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Synthesis of 1,2,3 triazole-linked benzimidazole through a copper-catalyzed click reaction

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Abstract: An efficient method has been developed for the synthesis of 1,2,3 triazole-linked benzimidazole through a copper-catalyzed click reaction in ethanol at 50°C. A broad range of aromatic azides were successfully reacted with *n*-propynylated benzimidazole *via* copper-catalyzed azide-alkyne cycloaddition reactions in the absence of a ligand. This method offers many advantages including short reaction times, low cost, and simple purification procedures.

Keywords: 1,2,3-triazole; Benzimidazole; Click reaction.

Introduction

Over the past few years, there has been a substantial amount of interest in the development and pharmacological evaluation of benzimidazole [1, 2]. The benzimidazole scaffold represents a class of heterocyclic compounds with significant pharmacological properties such as antitumor [3], anti-microbial [4, 5], anti-viral [6], and antihypertensive [7] properties. Furthermore, triazoles are widely used in agrochemicals, pharmaceuticals, photographic materials, dyes, and corrosion inhibitors [8-12]. Triazoles have also been reported to possess anti-fungal, anti-helminthic, and anti-bacterial properties [13-16].

The synthesis of 1,2,3-triazoles by copper-catalyzed alkyne-azide cycloaddition (CuAAC) reactions are established as noticeable “Click” chemistry reactions. Click reactions are one of the most beneficial catalytic techniques used for the synthesis of 1,2,3-triazoles because of its high reaction yield, wide substrate scope, and simple purification [17, 18]. A majority of published procedures for the CuAAC reactions favor simple copper salts like CuI, $Cu(AcO)_2$, and $CuSO_4$ as the catalysts [19-23]. Other copper(0) and copper(I) catalysts such as copper nano-size powder [24], copper nanoparticles adsorbed onto charcoal [25], and copper nanoclusters [26] have also shown good catalytic activities.

In view of the biological importance of benzimidazole and 1,2,3-triazoles; synthesis of the 1,2,3-triazole linked benzimidazole pharmacophore *via* efficient copper-catalyzed click reactions would produce novel molecular templates that are likely to exhibit interesting biological properties. Kulkarni *et al.* have reported the synthesis of 2-mercaptobenzimidazole-linked coumarinyl triazoles as anti-tubercular agents [27]. Eppakayala and co-workers have carried out the synthesis and biological evaluation of benzimidazole-linked 1,2,3-triazoles as potential anti-cancer agents [13]. Moreover, Rao *et al.* have described the synthesis of benzimidazole-appended triazole-linked 1,3-diconjugate of calix-[4]-arene as a ratiometric fluorescence off-on-off sensor for Cu^{2+} ions in an aqueous buffer solution [28].

In continuation of our interest in the synthesis of 1,2,3-triazole linked heterocyclic compounds [29-31], new derivatives of 1,2,3 triazole-linked benzimidazole have been synthesized *via* by Cu $(OAc)_2$ catalyst in ethanol.

Results and discussion

The reaction of 2-(methylthio)-1*H*-benzo[d]imidazole (1) with propargyl bromide (2) in DMF in the presence of K_2CO_3, as a base, afforded 2-(methylthio)-1-(prop-2-ynyl)-1*H*-benzo[d]imidazole (3) in good yield (Scheme 1). The structure of this compound was confirmed by ^1H NMR spectroscopy. The singlets observed at 2.75, 3.48, and 5.07 ppm are attributed to the SCH_3, CH, and CH_2 protons, respectively. The aromatic ring protons appeared as multiplets between 7.19 and 7.61 ppm.

Similarly, the reaction of 1*H*-benzo[d]imidazole-2(3H)-thione (4) with propargyl bromide (2) in DMF in the presence of K_2CO_3 afforded 1-(prop-2-ynyl)-2-(prop-2-ynylthio)-1H-benzo[d]imidazole 5 in good yield (Scheme 1).

