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REGULAR ARTICLE

Synthesis and in-vitro biological evaluation of 1,1-diaryl-2-(1,2,3)triazol-1-yl-ethanol derivatives as antifungal compounds flutriafol analogues

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Abstract. A small library of diverse 1,1-diaryl-2-(1,2,3)triazol-1-yl-ethanol derivatives was designed and prepared from CuAAC reaction as the key step. The molecular structure of some representative compounds was unambiguously determined from X-ray diffraction studies. In addition, synthesized 1,2,3-triazoles were evaluated for activity against filamentous fungi (*Mucor hiemalis*, *Aspergillus fumigatus*, *Trichosporon cutaneum*, and *Rhizopus oryzae*) and yeasts that belong to the genus Candida. Two compounds showed high activity against *C. utilis* (MIC 0.5 μg/mL) and A. fumigatus (MIC 4 μg/mL) which is close to itraconazole used as reference compound.

Keywords. 1, 2, 3-Triazoles; antifungal; flutriafol analogues.

1. Introduction

Flutriafol, 1-(4-Fluorophenyl)-1-(2-fluorophenyl)-2-[1,2,4]triazol-1-yl-ethanol (**1**), belongs to azole group of antifungal drugs, a group of medicines with a relatively broad spectrum used for the control of fungal diseases.[1,2] Flutriafol is one of the most active fungicides which are currently used for crop control on fruits, vegetables, and cereals.[3] An outstanding characteristic is that this molecule was designed by computer to better match the action site by inhibiting the C-14α-demethylase enzyme involved in the biosynthesis of fungal sterols.[4,5] However, Flutriafol represents a potentially dangerous pollution problem as a result of its persistence in soil and latent presence in groundwater.[6–9]

These elements encouraged us to initiate an investigation aimed to develop compounds similar to Flutriafol with high antifungal activity but low environmental impact. In this regard, copper-catalyzed azide-alkyne cycloaddition (CuAAC), the most widely used click reaction,[10–12] plays a prominent role in search and discovery of new drugs through modular preparation of libraries of molecules with diverse purposes. In this reaction, the formation of 1,2,3-triazol as assembly element is fundamental because the heterocycle generation is concomitant with the linkage process. Moreover, 1,2,3-triazoles are among the most common amide bond isosteres, as well as olefins rigid analogs and other heterocycles isosteres, with the additional advantage of marked stability under hydrolytic, oxidative, and reductive conditions. Hence, as 1,2,3-triazoles are recognized as important scaffolds in different compounds with widespread applications as antimicrobial, antiviral, and antitumor drugs, we considered that 1,2,3-triazoles are ideal structures to design a new synthetic strategy which would allow the preparation of Flutriafol derivatives (**2**) by changing the 1,2,4-triazole by 1,2,3-triazole

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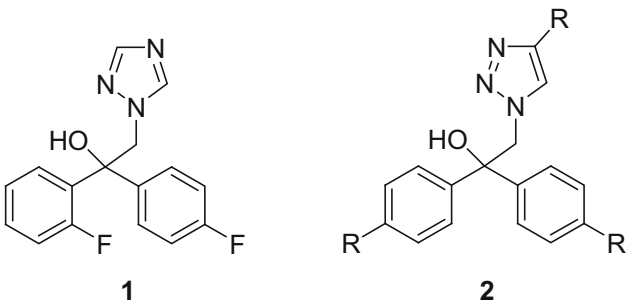


Scheme 1. Structure of Flutriafol (**1**) and general structure for molecules **2** proposed in this work.

moiety through CuAAC reaction. Herein is described a summary of our recent successful endeavours in this area (Scheme 1).

2. Experimental

2.1 *General remarks*

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. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance 300 MHz, and a Varian 500 MHz; 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* a direct inlet probe. Only the molecular and parent ions (m/z) are reported. IR spectra were recorded on a Bruker TENSOR 27 FT instrument.

For the X-ray diffraction studies, crystals of compounds **4**–**8** and **13** were obtained by slow evaporation of a dilute MeOH solution, and the reflections were acquired with a Bruker APEX DUO diffractometer equipped with an Apex II CCD detector. Three standard reflections every 97 reflections were used to monitor the crystal stability. The structures were solved by direct methods; missing atoms were found by difference-Fourier synthesis, and refined on F2 by a full-matrix least-squares procedure using anisotropic displacement parameters using SHELX-97. Crystallographic data for the structures reported herein have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 1863382 for compound **4**, No. 1863383 for compound **5**, No. 1863384 for compound **6**, No. 1863385 for compound **7**, No. 1863386 for compound **8** and No. 1863387 for compound **13**). Copies of available materials can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (facsimile: (44) 01223 336033); e-mail: deposit@ccdc.ac.uk.

2.2 *Synthesis of 2-(2-Chloro-5-nitrophenyl)-2-phenyloxirane (**4**)*

Trimethylsulfonium iodide (2.04 g, 10 mmol) and crushed KOH (1.7 g, 30 mmol) were successively added portionwise to a solution of (2-chloro-5-nitrophenyl) (phenyl) methanone **3** (1.30 g, 5 mmol) in *t*-BuOH (12.5 mL) at 30 °C. The resulting mixture was stirred at 40–50 °C for 11 h. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The resulting mixture was treated with H_2O (90 mL) and a 5% NaClO solution (12 mL). The product was extracted with ether (3 × 15 mL), the organic phases were joined and dried over Na_2SO_4 and the solvent was removed *in vacuo*. Crystallization afforded compound **4** (EtOH) as white solid (1.2 g, 92%), M.p. 160 °C. IR (ATR, ν_{max} cm^{-1}): 3096, 2915, 1517, 1343, 700. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (d, J = 2.7 Hz, 1H), 8.18 (dd, J = 8.8, 2.7 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.36–7.15 (m, 5H), 3.44 (d, J = 5.1 Hz, 1H), 3.31 (d, J = 5.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.7, 140.8, 139.5, 137.1, 130.6, 128.6, 128.5, 126.2, 125.5, 124.3, 60.1, 57.0. MS [EI+] m/z (%): 275 $[M]^+$ (20), 163 $[C_8H_5NO_3]^+$ (100), 199 $[C_8H_5NO_3]^+$ (68), 210 $[C_{13}H_8NO_2]^+$ (40). HRMS (EI): calcd. for $C_{14}H_{10}ClNO_3$: 275.0349; found: 275.0351.

