

## Ultrasound assisted Synthesis of Thiazolidine Thiones Containing 1,2,3-triazoles Using Cu/TiO<sub>2</sub>

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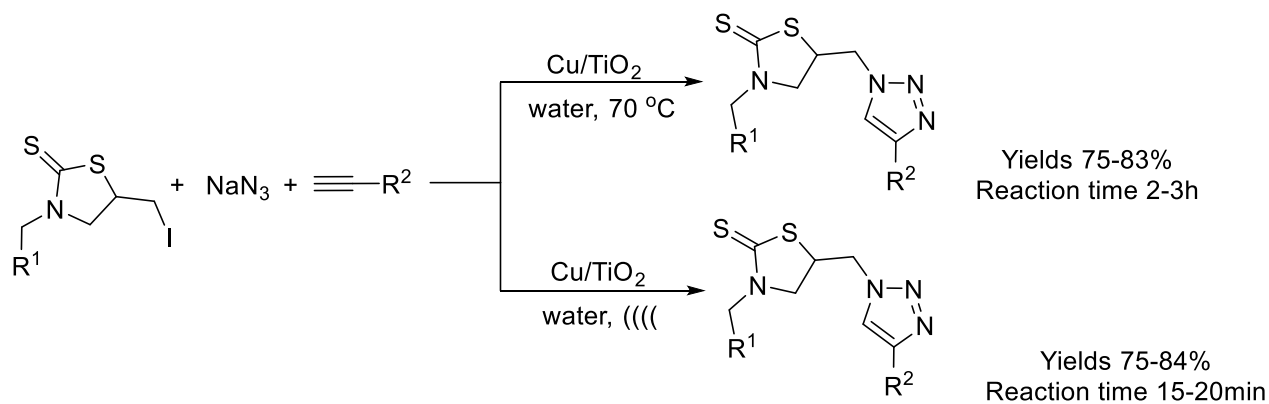
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### Abstract

Oxidised copper nanoparticles on TiO<sub>2</sub> have been found to effectively catalyze the multicomponent synthesis of 1,4-disubstituted 1,2,3-triazoles in water under both conventional heating and ultrasonic irradiation conditions. The Cu/TiO<sub>2</sub> nanocatalyst is easy to prepare, very versatile and recyclable. Following the optimized conditions, an array of 1,2,3-triazoles containing thiazolidine-2-thiones were synthesized from 5-iodomethylthiazolidine-2-thiones, sodium azide, and phenylacetylene. All the compounds were evaluated for antibacterial activity and some of them displayed varying levels of antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.



**Keywords:** 1,2,3-Triazole, thiazolidine-2-thione, heterogeneous catalyst, ultrasonic irradiation, 1,3-dipolar cycloaddition

## Introduction

1,2,3-Triazole and its derivatives are potential pharmacophore which received considerable attention over the past few years. They also exhibit wide range of biological properties such as anti HIV, antiallergic, antimicrobial, antifungal and antitumor.<sup>1-5</sup> In recent years, several different methods have been reported for the synthesis of 1,2,3-triazole derivatives and as a result, the multiple derivatives of triazole ring were synthesized.<sup>6-15</sup> For the 1,2,3 isomer, copper(I)-catalyzed 1,3-dipolar cycloaddition of substituted azides and terminal alkynes, [3+2] Huisgen's cycloaddition reaction, is the most common method for the synthesis of these compounds. Great efforts have been assigned in order to increase the general efficiency of the process adopted to numerous applications of the resulting 1,2,3-triazoles.<sup>16, 17</sup>

The high costs of transition-metal catalysts and toxic effects of many transition metals have inspired an increased interest in immobilizing catalysts onto a support, particularly for biological applications.<sup>18</sup> The supported reagents can assist the isolation, recovery and recycling of the catalyst by filtration, thus providing environmentally cleaner processes. The immobilization of metal on inorganic supports with high surface area improves the stability and dispersion of the particles and obtain active and recyclable heterogeneous nanocatalysts as a result.<sup>19, 20</sup> With these principles in mind, development of various synthetic modifications such as utilization of various catalysts based on copper ions immobilized on different inorganic supports have considerable advantages for overcoming some of drawbacks of classical Huisgen's cycloaddition reaction, such as harsh conditions, long reaction times and low to moderate yields with certain substrates.<sup>21-23</sup> No reports are available on the synthesis of 1,4-disubstituted 1,2,3-triazoles by use of Cu/TiO<sub>2</sub> nanocatalyst. Therefore, investigation of the preparation of 1,2,3-triazoles using Cu/TiO<sub>2</sub> nanocatalyst as a heterogeneous catalyst via copper-catalyzed azide alkyne cycloaddition (CuAAC) was carried out in this study.

Several heterocyclic moieties containing of nitrogen, sulfur, oxygen hetero-atom have been explored for the development of new generation antimicrobial agents.<sup>24</sup> Thiazolidine thiones are one of the most important classes of heterocycles that demonstrated the potential antibacterial and antifungal activities.<sup>25</sup> Thiazolidine thiones are five membered heterocycles of dithiocarbamates family consisting nitrogen and sulfur atoms attaching on the carbon of C=S bond, are one of the key building blocks in drug discovery and synthesis of valuable natural products.<sup>26, 27</sup>

The 1,2,3-triazole heterocycles have gained significant interest of synthetic organic chemists for present of this moiety in a number of compounds which show diverse biological activities.<sup>24,28,29</sup> In this communication, we wish to report the synthesis of a series of 1,2,3-triazoles containing thiazolidine-2-thiones moieties. Although there have been a lot of reports about the synthesis of 1,2,3-triazoles and their pharmacological properties, insufficient effort have been made to study thiazolidine-2-thiones containing 1,2,3-triazole groups. We wish to present herein our contribution to the 1,3-dipolar cycloaddition of alkynes and in-situ generated azides, from different precursors, catalyzed by Cu/TiO<sub>2</sub> in various solvents to achieve 1,4-disubstituted 1,2,3-triazoles. The reactions were carried out under both conventional heating and ultrasonic irradiation conditions (ultrasonic probe).

