¹H NMR (300 MHz, CDCl₃) δ 7.44 (s, 1H), 7.43–7.35 (m, 1H), 7.30–7.21 (m, 3H), 4.78 (s, broad, 1H), 4.64 (s, 2H), 4.53–4.38 (dddd, *J* = 14.0, 14.0, 7.1, 3.6 Hz), 4.28–4.20 (m, 1H), 3.66 (t, *J* = 6.4 Hz, 2H), 3.58–3.51 (dddd, *J* = 9.7, 9.7, 5.5, 5.0 Hz, 2H), 2.79 (t, *J* = 7.4 Hz, 2H), 2.17 (s, broad, 1H), 1.89 (p, *J* = 6.6 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 147.0, 134.8, 133.1, 129.3, 129.2, 126.6, 122.3, 71.2, 70.5, 68.8, 61.3, 52.6, 31.5, 21.7; IR (ATR, cm⁻¹): 3487, 2912, 2862, 1716, 1446, 1219; MS [EI+] *m/z* (%): 325 [M]⁺ (10), 126 [C₅H₈N₃O]⁺ (100). HRMS (EI): calcd. For C₁₅H₂₀ClN₃O₃: 325.1193; found: 325.1195.

2.2.7. 1-(2-Chlorobenzoyloxy)-3-[4-(4-nitro-phenoxy)methyl]-[1,2,3]triazol-1-yl]-propan-2-ol (**13**). White solid; yield: 55%; mp 85°C; ¹H NMR (300 MHz, CDCl₃) δ 8.20 (d, *J* = 8.2 Hz, 2H), 8.17 (d, *J* = 2.1 Hz, 2H), 7.81 (s, 1H), 7.43–7.23 (m, 4H), 7.08 (m, 2H), 4.63 (d, *J* = 1.1 Hz, 2H), 4.62 (dddd, *J* = 14.1, 14.0 7.1, 4.6 Hz, 2H), 4.30 (m, 1H), 3.64–3.49 (dddd, *J* = 9.7, 9.7, 5.0, 4.7 Hz, 2H), 2.16 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 162.7, 142.1, 141.4, 134.6, 132.9, 129.2, 129.2, 128.9, 126.5, 125.5, 124.4, 114.5, 71.0, 70.4, 68.75, 52.7; IR (ATR, cm⁻¹): 3253, 2878, 2856, 1336; MS [EI+] *m/z* (%): 418 [M]⁺ (5), 125 [C₇H₆Cl]⁺ (100). HRMS (EI): calcd. For C₁₉H₁₉ClN₄O₅: 418.1044; found: 418.1048.

2.2.8. 1-(2-Chlorobenzoyloxy)-3-[4-(4-chlorophenoxy)methyl]-[1,2,3]triazol-1-yl]-propan-2-ol (**14**). White solid; yield: 89%; mp 67–68°C; ¹H NMR (300 MHz, CDCl₃) δ 7.73 (s, 1H), 7.41 (dd, *J* = 9.6, 4.8 Hz, 1H), 7.30–7.20 (m, 5H), 6.94–6.89 (m, 2H), 5.16 (s, 2H), 4.63 (s, 2H), 4.60–4.40 (m, 2H), 4.29 (dd, *J* = 4.5, 3.7 Hz, 1H), 3.62–3.46 (m, 2H), 2.95 (s, broad, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 156.1, 143.0, 134.3, 132.8, 128.9, 128.9, 128.8, 128.7, 128.7, 126.2, 123.6, 115.4, 70.5, 70.1, 68.5, 61.5, 52.2; IR (ATR, cm⁻¹): 3168, 2921, 2869, 1489, 1237; MS [EI+] *m/z* (%): 407 [M]⁺ (2), 185 [C₉H₁₀ClO]⁺ (80), 127 [C₆H₄ClO]⁺ (100). HRMS (EI): calcd. For C₁₉H₁₉Cl₂N₃O₃: 407.0803; found: 407.0808.



SCHEME 2: Reagents and conditions: (a) NaBH_4 and MeOH. (b) Epichlorohydrin, NaOH, and $N\text{-Bu}_4\text{NBr}$. (c) NaN_3 , NH_4Cl , and MeOH- H_2O .



