Original Article

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Highly Efficient Synthesis of 1,4-Disubstituted 1,2,3-Triazole Derivatives under Ultrasonic Irradiation, Evaluation of Vasorelaxant Activities

Sakineh Ebrahimpourmoghaddam[1];PhD, Maryam Motevasel[2];PhD, Saghar Mowlazadeh Haghighi[1];PhD, Azar Purkhosrow[3];MSc, Hashem Sharghi[1];PhD, Ali Khalafinezhad[1];PhD, Elahe Sattarinezhad [3*];PhD

[1]Department of Chemistry, Shiraz University, Shiraz, Iran.
[2]Department of Medical Laboratory Sciences, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Pharmacology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract

1,4-Disubstituted 1,2,3-Triazole derivatives are exciting pharmacophores with a wide range of biological activities, including anticancer, antituberculosis, antifungal, antibacterial, and anti-HIV. Due to their diverse uses, many efforts have been made to synthesize these valuable medicinal scaffolds. Unfortunately, most of them have difficult and time-consuming procedures, low yields of the products, or environmentally toxic residues, therefore, it is necessary to develop easy methods with high efficiency and without harmful by-products. In the first part of this study, differently decorated 1,4-disubstituted 1,2,3-triazole derivatives were synthesized through a one-pot, two-step procedure from epoxides, alkynes and sodium azide in the presence of Cu_2O in water under ultrasonic irradiation with high efficiency and without any toxic residues. In the second part of this research, the vasorelaxant activity of these triazole derivatives was studied in isolated rat thoracic aorta. Based on the results, three compounds have potent vasorelaxant activity and can be considered in future evaluations for the development of new antihypertensive drugs.

Keywords: Triazole, Ultrasonic irradiation, Vasorelaxant

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1. Introduction

1,4-Disubstituted 1,2,3-triazoles are attractive pharmacophores with a wide range of biological activities such as anticancer (1, 2), antituberculosis (3), antifungal (4), antimicrobial (5, 6), antiviral (7), analgesic (8) and anti-HIV (9). Furthermore, they have many applications in industry as dyestuffs, corrosion inhibitors, light stabilizers, optical brighteners and fluorescent whiteners (10). Due to their amazing properties and extensive uses, numerous methods have been developed to synthesize these valuable pharmaceutical scaffolds (11).

Corresponding Author: Elahe Sattarinezhad, Department of Pharmacology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
Email: elahesat@yahoo.com

The traditional method for the synthesis of 1,2,3-triazoles is 1,3-dipolar cycloaddition reaction between alkynes and azide derivatives. This method requires multi-step procedures and high temperature and besides, leads to the production of a mixture of 1,4- and 1,5-disubstituted triazoles (12). A widely used copper-catalyzed variant of this reaction named "Huisgen reaction" makes it possible to conduct this reaction even at room temperature while using water as the green solvent (13). The reaction proceeds in the presence of a copper (I) catalyst to produce 1,4-disubstituted 1,2,3-triazoles exclusively (14). Copper (I) catalysis confers regiospecificity and enables us to use a wide variety of substrates. Despite all the advantage, Copper (I) is thermodynamically unstable and easily oxidates to copper (II) species and/or

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disproportionation to copper (0) and copper (II) species (15). This unfavorable property of copper (I) generally slows down the reaction rate and usually requires the use of ligands which in turn may lead to the formation of harmful by-products (16). Accordingly, it is necessary to use a method to accelerate the reaction without leaving undesirable residues.

Ultrasonic chemistry has received an increasing attention for the synthesis of organic materials. It can make numerous organic reactions proceed in shorter time and milder conditions (17). Moreover, this approach leads to the production of pure products with high yields using simple and environmentally friendly methods (18). However, there are few reports on ultrasound-assisted 1,3-dipolar cycloaddition reactions. Therefore, considering the advantages of the ultrasonic method and with special attention to the importance of green chemistry, we designed a one-pot, two-step, efficient, regioselective and safe synthetic procedure to synthesize different decorated 1,4-disubstituted 1,2,3-triazole derivatives from epoxides, sodium azide, and alkynes in water, catalyzed by Cu_2O under ultrasonic irradiation at room temperature.

The vasorelaxant activities of various types of triazole derivatives have been reported by some authors. Biagi et al. designed and synthesized a series of 1,5-diphenylsubstituted 1,2,3-triazoles and reported their vasorelaxant effects (19). Baragatti et al. produced a series of 5-substituted-triazolyl–benzimidazolones and triazolyl–benzotriazoles as well as1,5-Diarylsubstituted 1,2,3-triazoles and found them to be potent vasorelaxants (20).