2.3 *Synthesis of 2-Azido-1-(2-chloro-5-nitrophenyl)-1-phenylethanol (**5**)*

Compound **4** (1.45 g, 5.3 mmol) was added to a solution of NH_4Cl (1.2 g, 22.6 mmol) and NaN_3 (2.8 g, 43.07 mmol) in MeOH (8 mL) and H_2O (2 mL). The resulting mixture was heated at reflux temperature during 12 h. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. 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*. Purification by column chromatography (SiO_2, hexane/AcOEt 95:5) afforded 2-Azido-1-(2-chloro-5-nitro-phenyl)-1-phenyl-ethanol **5** as white solid (1.29 g, 77%), M.p. 124 °C. IR (ATR, ν_{max} cm^{-1}): 3565, 2864, 2099, 1515, 1344, 698. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (d, J = 2.7 Hz, 1H), 8.16 (dd, J = 8.7, 2.7 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.41–7.15 (m, 5H), 4.32–4.02 (m, 2H), 3.44 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.6, 142.48, 141.62, 139.2, 132.4, 128.7, 128.5, 126.1, 124.3, 124.1, 78.8, 58.1. MS [EI+] m/z(%): 318 $[M]^+$ (10), 241 $[M - C_6H_5]^+$ (100). HRMS (EI): calcd. for $C_{14}H_{11}ClN_4O_3$: 318.0520; found: 318.0527.

2.4 *General procedure for the synthesis of 1,1-diaryl-2-(1,2,3)triazol-1-yl-ethanol derivatives*

The appropriate alkyne (1 mol) was added in one portion to a solution of 2-azido-1-(2-chloro-5-nitrophenyl)-1-phenylethanol **5** (0.1g, .314 mmol), CuI (0.005 g, 0.02 mmol) and DIPEA (0.17 mL, 0.129 g, 1 mmol) in CH_2Cl_2 (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 an additional 24 h. The product was extracted with CH_2Cl_2 (3 × 15 mL), the organic phases were joined and dried over Na_2SO_4, the solvent was removed *in vacuo* and the final product was purified by crystallization.

1-(2-chloro-5-nitrophenyl)-1-phenyl-2-(4-phenyl-1,2,3-triazol-1-yl)ethanol (***6***). 2-azido-1-(2-chloro-5-nitrophenyl)-1-phenylethanol **5** and phenylacetylene afforded 1-(2-chloro-5-nitrophenyl)-1-phenyl-2-(4-phenyl-1,2,3-triazol-1-yl)ethanol **6** as white solid (85%), M.p. 160 °C. IR (ATR, ν_{max} cm^{-1}): 3296, 2973, 2866, 1528, 1343, 694. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.72 (d, J = 2.8 Hz, 1H), 8.01 (dd, J = 8.7, 2.7 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.67 (d, J = 4.2 Hz, 1H), 7.65 (s, 1H), 7.44–7.26 (m, 9H), 5.88 (d, J = 13.9 Hz, 1H), 5.23 (d, J = 13.8 Hz, 1H), 1.93 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.3, 146.4, 141.9, 141.5, 138.9, 132.1, 130.3, 128.7, 128.5, 128.1, 126.4, 125.7, 124.1, 124.1, 121.6, 77.1, 56.0. MS [EI+] m/z (%): 420 $[M]^+$ (10), 77 $[M\text{-}C_6H_5]^+$ (100). HRMS (EI): calcd. for $C_{22}H_{17}ClN_4O_3$: 420.0989; found: 420.0992.

1-(2-chloro-5-nitrophenyl)-1-phenyl-2-(4-p-tolyl-1,2,3-triazol-1-yl)ethanol (***7***). 2-azido-1-(2-chloro-5-nitrophenyl)-1-phenylethanol **5** and 1-ethynyl-4-methyl-benzene afforded 1-(2-chloro-5-nitrophenyl)-1-phenyl-2-(4-p-tolyl-1,2,3-triazol-1-yl)ethanol **7** as white solid (82%), M.p. 178 °C. IR (ATR, ν_{max} cm^{-1}): 3169, 2923, 2854, 1525, 1340, 698. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (d, J = 2.6 Hz, 1H), 8.10–7.92 (m, 2H), 7.77–7.12 (m, 10H), 6.69 (d, J = 2.4 Hz, 1H), 5.95 (d, J = 13.7 Hz, 1H), 5.29 (d, J = 13.8 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.0, 146.3, 142.6, 142.5, 139.2, 137.8, 132.0, 129.5, 128.6, 128.3, 128.0, 126.9, 125.6, 124.2, 124.0, 121.8, 76.4, 55.7, 21.4. MS [EI+] m/z (%):434 $[M]^+$ (10), 115 $[M\text{-}C_9H_8]^+$ (100). HRMS (EI): calcd. for $C_{23}H_{19}ClN_4O_3$: 434.1146; found: 434.1157.