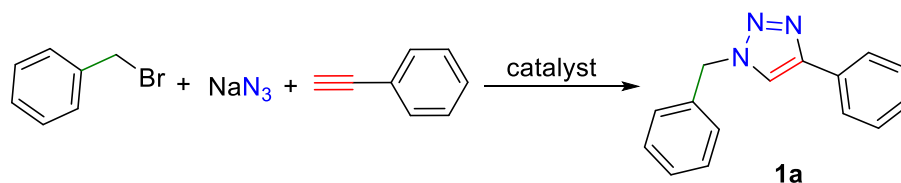
## Results and Discussion

In recent years, a main purpose in synthetic organic chemistry has been to develop environmentally greener and economically competitive processes for the efficient synthesis of biologically active compounds.<sup>30, 31</sup>

Because of the wide use of heterogeneous nanocatalysts in different area of organic chemistry, here we wish to report an efficient and environmentally benign method for the synthesis of 1,4-disubstituted 1,2,3-triazoles via 1,3-dipolar condensation reaction in the presence of Cu/TiO<sub>2</sub> nanocatalyst as recyclable and active catalyst in water at ambient temperature under both conventional and ultrasound irradiation conditions. Several attempts were made in order to optimize the reaction conditions such as equivalents of sodium azide, number of mol% of catalyst, and different solvent systems at room temperature and higher.

We initiated our study by examining the 1,3-dipolar cycloaddition between benzyl bromide, sodium azide, and phenylacetylene as a model reaction. The corresponding results are listed in table 1. We observed that when the reaction was catalyzed by the well-known CuI (5 mol%) in water, stirring at 78 °C for 24h, the corresponding 1,4-disubstituted 1,2,3-triazole **1a** was obtained in 75% yield (Table 1, entry 1). The desired product **1a** was formed in 88% yield in water at 100 °C when 10 mol% of CuI was used as catalyst (Table 1, entry 2). It was found that the reaction was sensitive to the amount of catalyst and temperature. Hence, to further improve the reactivity, the amount of catalyst and temperature were optimized. When the amount of Cu/TiO<sub>2</sub> was lowered from 5 mol% to 3 mol%, there was a drop in yield (Table 1, entry 3). When the amount of catalyst was increased from 5 mol% to 10 mol%, the yield of product **1a** was not changed. Nevertheless, further lowering or increasing the reaction temperature do dramatically decrease the yield (Table 1, entries 7, 8, 11).

**Table 1.** Optimization of different reaction parameter



Entry	Catalyst	Conventional <sup>a</sup>			Ultrasound Irradiation <sup>b</sup>		
		Amount of cat. (mol%)	Time (h)	Temp. (°C)	Yield <sup>c</sup> (%)	Time (min)	Yield <sup>c</sup> (%)
<b>Effect of Catalyst and Catalyst Loading</b>							
1	CuI	5	24	78	75	15	75 <sup>22</sup>
2	CuI	10	8	100	88	15	82
3	Cu/TiO <sub>2</sub>	3	2	70	80	15	80
4	Cu/TiO <sub>2</sub>	5	1	70	98	10	98
5	Cu/TiO <sub>2</sub>	10	1	70	98	10	98
6	TiO <sub>2</sub>	5	24	70	0	-	-
<b>Effect of Temperature</b>							
7	Cu/TiO <sub>2</sub>	5	4	r.t.	80		
8	Cu/TiO <sub>2</sub>	5	2	50	88		
9	Cu/TiO <sub>2</sub>	5	1	70	98		
10	Cu/TiO <sub>2</sub>	5	1	85	98		
11	Cu/TiO <sub>2</sub>	5	1	100	95		

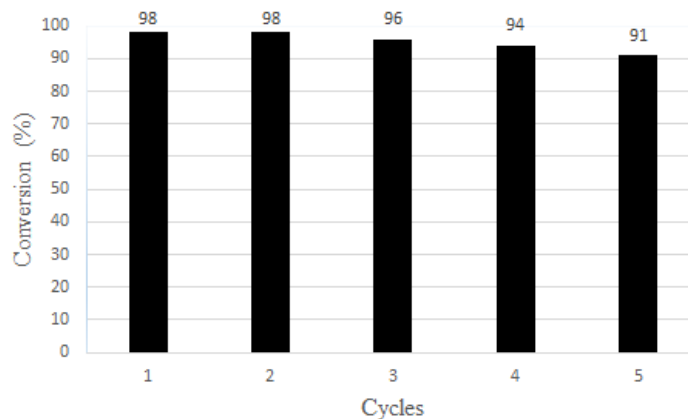
<sup>a</sup>Reaction conditions: benzyl bromide (1 mmol), sodium azide (1.2 mmol), phenylacetylene (1 mmol) were added to water as solvent (4 mL). <sup>b</sup>Ultrasonic probe (400 W, 24 kHz). <sup>c</sup>Isolated yields.

Extensive screening showed that Cu/TiO<sub>2</sub> nanocatalyst was the most effective catalyst. As a result, Cu/TiO<sub>2</sub> nanocatalyst was used in the subsequent investigations due to its efficiency, easy isolation, and reusability. Then we turned our attention to investigating the effect of solvents on formation of the 1,4-disubstituted 1,2,3-triazoles from benzyl bromide, sodium azide, and phenylacetylene in the presence of Cu/TiO<sub>2</sub> as a catalyst. Among the solvent used, CH<sub>3</sub>CN and DMF required longer reaction times and yields were 60 and 80%, respectively (Table 2, entries 3, 4). Reaction in water at 70 °C resulted in high catalytic activity and 98% yield of the desired product (Table 2, entry 5). Although use of ethanol as solvent resulted in moderate yield (75%), a mixture of ethanol and water (1:1) furnished the product in good yield. The reaction which performed under conventional stirring, required a reaction time 1-24 h clearly longer than those require when ultrasound was used (10-20min) (Table 2). It is important to note that ultrasound with frequencies less than 50 kHz and use of solid catalysts in the reaction mixture increase the reaction rate because of the local growth in both temperature and pressure due to the cavitation of some bubbles next to the surface of the catalyst/reactants.<sup>30</sup>