In the second part of this research, we evaluated the cuted 1,2,3-triazole derivatives in isolated rat thoracic aorta.

2. Material and methods

2.1. Materials

2.1.1. Chemicals and equipments

All chemicals were of analytical grade and were purchased from Fluka, Sigma or Merck.

Acetylcholine and all of the synthesized compounds were dissolved in dimethyl sulfoxide (DMSO). The final concentrations of DMSO in organ bath had no effect on the tissue response.

For recorded ^1H NMR and ^{13}C NMR spectra we used Brucker (250 MHz) Avanc DRX in pure deuterated DMSO-d6 and $CDCl_3$ solvents with tetramethylsilane (TMS) as internal standards. Mass spectra were recorded on a shimadzu GCMS-QP1000 EX INSTRUMENTS AT 70 or 20ev. Melting points were determined in open capillary tubes in a Barnstead Electrothermal 9100 BZ circulating oil melting point apparatus. Elemental analyses were performed on a thermo finnigan flash EA1112≠1CHNS. The reaction monitoring was accomplished by thin layer chromatography (TLC) on silica gel Poly Gram SILG/UV254 plates and gas chromatography (GC).

2.1.2. Animals

Male Sprague-Dawley rats (200-220 g) were used. The animals were housed in groups of 6-7 under standard conditions (12 h light/dark cycle, temperature: 20-25 °C, and humidity: 25-35%) with standard rat chow and tap water ad libitum. All animal procedures were approved by the Institution of Animal Care and Use Committee of Shiraz University of Medical Sciences.

2.2. Methods

2.2.1. Synthesis of 1,4-disubstituted 1,2,3-triazole compounds

1,4-disubstituted 1,2,3-triazole compounds were synthesized from epoxides, sodium azide, and alkynes in water, catalyzed by Cu_2O under ultrasonic (U.S.) irradiation at room temperature (rt) (Figure 1).

For initial screening experiments, the 1,3-dipolar cycloaddition reactions between styrene oxide, sodium azide and phenylacetylene in a 1:1.1:1 molar ratio at room temperature was selected as the model reaction (Figure 2).

In the next step, we investigated the effects of using various solvents and different amounts of

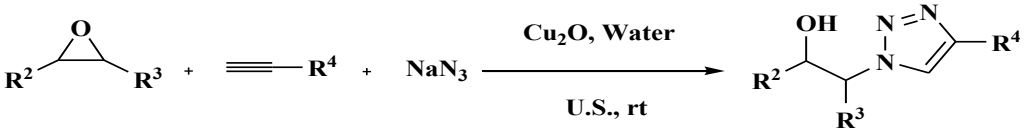
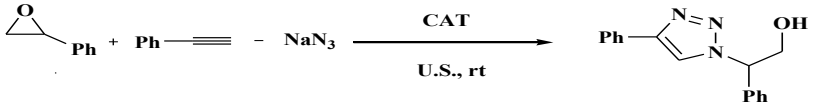


Figure 1. Synthesis of 1,4-disubstituted 1,2,3-triazole compounds from epoxides, sodium azide, and alkynes in water, catalyzed by Cu_2O under ultrasonic irradiation.



1-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethanol

Figure 2. 1,3-dipolar cycloaddition reaction between styrene oxide, sodium azide and phenylacetylene in a 1:1.1:1 molar ratio at room temperature under ultrasonic irradiation.

catalyst on the reaction time and the yields of the products (Table 1). After establishing the feasibility of the proposed method for the synthesis of the model compound, the scope of the methodology was briefly assessed by employing a set of various reactive precursors to produce 12 different 1,4-disubstituted 1,2,3-triazole compounds (Table 2).

For each reaction, epoxide (1 mmol), alkyne (1 mmol), and sodium azide (1.1 mmol) were mixed and stirred in water (2 mL) in the presence of 10 mol% of Cu_2O at room temperature in an uncapped vial under ultrasonic irradiation in temperature controlled experiments. Reactions were performed in a water bath at 25±1 °C. After the completion of the reaction, as monitored by thin layer chromatography (TLC) using n-hexane/ethyl acetate, the mixture was diluted by H_2O (5 mL), it was vacuum-filtered onto a sintered-glass funnel, and the residue was consecutively washed with ethyl acetate (30 mL) and water (5 mL). The combined supernatant and organic washings were extracted with ethyl acetate (3×10 mL); the combined organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum, followed by purification on silica gel using hexane/ethyl acetate as the eluent, produced the pure 1,4-disubstituted-1,2,3-triazole derivatives. All the newly synthesized triazoles were characterized in detail by IR, ^1H and ^{13}C NMR, mass spectroscopy, and elemental analysis. Full analytical and spectroscopic data for all of the compounds synthesized in this study are included in the Supporting Information.