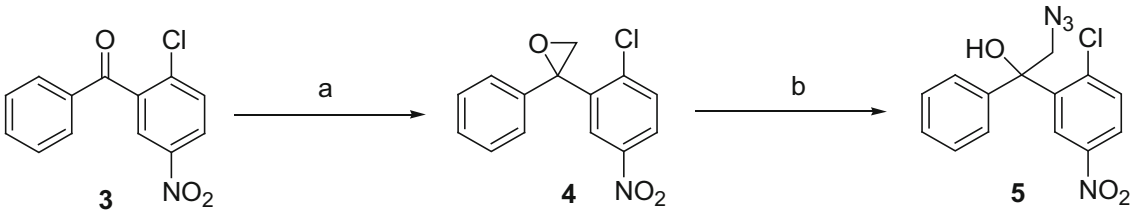
1-(2-chloro-5-nitrophenyl)-2-(4-(4-methoxyphenyl)-1,2,3-triazol-1-yl)-1-phenylethanol (***8***). 2-azido-1-(2-chloro-5-nitrophenyl)-1-phenylethanol **5** and 1-ethynyl-4-methoxy-benzene afforded 1-(2-chloro-5-nitrophenyl)-2-(4-(4-methoxyphenyl) -1,2,3-triazol-1-yl)-1-phenylethanol **8** as white solid (74%), M.p. 180 °C. IR (ATR, ν_{max} cm^{-1}): 3177, 2925, 2853, 1525, 1341, 699. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (d, J = 2.8 Hz, 1H), 8.00 (dd, J = 8.7, 2.8 Hz, 1H), 7.94 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.42–6.89 (m, 8H), 6.17 (s 1H) 5.89 (d, J = 13.8 Hz, 1H), 5.23 (d, J = 13.8 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 146.8, 146.2, 142.2, 142.1, 138.9, 131.8, 128.4, 128.2, 126.9, 126.6, 124.1, 123.8, 123.2, 121.0, 114.1, 76.4, 55.6, 55.2. MS [EI+] m/z (%):450 $[M]^+$ (5), 132 $[M\text{- }C_9H_8O]^+$ (100). HRMS (EI): calcd. for $C_{23}H_{19}ClN_4O_4$: 450.1095; found: 450.1097.

1-(2-chloro-5-nitrophenyl)-2-(4-(4-fluorophenyl)-1,2,3-triazol-1-yl)-1-phenylethanol (***9***). 2-azido-1-(2-chloro-5-nitrophenyl)-1-phenylethanol **5** and 1-ethynyl-4-fluoro-benzene afforded 1-(2-chloro-5-nitrophenyl)-2-(4-(4-fluorophenyl)-1,2,3-triazol-1-yl)-1-phenylethanol **9** as white solid (85%), M.p. 172 °C. IR (ATR, ν_{max} cm^{-1}): 3179, 2924, 2854, 1525, 1344, 699. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67–8.60 (m, 1H), 8.14–8.10 (m, 1H), 8.07–7.97 (m, 1H), 7.78–7.66 (m, 2H), 7.50–7.08 (m, 8H), 6.76 (s, 1H), 5.95 (dd, J = 13.7, 1.5 Hz, 1H), 5.29 (dd, J = 13.8, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 160.5, 146.06, 145.7, 142.3, 142.2, 138.9, 131.8, 128.4, 128.0, 127.3, 127.2, 127.0, 126.950, 126.700, 123.930, 123.800, 121.940, 115.7, 115.4, 76.0, 55.4. MS [EI+] m/z (%):438 $[M]^+$ (5), 120 $[M\text{-}C_8H_5F]^+$ (100). HRMS (EI): calcd. for $C_{22}H_{16}ClFN_4O_3$: 438.0895; found: 438.0899.

1-(2-chloro-5-nitrophenyl)-2-(4-(4-pentylphenyl)-1,2,3-triazol-1-yl)-1-phenylethanol (***10***). 2-azido-1-(2-chloro-5-nitrophenyl)-1-phenylethanol **5** and 1-ethynyl-4-pentylbenzene afforded 11-(2-chloro-5-nitrophenyl)-2-(4-(4-pentylphenyl)-1,2,3-triazol-1-yl)-1-phenylethanol **10** as white solid (89%), M.p. 132 °C. IR (ATR, ν_{max} cm^{-1}): 3157, 2925, 2854, 1726, 1518, 1341, 695. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73 (d, J = 2.5 Hz), 8.05 (dd, J = 8.6, 2.6 Hz, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.7 Hz, 1H), 7.40–7.13 (m, 7H), 5.82 (d, J = 13.9 Hz, 1H), 5.24 (d, J = 14.0 Hz, 1H), 4.34 (s, 1H), 2.58 (d, J = 7.6 Hz, 2H), 1.60 (m, 4H), 1.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6, 146.5, 143.3, 141.7, 140.9, 138.7, 132.2, 128.9, 128.8, 127.4, 126.2, 125.7, 124.3, 124.0, 121.1, 77.0, 56.3, 35.7, 31.47, 31.0, 22.5, 14.0. MS [EI+] m/z (%):490 $[M]^+$ (5), 149 $[M\text{-}C_7H_6N_3O]^+$ (100), 71$[M\text{-}C_5H_{11}]^+$ (20), 57 $[M\text{-}C_4H_9]^+$ (58). HRMS (EI): calcd. for $C_{27}H_{27}ClN_4O_3$: 490.1772; found: 490.1777.

1-(2-chloro-5-nitrophenyl)-2-[4-(4-nitrophenoxy)methyl-1,2,3-triazol-1-yl]-1-phenylethanol (***11***). 2-azido-1-(2-chloro-5-nitrophenyl)-1-phenylethanol **5** and 1-nitro-4-prop-2-ynyloxybenzene afforded 1-(2-chloro-5-nitrophenyl)-2-[4-(4-nitrophenoxy)methyl-1,2,3-triazol-1-yl]-1-phenylethanol **11** as white solid (87%), M.p. 170 °C. IR (ATR, ν_{max} cm^{-1}): 3170, 2920, 2851, 1511, 1340, 699. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54 (d, J = 2.8 Hz, 1H), 8.19–8.11 (m, 2H), 7.98 (dd, J = 8.5, 2.5 Hz, 2H), 7.50–7.32 (m, 6H), 7.06–6.97 (m, 2H), 6.59 (s, 1H), 5.97 (d, J = 13.7 Hz, 1H), 5.22 (d, J = 13.7 Hz, 1H), 5.16 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 146.0, 142.1, 142.0, 141.7, 141.5, 138.9, 131.8, 128.4, 128.2, 126.6, 125.7, 125.5, 123.9, 123.8, 114.8, 76.1, 62.0, 55.5. MS [EI+] m/z (%): 495 $[M]^+$ (5), 149 $[M\text{-}C_7H_6N_3O]^+$ (100). HRMS (EI): calcd. for $C_{23}H_{18}ClN_5O_6$: 495.0946; found: 495.0944.

