Doped Nano-Sized Copper(I) Oxide (Cu_2O) on Melamine–Formaldehyde Resin: a Highly Efficient Heterogeneous Nano Catalyst for 'Click' Synthesis of Some Novel 1*H*-1,2,3-Triazole Derivatives Having Antibacterial Activity

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A facile and simple protocol for the 1,3-dipolar cycloaddition of organic azides with terminal alkynes catalyzed by doped nano-sized Cu_2O on melamine–formaldehyde resin (nano-Cu_2O–MFR) as a new and convenient heterogeneous catalyst is described. In this method, 'click' cycloaddition of various structurally diverse β-azido alcohols and alkynes in the presence of nano-Cu_2O–MFR in H_2O/THF 1:2 furnished the corresponding 1,4-disubstituted 1*H*-1,2,3-triazole adducts **1a**–**1o** in good to excellent yields at room temperature (*Scheme* and *Table 3*). The nano-Cu_2O–MFR was characterized by scanning electron microscopy (SEM), X-ray diffraction (XRD), inductively coupled plasma (ICP) analysis, and FT-IR. The nano-Cu_2O–MFR could be easily recovered and recycled from the reaction mixture and reused for many consecutive trials without significant decrease in activity (*Table 4*). The *in vitro* antibacterial activities of all synthesized compounds were tested on several *Gram*-positive and/or *Gram*-negative bacteria (*Table 5*). The results demonstrate the promising antibacterial activity for some of the synthesized compounds.

Introduction. – The 1*H*-1,2,3-triazoles [1] are an important class of N-heterocyclic compounds with a wide range of applications in organic and medicinal chemistry. Many bioactive compounds with a broad spectrum of activities such as anti-inflammatory [2], antiviral [3], anticancer [4], anti-allergic [5], anticonvulsant [6], antibiotic [7], antibacterial [8], and antimicrobial activity [9], contain a 1*H*-1,2,3-triazole core in their scaffolds. Additionally, 1*H*-1,2,3-triazoles have also found industrial applications as dyes, corrosion inhibitors, photostabilizers, photographic materials, and agrochemicals [10].

The *Huisgen* 1,3-dipolar cycloaddition of azides and alkynes is one of the most widely used method for the synthesis of 1*H*-1,2,3-triazoles [11]. However, this noncatalyzed process exhibits several disadvantages, including the requirement for high temperature, low yields of the desired product, and poor regioselectivity affording a mixture of 1,4- and 1,5-disubstituted triazoles [12]. The synthetic utility of the *Huisgen* 1,3-dipolar cycloaddition between azides and alkynes was significantly improved since

Sharpless and co-workers [13] and *Meldal* and co-workers [14] have found that Cu^{I} salts dramatically accelerate the reaction. The Cu^{I}-catalyzed *Huisgen* cycloaddition, has enabled the practical and efficient preparation of 1,4-disubstituted 1*H*-1,2,3-triazoles, with favorable selectivity, which normally cannot be prepared *via* traditional *Huisgen* approaches. The required copper(I) catalysts are usually prepared by *in situ* reduction of copper(II) salts with ascorbate [15], oxidation of copper(0) [16], or by comproportionation of copper(0) and copper(II) [15][17]. The catalysts might be copper(0) nanosize clusters [18], or appropriate copper(I) salts (CuI or CuBr) with triphenylphosphine [19], iminopyridine [20], or mono- [13][14] or polydentate [21] N-ligands. To improve reuse and recovery, copper species have been immobilized onto various supports such as activated carbon [22], amine-functionalized polymers [23], zeolites [24], aluminium oxyhydroxide nanofiber [25], Wyoming montmorillonite [26], alumina [27], silica-supported N-heterocyclic carbenes [28], and amine-functionalized silica [29]. However, the immobilized catalysts on solid supports frequently suffer from leakage of catalysts, high reaction temperatures, low yields of product, low activity, and requiring additives.

Melamine–formaldehyde resin (MFR; melamine = 1,3,5-triazine-2,4,6-triamine) is the most useful thermosetting material [30]. MFR is extensively employed for manufacturing composites and panels as well as textile coatings in industry (for information about MFR, see [31]). The ability of MFR to host several cations has been established [32]. The presence of spaces and/or cavities between triazine cores, and also the presence of multi-coordinating N-atoms as well as the capability of forming H-bonds in this cavity turn MFR into a suitable solid support for absorbing metal salts (*Fig. 1*). Additionally, MFR contains many electron-deficient triazine cores that potentially can generate π–π^* interaction between rich π-electron reactants and also triazine cores. Therefore, this property makes MFR a suitable binding site for reactants. Considering the recently reported properties of MFR, we were encouraged to apply MFR as a useful support in organic transformations [33].

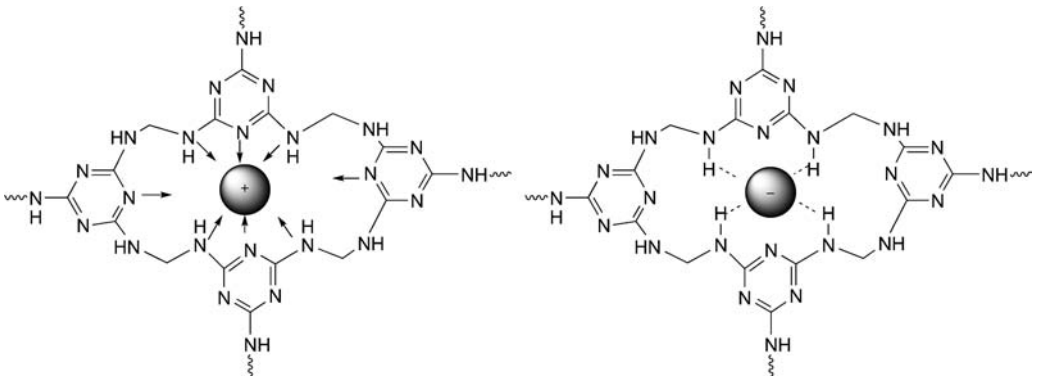
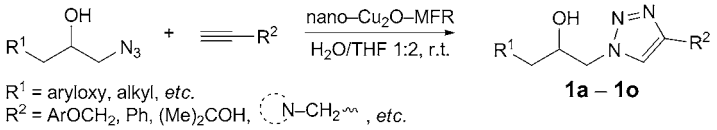


Fig. 1. *Schematic view for potential hosting of cation* (left) *and anion* (right) *by MFR*

In line with our efforts toward the synthesis of new bioactive compounds having 1*H*-1,2,3-triazole cores [34], hereby we establish that doped nano-sized Cu_2O on melamine–formaldehyde resin (nano-Cu_2O–MFR) is a highly efficient heterogeneous

catalyst for *Huisgen* 1,3-dipolar cycloaddition between different terminal alkynes and β-azido alcohols at room temperature resulting in 1*H*-1,2,3-triazole derivatives **1a**–**1o** (*Scheme*).