2.2.2. Assessment of vasorelaxant activity of 1,4-disubstituted 1,2,3-triazole compounds

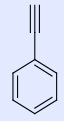
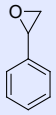
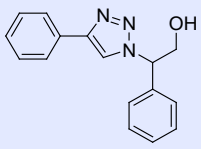
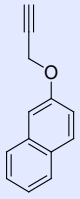
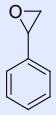
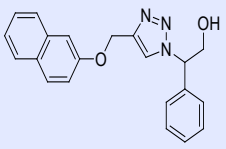
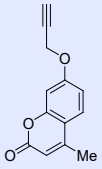
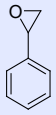
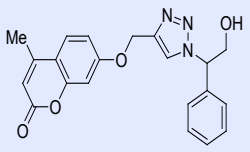
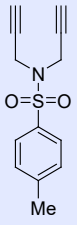
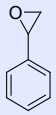
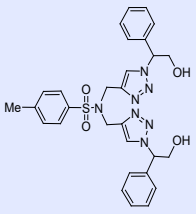
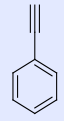
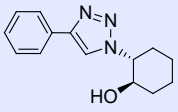
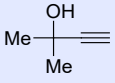
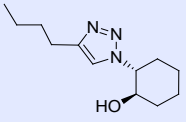
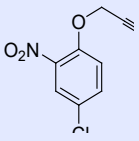
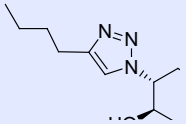
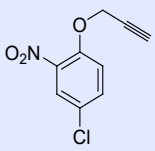
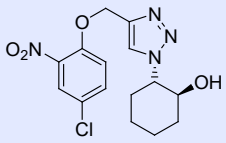
Animals were anesthetized with ketamine (60 mg/kg) and xylazine (8 mg/kg). The thoracic aorta was isolated and cut into four 4-mm rings. The rings were attached to hooks in an organ bath filled with bicarbonate-buffered physiological saline solutions (PSS buffer). Vascular tensions were recorded by a pressure transducer (K 30, Hugo Sachs Elektronik, Germany) using a software (HSE-ACAD, Hugo Sachs Elektronik, Germany). The PSS buffer solution was continuously

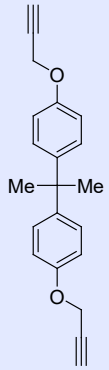
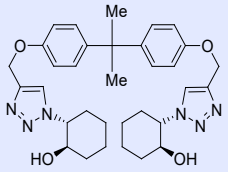
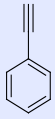
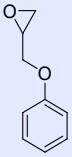
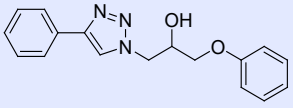
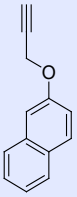
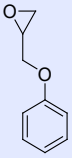
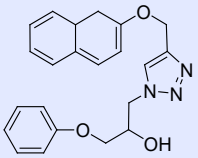
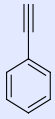
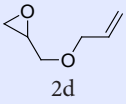
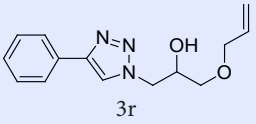
Table 1. Effects of various solvents and the catalyst concentrations on 1,3-dipolar cycloaddition reaction time and product yield.

Entry	Solvent	Catalyst (mol%)	Time [min]	Yield of product*[%]
1	#	Cu_2O (3.5 mol%)	60	0
2	Ethanol	Cu_2O (3.5 mol%)	30	70
3	water	Cu_2O (3.5 mol%)	30	95
4	DMSO	Cu_2O (3.5 mol%)	60	10
5	DMF	Cu_2O (3.5 mol%)	60	15
6	Toluene	Cu_2O (3.5 mol%)	60	5
7	Dioxane	Cu_2O (3.5 mol%)	60	10
8	Acetonitrile	Cu_2O (3.5 mol%)	60	50
9	Ethanol/water (1:1)	Cu_2O (3.5 mol%)	30	95
10	Dioxane/water (1:1)	Cu_2O (3.5 mol%)	30	80
11	water	Cu_2O (1.5 mol%)	30	65
12	water	Cu_2O (5.0 mol%)	25	95
13	water	Cu_2O (10.0 mol%)	25	98

* Isolated yields. #In the absence of solvent.

Table 2. 1,4-disubstituted 1,2,3-triazoles synthesized by reacting epoxides (1.0 mmol), terminal alkynes (1.0 mmol) and sodium azide (1.1 mmol) in the presence of Cu_2O (10 mol%) in water at room temperature under U.S. irradiation.