1-(2-chloro-5-nitrophenyl)-2-(4-(4-chlorophenoxymethyl)-1,2,3-triazol-1-yl)-1-phenylethanol (***12***). 2-azido-1-(2-chloro-5-nitrophenyl)-1-phenylethanol **5** and 1-chloro-4-prop-2-ynyloxybenzene afforded 1-(2-chloro-5-nitrophenyl)-2-(4-(4 -chlorophenoxymethyl)-1,2,3 -triazol-1 -yl)-1-phenylethanol **12** as white solid (59%), M.p. 118 °C. IR (ATR, ν_{max} cm^{-1}): 3152, 2929, 2872, 1522, 1342, 692. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.04 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 47.4 Hz, 1H), 7.29 (dd, J = 21.9, 15.5, 5.5 Hz, 8H), 6.95–6.75 (m, 2H), 5.81 (d, J = 14.0 Hz, 1H), 5.20 (d, J = 13.9 Hz, 1H), 5.03 (s, 2H), 3.98 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.6, 146.4, 143.6, 141.4, 140.8, 138.7, 132.2, 129.3, 129.0, 128.9, 126.1, 126.1, 124.6, 124.3,



Scheme 2. Reagents and conditions: (a) Trimethylsulfonium iodide, KOH, tBuOH, 40–50 °C, 11 h, (b) NaN_3, NH_4Cl, MeOH-H_2O, 12 h.

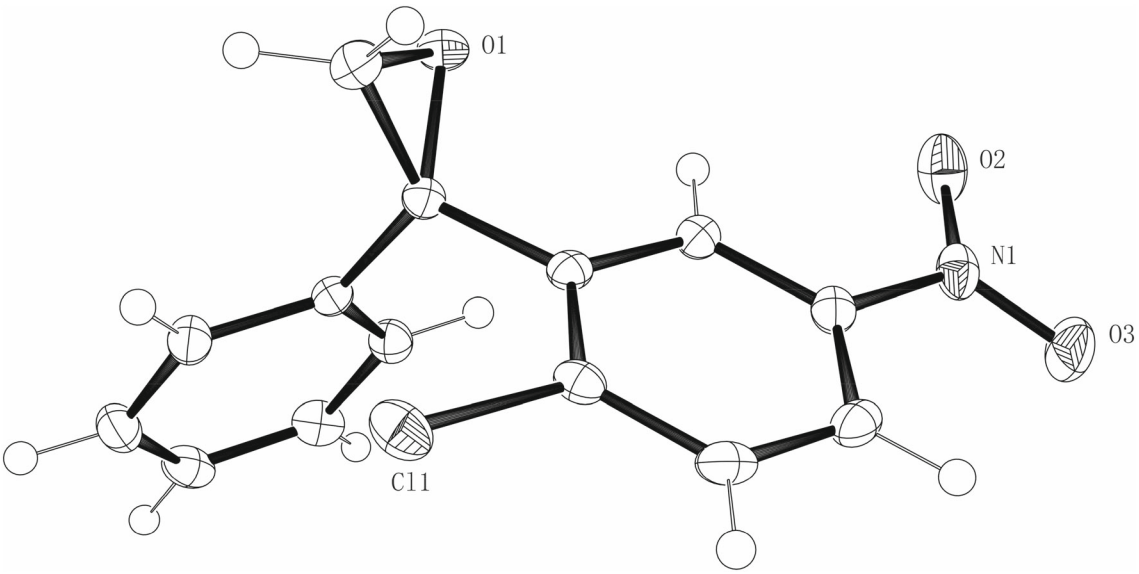


Figure 1. ORTEP diagram and atom labelling system for compound **4**.

123.8, 116.0, 77.5, 61.8, 56.2. MS [EI+] m/z (%):484 $[M]^+$ (10), 262 $[M\text{-}C_{13}H_9ClNO_3]^+$ (100). HRMS (EI): calcd. for $C_{23}H_{18}Cl_2N_4O_4$: 484.0705; found: 484.0708.

2-(4-(4-bromophenoxymethyl)-1,2,3-triazol-1-yl)-1-(2-chloro-5-nitrophenyl)-1-phenylethanol (***13***). 2-azido-1-(2-chloro-5-nitrophenyl)-1-phenylethanol **5** and 1-bromo-4-prop-2-ynyloxybenzene afforded 2-(4-(4-bromophenoxymethyl)-1,2,3-triazol-1-yl)-1-(2-chloro-5-nitrophenyl)-1-phenylethanol **13** as white solid (65%), M.p. 174 °C. IR (ATR, ν_{max} cm^{-1}): 3152, 3110, 2955, 2923, 1523, 1342, 696. ^1H NMR (300 MHz, $CDCl_3$): δ 8.62 (d, J = 2.5 Hz, 1H), 8.04 (dd, J = 8.2, 2.6 Hz, 1H), 7.67 (s, 1H), 7.36 (dd, J = 27.2, 18.6, 6.2 Hz, 8H), 6.78 (d, J = 8.5 Hz, 2H), 5.81 (d, J = 13.8 Hz, 1H), 5.21 (d, J = 14.0 Hz, 1H), 5.05 (s, 2H), 3.88 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 146.4, 143.6, 141.3, 140.7, 138.6, 132.2, 129.0, 126.0, 124.6, 124.4, 123.8, 116.5, 77.0, 61.8, 56.3. MS [EI+] m/z (%):528 $[M]^+$ (5), 262 $[M\text{-}C_{13}H_9ClNO_3]^+$ (100). HRMS (EI): calcd. for $C_{23}H_{18}BrClN_4O_4$: 528.0200; found: 528.0207.