Scheme. *Reaction of β-Azido Alcohols and Alkynes in the Presence of Nano-Cu_2O–MFR*. For R^1 and R^2, see *Table 3*.



To reveal the bioactivity of the synthesized 1*H*-1,2,3-triazoles **1a**–**1o**, they were screened for their *in vitro* antibacterial activity against some pathogenic *Gram*-negative (*Salmonella typhi* (PTCC-1609), *Pseudomonas aeruginosa* (PTCC-1074), and *Escherichia coli* (PTCC-1338)), and *Gram*-positive bacteria (*Staphylococcus epidermidis* (PTCC-1114) and *Bacillus subtilis* (PTCC-1023)).

Results and Discussion. – Scanning electron microscopy (SEM) and FT-IR spectrometry were utilized to evaluate the morphology and study the formation of nano-Cu_2O–MFR, respectively. The SEM image of nano-Cu_2O–MFR (*Fig. 2*) showed that a narrow size distribution was obtained when adopting the proposed synthetic procedure (see *Exper. Part*). The histogram based on the SEM image, and shown in *Fig. 3* clearly revealed the size distribution and the average size of the nano-Cu_2O–MFR.

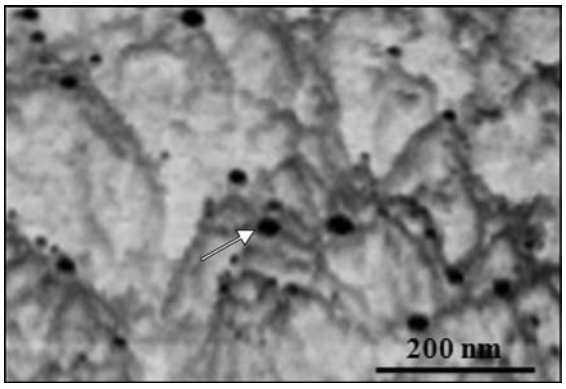


Fig. 2. *Scanning electron microscopy* (SEM) *image of nano-Cu_2O–MFR*

Metal oxides generally give IR absorption bands below 1000 cm^{-1}. In the FT-IR spectrum (KBr disk) of the solid nano-Cu_2O–MFR (*Fig. 4*), an asymmetric band appeared at 470 cm^{-1} which was assigned to the Cu–O bond.

Spectroscopic techniques such as inductively coupled plasma (ICP) analysis and patterned X-ray diffraction (XRD) were employed for the characterization of nano-

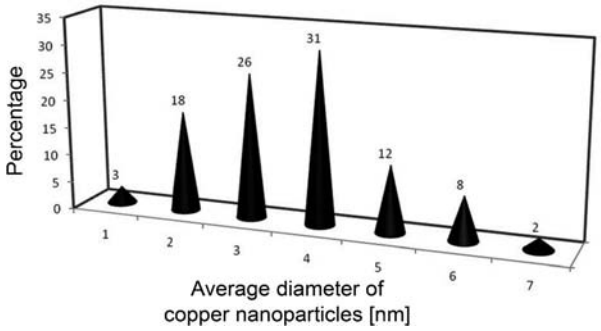


Fig. 3. *Histogram representing the average diameter of nano-Cu_2O–MFR*

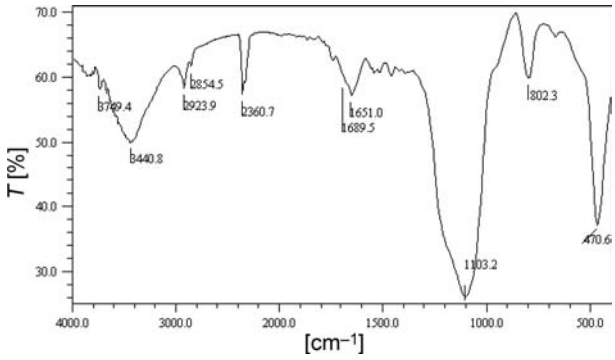


Fig. 4. *FT-IR Spectrum of nano-Cu_2O–MFR*

Cu_2O–MFR. In the XRD pattern of nano-Cu_2O–MFR (*Fig. 5*), the strong peaks correspond to the copper nanostructure, the relevant data of which have been reported in our previous study [35].

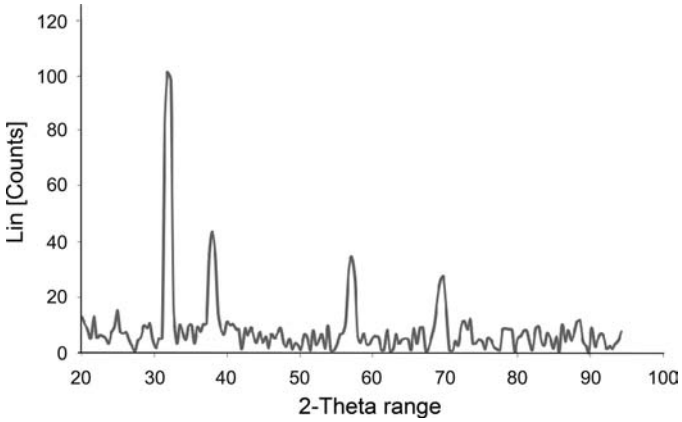
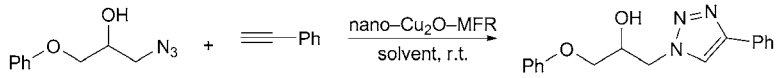


Fig. 5. *XRD Pattern of nano-Cu_2O–MFR*

To establish the optimized cycloaddition conditions, we chose the reaction of phenylacetylene and 1-azido-3-phenoxypropan-2-ol as the model substrates to afford 1-phenoxy-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propan-2-ol (**1a**). The effect of various solvents on this cycloaddition was studied with nano-Cu_2O–MFR (0.3 g, 0.072 mol-% of Cu) at room temperature (*Table 1*). A solution in H_2O/THF 1:2 (*Table 1*, *Entry 6*) proved to be the most appropriate, and this solvent mixture was thus the solvent of choice for all subsequent reactions. When H_2O or THF were employed alone, moderate yields of **1a** were obtained (*Entries 8 and 9*). Other solvents in a 1:2 mixture with H_2O, such as DMSO (*Entry 2*), DMF (*Entry 4*), and *t*-BuOH (*Entry 5*) led to the desired product in satisfactory yields; however, longer times were needed for the reactions to be completed. Other solvents afforded lower yields of **1a**.