**Table 2.** Effect of solvent on both conventional and sonochemical synthesis of 1,2,3-triazole

Entry	Solvent	Conventional <sup>a</sup>		Ultrasound Irradiation <sup>b</sup>	
		Time (h)	Yield <sup>c</sup> (%)	Time (min)	Yield <sup>c</sup> (%)
1	EtOH	3	75	15	70
2	EtOH/H <sub>2</sub> O (1:1)	2	96	15	96
3	DMF	6	80	15	75
4	CH <sub>3</sub> CN	24	60	20	40
5	H <sub>2</sub> O	1	98	10	98
6	neat	1	90	-	-

<sup>a</sup>Reaction conditions: benzyl bromide (1 mmol), sodium azide (1.2 mmol), phenylacetylene (1 mmol) were added to the selected solvent (4 mL) at 70 °C. <sup>b</sup>Ultrasonic probe (400 W, 24 kHz). <sup>c</sup>Isolated yields.



**Figure 1.** Recycling the Cu/TiO<sub>2</sub> in the synthesis of 1a.

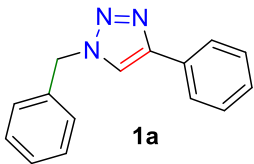
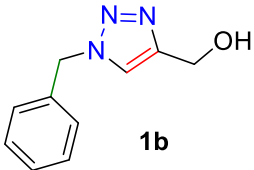
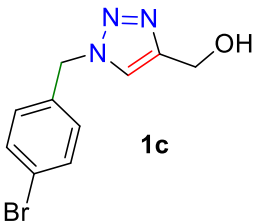
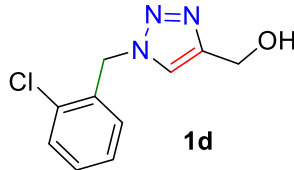
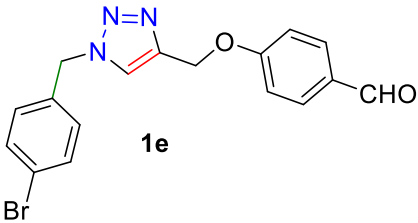
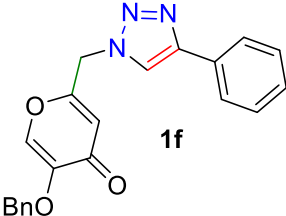
The best general condition were found to be 1.2 equiv. NaN<sub>3</sub>, 5 mol% Cu/TiO<sub>2</sub> in water at 70 °C until the reaction was complete (Table 2, entry 5). In addition, the catalyst could be easily recovered by filtration and reused leading to triazole 1a in excellent yields along five consecutive cycles (Figure 1). A wide range of 1,4-

disubstituted triazoles were synthesized from benzyl bromides and different terminal alkynes, and the results are summarized in Table 3. To the best of our knowledge, this was the first report describing the use of Cu/TiO<sub>2</sub> nanocatalyst in the multicomponent variant of the click reaction. Furthermore, this method was found to be equally effectual and straightforward for the preparation of 1,2,3-triazoles containing thiazolidine-2-thione moieties. It is worthwhile mentioning that all the reactions were carried out in the presence of air.

**Table 3.** Preparation of 1,4-disubstituted 1,2,3-triazoles catalyzed by Cu/TiO<sub>2</sub> nanocatalyst

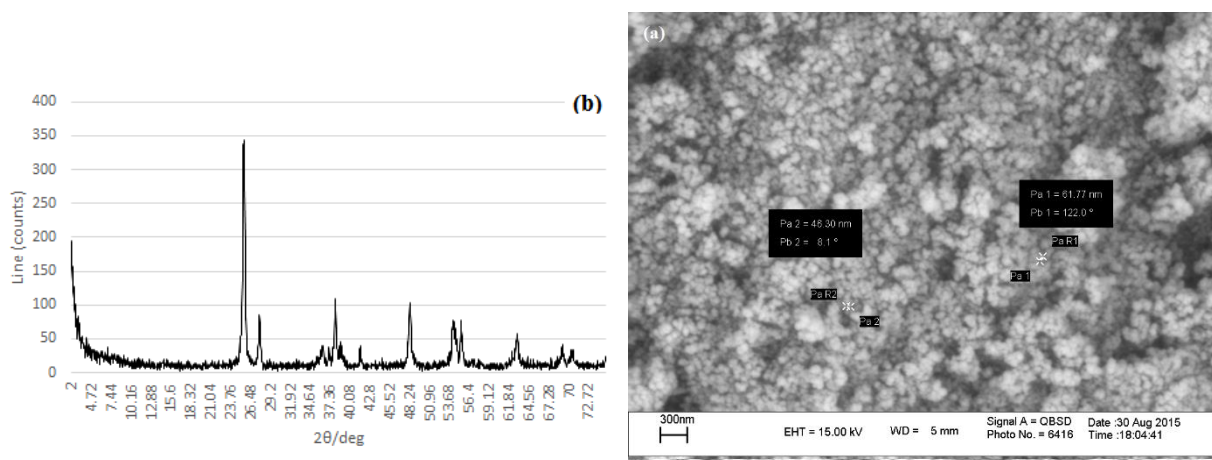
$$\text{R}^1\text{-CH}_2\text{-Br} + \text{NaN}_3 + \text{HC}\equiv\text{C-R}^2 \xrightarrow[\text{water, 70 }^\circ\text{C}]{\text{Cu/TiO}_2} \text{R}^1\text{-CH}_2\text{-N}_1\text{N}_2\text{C}_3\text{R}^2$$