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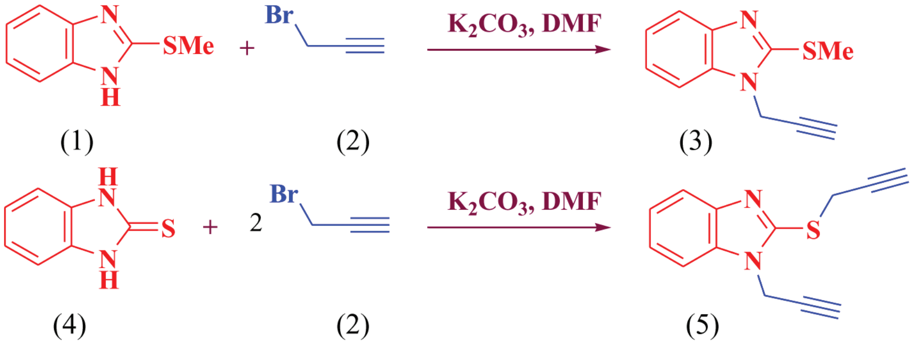
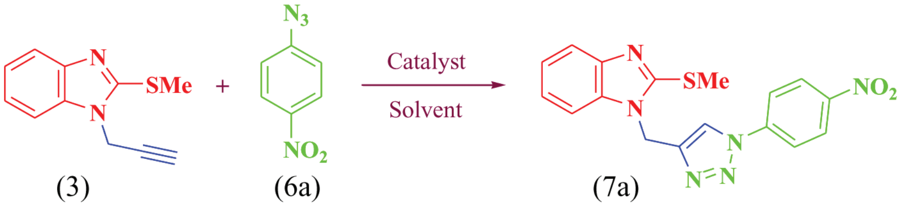


Scheme 1 Synthesis of 2-(methylthio)-1-(prop-2-ynyl)-1*H*-benzo[d]imidazole **(3)** and 1-(prop-2-ynyl)-2-(prop-2-ynylthio)-1*H*-benzo[d]imidazole **(5)**.

Table 1 Effects of various solvents, catalysts, and temperatures on reaction of compound (3) with 1-azido-4-nitrobenzene (6a).[a]



Scheme 2

Entry	Catalyst (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	$Cu(OAc)_2$ (10)	H_2O	50	2	70
2	$Cu(OAc)_2$ (10)	EtOH	50	1	95
3	$Cu(OAc)_2$ (10)	MeOH	50	2	73
4	$Cu(OAc)_2$ (10)	DMF	50	3	82
5	$Cu(OAc)_2$ (10)	CH_3CN	50	3	57
6	$Cu(OAc)_2$ (10)	1,4-dioxane	50	4	32
7	$Cu(OAc)_2$ (10)	THF	50	5	43
8	$Cu(OAc)_2$ (10)	CH_2Cl_2	50	4	35
8	$CuSO_4$ (10)	EtOH	50	1	74
9[c]	CuI (10)	EtOH	50	1	81
10	$Cu(OAc)_2$ (5)	EtOH	50	1	50
11	$Cu(OAc)_2$ (20)	EtOH	50	0.5	95
12	$Cu(OAc)_2$ (10)	EtOH	RT	5	45
13	$Cu(OAc)_2$ (10)	EtOH	80	1	94

[a] Reaction conditions: compound (3) (1.0 mmol), 1-azido-4-nitrobenzene (6a) (1.0 mmol), copper salt, sodium ascorbate (twice the amount of copper salt), solvent (5 mL).

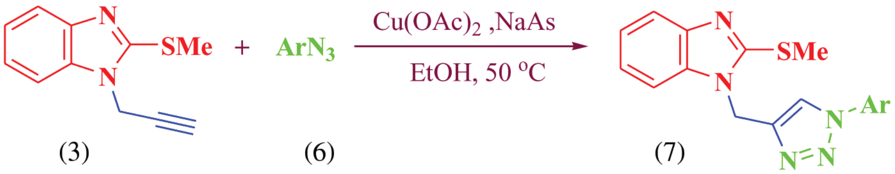
[b] Isolated yield.

[c] Without sodium ascorbate.