Table 1. *Effect of Various Solvents on the Conversion of Phenylacetylene into* **1a** *in the Presence of Nano-Cu_2O–MFR at Room Temperature*



1a

Entry	Solvent[a])	Time [min]	Yield [%][b])
1	H_2O/acetone	150	73
2	H_2O/DMSO	90	84
3	H_2O/$CHCl_3$	75	80
4	H_2O/DMF	110	86
5	H_2O/*t*-BuOH	80	89
6	H_2O/THF	30	93
7	H_2O/MeCN	110	75
8	H_2O	120	61
9	THF	100	70

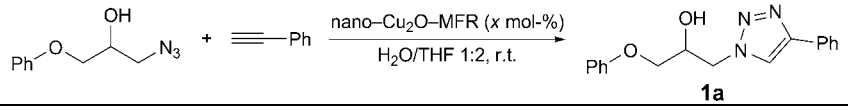
[a]) For *Entries 1–7*, a 1:2 mixture of H_2O/organic solvent was used. [b]) Yield of isolated product **1a**.

To determine the optimized amount of nano-Cu_2O–MFR, different amounts of catalyst were employed in the model reaction (*Table 2*). With 0.3 g (0.072 mol-% of Cu) of nano-Cu_2O–MFR, the reaction progressed properly (*Table 2*, *Entry 3*). Lower yields of **1a** were obtained with 0.1 and 0.2 g of the catalyst (*Entries 1* and *2*), and an extra amount of nano-Cu–MFR had no distinguishable effect on the progress of the reaction (*Entries 4 and 5*).

The appropriate stoichiometric ratio azide/alkyne for obtaining **1a** under the optimized conditions was found to be 1:1.2. This ratio must be precisely determined, since an enhanced molar ratio of the alkyne can lead to the appearance of by-products as the result of Cu(I)-catalyzed alkyne–alkyne coupling.

To establish the scope of this protocol, the optimized conditions were applied to various structurally diverse azides and alkynes (*Table 3*). The results showed that nano-Cu_2O–MFR is an efficient catalyst for the Cu(I)-catalyzed *Huisgen* cycloaddition between an azide and alkyne, producing the 1,4-disubstituted 1*H*-1,2,3-triazoles **1a**–**1o** mainly in excellent yields and short reaction times at room temperature. Thus, numerous functional groups in both the azide and alkyne were tolerated.

Table 2. *Effect of Different Amounts of Nano-Cu_2O–MFR on the Conversion of Phenylacetylene into* **1a** *at Room Temperature*



1a

Entry	Nano-Cu–MFR [mol-%]	Time [min]	Yield [%][a])
1	0.024	80	87
2	0.048	60	90
3	0.072	30	93
4	0.096	30	93
5	0.12	40	90

[a]) Yield of isolated product **1a**.

Compounds **1a**–**1o** were fully characterized, and their structures were confirmed by ^{1}H- and ^{13}C-NMR, and IR spectroscopy, and mass spectrometry, and elemental analysis. Structural assignments of the triazolylmethyl alcohols **1a** and **1b** were made by comparison of their ^{1}H- and ^{13}C-NMR spectra with those reported in [36]. In particular, a *s* at δ(H) 7.50–8.20 in the ^{1}H-NMR spectra is a criterion for a proton at C(5) of the 1*H*-1,2,3-triazole moiety, which perfectly agrees with the literature data.

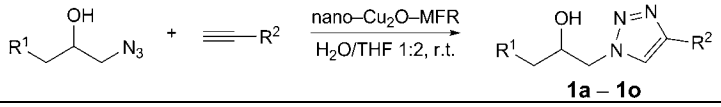
The synthesis of β-azido alcohols used in this research was achieved *via* the regioselective ring opening reaction of corresponding oxiranes with sodium azide in quantitative yields [34b]. The prerequisite terminal alkynes for *Entries 4, 5* and *11–15* of *Table 3* were obtained by means of an S_N2-type reaction of propargyl bromide (= 3-bromoprop-1-yne) and corresponding nucleophiles. This strategy permitted the incorporation of bioactive moieties in the structure of the alkynes and finally the 1*H*-1,2,3-triazole adducts. For instance, a therapeutic agent such as theophylline (= 3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione) was incorporated in the structure of compounds **1k** and **1l** (*Table 3*, *Entries 11* and *12*). This approach allows the synthesis of many adducts with potential biological activities in various medicinal domains.

As expected, disubstituted alkynes such as diphenylacetylene were inactive in the cycloaddition with β-azido alcohols (*Table 3*, *Entry 16*). This behavior is completely consistent with the mechanism of the Cu^I-catalyzed azide–alkyne cycloaddition in which the formation of a copper(I) acetylide species is inevitable.

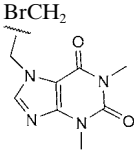
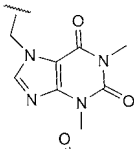
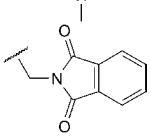
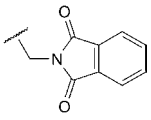
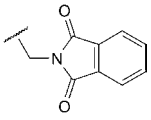
The applicability of this protocol on a preparative scale, was testet with the 1,3-dipolar cycloaddition of the model substrates phenylacetylene and 1-azido-3-phenoxypropan-2-ol on a 100-mmol scale, which gave **1a** efficiently after 30 min in 88% yield under optimized conditions. This compares well to the smaller-scale synthesis (*Table 3*, *Entry 1*).