Entry	Alkyne	Epoxide	Product	Time [min]	Yield [%]
1	 1a	 2a	 3a	30	95
2	 1e	 2a	 3e	40	95
3	 1f	 2a	 3f	35	90
4	 1g	 2a	 3g	50	90
5	 1a	 2b	 3j	30	90
6	 1c	 2b	 3l	45	92
7	 1j	 2b	 3l	35	90
8	 1j	 2b	 3m	40	87

9	 1h	 2b	 3o	55	85
10	 1a	 2c	 3p	30	95
11	 1e	 2c	 3q	40	90
12	 1a	 2d	 3r	50	85

bubbled with O_2 (95%) and CO_2 (5%) while being refreshed every 20 minutes. The temperature was maintained at 37 °C. The aortic rings were stabilized for an hour with a resting vascular tension of 1g. After the equilibration period, cumulative concentrations of phenylephrine were added to the organ bath to reach a concentration capable of producing the maximal contraction of the aortic rings (10^{-7}–10^{-6} M). After that, cumulative concentrations of triazole compounds (10^{-9}–10^{-4} M) were added to the chambers while the vascular tensions of the aortic rings were recorded. Concentration-response curves were plotted and log IC_{50} (the logarithm of the concentration that relaxes the vessel to 50% of its initial contraction), and maximal vasorelaxant effects (E_{max}) were obtained.

2.2.3. Statistical analysis

Data were presented as mean±S.E.M. and analyzed using SPSS software. One way analyses of variance (ANOVA) and post hock Tukey's were used. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Synthesis of 1,4-disubstituted 1,2,3-triazole compounds

As shown in Table 2, we synthesized 12 different 1,4-disubstituted 1,2,3-triazole compounds using Cu (I) catalyst with high efficiency under ultrasound irradiation.

3.2. Vasorelaxant activity of 1,4-disubstituted 1,2,3-triazole compounds

The results of pharmacological evaluations are presented in Table 3. Comparison of log IC_{50} values revealed that compounds 3f, 3g and 3l have potent vasorelaxant activity. In addition, compounds 3f and 3l showed maximal vasorelaxant response (E_{max}) even higher than Ach. Other triazoles synthesized in this study, although showing some degree of vasorelaxant activity, were un-

Table 3. Potencies and maximal efficacies of vasorelaxant 1,4-disubstituted 1,2,3-triazole compounds

Entry	Compound	Log IC_{50}	E_{max}
1	Acetylcholine	-6.18±0.19	90.66±4.17
2	3f	-6.72±0.64	92.66±7.33
3	3g	-6.94±0.76	69.37±3.52
4	3l	-7.28±0.52	96.57±3.42

able to significantly reduce aortic tension (data not shown).

4. Discussion

In this study, we synthesized some potent vasorelaxant 1,4-disubstituted 1,2,3-triazole compounds from epoxides, sodium azide, and terminal alkynes in water, catalyzed by Cu_2O under ultrasonic irradiation. While the catalyst promoted the reaction to proceed in a regioselective manner (21), the ultrasound accelerated the reaction rate and provided easier manipulation (22, 23). Despite all the advantages of ultrasound, the number of studies that have used it to accelerate the 1,3-dipolar cycloaddition reactions is not significant. In a study by Reddy *et al*., 1,2,3- triazole derivatives were synthesized using Cu (I) as the catalyst with the help of ultrasound waves (24). Jiang et al. described a method for 1,3-dipolar cycloaddition using $Cu(OAc)_2$/metallic copper as the catalyst under ultrasound irradiation (25). Cravatto *et al.* reported an ultrasound-assisted 1,3-dipolar cycloaddition in 1,4-dioxane/ water using metallic copper as the catalyst, at a relatively high temperature (26). It is quite certain that conducting organic reactions in water is preferred due to environmental concerns. In comparison with other solvents, water is safe, nontoxic, economical and recyclable. In the process of optimizing the reaction conditions, we found that the best results were obtained using water as the solvent system. Therefore; our method is an example of green chemistry. Moreover, deprotonation of the π complex alkyne to form the copper acetylide can occur without the addition of a base in water, but in organic solvents, the formation of copper acetylide is unfavorable and a base is required for deprotonation (27). For the synthesis of various 1,4-disubstituted 1,2,3-triazoles, we employed various precursors and expanded the scope of the methodology. It was shown that with the help of ultrasound, various epoxides simply reacted with different terminal alkynes and sodium azide in the presence of Cu (I) to produce the desired 1,4-disubstituted 1,2,3-triazole derivatives in high yields. We were pleased that the cycloaddition reaction tolerates changes in terminal alkynes and epoxides meaning that steric and electronic variations in the reactants do not affect the reaction efficiency. Similar series of 1,4-disubstituted 1,2,3-triazole compounds have been synthesized using a supported catalyst system prepared by immobilization of a copper (II) complex of 4'-phenyl-2,2':6',2''-terpyridine on activated multi-