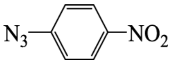
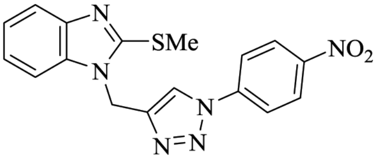
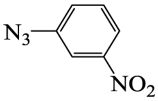
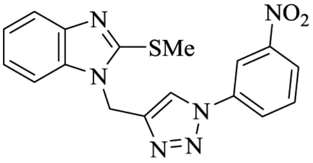
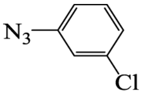
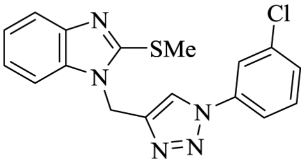
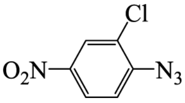
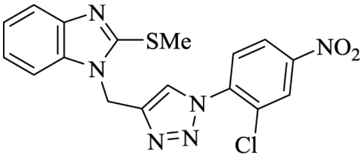
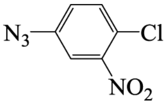
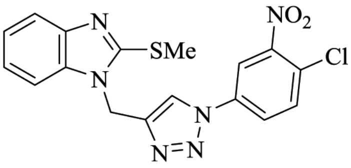
The ^1H NMR spectrum for (5) shows two singlets for the CH protons at 3.26 and 3.49 ppm, respectively, a singlet for the S-CH_2 protons at 4.23 ppm, a singlet for the N-CH_2 protons at 5.12 ppm, and two multiplets for the aromatic ring protons at 7.23-7.30 ppm and 7.6-7.65 ppm, respectively.

Compound **3** (1.0 mmol) and 1-azido-4-nitrobenzene (6a) (1.0 mmol) were selected as the model substrates to establish the optimum model reaction conditions. The results obtained were tabulated in Table 1 (Scheme 2). To optimize the reaction conditions, the above model reaction was carried out in the presence of $Cu(OAc)_2$ (10 mol%), as a catalyst, and sodium ascorbate (20 mol%), and the effects of various solvents, catalysts, and reaction temperatures were studied. The reactions were performed using various solvents including H_2O, EtOH, MeOH, DMF, CH_3CN, 1,4-dioxane, THF, and dichloromethane (DCM) at 50°C (Table 1). As shown in Table 1, the highest reaction yield was obtained when ethanol was used as the solvent (Table 1, entry 2). The concentration of the catalytic copper salt was optimized, as shown in Table 1. Decreasing the loading of

Table 2 Synthesis of 2-(methylthio)-1-((1-aryl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-benzo[*d*]imidazole (7).[a]



Scheme 3

Entry	ArN_3	Product	Time (h)	Mp (°C)	Yield (%)[b]
1	 **(6a)**	 **(7a)**	1	162-164	95
2	 **(6b)**	 **(7b)**	2	173-175	90
3	 **(6c)**	 **(7c)**	3	142-143	80
4	 **(6d)**	 **(7d)**	2	155-159	85
5	 **(6e)**	 **(7e)**	2	183-186	88

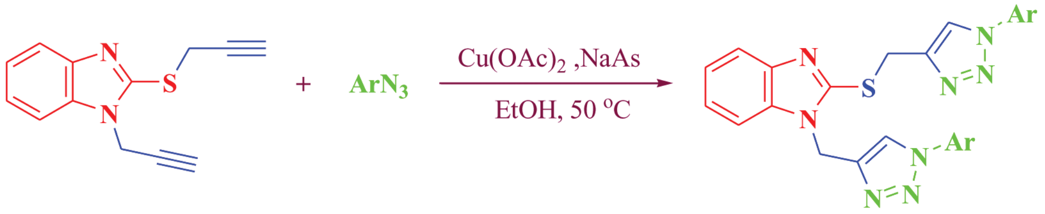
[a] Reaction conditions: compound (3) (1.0 mmol), aryl azide (6) (1.0 mmol), $Cu(OAc)_2$ (10.0 mol%), NaAs (20 mol%), ethanol (5 mL), 50°C.
[b] Isolated yield.

the catalyst to 5 mol% lowered the reaction yield dramatically (Table 1, entry 10). However, increasing the amount of catalyst to 20 mol% only shortened the reaction time and did not have any effect on the reaction yield (Table 1, entry 11). Furthermore, the effect of temperature on the conversion was studies. At room temperature and 10 mol% catalyst, the reaction had a low reaction yield (Table 1, entry 12). Increasing the temperature to 80°C did improve the overall reaction yield (Table 1, entry 13) from 45% to 94%.