The reusability of nano-Cu_2O–MFR was also investigated in the 'click' cycloaddition of the model substrates in several runs (*Table 4*). After each run, the solution was vacuum-filtered through a sintered-glass funnel, and the solid was washed successively with THF and dried in a vacuum oven at 100° for 30 min. The catalyst was then reused directly without further purification, and no fresh catalyst was added in subsequent runs. Thus, according to the results (*Table 4*), the catalyst can be recovered,

Table 3. *Nano-Cu_2O–MFR-Catalyzed 'Click' Cycloaddition of β-Azido Alcohols with Alkynes in H_2O/THF 1:2 at Room Temperature*

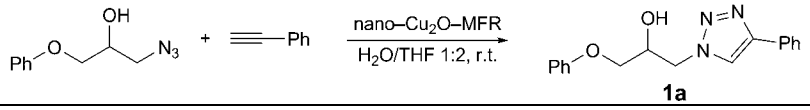


1a – 1o

Entry	β-Azido alcohol (R^1)	Alkyne (R^2)	Product **1**[a])	Time [h]	Yield[b]) [%]
1	PhO	Ph	**1a**	0.5	93
2		Ph	**1b**	0.5	92
3	CH_2=C(Me)COO	Ph	**1c**	1	83
4	2,4-Cl_2–C_6H_3O	4-Cl–C_6H_4–O–CH_2	**1d**	1	80
5	4-Bn–C_6H_4O	4-Cl–C_6H_4–O–CH_2	**1e**	1	81
6	PhO	$Me_2C(OH)$	**1f**	0.75	85
7	4-Bn–C_6H_4O	$Me_2C(OH)$	**1g**	0.5	91
8	4-MeO–C_6H_4O	$Me_2C(OH)$	**1h**	0.5	93
9	PhO	$HOCH_2$	**1i**	0.33	88
10	4-Cl–C_6H_4O	$BrCH_2$	**1j**	0.33	86
11	4-MeO–C_6H_4O		**1k**	0.33	90
12	Me		**1l**	0.5	88
13	4-MeO–C_6H_4O		**1m**	0.5	93
14	Naphthalen-2-yloxy		**1n**	0.5	92
15			**1o**	1	83
16		Ph–C≡C–Ph	n.r.[c])	10	–

[a]) All products were characterized by ^{1}H- and ^{13}C-NMR, IR, CHN and MS analysis. [b]) Yield of isolated product. [c]) No reaction.

Table 4. *The Reusability of Nano-Cu–MFR in Successive Runs for* the *Synthesis of* **1a**



1a

Run	Time [min]	Yield [%][a])
1	30	93
2	40	90
3	48	90
4	56	88
5	60	85

[a]) Yield of isolated product **1a**.

recycled, and reused for many consecutive trials without significant loss of its activity. The amount of leached copper from nano-Cu_2O–MFR was negligible (0.0015% after five runs), as indicated by the Cu^I contents in both fresh catalyst and recycled catalyst (after five runs) determined by ICP analysis.

Compounds **1a**–**1o** were evaluated for their *in vitro* antibacterial activity against several *Gram*-negative (*Salmonella typhi*, *Pseudomonas aeruginosa,* and *Escherichia coli*) and *Gram*-positive (*Staphylococcus epidermidis*, and *Bacillus subtilis*) bacteria (*Table 5*). The antibacterial activity of **1a**–**1o** was compared with that of gentamycin and ampicillin as reference drugs for *Gram*-negative and *Gram*-positive bacteria, respectively.

The minimum inhibitory concentration (*MIC*) values of the examined compounds were measured by a serial dilution assay by using the disc-plate method (*Table 5*). Among the synthesized compounds, **1d** and **1e** were the most potent compounds against *Gram*-positive bacteria. In the case of *S. epidermidis*, compound **1a** also demonstrated promising activity; however its antibacterial activity was weaker ($MIC > 37.5$ μg/ml) than that of **1d** and **1e**. Other tested compounds were inactive or showed varying antibacterial activity against the two examined *Gram*-positive bacteria. In general, compounds **1m** and **1n** were the most active compounds against all examined *Gram*-negative bacteria. Compound **1n** demonstrated a comparable activity ($MIC > 18.75$ μg/ml) against *P. aeruginosa* in comparison with gentamycin as the reference drug ($MIC >$ 12.5 μg/ml), whereas **1b**, **1g**, and **1m** showed lower activity in comparison with **1n**. Additionally, compounds **1m**, **1n**, **1g**, and **1j** exhibited a promising antibacterial activity against *S. typhi*. On the other hand, compounds **1d** and **1l**–**1n** had the best activity against *E. coli* ($MIC > 37.5$ μg/ml).

Concerning the structure–activity relationship (SAR), as the *MIC* results indicate, the antibacterial activity of the synthesized compounds seems to depend on the substituent at the 1,2,3-triazol-1-yl cores. As expected, the maximum antibacterial activity against *Gram*-positive bacteria was observed when a 4-chlorophenoxy was methyl-linked at C(4) of the 1,2,3-triazol-1-yl core (compounds **1d** and **1e**). The activity of **1d** and **1e** can be explained by the intrinsic antibacterial activity of chlorophenols [37]. Compounds **1m** and **1n** having a phthalimide moiety linked to the methyl group at

Table 5. In vitro *Antibacterial Study of Compounds* **1a**–**1o**[a])

Compound	*MIC* [μg/ml]				
	S. epidermidis	*B. subtilis*	*P. aeruginosa*	*S. typhi*	*E. coli*
1a	> 37.5	> 75	100	> 50	> 75
1b	> 50	> 50	> 37.5	> 75	> 50
1c	> 100	> 75	> 50	> 50	> 75
1d	> 25	> 25	> 50	100	> 37.5
1e	> 25	> 25	> 50	> 50	> 75
1f	> 75	> 75	> 50	> 50	> 50
1g	100	> 50	> 37.5	> 37.5	> 50
1h	100	100	> 75	> 75	> 50
1i	100	> 75	> 75	> 50	> 50
1j	> 50	100	> 75	> 37.5	> 50
1k	100	> 50	> 50	> 50	> 75
1l	> 75	100	> 50	> 75	> 37.5
1m	> 75	> 50	> 25	> 25	> 37.5
1n	> 75	> 50	> 18.75	> 25	> 37.5
1o	> 75	> 50	100	100	> 75
Ampicillin[b])	> 18.75	> 12.5	–	–	–
Gentamycin[c])	–	–	> 12.5	> 12.5	> 12.5

[a]) Examined bacteria: *Staphylococcus epidermidis* (PTCC 1114), *Bacillus subtilis* (PTCC 1023), *Pseudomonas aeruginosa* (PTCC 1047), *Salmonella typhi* (PTCC 1609), and *Escherichia coli* (PTCC 1338). [b]) Reference drug for *Gram*-positive bacteria. [c]) Reference drug for *Gram*-negative bacteria.

C(4) of the 1,2,3-triazol-1-yl core demonstrated good activity against all examined *Gram*-negative bacteria. However, **1o** showed a different antibacterial activity against the five examined bacteria although it contains a phthalimide core. The presence of the theophylline moiety in **1k** and **1l** did not enhance the activity against the microorganisms. The quantitative structural–activity relationships (QSAR) of **1a**–**1o** are under investigation, and results will be reported in due course.