1-(2-chloro-5-nitrophenyl)-1-phenyl-2-(4-(4-trifluoromethylphenyl)-1,2,3-triazol-1-yl)ethanol (***14***). 2-azido-1-(2-chloro-5-nitrophenyl)-1-phenylethanol **5** and 1-ethynyl-4-trifluoromethylbenzene afforded 1-(2-chloro-5-nitrophenyl)-1-phenyl-2-(4-(4-trifluoromethylphenyl)-1,2,3-triazol-1-yl) ethanol **14** as white solid (83%), M.p. 106 °C. IR (ATR, ν_{max} cm^{-1}): 3253, 3160, 2960, 2924, 1527, 1322, 696. ^1H NMR (300 MHz, $CDCl_3$): δ 8.71 (d, J = 2.7 Hz, 1H), 8.08 (dd, J = 8.7, 2.7 Hz, 1H), 7.98 (s, 1H), 7.83 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.7 Hz, 1H), 7.42–7.23 (m, 5H), 5.87 (d, J = 14.0 Hz, 1H), 5.26 (d, J = 14.0 Hz, 1H), 3.92 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5, 145.3, 140.4, 139.8, 137.8, 131.4, 128.2, 128.1, 125.0, 124.8 (d, J_{C-F} = 4.6 Hz), 123.5, 122.9, 121.2, 55.5. MS [EI+] m/z (%):488 $[M]^+$ (5), 226 $[C_{10}H_7F_3N_3]^+$ (100). HRMS (EI): calcd. for $C_{23}H_{16}ClF_3N_4O_3$: 488.0863; found: 488.0865.

2-{1-[2-(2-chloro-5-nitrophenyl)-2-hydroxy-2-phenylethyl]-1,2,3-triazol-4-yl)methyl}-isoindole-1,3-dione (***15***). 2-azido-1-(2-chloro-5-nitrophenyl)-1-phenylethanol **5** and 2-Prop-2-ynylisoindole-1,3-dione afforded 2-{1-[2-(2-chloro-5-nitrophenyl)-2-hydroxy-2-phenylethyl]-1,2,3-triazol-4-yl) methyl}-isoindole-1,3-dione **15** as white solid (82%), M.p. 174 °C. IR (ATR, ν_{max} cm^{-1}): 3154, 3069, 2921, 2852, 1715, 1523, 1338, 697. ^1H NMR (300 MHz, $CDCl_3$): δ 8.57 (d, J = 2.7 Hz, 1H), 8.02 (dd, J = 8.7, J = 2.8 Hz, 1H), 7.87–7.78 (m, 2H), 7.76–7.70 (m, 2H), 7.55 (s, 1H), 7.49–7.21 (m, 6H), 5.79 (d, J = 14.0 Hz, 1H), 5.24 (d, J = 14.0 Hz,

Table 1. Crystal data and structure refinement of X-ray diffraction for compounds **4**–**8** and **13**.

Crystal data	**4**	**5**	**6**	**7**	**8**	**13**
Empirical formula	$C_{14}H_{10}ClNO_3$	$C_{14}H_{10}ClN_4O_3$	$C_{24}H_{23}ClN_4O_4S$	$C_{23}H_{19}ClN_4O_3$	$C_{46}H_{32}Cl_2N_8O_8$	$C_{23}H_{18}BrClN_4O_4$
Formula weight	275.68	317.71	498.97	434.87	894.94	530.97
Temperature (K)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)
Wavelength Å	0.71073	0.71073	0.71073	1.54178	1.54178	0.71073
Crystal system	Monoclinic	Triclinic	Triclinic	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1/c$	P-1	P-1	$P2_1/c$	$P2_1/c$	Pbca
Unitcell dimensions (Å, °)						
a	8.20880(10)	7.7690(4)	11.2777(4)	11.6542(2)	11.8721(2)	17.7425(7)
b	18.0143(3)	9.5031(5)	13.0110(5)	15.8062(2)	15.5280(3)	11.8317(5)
c	8.22110(10)	9.8940(5)	16.0874(6)	23.6310(4)	23.4708(4)	20.9612(8)
a	90	109.6847(10)	92.3399(8)	90	90	90
β	91.3672(7)	93.5364(10)	92.4305(8)	101.2643(9)	104.3411(8)	90
γ	90	92.6945(10)	93.4349(8)	90	90	90
Volume ($Å^3$)	1215.36(3)	684.68(6)	2351.98(15)	4269.18(12)	4192.01(13)	4400.3(3)
Z	4	2	4	8	4	8
Calculated density D (mgm^{-3})	1.507	1.541	1.409	1.353	1.418	1.603
F(000)	568	326	1040	1808	1854	2148
Absorption coefficient μ (mm^{-1})	0.317	0.298	0.291	1.860	1.957	2.057
Crystal size (mm^3)	0.303 × 0.221 × 0.103	0.302 × 0.282 × 0.275	0.373 × 0.254 × 0.195	0.316 × 0.136 × 0.130	0.338 × 0.243 × 0.216	0.509 × 0.332 × 0.132
θ_{max}(°)	27.445	32.576	27.542	70.068	70.069	27.443
θ_{min}(°)	2.261	2.194	1.268	3.384	3.446	1.943
h	-10 → 10	-11 → 11	-14 → 14	-11 → 11	-14 → 14	-23 → 22
k	-23 → 23	-14 → 14	-16 → 16	-19 → 19	-18 → 18	-15 → 15
l	-10 → 10	-14 → 14	-20 → 20	-28 → 26	-25 → 28	-26 → 27
Reflections collected	26502	17905	34624	71787	39753	52814
Independent reflection	2781 [R(int) = 0.0276]]	4985 [R(int) = 0.0203]	10807 [R(int) = 0.0190	7818 [R(int) = 0.0309]	7941 [R(int) = 0.0213]	5025 [R(int) = 0.0415]
Data/ restraints/ parameters	2781 / 0 / 172	4985 / 2400/ 598	10807 / 137/ 660	7818 / 471/ 649	7941 / 1046/ 734	5025 / 393/ 366
Goodness-of-fit on F^2	1.061	1.064	1.063	1.042	1.128	1.128
Final R indices $[I > 2\sigma(I)]$	$R1 = 0.0360$,[a] $wR2 = 0.0948$	$R1 = 0.0739$,[a] $wR2 = 0.2038$	$R1 = 0.0426$,[a] $wR2 = 0.1172$	$R1 = 0.0341$,[a] $wR2 = 0.0919$	$R1 = 0.0382$,[a] $wR2 = 0.0928$	$R1 = 0.0297$,[a] $wR2 = 0.0773$
R indices (all data)	$R1 = 0.0387$,[a] $wR2 = 0.0966$	$R1 = 0.0784$,[a] $wR2 = 0.2079$	$R1 = 0.0485$,[a] $wR2 = 0.1223$	$R1 = 0.0372$,[a] $wR2 = 0.0944$	$R1 = 0.0392$,[a] $wR2 = 0.0934$	$R1 = 0.0343$,[a] $wR2 = 0.0800$