In order to illustrate the versatility of this method, a series of aromatic azides were studied under the optimized reaction conditions, and the results obtained were tabulated in Table 2 (Scheme 3). A broad scope of different aromatic azides was tested, and 2-(methylthio)-1-((1-aryl-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-benzo[*d*]imidazoles (7) were obtained in good-to-excellent yields. As shown in Table 2, the steric effects of the substituents at the *ortho*-position of the aromatic azides did not have a clear effect on the reaction yields.

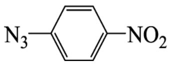
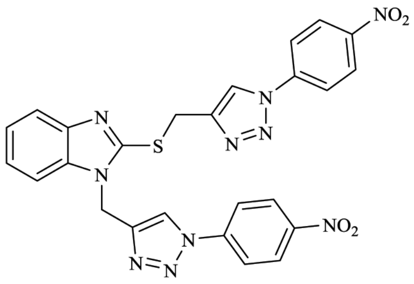
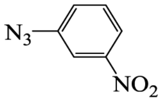
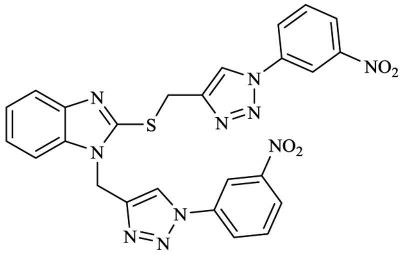
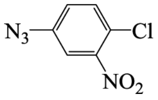
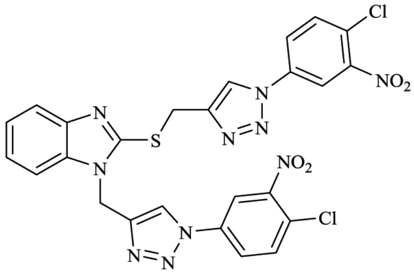
To extend the scope of our work, the click reaction of compound (5) with aromatic azides (6) were studied in the presence of 10 mol% of $Cu(OAc)_2$ and 20 mol% of sodium ascorbate in ethanol at 50°C (Table 3, and

Table 3 2-((1-aryl-1*H*-1,2,3-triazol-4-yl)methylthio)-1-((1-aryl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-benzo[*d*]imidazole (8).[a]



(5) (6) (8)

Scheme 4

Entry	ArN_3	Product	Time (h)	Mp (°C)	Yield (%)[b]
1	 **(6a)**	 **(8a)**	3	181-182	83
2	 **(6b)**	 **(8b)**	4	203-204	85
3	 **(6c)**	 **(8c)**	3	193-195	80

[a] Reaction conditions: compound (5) (1.0 mmol), aryl azide (6) (1.0 mmol), $Cu(OAc)_2$ (10.0 mol%), NaAs (20 mol%), ethanol (5 mL), 50°C.

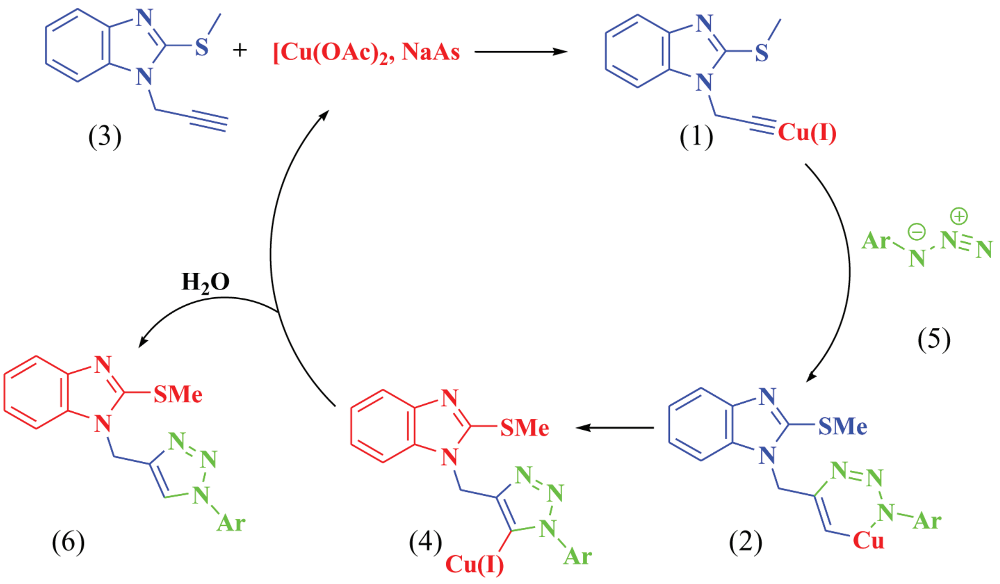
[b] Isolated yield.