**1**

Entry	Product	Conventional		Ultrasound Irradiation <sup>a</sup>	
		Time (min)	Yield <sup>b</sup> (%)	Time (min)	Yield <sup>b</sup> (%)
1	 <b>1a</b>	60	98	10	98
2	 <b>1b</b>	50	95	8	96
3	 <b>1c</b>	45	98	8	98
4	 <b>1d</b>	90	94	12	95
5	 <b>1e</b>	75	97	10	96
6	 <b>1f</b>	90	98	12	98

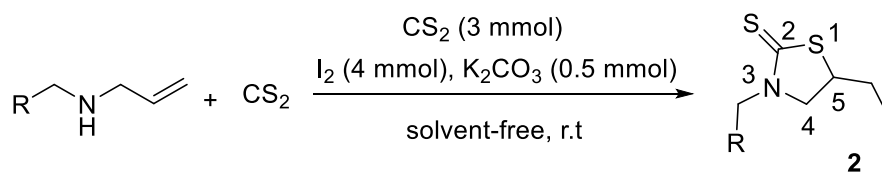
<sup>a</sup>Ultrasonic probe (400 W, 24 kHz). <sup>b</sup>Isolated yields.

The Cu/TiO<sub>2</sub> nanocatalysts were prepared by the mixture of copper nitrate and TiO<sub>2</sub> in deionized water via ultrasound-enhanced impregnation (UIM) method. Ultrasonic process significantly improve the dispersion of CuO on TiO<sub>2</sub> and the surface acid property as well as catalytic activity, especially at low temperatures. This catalyst mainly contains the easily reducible Cu<sup>2+</sup> and CuO species, and highly dispersed CuO sites.<sup>30</sup> It is worth noting that mixed Cu/Cu-oxide and, more recently, CuO nanoparticles are effective catalysts for the Huisgen's cycloaddition reaction.<sup>8</sup> The synthesized Cu/TiO<sub>2</sub> nanocatalyst was characterized by X-ray diffraction (XRD) and scanning electron microscopy (SEM). Through XRD patterns, the average crystal size of Cu/TiO<sub>2</sub> nanocatalyst was calculated as about 40 nm, which is in good agreement with the SEM observation (Figure 2).

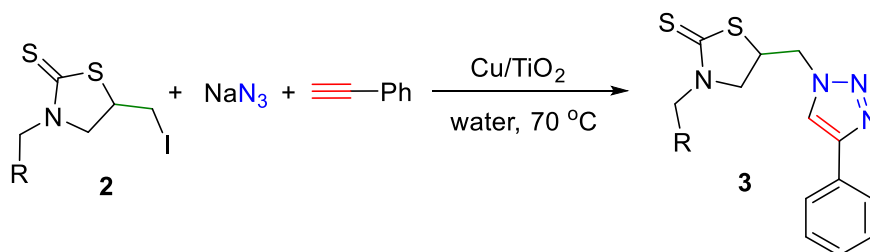


**Figure 2.** The SEM image (a) and the XRD pattern (b) of Cu/TiO<sub>2</sub>.

In view of the biological importance of triazoles and sulfur heterocycles, a focused library of 1,2,3-triazoles containing thiazolidine-2-thione moieties have been synthesized (Table 4). Synthesis of thiazolidine-2-thione heterocycles has been carried out by the recently reported procedures by our group (Scheme 1).<sup>32</sup>



**Scheme 1.** Synthesis of thiazolidine-2-thiones.

**Table 4.** One-pot three-component synthesis of 1,2,3-triazoles containing thiazolidine-2-thiones moieties

Entry	Product	R	Conventional		Ultrasound Irradiation <sup>a</sup>	
			Time (h)	Yield <sup>b</sup> (%)	Time (min)	Yield <sup>b</sup> (%)
1	<b>3a</b>	C <sub>6</sub> H <sub>11</sub>	2	83	15	84
2	<b>3b</b>	C <sub>6</sub> H <sub>5</sub>	2	82	15	82
3	<b>3c</b>	2-ClC <sub>6</sub> H <sub>4</sub>	2.5	75	20	75
4	<b>3d</b>	4-ClC <sub>6</sub> H <sub>4</sub>	2	83	15	83
5	<b>3e</b>	4- <i>i</i> -prC <sub>6</sub> H <sub>4</sub>	2	82	15	83
6	<b>3f</b>	2-thienyl	3	78	20	77
7	<b>3g</b>	5-methyl-2-furyl	2.5	83	15	83

<sup>a</sup>Ultrasonic probe (400 W, 24 kHz). <sup>b</sup>Isolated yields.

All the products were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR spectroscopy, and elemental analysis. In the <sup>1</sup>H NMR spectra, the formation of triazole was confirmed by the appearance of characteristic singlet in <sup>1</sup>H NMR due to triazolyl protons in the region of 7.40-7.60. The C-atom signals corresponding to C=S of thiazolidine-2-thione rings observed in the region of 193-195 ppm.

**Table 5.** Antibacterial activity of novel triazoles **3(a-g)**; inhibition diameter zone in millimeters (mm)

Entry	Compound	Inhibition	
		<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>
		ATCC 29213	ATCC 25922
1	<b>3a</b>	- <sup>a</sup>	-
2	<b>3b</b>	-	-
3	<b>3c</b>	8	7
4	<b>3d</b>	7	6
5	<b>3e</b>	-	-
6	<b>3f</b>	-	8
7	<b>3g</b>	10	8
8	<b>Gentamycin</b>	27	26

<sup>a</sup>Inactive

The thiazolidine-2-thiones containing 1,2,3-triazoles group **3(a-g)** were tested for their *in vitro* antibacterial activity by the disc diffusion method<sup>33</sup>, the data are listed in Table 5. As shown in Table 5, it has been found that compounds **3c**, **3d** and **3g** possess different inhibitory activities against both gram-positive

(*Staphylococcus aureus*) and gram-negative (*Escherichia coli*) bacterium (Table 5, entries 3, 4, and 7), while compound **3f** showed moderate inhibitory activity against *Escherichia coli* bacteria (Table 5, entry 6).