[a] $= R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, [b] $= wR_2 = [\Sigma w(F_o^2\text{-}F_c^2)^2/\Sigma(F_o^2)^2]^{1/2}$.

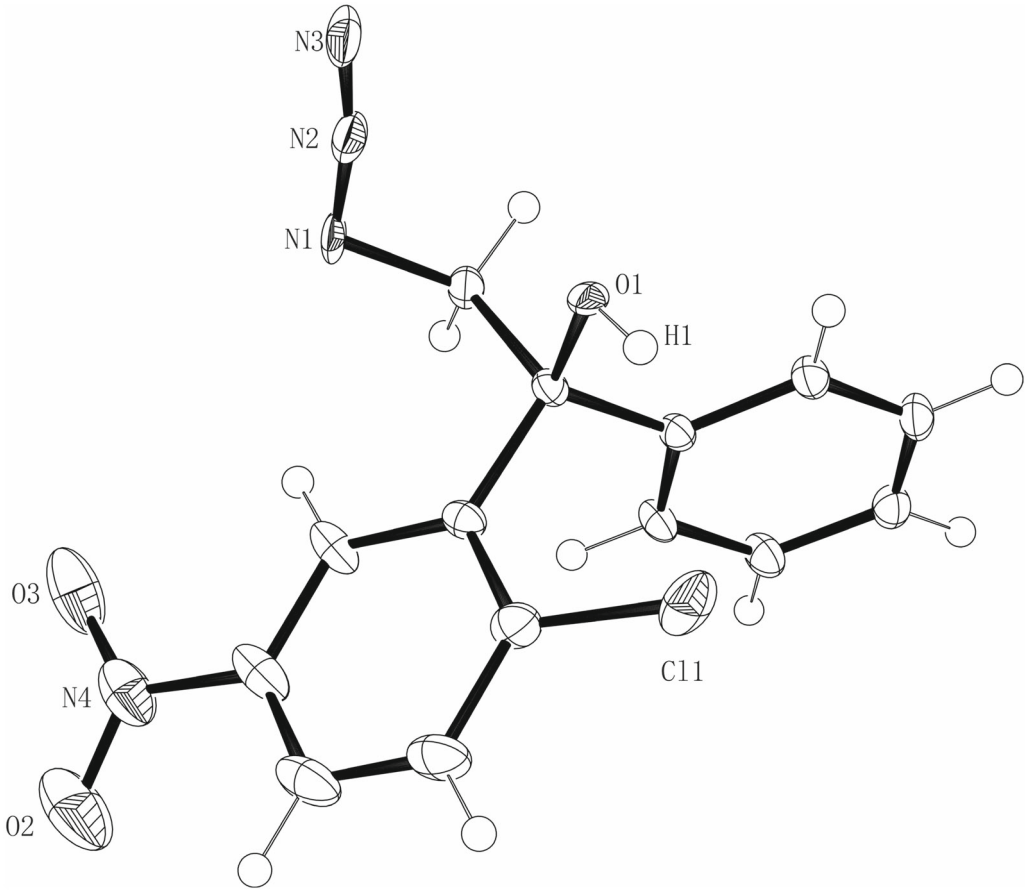
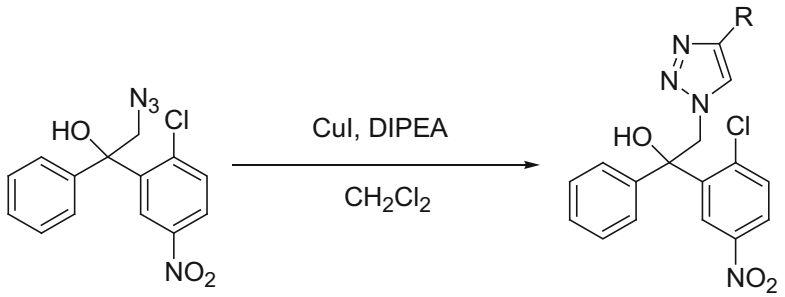


Figure 2. ORTEP diagram and atom labelling system for compound **5**.



Scheme 3. Synthesis 1,1-diaryl-2-(1,2,3)triazol-1-yl-ethanol derivatives from azido alcohol **5**.

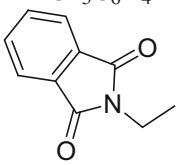
1H), 4.82 (q, J = 15.2 Hz, 2H), 3.95 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.4, 142.4, 141.2, 140.6, 138.2, 133.9, 132.0, 131.72, 128.8, 128.7, 125.9, 124.4, 124.2, 123.8, 123.3, 76.8, 55.8, 32.5. MS [EI+] m/z (%):503 $[M]^+$ (5), 160 $[C_9H_6NO_2]^+$ (100). HRMS (EI): calcd. for $C_{25}H_{18}ClN_5O_5$: 503.0996; found: 503.0997.