Scheme 4). As shown in this table, different aryl azides reacted successfully in the developed catalytic system. The corresponding products were isolated in good-to-high yields.

The copper-catalyzed click reaction mechanism comprises the multi-general steps shown in Scheme 5: a) 2-(methylthio)-1-(prop-2-ynyl)-1*H*-benzo[d]imidazole (3) was converted to its corresponding copper(I) acetylide intermediate (1) in the presence of $Cu(OAc)_2$/NaAs; b) the formation of six-membered ring copper metallacycle (2) by treatment of intermediate (1) with aromatic azide (5); c) cyclization takes place to yield the copper triazole intermediate (4); d) proteolysis of the Cu-C bond gives product (6) and regenerates the catalyst.

Conclusion

An efficient and versitile method for the synthesis of triazole-linked bezimidazole derivatives has been developed utilising the click reaction of propynylated



Scheme 5 Proposed mechanism.

benzimidazole compound 2-(methylthio)-1-(prop-2-ynyl)-1*H*-benzo[*d*]imidazole (3) or 1-(prop-2-ynyl)-2-(prop-2-ynylthio) -1*H*-benzo[*d*]imidazole (5) with aromatic azides catalyzed by Cu $(OAc)_2$. The short reaction time, mild experimental conditions, simple purification procedures and good-to-high yields are some advantages of this method.

Experimental

General

The reagents and solvents used were supplied from Merck, Fluka or Aldrich. Melting points were determined using an electro-thermal C14500 apparatus. The reaction progress and the purity of compounds were monitored using TLC analytical silica gel plates (Merck 60 F250). The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectroscopies were run on a Bruker Advance DPX-250 FT-NMR spectrometer. The chemical shift values were given as δ values against tetramethylsilane (TMS) as the internal standard, and the J values were given in Hz. The microanalyses were performed on a Perkin-Elmer 240-B microanalyzer.

Synthesis of 2-(methylthio)-1-(prop-2-ynyl)-1*H*-benzo[*d*]imidazole (3)

Propargyl bromide (2) (1.2 mmol, 0.1 mL) was added slowly to a stirring mixture of 2-(methylthio)-1*H*-benzo[d] imidazole (1) (1.0 mmol, 0.16 g) and K_2CO_3 (2.0 mmol, 0.20 g) in dry DMF (3 mL) at room temperature, and the resulting mixture was stirred at room temperature for 10 h. Upon completion of the reaction, the solvent was evaporated under vacuum, and the resulting product was washed with water. The residue was purified by crystallization from EtOH to give the title compound. Yield, 90%; White powder; Mp., 202-204°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.75 (s, 3H, CH_3), 3.48 (s, 1H, CH), 5.07 (s, 2H, CH_2), 7.19-7.23 (m, 2H, ArH), 7.56-7.61 (m, 2H, ArH); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 14.9, 76.3, 78.1, 110.0, 118.1, 122.1, 122.2, 136.1, 143.3, 152.6, 162.8; Anal. Calcd. for $C_{11}H_{10}N_2S$: C, 65.32; H, 4.98; N, 13.85%; Found: C, 65.13; H, 4.89; N, 13.69%.