## Conclusions

In conclusion, we have employed a new heterogeneous catalyst for the multicomponent [3+2] Huisgen's 1,3-dipolar cycloaddition in water. The catalyst consists of oxidized copper nanoparticles on TiO<sub>2</sub> and it is readily prepared from copper nitrate in deionized water via ultrasound-enhanced impregnation (UIM) method. A wide range of 1,4-disubstituted-1,2,3-triazoles has been synthesized with excellent yield in aqueous media promoted by both conventional heating and ultrasonic irradiation conditions (ultrasonic probe). Ultrasonic irradiation dramatically reduces the reaction time and temperature. The protocol was also applicable for the synthesis of novel 1,2,3-triazoles containing thiazolidin-2-thione groups in good yield. The catalyst is reusable in the same reaction medium. The antibacterial activity revealed that some of these new compounds showed weak to moderate activities.

## Experimental Section

**General.** Reagents were prepared in laboratory or were commercial products of analytical purity (Merck, Fluka, and Aldrich) and used as received. The Mueller-Hinton agar which was used in antibacterial susceptibility testing, was purchased from Merck. The <sup>1</sup>H NMR and <sup>13</sup>C NMR were recorded with a Bruker FT-400 MHz spectrometer at room temperature and CDCl<sub>3</sub> as a solvent. The FTIR spectra were recorded on a Bruker-Tensor 270 spectrometer. Elemental analyses were carried out with a Heareus CHN-ORAPID instrument. Analyses were consistent within ca. 0.4 theoretical values. The reaction were carried out using an ultrasonic processor UP400S (400 W, 24 kHz). Power X-ray diffraction pattern of the prepared catalyst was recorded on a Bruker AXS model D8 Advance diffractometer using CuK<sub>α</sub> radiation (λ = 1.542 Å), with the Bragg angle ranging from 2° to 70°. The morphology of the catalyst was observed by scanning electron microscopy (SEM) LEO 1430 VP. Reactions were monitored by thin layer chromatography (silica gel 60 F253, ultraviolet 254 nm).

**Preparation of Cu/TiO<sub>2</sub> nanocatalyst.** The catalyst were prepared according to the literature.<sup>34</sup>

**General procedure for the synthesis of 1,4-disubstituted-1,2,3-triazoles (1a-1f) by thermal heating methodology.** Terminal alkynes (1 mmol), benzyl halide (1 mmol), and sodium azide (1.2 mmol) in 4 mL H<sub>2</sub>O were introduced in a 10 mL vessel. Sequentially 5 mol% of Cu/TiO<sub>2</sub> was added to the mixture. The reaction mixture was warmed to 70 °C, and monitored by TLC until total conversion of the starting materials. The heterogeneous catalyst was removed by a simple filtration. The product was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with water, dried with Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was removed in vacuum to give corresponding triazole, which did not require any further purification.

**General procedure for the synthesis of 1,4-disubstituted-1,2,3-triazoles (1a-1f) by ultrasound methodology.** Terminal alkynes (1 mmol), benzyl halide (1 mmol), sodium azide (1.2 mmol), and 5 mol% of Cu/TiO<sub>2</sub> in 4 mL H<sub>2</sub>O were introduced in a 10 mL thick-walled flask. The flask was attached to a 12-mm-tip-diameter probe, and



the reaction mixture was sonicated at ambient temperature. After completion of the reaction mixture (monitored by TLC), the work-up and purification steps were carried out as described above.

**1-Benzyl-4-phenyl-1H-1,2,3-triazole (1a).** white solid; mp 135-137 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  5.57 (s, 2H,  $\text{CH}_2$ ), 7.30-7.33 (m, 3H, Ph-H), 7.36-7.42 (m, 5H, Ph-H), 7.69 (s, 1H, triazolyl), 7.80 (d,  $J$  7.5 Hz, 2H, Ph-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  52.8, 118.5, 124.4, 126.7, 126.9, 127.4, 127.6, 127.8, 129.4, 133.6, 146.8; IR (KBr)  $\nu/\text{cm}^{-1}$  3139, 3077, 1452, 1359, 1219, 1071, 1041, 767, 730, 694; Anal. Calcd for  $\text{C}_{15}\text{H}_{13}\text{N}_3$ : C, 76.57; H, 5.57; N, 17.86; found: C, 76.71; H, 5.74; N, 17.58.

**(1-Benzyl-1H-1,2,3-triazol-4-yl)methanol (1b).** white solid; mp 52-54 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  3.52 (bs, 1H, OH), 4.58 (s, 2H,  $\text{CH}_2$ ), 5.49 (s, 2H,  $\text{CH}_2$ ), 7.18-7.27 (m, 2H, Ph-H), 7.30-7.39 (m, 3H, Ph-H), 7.45 (s, 1H, triazolyl);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  53.1 ( $\text{CH}_2$ ), 55.3 ( $\text{CH}_2$ ), 120.6, 127.1, 127.8, 128.1, 136.4, 147.1; IR (KBr)  $\nu/\text{cm}^{-1}$  3256 (OH), 3113, 1488, 1228, 1125, 1064, 1039, 1009, 854, 781; Anal. Calcd for  $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}$ : C, 63.48; H, 5.86; N, 22.21; found: C, 63.65; H, 6.02; N, 21.96.

**(1-(4-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methanol (1c).** white solid; mp 108-110 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  3.27 (bs, 1H, OH), 4.74 (s, 2H,  $\text{CH}_2$ ), 5.45 (s, 2H,  $\text{CH}_2$ ), 7.13 (d,  $J$  8.3 Hz, 2H, Ph-H), 7.46 (s, 1H, triazolyl), 7.48 (d,  $J$  8.4 Hz, 2H, Ph-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  52.4 ( $\text{CH}_2$ ), 55.2 ( $\text{CH}_2$ ), 120.6, 121.9, 128.7, 131.3, 132.5, 147.3; IR (KBr)  $\nu/\text{cm}^{-1}$  3256 (OH), 3113, 1488, 1228, 1125, 1064, 1041, 1010, 854, 781; Anal. Calcd for  $\text{C}_{10}\text{H}_{10}\text{BrN}_3\text{O}$ : C, 44.80; H, 3.76; N, 15.67; found: C, 45.05; H, 3.92; N, 15.42.