SCHEME 3: Reaction of azido alcohol **6** with phenylacetylene.

2.2.9. *1-(2-Chlorobenzoyloxy)-3-[4-(6-methoxynaphthalen-2-yl)-[1,2,3]triazol-1-yl]-propan-2-ol (15)*. White solid; yield: 94%; mp 100°C ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.10 (s, 1H), 7.90 (s, 1H), 7.79 (dt, $J = 8.5, 1.8$ Hz, 1H), 7.72 (s, 1H), 7.68 (dd, $J = 8.8, 1.8$ Hz, 1H), 7.40 (dd, $J = 17.1, 9.3$ Hz), 7.29–7.20 (m, 3H), 7.16–7.09 (m, 2H), 4.66 (s, 2H), 4.60–4.46 (ddd, $J = 3.5, 13.9, 6.7$ Hz, 2H), 4.36 (s, 1H), 3.92 (s, 3H), 3.65–3.57 (dddd, $J = 9.7, 4.9, 9.7, 5.5$ Hz, 2H), 2.16 (s, broad, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 157.9, 147.6, 135.1, 134.3, 133.4, 129.7, 129.6, 129.5, 129.2, 128.8, 127.3, 126.9, 125.5, 124.9, 121.2, 119.2, 105.7, 71.5, 70.8, 69.2, 55.3, 53.3; IR (ATR, cm^{-1}): 3391, 3131, 2921, 2852, 1606, 1216; MS [EI+] m/z (%): 423 [M]⁺ (10), 226 [$\text{C}_{13}\text{H}_{10}\text{N}_3\text{O}$]⁺ (80), 185 [$\text{C}_9\text{H}_{10}\text{ClO}$]⁺ (35), 125 [$\text{C}_7\text{H}_6\text{Cl}$]⁺ (100). HRMS (EI): calcd. For $\text{C}_{23}\text{H}_{22}\text{ClN}_3\text{O}_3$: 423.1350; found: 423.1356.

2.2.10. *1-(2-Chlorobenzoyloxy)-3-[4-(4-fluorophenyl)-[1,2,3]triazol-1-yl]-propan-2-ol (16)*. Colorless oil; yield: 66%; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.82 (s, 1H), 7.77–7.70 (m, 2H), 7.53 (dd, $J = 5.7, 3.3$ Hz, 1H), 7.38 (td, $J = 7.4, 2.2$ Hz, 1H), 7.26 (ddt, $J = 7.6, 2.2, 1.1$ Hz, 1H), 7.30–7.21 (m, 2H), 7.09 (t, $J = 7.4$ Hz, 1H), 4.65 (d, $J = 0.8$ Hz, 2H), 4.61–4.46 (dd, $J = 14.0, 7.0$ Hz, 2H), 4.31 (p, $J = 5.2$ Hz, 1H), 3.64–3.54 (dd, $J = 9.7, 5.7$ Hz, 2H), 2.17 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 164.1, 160.8, 146.5, 134.8, 133.2, 129.5, 129.4, 129.1, 127.2, 127.1, 126.7, 126.4, 120.8, 115.7, 115.5, 71.2, 70.6, 69.0, 52.9; IR (ATR, cm^{-1}): 3365, 2922, 2864, 1497, 1224; MS [EI+] m/z (%): 361 [M]⁺ (25), 164 [$\text{C}_8\text{H}_7\text{FN}_3$]⁺ (100). HRMS (EI): calcd. For $\text{C}_{18}\text{H}_{17}\text{ClFN}_3\text{O}_2$: 361.0993; found: 361.0997.