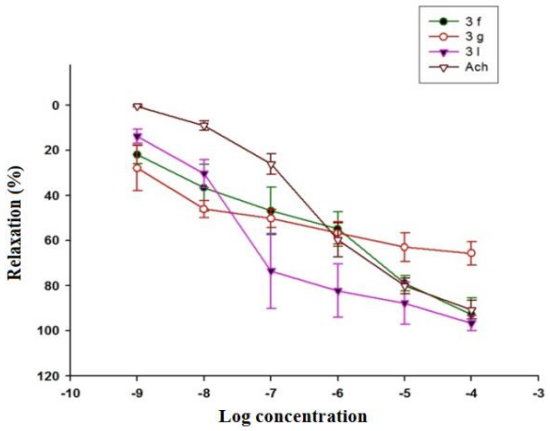


Figure 3. The vasorelaxant effect of 1,4-disubstituted 1,2,3-triazole compounds (10^{-9}-10^{-4} M) on vasocontraction induced by phenylephrine (10^{-7}–10^{-6} M).

walled carbon nanotubes (10). In another research, 1-(2-Hydroxyethyl)-1H-1,2,3-triazole derivatives were synthesized by copper-catalyzed 1,3-dipolar cycloaddition of 2-azido alcohols and terminal alkynes (28). Compared to these methods, the method we reported in this study is much simpler and less expensive. Vasorelaxant activity of various types of triazole derivatives have been reported by some researches (29, 30). The exact mechanisms by which triazole-based compounds exert their vasorelaxant effect have not been fully elucidated, but it has been suggested that some of triazole derivatives may activate the big-conductance calcium-activated potassium channels (BK_{Ca}) (31). Other mechanisms such as angiotensin II or vasopressin I receptor antagonism also have been proposed (32). Future studies are needed to reveal the possible mechanisms of vasorelaxant activity of these compounds to design more active and selective vasorelaxant molecules.

5. Conclusion

In this work, we reported an efficient and practical procedure for the synthesis of 1,4 disubstituted 1,2,3-triazole compounds under ultrasonic waves. The potent vasorelaxant 1,4-disubstituted 1,2,3-triazole derivatives obtained in this study may serve as valuable therapeutic candidates for the design of new antihypertensive drugs.

Supporting Information

Analytical and Spectroscopic Data for Representative Compounds

2-Phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethanol (3a):

Colorless powder; 97% yield. M.p. = 126.5 °C. IR (KBr): 694(s), 760(s), 1030(m), 1049(s), 1076(s), 1118(w), 1223(m), 1427(m), 1458(s), 2928(m), 3093(m), 3398(br) cm^{-1} . ^1H NMR ($CDCl_3$, 250 MHz): δ = 3.62(s, 1H), 4.15(dd, J_1 = 12.7, J_2 = 3.8 Hz, 1H), 4.56(dd, J_1 = 12.4, J_2 = 8.2 Hz, 1H), 5.60(dd, J_1 = 8.2, J_2 = 3.7 Hz, 1H), 7.17-7.26(m, 5H), 7.28(s, 1H), 7.29- 7.34(m, 2H), 7.62-7.69(m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 64.7, 67.3, 120.7, 126.0, 127.2, 128.2, 128.8, 129.0, 130.2, 136.2, 147.4 ppm. MS: m/z (%) = 267(0.2) $[M+2]^+$, 266(2.89) $[M+1]^+$, 265(6.9) $[M]^+$, 218(3.7), 206(43.1), 178(9.5), 116(100.0), 77(40). $C_{16}H_{15}N_3O$ (265.310): C 72.43, H 5.70; found C 72.56, H 5.57.