In summary, the preparation, characterization, and application of nano-Cu_2O–MFR as a highly efficient heterogeneous catalyst in the 1,3-dipolar cycloaddition of various β-azido alcohols and alkynes were examined. The cycloadditions proceeded under very mild conditions and efficiently in H_2O/THF 1:2 at room temperature. This protocol allowed the facile and regioselective synthesis of 1,4-disubstituted 1*H*-1,2,3-triazoles in good to excellent yields. The nano-Cu_2O–MFR was shown to be a chemically and thermally stable, cheap, and environmentally compatible heterogeneous nanocatalyst that could be reused for many consecutive experiments without any significant loss of its activity. Antibacterial screening of all synthesized compounds was conducted, revealing promising antibacterial activity against some *Gram*-positive and *Gram*-negative bacteria.

We thank the Shiraz University of Technology and Shiraz University of Medical Sciences Councils for partial support of this work.

Experimental Part

1. *General.* All chemicals were obtained from commercial sources. Solvents were purified and stored over 3-Å molecular sieves. TLC: *SILG/UV 254* silica-gel plates. Column chromatography (CC): silica gel *60* (SiO_2; 0.063–0.200 mm, 70–230 mesh; *ASTM*). M.p.: *Büchi-510* apparatus; open capillaries; uncorrected. IR Spectra: S*himadzu-FT-IR-8300* spectrophotometer; ν in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-Avance-DPX-250* spectrometer; at 250 and 62.5 MHz, resp.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. GC/MS: *Shimadzu-GC/MS-QP-1000-E*X apparatus; in *m*/*z* (rel.%). Elemental analyses (CHNS): *Perkin-Elmer-240-B* micro-analyzer.

2. *Nano-Cu_2O–Melamine-Formaldehyde Resin* (nano-Cu_2O–MFR). A suspension of pure MFR (0.5 g) in 0.01M aq. NaOH (20 ml) was refluxed for 12 h. Then, the mixture was cooled, the extra soln. decanted, and the remaining suspension containing MFR centrifuged at 5000 rpm. The separated MFR powder was dried in a vacuum oven at 250° for 4 h. To dry MFR (0.3 g), solid CuI (0.045 g, 0.24 mmol) was added, and the mixture was mechanically homogenized in a ball mill and exposed to microwave irradiation at 800 W for 5 min. Afterward, the sample was sonicated in a sonicator at 400 W (freq. 50 MHz), and nano-Cu_2O–MFR was dried in a vacuum oven at 250° for 2 h. Scanning electron microcopy (*SEM-XL-30-FEG* instrument (*Philips*; 20 KV) inductively coupled plasma (ICP) analysis and patterned X-ray diffraction (XRD, *D8 Advance*, *Bruker AXS*) were employed for the characterization of nano-Cu_2O–MFR.

3. *1,3-Dipolar Cycloaddition of β-Azido Alcohols with Terminal Alkynes: General Procedure.* A mixture of alkyne (6 mmol), nano-Cu_2O–MFR (0.3 g, 0.072 mol-% of Cu), and the appropriate *β*-azido alcohol (5 mmol) in H_2O/THF 1:2 (12 ml) was stirred at r.t. until TLC monitoring indicated no further progress in the conversion (*Table 3*). The catalyst was filtered off and the filtrate concentrated. The remaining foam was dissolved in $CHCl_3$ (50 ml), the soln. washed with H_2O (2 × 50 ml), dried (Na_2SO_4), and concentrated, and the crude product purified by CC (SiO_2).

*1-Phenoxy-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propan-2-ol* (=*α-(Phenoxymethyl)-4-phenyl-1*H*-1,2,3-triazole-1-ethanol*; **1a**): CC (AcOEt/hexane 2:1) yielded 1.37 g (93%). Colorless solid. M.p. 125–126°. IR (KBr): 3420 (br.), 3071*s*, 2927*m*, 1661*s*, 1595*m*, 1490*s*. ^1H-NMR ($CDCl_3$): 3.84 (*s*, OH, exchangeable with D_2O); 4.03–4.09 (*m*, NCH_2CH); 4.51 (*dd*, *J* = 3.6, 12.8, ArOCH_2); 4.66–4.78 (*m*, C*H*OH); 6.92–7.04 (*m*, 3 arom. H); 7.60–7.64 (*m*, 5 arom. H); 7.69–7.73 (*m*, 2 arom. H); 7.87 (*s*, H–C(5) of triaz.). ^{13}C-NMR ($CDCl_3$): 53.56; 68.63; 68.94; 114.55; 121.47; 121.62; 125.54; 128.15; 128.82; 129.66; 130.09; 147.23; 158.27. MS: 295.13 (7.1, M^+). Anal. calc. for $C_{17}H_{17}N_3O_2$ (295.34): C 69.14, H 5.80, N 14.23; found: C 69.05, H 5.91, N 14.15.

*2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)cyclohexanol* (**1b**): CC (AcOEt/hexane 2:1) yielded 1.11 g (92%). White solid. M.p. 181–182°. IR (KBr): 3300 (br.), 3045*s*, 2974*m*, 1590*s*, 1586*m*, 1455*s*. ^1H-NMR ($CDCl_3$): 1.25–1.46 (*m*, CH_2, CH); 1.87–2.21 (*m*, 2 CH_2, CH); 3.66 (*s*, OH, exchangeable with D_2O); 4.11 (br. *s*, NC*H*C*H*OH); 7.30–7.33 (*m*, 3 arom. H); 7.62–7.72 (*m*, 2 arom. H, H–C(5) of triaz.). ^{13}C-NMR ($CDCl_3$): 24.03; 24.78; 31.49; 33.75; 67.56; 72.53; 125.47; 128.09; 128.75; 131.28; 133.62; 147.39. MS: 243.14 (6.4, M^+). Anal. calc. for $C_{14}H_{17}N_3O$ (243.30): C 69.11, H 7.04, N 17.27; found: C 69.18, H 7.00, N 17.35.

*2-Hydroxy-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propyl 2-Methylprop-2-enoate* (**1c**): CC (AcOEt/hexane 2:1) yielded 1.19 g (83%). White solid. M.p. 105–106°. IR (KBr): 3346 (br.), 3050*s*, 2982*m*, 1596*s*, 1585*m*, 1458*s*. ^1H-NMR ((D_6)DMSO): 2.46 (*s*, Me); 3.31–3.39 (*m*, NCH_2CH); 3.86 (*s*, OH, exchangeable with D_2O); 4.02 (br. *s*, =CH_2); 4.18 (*dd*, *J* = 8.0, 13.5, OCH_2); 4.48–4.54 (*m*, C*H*OH); 7.28–7.43 (*m*, 3 arom. H); 7.80–7.83 (*m*, 2 arom. H); 8.45 (*s*, H–C(5) of triaz.). ^{13}C-NMR ((D_6)DMSO): 18.25; 53.51; 63.73; 70.88; 122.70; 125.52; 128.14; 129.31; 131.39; 133.52; 136.71; 146.41; 167.36. MS: 287.13 (4.7, M^+). Anal. calc. for $C_{15}H_{17}N_3O_3$ (287.31): C 62.71, H 5.96, N 14.63; found: C 62.60, H 6.05, N 14.69.