2.2.11. *1-(2-Chlorobenzoyloxy)-3-[4-(2,4-difluorophenyl)-[1,2,3]triazol-1-yl]-propan-2-ol (17)*. White solid; yield: 67%; mp 77°C ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.31–8.15 (m, 1H), 8.00 (s, 1H), 7.47–7.33 (m, 2H), 7.26 (dd, $J = 5.9, 3.5$ Hz, 2H), 6.99 (td, $J = 8.4, 2.6$ Hz, 1H), 6.88 (ddd, $J = 11.1, 8.9, 2.6$ Hz, 1H), 4.66 (s, 2H), 4.61–4.49 (ddd, $J = 14.1, 6.9, 3.7$ Hz, 2H), 4.37–4.27 (m, 1H), 3.65–3.55 (dddd, $J = 9.7, 9.6, 5.6, 4.6$ Hz, 2H), 1.65 (s, broad, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 163.4, 160.1, 139.6, 134.9, 134.3, 132.6, 128.8, 128.5, 126.1, 123.21, 114.2, 111.1, 103.6, 70.74, 70.1, 68.5, 52.4; IR (ATR, cm^{-1}): 3194, 3151, 2908, 1361; MS [EI+] m/z (%): 379 [M]⁺ (10), 239 [$\text{C}_{10}\text{H}_{11}\text{F}_2\text{N}_3\text{O}$]⁺ (100). HRMS (EI): calcd. For $\text{C}_{18}\text{H}_{16}\text{ClF}_2\text{N}_3\text{O}_2$: 379.0889; found: 379.0891.

2.2.12. *1-(2-Chlorobenzoyloxy)-3-[4-(2-trifluoromethylphenyl)-[1,2,3]triazol-1-yl]-propan-2-ol (18)*. Colorless oil; yield: 68%; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.91 (s, 1H), 7.90 (d, $J = 6.9$ Hz, 1H), 7.73 (dd, $J = 8.0, 1.4$ Hz, 1H), 7.47 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.42 (ddd, $J = 6.9, 3.7, 1.6$ Hz, 1H), 7.37–7.32 (m, 1H), 7.23 (td, $J = 6.5, 5.7, 3.7$ Hz, 2H), 4.63 (d, $J = 1.2$ Hz, 2H), 4.63–4.50 (dddd, $J = 14.1, 14.0, 6.8, 3.9$ Hz, 2H), 4.30 (dq, $J = 9.8, 5.3$ Hz, 1H), 3.60–3.51 (dddd, $J = 9.8, 9.7, 5.6, 4.9$ Hz, 2H), 1.26 (s, broad, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 163.4, 160.1, 139.6, 134.9, 134.3, 132.6, 128.8, 128.5, 126.1, 123.21, 114.2, 111.1, 103.6, 70.74, 70.1, 68.5, 52.4; IR (ATR, cm^{-1}): 3344, 1354, 1168.86, 1107; MS [EI+] m/z (%): 411 [M]⁺ (5), 125 [$\text{C}_7\text{H}_6\text{Cl}$]⁺ (100). HRMS (EI): calcd. For $\text{C}_{19}\text{H}_{17}\text{ClF}_3\text{N}_3\text{O}_2$: 411.0961; found: 411.0965.

2.3. *Theoretical Calculations*. All the electronic structure computations were carried out with NWChem package [14]. A frequency analysis was applied to the optimized geometries to verify the corresponding stability criterion. The PBEPBE [15] exchange and correlation functional was used with the 6-311+g** Pople's basis set. All the reactivity parameters were computed from a finite differences approach.

3. Results and Discussion

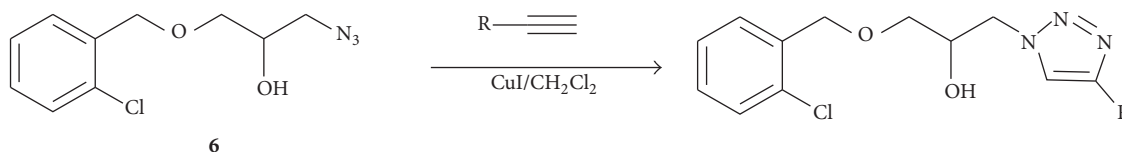
3.1. *Chemistry*. The first experiments were carried out with the objective to prepare 1-azido-3-(2-chloro-benzyl-oxo)-propan-2-ol, **6** (Scheme 2). Initially, 2-chlorophenyl methanol **4** prepared from reduction of 4-chlorobenzaldehyde **3** was reacted with epichlorohydrin to give the aryl epoxide **5** [9, 15] which was opened with sodium azide to afford azido alcohol **6** in a 62% global yield from 4-chlorobenzaldehyde **3**.