2-{4-[(1-naphthyloxy)methyl]-1H-1,2,3-triazol-1-yl}-2-phenylethanol (3e):

Cream solid; 84% yield. M.p. = 89-91 °C. IR (KBr): 698(s), 765(s), 1085(s), 1256(s), 1579(s), 2854(m), 2931(m), 3398(br) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 3.56(s, 1H), 4.19(dd, J_1 = 12.0, J_2 = 3.5 Hz, 1H), 4.58(dd, J_1 = 12.5, J_2 = 7.5 Hz, 1H), 5.34(s, 2H), 5.64(dd, J_1 = 7.5, J_2 = 5.0 Hz, 1H), 6.92(d, J = 7.5 Hz, 1H), 7.12-7.47(m, 9H), 7.65(s, 1H), 7.78(d, J = 7.5 Hz, 1H), 8.25(d, J = 7.5 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 62.3, 64.9, 67.3, 105.4, 120.9, 121.9, 125.2, 125.5, 125.7, 126.4, 127.1, 127.4, 128.9, 129.1, 134.5, 135.9, 144.2, 153.9 ppm. MS: m/z (%) = 346(5.1) $[M+1]^+$, 345(8.7) $[M]^+$, 225(5.1), 174(31.8), 144(100.0), 121(68.9), 81(33.8), 57(66.8). $C_{21}H_{19}N_3O_2$ (345.394): C 73.03, H 5.54; found C 73.11, H 5.40.

7-{[1-(2-hydroxy-2-phenylethyl)-1H-1,2,3-triazol-4-yl]methoxy}-4-methyl-4a,8a-dihydro-2H-chromen-2-one (3f):

Cream solid; 74% yield. M.p. = 157-158 °C. IR (KBr): 825(w), 1085(s), 1072(m), 1137(m), 1386(m), 1614(s), 1732(s), 2830(w), 3271(br) cm^{-1} . ^1H NMR ([D6]DMSO, 250 MHz): δ = 3.40(s, 3H), 3.96-4.00(m, 1H), 4.26-4.29(m, 1H), 5.23(s, 2H), 5.32-5.35(m, 1H), 5.80(s, 1H), 6.16(s, 1H), 6.96-7.10(m, 2H), 7.60-7.64(m, 4H), 7.95-8.16(m, 1H), 8.47(s, 1H) ppm. 4 ^{13}C NMR ([D6]DMSO, 62.9 MHz): δ = 23.2, 66.9, 68.2, 71.4, 106.7, 116.7, 117.7, 118.5, 129.7, 131.6, 132.3, 133.4, 133.8, 142.4, 146.9, 158.6, 159.8, 165.3, 166.2 ppm. MS: m/z (%) = 377(11.8) $[M]^+$, 202(27.0), 174(47.6), 144(60.8), 121(100.0), 103(83.3), 54(89.8). $C_{21}H_{19}N_3O_4$ (377.393): C 66.83, H 5.07; found C 66.96, H 4.92.

N,N-bis{[1-(2-hydroxy-1-phenylethyl)-1H-1,2,3-triazol-4-yl]methyl}-4-methyl benzene sulfonamide (3g):

White solid; 82% yield. M.p. = 185-187 °C. IR (KBr): 698(s), 904(w), 1060(m), 1159(s), 1342(s), 1452(m), 2858(w), 3413(br) cm-1 . ^1H NMR ([D6]DMSO, 250 MHz): δ = 2.24(s, 2H), 3.45(s, 3H), 3.96(m, 2H), 4.18(m, 2H), 4.45(s, 4H), 5.32(m, 2H), 5.74(m, 2H), 7.12(d, J = 7.5 Hz, 2H), 7.31(m, 10H), 7.53(d, J = 7.5 Hz, 2H), 8.47(s, 2H) ppm. ^{13}C NMR ([D6]DMSO, 62.9 MHz): δ = 26.1, 46.7, 68.3, 71.2, 128.8, 131.3, 132.1, 133.4, 133.8, 134.7, 141.5, 142.4, 146.9, 148.2 ppm. MS: m/z (%) = 574(0.4) $[M]^+$, 510(2.3), 418(73.2), 298(12.3), 187(12.7), 144(20.8), 91(100.0). $C_{29}H_{31}N_7O_4S$ (573.666): C 60.72, H 5.45; found C 60.58, H 5.36.

2-(4-Phenyl-1H-1,2,3-triazol-1-yl)cyclohexanol (3j):

Colourless solid; 91% yield. M.p. = 179-180 °C. IR (KBr): 698 (s), 771 (s), 980 (w), 1057 (s), 1088 (s), 1238 (s), 1439 (s), 2862 (w), 2943 (s), 3124 (m), 3310 (br) cm-1; ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.39-2.25 (m, 8 H), 4.09-4.17 (m, 3H), 7.23- 7.36 (m, 3 H), 7.36 (dd, J_1 = 8.2, J_2 = 1.7 Hz, 2H), 7.69 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 24.1, 24.8, 31.5, 33.8, 67.4, 72.5, 120.1, 125.4, 127.9, 128.7, 130.2

ppm. MS: m/z (%) = 244 (2.6) $[M+1]^+$, 243 (6.7) $[M]^+$, 215 (1.5), 203 (2.6), 174 (1.7), 158 (3.7), 117 (100.0), 81 (55.7), 55 (23.5). $C_{14}H_{17}N_3O$ (243.307): C 69.11, H 7.04; found C 69.03, H 6.89.