2.5 *In vitro antifungal activities*

The antifungal activity of compounds **6–15** was screened using reference strains of yeasts from American Type Culture Collection: *Candida albicans* ATCC-10231, *Candida utilis* ATCC-9226, *Candida glabrata* ATCC-34138, and *Candida krusei* ATCC-14243, as well as filamentous fungi: Aspergillus fumigatus ATCC-16907, *Trichosporon cutaneum* ATCC-28592, *Rhizopus oryzae* ATCC-10329 and *Mucor hiemalis* ATCC-8690.

The MICs of compounds **6–15** and the control antifungal agents were determined consistently using the broth microdilution method for yeasts developed by the Clinical and Laboratory Standards Institute and published in the document M27-A3.[18] For all organisms, RPMI 1640 medium with 0.165 M morpholinepropanesulfonic acid (MOPS) buffer (pH 7.0) was used as the test medium. MICs were determined after incubation at 30 °C for 16 to 24 h and defined by the

Table 2. Synthesis of 1,1-diaryl-2-(1,2,3)triazol-1-yl-ethanol derivatives.

Compound	R	Reaction time, h	% Yield
6	Ph	24	85
7	4-$CH_3C_6H_4$	24	82
8	4-$CH_3OC_6H_4$	24	74
9	4-FC_6H_4	24	85
10	4-$(C_5H_{11})C_6H_4$	24	89
11	CH_2O(4-NO_2)C_6H_4	24	87
12	CH_2O(4-Cl)C_6H_4	24	59
13	CH_2O(4-Br)C_6H_4	24	65
14	4-$CF_3C_6H_4$	24	83
15		24	82

criteria of the CLSI procedures. The visual reading was made with the help of an inverted mirror. The MIC of azoles is the lowest concentration that results in total inhibition of growth (100%).

3. Results and Discussion

3.1 *Chemistry*

Based on Flutriafol structural features and considering that this molecule bears tertiary alcohol with a 1,2,4-triazolylmethyl group and two different substituted fluorophenyl groups, we prepared 1,1-diaryl epoxide **4** from Corey-Chaykovsky epoxidation on benzophenone **3** through an adaptation of the methodology described by the groups of Xu[13] and Fuentes-Benites[14] (Scheme 2). The structure of epoxide **4** was established by conventional spectroscopic techniques and confirmed by X-ray crystallography studies determined on crystals of this compound which showed a C(1)-O(1)-C(2) angle (60.77°) distinctive of an oxirane ring (Figure 1).[15] Crystallographic data and structural refinement parameters of **4** and the other crystalline compounds are summarized in Table 1.

Ring opening reaction of epoxide **4** with sodium azide afforded the azido alcohol **5** in 77% yield. Single-crystal X-ray diffraction analysis of compound **5** reveals distances among nitrogen atoms in the azide group, N1–N2 =1.230 Å and N2–N3 =1.149 Å, indicating electronic delocalization with a similar behavior to other reported organic azides (Figure 2).[16] Azido alcohol **5** was taken as departure material which was reacted with different alkynes in presence of catalytic amounts of copper (I) iodide[17] through an optimized synthetic procedure that gave the corresponding 1,1-diaryl-2-(1,2,3)triazol-1-yl-ethanol derivatives **6–15** (Scheme 3). Results summarized in Table 2 show that this process occurs with high efficiency and functional group tolerance. All -(1,2,3)triazol-1-yl-ethanol derivatives were characterized by the conventional spectroscopic techniques and compounds **6**, **7**, **8** and **13** were crystalline solids which were studied by X-ray crystallography, confirming the proposed structure for these compounds. The ORTEP representations of compounds **6**, **7**, **8** and **13** are shown in Figure 3.

3.2 *Biological evaluation*

Compounds **6–15** were evaluated for their *in vitro* antimicrobial activity against four yeast specimens: *Candida albicans* ATCC 10231, *Candida utilis* ATCC 9226 and *Candida glabrata* ATCC 34138 and *Candida krusei* ATCC 14243, and four filamentous fungi *Mucor hiemalis* ATCC 8690, Aspergillus fumigatus 16907, *Trichosporon cutaneum* ATCC 28592 and *Rhizopus oryzae*. The antifungal activity of the evaluated compounds is summarized in Table 3. The microdilution methods M38-A (filamentous fungi) and M27-A3 (yeast), described by CLSI were adopted as the standard protocols. The tests were done in triplicate.

The antifungal activity of compound **6–15** was compared to an antifungal drug standard, itraconazole. The minimum inhibitory concentration (MIC) values of compounds and standard drug, expressed in micrograms per millilitre, were determined in 96-well plates by using RPMI 1640 medium buffered with MOPS (3-(N-Morpholino)propanesulfonic acid).

Among 1,1-diaryl-2-(1,2,3)triazol-1-yl-ethanol derivatives, compound **15** showed in *C. utilis* yeast strains an activity comparable to standard itraconazole, as well as susceptible-dose dependent (SDD) according to the parameters of M27-A3 reference method (Table 4),[18] which indicates that although this compound has a high activity, this condition does not imply sensitive therapeutic success, probably due to a higher dose is required to increase its activity with possible subsequent adverse or secondary effects.

On the other hand, the tested triazoles displayed well *in vitro* antifungal activity against filamentous fungi, observing that strains of *Aspergillus fumigatus* and *Rhizopus oryzae* were more sensitive to these compounds. Moreover, compound **11** was found to have the same activity as itraconazole in the *T. cutaneum* strain, while moderate activity in the strains of Aspergillus fumigatus and *Rhizopus oryzae*. Regarding the structures of the synthesized compounds, the substituent