*1-{4-[(4-Chlorophenoxy)methyl]-1*H*-1,2,3-triazol-1-yl}-3-(2,4-dichlorophenoxy)propan-2-ol* (=*4-[(4-Chlorophenoxy)methyl]-α-[(2,4-dichlorophenoxy)methyl]-1*H*-1,2,3-triazole-1-ethanol*; **1d**): CC (AcOEt/hexane 2:1) yielded 1.71 g (80%). Pale yellow solid. M.p. 129–130°. IR (KBr): 3264 (br.), 3028*s*, 2921*m*, 1647*s*, 1590*m*, 1491*s*. ^1H-NMR ((D_6)DMSO): 3.97–4.08 (*m*, NCH_2CH); 4.28 (*s*, OH, exchangeable with D_2O); 4.45 (*dd*, *J* = 7.5, 13.8, 1 H, ArOCH_2); 4.61 (*dd*, *J* = 3.2, 13.8, 1 H, ArOCH_2); 5.13 (*s*, OCH_2C=C); 5.66–5.68 (*m*, C*H*OH); 7.02–7.34 (*m*, 6 arom. H); 7.51 (*s*, 1 arom. H); 8.19 (*s*, H–C(5) of triaz.). ^{13}C-NMR ((D_6)DMSO): 52.52; 61.32; 67.58; 70.64; 115.17; 116.36; 122.54; 124.52;

124.75; 125.61; 128.00; 128.68; 129.14; 142.14; 152.79; 156.82. MS: 427.03 (2.6, M^+). Anal. calc. for $C_{18}H_{16}Cl_3N_3O_3$ (427.70): C 50.43, H 3.76, Cl 24.81, N 9.80; found: C 50.57, H 3.81, Cl 24.87, N 9.71.

*1-(4-Benzylphenoxy)-3-[4-[(4-chlorophenoxy)methyl]-1*H*-1,2,3-triazol-1-yl]propan-2-ol* (=*4-[(4-Chlorophenoxy)methyl]-α-[[4-(phenylmethyl)phenoxy]methyl}-1*H*-1,2,3-triazole-1-ethanol*; **1e**): CC (AcOEt/hexane 2:1) yielded 1.82 g (81%). White solid. M.p. 110–111°. IR (KBr): 3262 (br.), 3029*s*, 2912*m*, 1604*s*, 1575*m*, 1492*s*. ^{1}H-NMR ((D$_6$)DMSO): 3.59 (*s*, PhCH_2), 3.85–3.88 (*m*, NCH_2CH); 4.10 (*s*, OH, exchangeable with D$_2$O); 4.39 (*dd*, *J* = 7.6, 13.8, 1 H, ArOCH_2); 4.56 (*dd*, *J* = 3.3, 13.8, 1 H, ArOCH_2); 5.13 (*s*, OCH$_2$C≡C); 5.57–5.59 (*m*, C*H*OH); 6.83 (*d*, *J* = 8.3, 2 arom. H); 7.04–7.56 (*m*, 11 arom. H); 8.18 (*s*, H–C(5) of triaz.). ^{13}C-NMR ((D$_6$)DMSO): 40.44; 52.63; 61.31; 67.77; 69.47; 114.46; 116.42; 124.50; 125.61; 125.79; 128.31; 128.51; 129.18; 129.64; 133.53; 141.63; 142.02; 156.60; 156.86. MS: 449.15 (3.2, M^+). Anal. calc. for $C_{25}H_{24}ClN_3O_3$ (449.93): C 66.74, H 5.38, Cl 7.88, N 9.34; found: C 66.86, H 5.34, Cl 7.81, N 9.45.

*1-[4-(2-Hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl]-3-phenoxypropan-2-ol* (=*4-(1-Hydroxy-1-methylethyl)-α-(phenoxymethyl)-1*H*-1,2,3-triazole-1-ethanol*; **1f**): CC (AcOEt/hexane 2:1) yielded 1.17 g (85%). White solid. M.p. 92–93°. IR (KBr): 3316 (br.), 3100*s*, 2970*m*, 1597*m*, 1588*m*, 1468*s*. ^{1}H-NMR ((D$_6$)DMSO): 1.39 (*s*, 2 Me), 3.84–3.86 (*m*, NCH_2CH); 4.15 (*s*, CHO*H*, exchangeable with D$_2$O); 4.29 (*dd*, *J* = 7.3, 13.8, 1 H, ArOCH_2); 4.44 (*dd*, *J* = 3.8, 13.8, 1 H, ArOCH_2); 5.03 (*s*, (Me)$_2$CO*H*, exchangeable with D$_2$O); 5.48–5.50 (*m*, C*H*OH); 6.85–6.88 (*m*, 3 arom. H); 7.18–7.24 (*m*, 2 arom. H); 7.78 (*s*, H–C(5) of triaz.). ^{13}C-NMR ((D$_6$)DMSO): 30.69; 52.42; 67.01; 67.86; 69.40; 114.46; 120.73; 121.44; 129.45; 155.50; 158.28. MS: 277.14 (1.3, M^+). Anal. calc. for $C_{14}H_{19}N_3O_3$ (277.32): C 60.63, H 6.91, N 15.15; found: C 60.75, H 6.83, N 15.10.

*1-(4-Benzylphenoxy)-3-[4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-y])propan-2-ol* (=*4-(1-Hydroxy-1-methylethyl)-α-{[4-(phenoxymethyl)phenoxy]methyl}-1*H*-1,2,3-triazole-1-ethanol*; **1g**): CC (AcOEt/hexane 2:1) yielded 1.67 g (91%). White solid. M.p. 86–87°. IR (KBr): 3329 (br.), 3065*s*, 2971*m*, 1643*s*, 1584*m*, 1511*m*, 1453*s*. ^{1}H-NMR ((D$_6$)DMSO): 1.22 (*s*, 2 Me); 3.18 (*s*, PhCH_2); 3.63–3.65 (*m*, NCH_2CH); 3.95 (*s*, CHO*H*, exchangeable with D$_2$O); 4.09 (*dd*, *J* = 7.5, 13.7, 1 H, ArOCH_2); 4.25 (*dd*, *J* = 2.7, 13.4, 1 H, ArOCH_2); 4.88 (*s*, Me$_2$CO*H*, exchangeable with D$_2$O); 5.29–5.31 (*m*, C*H*OH); 6.60 (*d*, *J* = 8.2, 2 arom. H); 6.86–7.04 (*m*, 7 arom. H); 7.61 (*s*, H–C(5) of triaz.). ^{13}C-NMR ((D$_6$)DMSO): 30.71; 40.40; 52.44; 67.01; 67.87; 69.52; 114.46; 121.56; 125.79; 128.31; 128.51; 129.65; 133.52; 141.62; 155.66; 156.62. MS: 367.19 (5.1, M^+). Anal. calc. for $C_{21}H_{25}N_3O_3$ (367.44): C 68.64, H 6.86, N 11.44; found: C 68.50, H 6.81, N 11.53.