Azido alcohol **6** was the starting material for the following CuAAC experiments. In a model reaction, compound **6** was treated with phenylacetylene in presence of diverse Cu(I) catalytic sources according to that described by Rostovtsev et al. [16], Tornøe et al. [17] and our group [18, 19] (Scheme 3), obtaining compound **7** as only reaction product. From these experiments presented in Table 1, we selected CuI-DIPEA for CuAAC reaction because a best yield (85%) was reached using this catalytic system.

Taking these optimized conditions, a synthetic procedure was developed and a series of (2-chlorobenzoyloxy)-1,2,3-triazolyl-propan-2-ol derivatives was prepared from azido

TABLE 1: Effect of catalyst, reducing agent, base, and solvent.

Entry	Copper salt	Reducing agent	Base	Solvent	% yield
7	CuSO ₄	Glucose	NaOH	MeOH-H ₂ O	34
8	CuSO ₄	Sodium ascorbate	none	tBuOH-H ₂ O	28
9	CuI	None	NaOH	MeOH-H ₂ O	40
10	CuI	None	DIPEA	MeOH	35
11	CuI	None	DIPEA	CH ₂ Cl ₂	85



SCHEME 4

TABLE 2: 1,2,3-Triazoles prepared via CuAAC.

Compound	R ¹	% yield
7	Ph	85
8	CH ₂ O(4-CH ₃)C ₆ H ₄	99
9	CH ₂ O(4-OCH ₃)C ₆ H ₄	46
10	4-CH ₃ C ₆ H ₄	51
11		66
12	(CH ₂) ₃ OH	84
13	CH ₂ O(4-NO ₂)C ₆ H ₄	55
14	CH ₂ O(4-Cl)C ₆ H ₄	89
15		94
16	4-FC ₆ H ₄	66
17	2,4-FC ₆ H ₃	67
18	2-CF ₃ C ₆ H ₄	68

alcohol **6** with different alkynes. The results in Table 2 show that this process occurs with high efficiency and functional group tolerance; see Scheme 4.

3.2. DFT Characterization. In order to compare triazoles **7–18** with compound **1** and to establish possible SSRI candidates, a theoretical study was carried out. The global reactivity indexes of studied compounds are presented in Table 3, electronic affinity (*A*), ionization potential (*I*), chemical potential (μ), chemical softness (*S*), and electrophilicity (ω). The obtained results are gathered in Table 3.

Ionization potential (*I*) is defined as the energy needed to remove an electron from a molecule. According to obtained

results, the molecule **12** showed the highest ionization potential value, and the molecule **15** has the closest value to **1**, showing that electron-rich aromatic rings are necessary to mimic the properties of molecule **1**. On the other hand, the presence of electron attracting groups in the aromatics increases the value of *I*; the aliphatic moieties have the same effect.

Electron affinity (EA) measures the ability of a molecule to accept electrons and form anions. There are some EA negative in the obtained values, because the molecules released energy in the process of electron acceptance. In a general view, only the half of the molecules has positive EA values like one. Nevertheless, the computed values are different compared with **1**, with the molecules **16** with a behavior closest to **1**.

Chemical potential (μ) measures the escaping tendency of an electronic cloud in the ground state system. The obtained results shown that molecule **1** has higher value (less negative) than synthesized triazolyl derivatives, making compound **1** a better electron donor than obtained compounds. Nevertheless, almost all the compounds have pretty close values to **1**, except for compound **7** and in minor degree **12**.

Chemical softness (*S*) is related to polarizability. The values *S* for compounds **14** and **18** are remarkably close to the value of compound **1**, suggesting a similar facility to charge transfer; other compounds with similar values are **15–17**, respectively. As matter of fact, the trifluorobenzyl group in compound **18** shows similar characteristics to indolyl moiety in compound **1**.

Electrophilicity (ω) gives an idea of the stabilization energy when the system acquires electrons from the environment up to saturation. Since the electrophilicity power is computed through ($\mu^2/2\eta$), the differences in electrophilicity power (ω) between the compounds are mainly due to differences in their chemical potential. In this regard, the results suggest that triazole moiety is a better nucleophile for compounds **7–18** than tetrahydropyridine system in compound **1**. In a general way all the parameters obtained by DFT calculations show the necessity of having an electron-rich aromatic bond to mimic the indolyl moiety in compound **1**.

TABLE 3: Global reactivity indexes in eV.