**(1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methanol (1d).** yellow solid; mp 97-99 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  2.66 (bs, 1H, OH), 4.78 (s, 2H,  $\text{CH}_2$ ), 5.65 (s, 2H,  $\text{CH}_2$ ), 7.20 (d,  $J$  8.1 Hz, 1H, Ph-H), 7.24-7.33 (m, 2H, Ph-H), 7.43 (d,  $J$  7.8 Hz, 1H, Ph-H), 7.56 (s, 1H, triazolyl);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  50.4 ( $\text{CH}_2$ ), 55.6 ( $\text{CH}_2$ ), 120.9, 126.6, 128.9, 129.3, 129.4, 131.9, 133.0, 147.7; IR (KBr)  $\nu/\text{cm}^{-1}$  3222(OH), 3117, 1472, 1440, 1222, 1120, 1038, 1014, 757, 680; Anal. Calcd for  $\text{C}_{10}\text{H}_{10}\text{ClN}_3\text{O}$ : C, 53.70; H, 4.51; N, 18.79; found: C, 53.95; H, 4.82; N, 18.46.

**4-((1-(4-Bromobenzyl)-1H-1,2,3-triazol-1-yl)methoxy)benzaldehyde (1e).** white solid; mp 73-75 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  5.27 (s, 2H,  $\text{CH}_2$ ), 5.50 (s, 2H,  $\text{CH}_2$ ), 7.08 (d,  $J$  8.7 Hz, 2H, Ph-H), 7.16 (d,  $J$  8.3 Hz, 2H, Ph-H), 7.51 (d,  $J$  8.3 Hz, 2H, Ph-H), 7.56 (s, 1H, triazolyl), 7.83 (d,  $J$  8.7 Hz, 2H, Ph-H), 9.88 (s, 1H, CHO);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  56.6 ( $\text{CH}_2$ ), 61.1 ( $\text{CH}_2$ ), 114.0, 121.7, 122.1, 128.7, 129.4, 131.0, 131.4, 132.0, 142.9, 145.00, 189.8 (CHO); IR (KBr)  $\nu/\text{cm}^{-1}$  3156, 2927, 2835 (CHO), 1677, 1606, 1574, 1256, 1158, 1009, 801; Anal. Calcd for  $\text{C}_{17}\text{H}_{14}\text{BrN}_3\text{O}_2$ : C, 54.86; H, 3.79; N, 11.29; found: C, 55.05; H, 3.92; N, 10.94.

**5-(Benzyloxy)-2-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)-4H-pyran-4-one (1f).** yellow solid; mp 182-184 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  5.03 (s, 2H,  $\text{CH}_2$ ), 5.39 (s, 2H,  $\text{CH}_2$ ), 6.35 (s, 1H, pyranyl), 7.30-7.36 (m, 6H, Ph-H), 7.41-7.45 (t,  $J$  7.4 Hz, 2H, Ph-H), 7.51 (s, 1H, triazolyl), 7.81 (d,  $J$  7.8 Hz, 2H, Ph-H), 7.84 (s, 1H, pyranyl);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  49.7 ( $\text{CH}_2$ ), 70.8 ( $\text{CH}_2$ ), 114.0, 119.0, 124.8, 126.7, 127.5, 127.6, 127.7, 127.9, 128.8, 134.3, 140.3, 146.4, 147.7, 158.3, 172.9 (C=O); IR (KBr)  $\nu/\text{cm}^{-1}$  3088, 2878, 1655 (C=O), 1621, 1588, 1433, 1222, 1162, 1080; Anal. Calcd for  $\text{C}_{21}\text{H}_{17}\text{N}_3\text{O}_3$ : C, 70.18; H, 4.77; N, 11.69; found: C, 70.43; H, 4.98; N, 11.36.

**General procedure for the synthesis of 1,2,3-triazoles containing thiazolidine-2-thione groups (3a-3g) by thermal heating methodology.** Terminal alkynes (1 mmol), 5-iodomethylthiazolidine-2-thiones (1 mmol), sodium azide (1.2 mmol), and 5 mol% of Cu/TiO<sub>2</sub> in water (4 mL) were introduced in a 10 mL vessel. The reaction mixture was warmed to 70 °C, and monitored by TLC until total conversion of the starting materials. The heterogeneous catalyst was removed by a simple filtration. The product was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with water and dried with Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was removed in vacuum to give corresponding triazole. The product was purified by preparative column chromatography using *n*-hexane/ethyl acetate (5:3) as eluent to give the product.

### General procedure for the synthesis of 1,2,3-triazoles containing thiazolidine-2-thione groups (3a-3g) by ultrasound methodology

Terminal alkynes (1 mmol), 5-iodomethylthiazolidine-2-thiones (1 mmol), sodium azide (1.2 mmol), and 5 mol% of Cu/TiO<sub>2</sub> in water (4 mL) were introduced in a 10 mL thick-walled flask. The flask was attached to a 12-mm-tip-diameter probe, and the reaction mixture was sonicated at ambient temperature. After completion of the reaction mixture (monitored by TLC), the work-up and purification steps were carried out as described above.