*1-[4-(2-Hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl]-3-(4-methoxyphenoxy)propan-2-ol* (=*4-(1-Hydroxy-1-methylethyl)-α-[(4-methoxyphenoxy)methyl]-1*H*-1,2,3-triazole-1-ethanol*; **1h**): CC (AcOEt/hexane 2:1) yielded 1.42 g (93%). White solid. M.p. 70–71°. IR (KBr): 3310 (br.), 3080*s*, 2976*m*, 1590*m*, 1584*m*, 1475*s*. ^{1}H-NMR (CDCl$_3$): 1.44 (*s*, 2 Me); 3.64 (*s*, MeO); 3.79–3.83 (*m*, NCH_2CH); 4.27–4.34 (*m*, ArOCH_2, CHO*H*); 4.47–4.53 (*m*, C*H*OH, (Me)$_2$CO*H*); 6.66–6.74 (*m*, 4 arom. H); 7.54 (*s*, H–C(5) of triaz.). ^{13}C-NMR (CDCl$_3$): 30.89; 53.29; 55.64; 68.09; 68.65; 69.81; 114.66; 115.52; 121.59; 152.34; 154.14; 155.08. MS: 307.15 (5.8, M^+). Anal. calc. for $C_{15}H_{21}N_3O_4$ (307.34): C 58.62, H 6.89, N 13.67; found: C 58.73, H 6.85, N 13.79.

*1-[4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]-3-phenoxypropan-2-ol* (=*4-(Hydroxymethyl)-α-(phenoxymethyl)-1*H*-1,2,3-triazole-1-ethanol*; **1i**): CC (AcOEt/hexane 2:1) yielded 1.09 g (88%). Bright yellow oil. IR (film): 3325 (br.); 3063*s*, 2981*m*, 1595*s*, 1580*m*, 1464*s*. ^{1}H-NMR (CDCl$_3$): 3.94–3.95 (*m*, NCH_2CH); 4.34–4.37 (*m*, ArOCH_2); 4.54–4.59 (*m*, CH_2OH, C*H*OH); 4.91 (*s*, CHO*H*, exchangeable with D$_2$O); 5.35 (*s*, CH$_2$O*H*, exchangeable with D$_2$O); 6.83–6.95 (*m*, 3 arom. H); 7.19–7.25 (*m*, 2 arom. H); 7.75 (*s*, H–C(5) of triaz.). ^{13}C-NMR (CDCl$_3$): 53.26; 53.28; 56.12; 68.75; 114.46; 121.51; 123.69; 129.63; 148.57; 158.05. MS: 249.11 (11.5, M^+). Anal. calc. for $C_{12}H_{15}N_3O_3$ (249.27): C 57.82, H 6.07, N 16.86; found: C 57.95, H 6.14, N 16.78.

*1-[4-(Bromomethyl)-1*H*-1,2,3-triazol-1-yl]-3-(4-chlorophenoxy)propan-2-ol* (=*(4-Bromomethyl)-α-[(4-chlorophenoxy)methyl]-1*H*-1,2,3-triazole-1-ethanol*; **1j**): CC (AcOEt/hexane 2:1) yielded 1.49 g (86%). Bright yellow oil. IR (film): 3400 (br.), 3025*s*, 2983*m*, 1592*s*, 1587*m*, 1452*s*. ^{1}H-NMR (CDCl$_3$): 3.87–3.91 (*m*, NCH_2CH); 4.39–4.43 (*m*, ArOCH_2); 4.52–4.55 (*m*, C*H*OH); 4.72 (*s*, CH$_2$Br); 4.95 (*s*, CHO*H*, exchangeable with D$_2$O); 6.84 (*d*, *J* = 8.4, 2 arom. H);7.09 (*d*, *J* = 8.4, 2 arom. H); 7.75 (*s*, H–C(5) of triaz.). ^{13}C-NMR (CDCl$_3$): 53.12; 53.58; 56.52; 68.83; 115.76; 122.40; 125.94; 129.47; 149.71; 160.28.

MS: 344.99 (7.3, M^+). Anal. calc. for $C_{12}H_{13}BrClN_3O_2$ (346.61): C 41.58, H 3.78, Br 23.05, Cl 10.23, N 12.12; found: C 41.64, H 3.70, Br 23.17, Cl 10.18, N 12.25.

*3,7-Dihydro-7-{[1-[2-hydroxy-3-(4-methoxyphenoxy)propyl]-1*H*-1,2,3-triazol-4-yl}methyl]-1,3-dimethyl-1*H*-purine-2,6-dione* (**1k**): CC (AcOEt) yielded 1.98 g (90%). White solid. M.p. 183–184°. IR (KBr): 3222 (br.), 3127*s*, 2931*m*, 1725*s*, 1710*s*, 1657*s*, 1549*m*, 1439*s*. ^{1}H-NMR ((D$_6$)DMSO): 3.16 (*s*, Me–N(3)); 3.35 (*s*, Me–N(1)); 3.65 (*s*, MeO); 3.80–3.83 (*m*, NC*H*$_2$CH); 4.15 (*s*, OH, exchangeable with D$_2$O); 4.35 (*dd*, *J* = 7.5, 13.8, 1 H, ArOC*H*$_2$); 4.51 (*dd*, *J* = 3.3, 13.8, 1 H, ArOC*H*$_2$); 5.49–5.51 (*m*, C*H*OH); 5.54 (*s*, NCH$_2$C=C); 6.75–6.83 (*m*, 4 arom. H); 8.07 (*s*, H–C(5) of triaz.); 8.13 (*s*, H–C(8) of theophyl.). ^{13}C-NMR ((D$_6$)DMSO): 27.42; 29.28; 41.04; 52.68; 55.21; 67.75; 69.96; 105.72; 114.40; 115.31; 124.77; 141.99; 142.27; 148.17; 150.85; 152.22; 153.43; 154.29. MS: 441.18 (10.3, M^+). Anal. calc. for $C_{20}H_{23}N_7O_5$ (441.44): C 54.42, H 5.25, N 22.21; found: C 54.31, H 5.39, N 22.27.