(1R)-2-[4-(1-hydroxy-1-methylethyl)-1H-1,2,3-triazol-1-yl]cyclohexanol (3k):

White solid; 92% yield. M.p. = 144-146 °C. IR (KBr): 630(m), 964(m), 1228(m), 1639(m), 2864(m), 2943(s), 3350(br), 3562(m) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.41-1.45(m, 2H), 1.60(s, 6H), 1.85-1.88(m, 4H), 2.15-2.19(m, 2H), 3.01(s, 1H), 3.71(s, 1H), 3.98-4.13(m, 2H), 7.48(s, 1H) ppm. ^{13}C NMR (CDCl3, 62.9 MHz): δ = 24.0, 24.8, 29.9, 31.6, 33.8, 67.0, 67.9, 72.4, 119.5, 154.4 ppm. MS: m/z (%) = 226(9.0) $[M+1]^+$, 210(7.3), 149(10.1), 111(19.9), 91(22.4), 71(36.8), 57(100.0). $C_{11}H_{19}N_3O_2$ (225.287): C 58.64, H 8.50; found C 58.51, H 8.36.

(1R)-2-(4-butyl-1H-1,2,3-triazol-1-yl)cyclohexanol (3l):

White solid; 85% yield. M.p. = 76-77 °C. IR (KBr): 962(w), 1070(s), 1218(m), 1450(s), 2858(s), 2937(s), 3258(br) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.87(t, J = 7.5 Hz, 3H), 1.27-1.39(m, 6H), 1.52-1.55(m, 2H), 1.79-1.82(m, 3H), 2.06-2.11(m, 2H), 2.53-2.59(m, 2H), 3.94-4.09(m, 2H), 7.32(s, 1H) ppm. ^{13}C NMR (CDCl3, 62.9 MHz): δ = 13.8, 22.3, 24.0, 24.3, 25.2,5 31.4, 31.7, 33.9, 66.7, 72.3, 120.5, 147.3 ppm. MS: m/z (%) = 223(1.8) $[M]^+$, 194(1.5), 99(11.2), 81(100.0). $C_{12}H_{21}N_3O$ (223.315): C 64.54, H 9.48; found C 64.45, H 9.61.

2-{4-[(4-chloro-2-nitrophenoxy)methyl]-1H-1,2,3-triazol-1-yl}cyclohexanol (3m):

Pale yellow solid; 82% yield. dc. = 145 °C. IR (KBr): 812(m), 1074(m), 1278(s), 1342(s), 1529(s), 1610(m), 2854(m), 2931(m), 3398(br) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.23-2.08(m, 8H), 2.66(s, 1H), 3.99-4.01(m, 1H), 4.14-4.18(m, 1H), 5.34(s, 2H), 7.31(s, 1H), 7.25-7.35(m, 1H), 7.47-7.52(m, 1H), 7.76(s, 1H) ppm. ^{13}C NMR ([D6]DMSO, 62.9 MHz): δ = 23.6, 24.3, 31.6, 34.7, 63.0, 66.0, 71.1, 117.3, 124.2, 124.4, 133.7, 133.9, 139.8, 140.9, 149.4 ppm. MS: m/z (%) = 352(13.5) $[M]^+$, 264(22.1), 236(16.0), 173(22.8), 157(25.5), 121(31.3), 97(43.6), 81(100.0), 55(92.0). $C_{15}H_{17}C_1N_4O_4$(352.773): C 51.07, H 4.86; found C 51.18, H 4.73.

2-[4-({4-[1-(4-{[1-(3-hydroxycyclohexyl)-1H-1,2,3-triazol-4-yl]methoxy}phenyl)-1-methylethyl]phenoxy}methyl)-1H- 1,2,3-triazol-1-yl] cyclohexanol (3o):

White solid; 84% yield. dc. = 200 °C. IR (KBr): 906(w), 1055(m), 1161(s), 1338(s), 1456(s), 2860(m), 2935(m), 3392(br) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 131(s, 6H), 1.42-2.12(m, 16H), 3.80(s, 2H), 3.94(m, 2H), 4.33(m, 2H), 4.90(s, 4H), 6.63(d, J = 7.5 Hz, 4H), 6.87(d, J = 7.5 Hz, 4H), 7.41(s, 2H), ppm. ^{13}C NMR (CDCl3, 62.9 MHz): δ = 21.5, 24.1, 24.7, 30.6, 33.5, 43.0, 67.3, 72.6, 123.8, 124.6, 127.3, 129.9, 141.7, 142.2. ppm. MS: m/z (%) = 586(0.5) $[M]^+$, 530(0.8), 465(1.8), 430(1.7), 374(100.0), 285(18.7), 195(10.3), 152(18.2), 81(49.5). $C_{33}H_{42}N_6O_4$ (586.724): C 67.55, H 7.22; found C 67.68, H 7.09.