**3-(Cyclohexylmethyl)-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)thiazolidine-2-thione (3a).** pale yellow solid; mp 141-143 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 1.01-1.27 (m, 5H, cyclohexyl), 1.59-1.85 (m, 6H, cyclohexyl), 3.92 (d, *J* 11.7 Hz, 1H, C4), 4.01-4.12 (m, 2H, C4, C5), 4.41-4.47 (dd, *J* 14.1, 7.7 Hz, 1H, CH\*-CH-N), 4.56-4.61 (dd, *J* 14.1, 5.4 Hz, 1H, CH\*-CH-N), 5.00 (d, *J* 15.0 Hz, 1H, N-CH-C<sub>6</sub>H<sub>11</sub>), 5.23 (d, *J* 15.0 Hz, 1H, N-CH-C<sub>6</sub>H<sub>11</sub>), 7.41 (d, *J* 7.3 Hz, 1H, Ph-H), 7.42-7.46 (t, *J* 7.5 Hz, 2H, Ph-H), 7.53 (s, 1H, triazolyl), 7.79 (d, *J* 7.3 Hz, 2H, Ph-H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 24.6, 25.1, 29.6, 29.8, 35.5, 37.9, 41.1, 54.3, 59.5 (N-CH<sub>2</sub>-C<sub>6</sub>H<sub>11</sub>), 120.2, 127.1, 127.3, 127.9, 133.7, 143.1, 194.2 (C=S); IR (KBr) ν/cm<sup>-1</sup> 2955, 2921, 2851, 1478, 1384, 1319 (C=S), 1040; Anal. Calcd for C<sub>19</sub>H<sub>24</sub>N<sub>4</sub>S<sub>2</sub>: C, 61.26; H, 6.49; N, 15.04. Found: C, 61.55; H, 6.72; N, 14.79.

**3-Benzyl-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)thiazolidine-2-thione (3b).** pale yellow solid; mp 157-159 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 3.75-3.80 (dd, *J* 15.4, 5.1 Hz, 1H, C4), 3.97-4.04 (m, 2H, C4, C5), 4.32-4.37 (dd, *J* 14.0, 7.4 Hz, 1H, CH\*-CH-N), 4.54-4.59 (dd, *J* 14.0, 4.9 Hz, 1H, CH\*-CH-N), 4.69 (d, *J* 14.4 Hz, 1H, N-CH-Ph), 5.10 (d, *J* 14.4 Hz, 1H, N-CH-Ph), 7.34-7.45 (m, 9H, Ph-H and 1H of triazolyl), 7.75 (d, *J* 7.2 Hz, 2H, Ph-H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 40.9 (S-CH), 51.3, 51.7, 56.6, 119.6, 124.8, 127.5, 127.5, 127.6, 127.8, 128.2, 128.9, 134.0, 146.9, 193.1 (C=S); IR (KBr) ν/cm<sup>-1</sup> 3031, 2923, 1599, 1483, 1428, 1384, 1321 (C=S), 1178, 1077, 1026; Anal. Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>S<sub>2</sub>: C, 62.27; H, 4.95; N, 15.29; found: C, 62.55; H, 5.22; N, 14.96.

**3-(2-Chlorobenzyl)-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)thiazolidine-2-thione (3c).** yellow solid; mp 128-130 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 3.81-3.85 (m, 1H, C4), 4.00-4.14 (m, 2H, C4, C5), 4.45-4.50 (dd, *J* 14.2, 6.7 Hz, 1H, CH\*-CH-N), 4.56-4.61 (dd, *J* 14.4, 5.5 Hz, 1H, CH\*-CH-N), 4.85 (d, *J* 14.9 Hz, 1H, N-CH-Ph), 5.21 (d, *J* 14.9 Hz, 1H, N-CH-Ph), 7.23-7.37 (m, 4H, Ph-H), 7.40-7.44 (m, 3H, Ph-H), 7.59 (s, 1H, triazolyl), 7.76 (d, *J* 7.3 Hz, 2H, Ph-H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 41.1 (S-CH), 48.8, 51.9, 56.8, 119.6, 124.7, 126.6, 127.4, 127.8, 128.9, 129.0, 129.0, 129.7, 131.3, 132.8, 146.9, 193.5 (C=S); IR (KBr) ν/cm<sup>-1</sup> 3130, 3060, 2929, 1678, 1479, 1436, 1355, 1317 (C=S), 1219, 1183, 1045; Anal. Calcd for C<sub>19</sub>H<sub>17</sub>ClN<sub>4</sub>S<sub>2</sub>: C, 56.92; H, 4.27; N, 13.97; found: C, 57.25; H, 4.52; N, 13.74.

**3-(4-Chlorobenzyl)-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)thiazolidine-2-thione (3d).** yellow solid; mp 124-126 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 3.83-3.87 (m, 1H, C4), 4.02-4.04 (m, 2H, C4, C5), 4.38-4.44 (dd, *J* 14.1, 6.8 Hz, 1H, CH\*-CH-N), 4.59-4.63 (dd, *J* 14.1, 4.1 Hz, 1H, CH\*-CH-N), 4.77 (d, *J* 14.5 Hz, 1H, N-CH-Ph), 4.92 (d, *J* 14.5 Hz, 1H, N-CH-Ph), 7.26-7.38 (m, 5H, Ph-H), 7.43-7.47 (t, *J* 7.4 Hz, 2H, Ph-H), 7.50 (s, 1H, triazolyl), 7.78 (d, *J* 7.4 Hz, 2H, Ph-H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ<sub>C</sub> 40.9, 50.6, 51.9, 56.7, 120.0, 124.8, 127.6, 127.9, 128.2, 128.3, 128.9, 129.3, 137.1, 144.3, 194.1 (C=S); IR (KBr) ν/cm<sup>-1</sup> 3126, 3081, 2924, 1732, 1486, 1468, 1432, 1356, 1304, 1214, 1179, 1090, 1042, 1017; Anal. Calcd for C<sub>19</sub>H<sub>17</sub>ClN<sub>4</sub>S<sub>2</sub>: C, 56.92; H, 4.27; N, 13.97; found: C, 57.28; H, 4.53; N, 13.67.