*3,7-Dihydro-7-{[1-(2-hydroxybutyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1,3-dimethyl-1*H*-purine-2,6-dione* (**1l**): CC (AcOEt) yielded 1.46 g (88%). White solid. M.p. 144–145°. IR (KBr): 3252 (br.), 3107*s*, 2961*m*, 1719*s*, 1708*s*, 1665*s*, 1542*m*, 1431*s*. ^{1}H-NMR ((D$_6$)DMSO): 0.82 (*t*, *J* = 7.2, *Me*CH$_2$); 1.13–1.38 (*m*, *Me*CH$_2$); 3.16 (*s*, Me–N(3)); 3.35 (*s*, Me–N(1)); 3.68 (*s*, OH, exchangeable with D$_2$O); 4.12 (*dd*, *J* = 7.6, 13.7, 1 H, CH$_2$N); 4.28 (*dd*, *J* = 3.2, 13.7, 1 H, CH$_2$N); 4.94–4.97 (*m*, C*H*OH); 5.52 (*s*, NCH$_2$C=C); 8.00 (*s*, H–C(5) of triaz.); 8.11 (*s*, H–C(8) of theophyl.). ^{13}C-NMR ((D$_6$)DMSO): 9.57; 27.04; 27.42; 29.29; 41.04; 55.04; 70.21; 105.69; 124.47; 141.85; 142.28; 148.16; 150.86; 154.29. MS: 333.15 (11.7, M^+). Anal. calc. for $C_{14}H_{19}N_7O_3$ (333.35): C 50.44, H 5.75, N 29.41; found: C 50.49, H 5.87, N 29.54.

*2-{[1-[2-Hydroxy-3-(4-methoxyphenoxy)propyl]-1*H*-1,2,3-triazol-4-yl}methyl]-1*H*-isoindole-1,3(2*H*)-dione* (**1m**): CC (AcOEt/hexane 4:1) yielded: 1.89 g (93%). White solid. M.p. 141–142°. IR (KBr): 3326 (br.), 3145*s*, 2990*m*, 2971*m*, 1764*s*, 1709*s*, 1506*m*, 1427*s*. ^{1}H-NMR ((D$_6$)DMSO): 3.64 (*s*, MeO); 3.81–3.83 (*m*, NC*H*$_2$CH); 4.17 (*s*, OH, exchangeable with D$_2$O); 4.33 (*dd*, *J* = 7.8, 13.8, 1 H, ArOC*H*$_2$); 4.50 (*dd*, *J* = 3.4, 13.8, 1 H, ArOC*H*$_2$); 4.83 (*s*, NCH$_2$C=C); 5.50–5.52 (*m*, C*H*OH); 6.81–6.85 (*m*, 4 arom. H); 7.80–7.82 (*m*, 4 arom. H); 8.03 (*s*, H–C(5) of triaz.). ^{13}C-NMR ((D$_6$)DMSO): 32.84; 52.67; 55.22; 67.79; 70.04; 114.46; 115.38; 123.09; 124.13; 131.48; 134.41; 141.92; 152.25; 153.44; 167.26. MS: 408.14 (3.9, M^+). Anal. calc. for $C_{21}H_{20}N_4O_5$ (408.41): C 61.76, H 4.94, N 13.72; found: C 61.70, H 5.03, N 13.76.

*2-{[1-[2-Hydroxy-3-(naphthalen-2-yloxy)propyl]-1*H*-1,2,3-triazol-4-yl}methyl]-1*H*-isoindol-1,3(2*H*)-dione* (**1n**): CC (AcOEt/hexane 4:1) yielded 1.97 g (92%). Pale yellow solid. M.p. 208–209°. IR (KBr): 3366 (br.), 3152*m*, 3087*s*, 2931*m*, 1775*s*, 1723*s*, 1628*s*, 1558*m*, 1423*s*. ^{1}H-NMR ((D$_6$)DMSO): 4.03–4.05 (*m*, NC*H*$_2$CH); 4.28 (*s*, OH, exchangeable with D$_2$O); 4.42 (*dd*, *J* = 7.5, 13.8, 1 H, ArOC*H*$_2$); 4.57 (*dd*, *J* = 3.6, 13.8, 1 H, ArOC*H*$_2$); 4.84 (*s*, NCH$_2$C=C); 5.61–5.64 (*m*, C*H*OH); 7.12–7.42 (*m*, 4 arom. H); 7.74–7.86 (*m*, 7 arom. H); 8.08 (*s*, H–C(5) of triaz.). ^{13}C-NMR ((D$_6$)DMSO): 32.87; 52.68; 67.71; 69.52; 106.72; 118.57; 123.09; 123.59; 124.19; 126.33; 126.64; 127.43; 128.48; 129.24; 131.49; 134.13; 134.42; 141.97; 156.14; 167.27. MS: 428.15 (7.5, M^+). Anal. calc. for $C_{24}H_{20}N_4O_4$ (428.44): C 67.28, H 4.71, N 13.08; found: C 67.36, H 4.63, N 13.19.

*2-{[1-(2-Hydroxycyclohexyl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-isoindol-1,3(2*H*)-dione* (**1o**): CC (AcOEt/hexane 2:1) yielded 1.35 g (83%). White solid. M.p. 170–171°. IR (KBr): 3290 (br.), 3100*s*, 2985*m*, 1593*s*, 1580*m*, 1465*s*. ^{1}H-NMR (CDCl$_3$): 0.94–0.99 (*m*, 2 CH$_2$); 1.65–1.82 (*m*, 2 CH$_2$); 3.30 (*s*, OH, exchangeable with D$_2$O); 3.94–3.97 (*m*, C*H*OH); 4.12–4.22 (*m*, NCH); 4.96 (*s*, NCH$_2$C=C); 7.26 (*s*, H–C(5) of triaz.); 7.68–7.71 (*m*, 2 arom. H); 7.81–7.84 (*m*, 2 arom. H). ^{13}C-NMR (CDCl$_3$): 14.11; 23.93; 24.65; 29.34; 31.61; 33.67; 72.43; 123.45; 131.98; 134.09; 134.73; 147.28; 167.66. MS: 326.14 (9.7, M^+). Anal. calc. for $C_{17}H_{18}N_4O_3$ (326.35): C 62.57, H 5.56, N 17.17; found: C 62.45, H 5.63, N 17.10.

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Received April 29, 2012