	A	I	μ	S	ω
1	0.113	6.546	-3.216	0.155	0.804
7	-1.042	7.717	-8.879	0.056	2.219
8	-0.162	7.593	-3.878	0.128	0.969
9	-0.129	7.250	-3.689	0.135	0.922
10	-0.105	7.510	-3.808	0.131	0.952
12	-0.158	8.362	-4.260	0.117	1.065
13	0.911	8.253	-3.671	0.136	0.917
14	0.347	7.312	-3.482	0.143	0.870
15	0.526	6.619	-3.044	0.164	0.761
16	0.271	7.397	-3.562	0.140	0.890
17	0.371	7.537	-3.583	0.139	0.895
18	0.568	7.688	-3.559	0.140	0.889

$$\mu = 1/2(\varepsilon_I + \varepsilon_A); \eta = \varepsilon_A - \varepsilon_I; S = 1/; \omega = \mu^2/2\eta.$$

TABLE 4: Local reactivity indexes for selected atoms.

Compound		f^+	f^-	s^+	s^-
7	N1	0.01	0.04	0.01	0.06
	N2	0.02	0.08	0.03	0.12
	N3	0.02	0.04	0.03	0.06
8	N1	0.00	0.02	0.00	0.07
	N2	0.01	0.03	0.03	0.10
	N3	0.02	0.01	0.07	0.03
9	N1	0.00	0.04	0.00	0.14
	N2	0.02	0.08	0.07	0.29
	N3	0.01	0.04	0.03	0.14
10	N1	0.01	0.04	0.03	0.14
	N2	0.02	0.08	0.07	0.28
	N3	0.02	0.03	0.07	0.10
12	N1	0.00	0.03	0.00	0.11
	N2	0.01	0.10	0.03	0.37
	N3	0.01	0.04	0.03	0.14
13	N1	0.01	0.03	0.04	0.12
	N2	0.02	0.06	0.08	0.23
	N3	0.00	0.03	0.00	0.12
14	N1	0.02	0.01	0.08	0.13
	N2	0.05	0.03	0.22	0.27
	N3	0.03	0.02	0.13	0.13
15	N1	0.01	0.03	0.04	0.11
	N2	0.03	0.05	0.11	0.19
	N3	0.02	0.03	0.07	0.11
16	N1	0.02	0.02	0.07	0.07
	N2	0.02	0.03	0.07	0.11
	N3	0.03	0.04	0.11	0.15
17	N1	0.00	0.04	0.00	0.15
	N2	0.02	0.07	0.07	0.27
	N3	0.02	0.04	0.07	0.17
18	N1	0.02	0.02	0.08	0.08
	N2	0.02	0.04	0.08	0.16
	N3	0.03	0.03	0.12	0.12