1-Phenoxy-3-(4-phenyl-1H-1,2,3-triazol-1-yl) propan-2-ol (3p):

Colorless solid; 75% yield. M.p. = 125-126 °C. IR (KBr): 690 (s), 752 (s), 1041 (m), 1080 (m), 1119 (w), 1250 (s), 1493 (w), 1597 (m), 1724 (w), 2920 (w), 3074 (w), 3425 (b) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ = 3.88 (s, 1H), 4.01-4.05 (m, 2H), 4.55 (dd, J_1 = 12.7, J_2 = 3.5 Hz, 2H), 4.68-4.77 (m, 1H), 6.90-7.02 (m, 3H), 7.6-7.02 (m, 5H), 7.69-7.72 (m, 2H), 7.85 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 53.5, 68.6, 68.9, 114.5, 121.4, 121.6, 125.5, 128.1, 128.8, 129.6, 130.0, 147.2, 158.2 ppm. MS: m/z (%) = 297 (1.6) $[M+2]^+$, 296 (4.4) $[M+1]^+$, 295 (7.1) $[M]^+$, 279 (7.3), 243 (3.7), 222 (5.1), 202 (9.0), 167 (22.1), 149 (62.5), 117 (35.7), 94 (24.2), 77 (51.8), 57 (100.0). $C_{17}H_{17}N_3O_2$ (295.336): C 69.14, H 5.80; found C 69.03, H 5.93.

1-{4-[(1-naphthyloxy)methyl]-1H-1,2,3-triazol-1-yl}-3-phenoxy-2-propanol (3q):

Brown solid; 75% yield. M.p. = 120-122 °C. IR (KBr): 792(m), 1097(s), 1240(s), 1460(s), 1598(s), 2875(m), 2931(m), 3330(br) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ = 3.66(s, 1H), 3.84(m, 2H), 4.36-4.59(m, 3H), 5.23(s, 2H), 6.76-6.81(m, 4H), 7.14-7.32(m, 6H), 7.69-7.71(m, 2H), 8.12(d, J = 7.5 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 53.0, 62.2, 68.7, 105.3, 114.4, 120.8, 121.9, 124.4, 125.3, 125.7, 126.4, 127.4, 129.6, 134.5, 144.1, 153.8, 158.0 ppm. MS: m/z (%) = 377(0.9) $[M]^+$, 280(2.3), 149(17.4), 85(40.8), 57(100.0). $C_{22}H_{23}N_3O_3$ (377.436): C 70.01, H 6.14; found C 69.88, H 6.25.

1-(Allyloxy)-3-(4-phenyl-1H-1,2,3-triazol-1-yl) propan-2-ol (3r):

Colourless solid; 87% yield. M.p. = 71.5–72 8C. IR (KBr): 698 (m), 721 (m), 860 (m), 957 (m), 1076 (s), 1165 (s), 1358 (w), 1458 (w), 2970 (m), 3128 (m), 3356 (br) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ=3.19 (d, J = 5.0 Hz, 2H), 3.70 (d, J = 5.46 Hz, 2H), 3.96-4.11 (m, 2H), 4.27 (dd, J_1 = 13.2, J_2 = 2.6 Hz, 1H), 4.51 (s, 1 H), 4.93 (dd, J_1 = 17.2, J_2 = 10.3 Hz, 1H), 4.99- 5.01 (m, 1 H), 5.53-5.64 (m, 1H), 6.94-7.06 (m, 3 H), 7.36 (dd, J_1 = 8.2, J_2 = 1.7 Hz, 2H), 7.58 (s, 1H) ppm. ^{13}C NMR($CDCl_3$, 62.9 MHz): δ = 53.5, 68.9, 71.3, 72.3, 117.4, 121.0, 125.4, 128.0, 128.7, 129.7, 134.2, 147.0 ppm. MS: m/z (%) = 260 (5.4) $[M+1]^+$, 259 (10.5) $[M]^+$, 230 (4.8), 203 (11.1), 158 (14.9), 132 (16.0), 116 (100.0), 93 (4.2), 77 (46.2), 57 (37.7). $C_{14}H_{17}N_3O_2$ (295.304): C 64.85, H 6.61; found C

64.97, H 6.49.

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Conflict of Interest

The authors declare no conflict of interest.

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