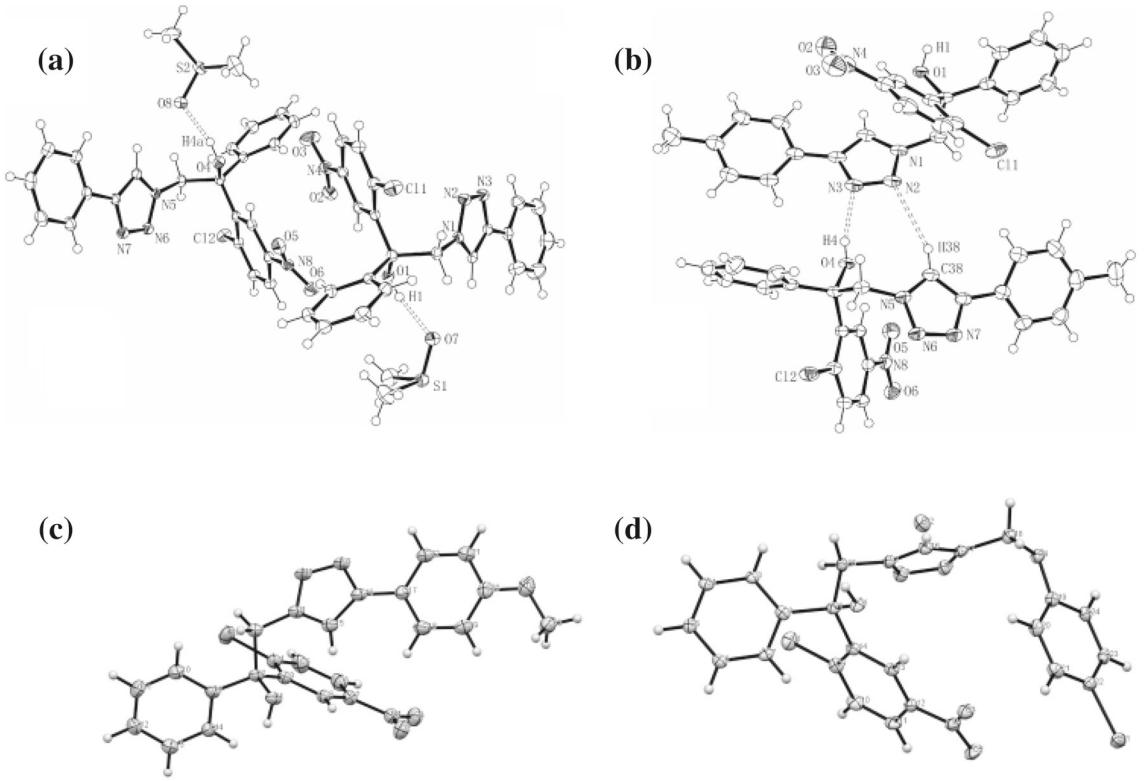


Figure 3. ORTEP diagram and atom labelling system for compounds **6** (a), **7** (b), **8** (c) and **13** (d).

Table 3. *In vitro* antifungal activities of synthesized compounds MIC (μg/mL).

Compound	*C.alb*	*C.uti*	*C.gla*	*C.kru*	*M.hie*	*A.fum*	*T.cut*	*R.ory*
6	16	4	4	16	16	16	16	16
7	16	4	8	16	8	16	16	16
8	16	2	8	16	16	16	16	16
9	8	4	8	16	16	4	16	16
10	16	8	16	16	16	8	16	16
11	16	8	16	16	8	4	8	4
12	16	8	16	16	16	8	16	16
13	16	2	16	16	16	8	16	16
14	16	4	16	16	16	8	16	16
15	8	0.5	8	16	8	4	8	4
Standard[a]	0.03	0.25	1	0.25	4	1	8	1

Abbreviations: *C. alb., Candida albicans*; *C. uti., Candida utilis*; *C. gla., Candida glabrata*; *C. kru., Candida krusei*; *M. hie., Mucor hiemalis; A. fum., Aspergillus fumigatus; T. cut., Trichosporon cutaneum; R. ory*., Rhizopus oryzae.
[a]Itraconazole.

groups on aromatic rings appear to be important. The presence of electron withdrawing substituent groups seems to be a major factor in antimicrobial activity increase. For example, compound **11** containing an electron-withdrawing substituent (–NO_2), shows lower MIC in strains of filamentous fungi compared to compounds having methyl, halogens and aliphatic chains as substituent groups.

Although a toxicity evaluation study on the synthesized triazoles was not done, previous reports indicate that 1,2,3-triazoles display low cytotoxicity against diverse cells [19–21] which suggest that synthesized triazoles could be also harmless. Future studies about the toxicity of 1,1-diaryl-2-(1,2,3)triazol-1-yl-ethanol derivatives will be done to determine this biological property and to compare to Flutriafol toxicity.

Table 4. Sensitivity of yeast strains according to the document M27-A3: Susceptible (S), dose-dependent sensitive (SDD) and resistant (R).

Compound	*C. alb*	*C. uti*	*C. gla*	*C. kru*
6	R	R	R	R
7	R	R	R	R
8	R	R	R	R
9	R	R	R	R
10	R	R	R	R
11	R	R	R	R
12	R	R	R	R
13	R	R	R	R
14	R	R	R	R
15	R	SDD	R	R
Standard[a]	S	SDD	R	SDD

Abbreviations: *C. alb., Candida albicans*; *C. uti., Candida utilis*; *C. gla., Candida glabrata*; *C. kru., Candida krusei*; [a]Itraconazole.

4. Conclusions

In summary, a series of 1,1-diaryl-2-(1,2,3)triazol-1-yl-ethanol derivatives analogues to Flutriafol was obtained from click chemistry approach through a short synthetic sequence and using inexpensive starting materials. In addition, the structure of some final products, as well as some intermediates, was unequivocally determined by X-ray crystallography studies. Antifungal activity found in some 1,1-diaryl-2-(1,2,3)triazol-1-yl-ethanol derivatives suggests that this kind of compounds could open a new trend which may lead to the research about design, synthesis and optimization of novel promising antifungal compounds from mild and environmentally friendly synthetic methods according to the aim of Click Chemistry.

Supplementary Information (SI)

Characterization of t1,1-diaryl-2-(1,2,3)triazol-1-yl-ethanol derivatives, ^{1}H NMR and ^{13}C NMR, as well as crystallographic data. Supplementary Information is available on www.ias.ac.in/chemsci.

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