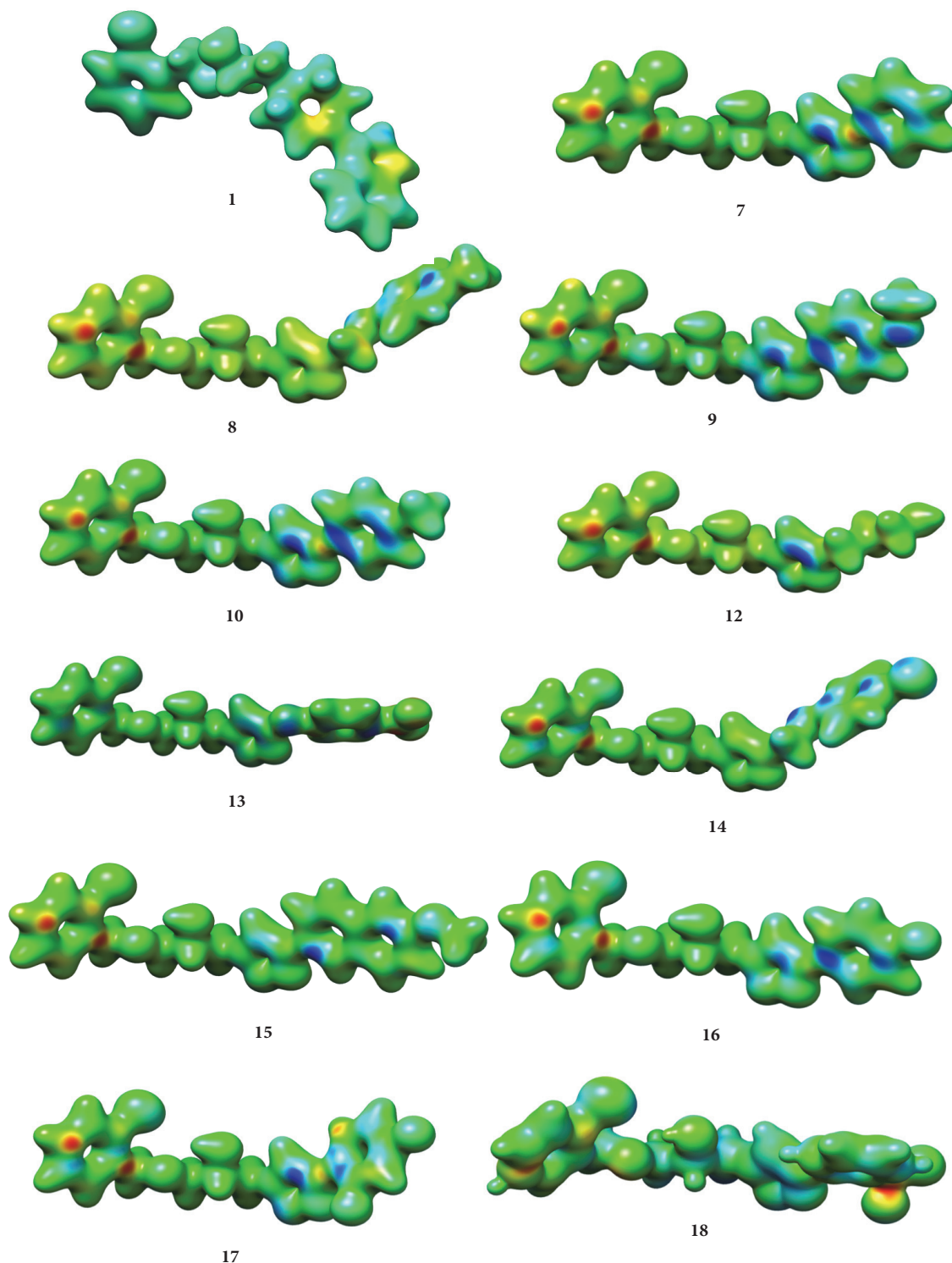


FIGURE 1: Dual descriptor f^{\pm} for the molecules studied in this work.

The local properties of synthesized compounds are hard to analyze due to the diverse nature of substituent groups used in this study. For this reason, the three nitrogen atoms in triazole ring were used as a probe for the local properties in the prepared molecules. As shown in Table 4, the highest values of f^- can be observed for N2 atom in all molecules,

indicating that this atom is the most susceptible to a nucleophilic attack. In addition, a visible tendency for the case of f^+ was not found. The local softness (s) followed the same tendencies as Fukui functions; nevertheless, this function could be comparable between molecules, being higher in compounds 14–18 on N2 atom.

Other important index is known as dual descriptor f^\pm which contains information about the chemical philicity (electrophilicity/nucleophilicity). In this case, the graphic maps are generally sufficient for rationalizing the chemical reactivity. The maps of dual descriptor for the set of molecules studied in this work are represented in Figure 1, displaying the most probable sites for a possible nucleophilic-electrophilic attack. In a general way, the most electrophilic sites are found on the chlorobenzyl moiety, while the most nucleophilic sites are located on the opposite side of the molecule independent of the electronic nature of substituent group. These elements reveal some similarities between compound **1** and synthesized compounds with nearest values for compounds **14–18**. The calculated parameters also allow establishing interaction sites in these molecules.

4. Conclusions

A new class of derivatives of chlorobenzoyloxy triazolylpropan-2-ol was obtained from CuAAC reaction using commercially available raw materials through simple and efficient methods. Theoretical calculations indicate that a high similarity can be found between these products and the leading molecule **1**; consequently, a good SSRI ability would be expected for these compounds, suggesting more studies about this topic. Also, DFT descriptors show that the presence of an electron-rich aromatic ring is necessary to mimic the indolyl moiety present in compound **1**.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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