**3-(4-Isopropylbenzyl)-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)thiazolidine-2-thione (3e).** white solid; mp 163-165 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ<sub>H</sub> 1.24 (d, *J* 6.9 Hz, 6H, 2CH<sub>3</sub>), 2.89-2.94 (dd, *J* 13.7, 6.8 Hz, 1H, C4), 3.81 (d, *J* 11.0 Hz, 1H, Ph-CH(CH<sub>3</sub>)<sub>2</sub>), 3.99-4.06 (m, 2H, C4, C5), 4.35-4.40 (dd, *J* 14.0, 7.6 Hz, 1H, CH\*-CH-N), 4.56-4.61 (dd, *J* 13.9, 5.1 Hz, 1H, CH\*-CH-N), 4.70 (d, *J* 14.4 Hz, 1H, N-CH-Ph), 5.04 (d, *J* 14.4 Hz, 1H, N-CH-Ph), 7.24-7.29 (m, 4H, Ph-H), 7.35-7.37 (m, 2H, Ph-H, triazolyl), 7.41-7.45 (t, *J* 7.4 Hz, 2H, Ph-H), 7.75 (d, *J* 7.2 Hz,

2H, Ph-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  22.8 ( $\text{CH}_3$ ), 23.0 ( $\text{CH}_3$ ), 32.9 (S- $\text{CH}_2$ ), 41.0, 51.1, 51.8, 56.7, 119.5, 122.7, 123.1, 124.8, 126.2, 127.5, 127.9, 131.9, 135.6, 144.8, 194.7 (C=S); IR (KBr)  $\nu/\text{cm}^{-1}$  3129, 2922, 1685, 1557, 1481, 1421, 1368, 1320 (C=S), 1177, 1026; Anal. Calcd for  $\text{C}_{22}\text{H}_{24}\text{N}_4\text{S}_2$ : C, 64.67; H, 5.92; N, 13.71; found: C, 64.95; H, 6.24; N, 13.43.

**5-((4-Phenyl-1H-1,2,3-triazol-1-yl)methyl)-3-(thiophen-2-ylmethyl)thiazolidine-2-thione (3f).** pale yellow solid; mp 148-150 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  3.91 (d,  $J$  11.5 Hz, 1H, C4), 4.01-4.11 (m, 2H, C4, C5), 4.41-4.46 (dd,  $J$  14.1, 7.7 Hz, 1H,  $\text{CH}^*\text{-CH-N}$ ), 4.56-4.61 (dd,  $J$  14.1, 5.4 Hz, 1H,  $\text{CH}^*\text{-CH-N}$ ), 4.89 (d,  $J$  15.0 Hz, 1H, N-CH-Ph), 5.23 (d,  $J$  15.0 Hz, 1H, N-CH-Ph), 7.01 (t,  $J$  4.2 Hz, 1H, thienyl), 7.08 (d,  $J$  2.8 Hz, 1H, thienyl), 7.33-7.37 (m, 2H, thienyl and Ph-H), 7.42-7.46 (t,  $J$  7.5 Hz, 2H, Ph-H), 7.50 (s, 1H, triazolyl), 7.78 (d,  $J$  7.3 Hz, 2H, Ph-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  41.0 (S- $\text{CH}_2$ ), 45.8, 51.8, 56.4, 119.6, 124.8, 125.6, 126.1, 127.3, 127.5, 127.9, 128.9, 135.5, 143.0, 193.5 (C=S); IR (KBr)  $\nu/\text{cm}^{-1}$  3081, 2922, 1480, 1440, 1362, 1310, 1257, 1219, 1182, 1137, 1078, 1042; Anal. Calcd for  $\text{C}_{17}\text{H}_{16}\text{N}_4\text{S}_3$ : C, 54.81; H, 4.33; N, 15.04; found: C, 55.10; H, 4.62; N, 14.77.

**3-((5-Methylfuran-2-yl)methyl)-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)thiazolidine-2-thione (3g).** yellow solid; mp 135-137 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  2.25 (s, 3H,  $\text{CH}_3$ ), 3.97-4.06 (m, 2H, C4, C5), 4.08-4.13 (dd,  $J$  12.5, 6.9 Hz, C4), 4.49-4.54 (dd,  $J$  14.1, 7.2 Hz, 1H,  $\text{CH}^*\text{-CH-N}$ ), 4.55-4.60 (dd,  $J$  14.1, 5.7 Hz, 1H, 1H,  $\text{CH}^*\text{-CH-N}$ ), 4.71 (d,  $J$  15.3 Hz, 1H, N-CH-Ph), 4.91 (d,  $J$  15.3 Hz, 1H, N-CH-Ph), 5.94 (d,  $J$  2.0 Hz, 1H, furyl), 6.26 (d,  $J$  2.0 Hz, 1H, furyl), 7.32-7.36 (m, 1H, Ph-H), 7.41-7.44 (t,  $J$  7.5 Hz, 2H, Ph-H), 7.73 (s, 1H, triazolyl), 7.79 (d,  $J$  7.3 Hz, 2H, Ph-H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  12.6 ( $\text{CH}_3$ ), 41.2 (S- $\text{CH}_2$ ), 44.3, 51.8, 57.1, 105.7, 110.2, 119.6, 124.8, 127.4, 127.9, 129.0, 145.1, 147.0, 152.0, 192.8 (C=S); IR (KBr)  $\nu/\text{cm}^{-1}$  3142, 2943, 1563, 1473, 1426, 1347 (C=S), 1306, 1262, 1216, 1182, 1019; Anal. Calcd for  $\text{C}_{18}\text{H}_{18}\text{N}_4\text{OS}_2$ : C, 58.35; H, 4.90; N, 15.12; found: C, 58.61; H, 5.13; N, 14.88.

### Inhibition test of triazoles 3(a-g)

The newly synthesized compounds **3(a-g)** were evaluated for their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* bacterium by disc diffusion method. The bacterial suspensions were adjusted to 0.5 McFarland standards (which gives a final bacterial concentration of  $1.5 \times 10^8$  CFU.mL $^{-1}$ ). The Mueller-Hinton agar were inoculated with bacterial suspension using a sterile cotton swab. The filter paper discs (6 mm in diameter) impregnated with the solution of tested compounds in dimethyl sulfoxide (DMSO) (20  $\mu\text{l}$ /disc, corresponding to 2 mg/disc) and placed onto the agar plates. DMSO was used as a negative control whereas Gentamycin was used as positive control (2  $\mu\text{g}$ /disc). The plates were incubated at 37 °C for 24h. Antimicrobial activities were expressed as inhibition diameter zones in millimeters (mm). The experiments were carried out in triplicates and the average zone of inhibition was calculated.

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