1-(prop-2-ynyl)-2-(prop-2-ynylthio)-1*H*-benzo[*d*] imidazole (5)

To a mixture of 1*H*-benzo[d]imidazole-2(3H)-thione (4) (1.0 mmol, 0.15 g) and K_2CO_3 (3.0 mmol, 0.4 g) in dry DMF (4 mL) were added propargyl bromide (2) (2.4 mmol, 0.2 mL). The reaction mixture was stirred at room temperature until the disappearance of compound (4) (monitored by TLC). The solvent was evaporated to dryness, the crude product was washed with H_2O, and the precipitate formed was purified by recrystallization from methanol. Yield, 86%; White powder; Mp., 224-226°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.26 (s, 1H, CH),3.49 (s, 1H, CH), 4.23 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 7.23-7.30 (m, 2H, ArH), 7.60-7.65 (m, 2H, ArH); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 21.0, 74.7, 76.4, 76.5, 78.1, 80.2, 81.6, 83.1, 110.4, 118.5, 122.5, 122.6, 136.0, 143.2, 149.8; Anal. Calcd. for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38%; Found: C, 69.18; H, 4.53; N, 12.55%.

Synthesis of 2-(methylthio)-1-((1-aryl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-benzo[*d*]imida-zole (7a-e)

A round-bottomed flask was charged with 2-(methylthio)-1-(prop-2-ynyl)-1*H*-benzo[*d*]imidazole (3) (1.0 mmol, 0.2 g), an aromatic azide (6) (1.0 mmol), $Cu(OAc)_2$ (0.1 mmol, 0.18 g), sodium ascorbate (0.2 mmol, 0.4 g), and ethanol (3.0 mL). The resulting mixture was stirred at 50°C until the disappearance of compound (3) (monitored by TLC). Upon completion of the reaction, the resulting mixture was washed with a (1:1) mixture of H_2O and conc. NH_3 to remove the catalyst. The residue was finally purified by flash column chromatography (hexane/ethyl acetate = 10:1) to give the desired product (Table 2).

2-(methylthio)-1-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-benzo[*d*]imid- azole (7a)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.76 (s, 3H, CH_3), 5.55 (s, 2H, CH_2), 7.18-7.22 (m, 2H, ArH), 7.56-7.58 (d, 1H, *J* = 6.2 Hz, ArH), 7.62-7.65 (d, 1H, *J* = 6.2 Hz, ArH), 8.18-8.21 (d, 2H, *J* = 9.3 Hz, ArH), 8.40-8.43 (d, 2H, *J* = 9.3 Hz, ArH), 9.06 (s, 1H, CH of triazole); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 14.9, 110.2, 118.0, 121.1, 122.0, 122.1, 122.7, 125.9, 141.1, 143.5, 144.2, 147.2; Anal. Calcd. for $C_{17}H_{14}N_6O_2S$: C, 55.73; H, 3.85; N, 22.94%; Found: C, 55.92; H, 3.94; N, 23.11%.

2-(methylthio)-1-((1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-benzo[*d*]imid- azole (7b)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.76 (s, 3H, CH_3), 5.54 (s, 2H, CH_2), 7.14-7.22 (m, 2H, ArH), 7.56-7.58 (m, 2H, ArH), 7.62-7.64 (m, 2H, ArH), 7.80-7.86 (t, 1H, *J* = 7.3 Hz, ArH), 8.27-8.29 (d, 1H, *J* = 7.3 Hz, ArH), 8.35-8.38 (d, 1H, *J* = 7.3 Hz, ArH), 8.70 (s, 1H, ArH), 9.09 (s, 1H, CH of triazole); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 14.8, 110.2, 115.2, 118.0, 122.0, 122.1, 122.7, 123.5, 126.5, 131.8, 137.4, 143.5, 144.0, 148.8; Anal. Calcd. for $C_{17}H_{14}N_6O_2S$: C, 55.73; H, 3.85; N, 22.94%; Found: C, 55.91; H, 3.77; N, 22.79%.

1-((1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-(methylthio)-1*H*-benzo[*d*]imid- azole (7c)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.79 (s, 3H, CH_3), 5.57 (s, 2H, CH_2), 7.21 (d, 2H, ArH), 7.56-7.63 (m, 4H, ArH), 7.90-7.92 (d, 1H, *J* = 6.0 Hz, ArH), 8.04 (s, 1H, ArH), 8.96 (s, 1H, CH of triazole); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 15.0, 19.0, 56.5, 110.2, 117.5, 118.0, 122.1, 122.1, 122.7, 125.0, 125.2, 133.5, 136.0, 143.4, 144.2, 148.4; Anal. Calcd. for $C_{17}H_{14}ClN_5S$: C, 57.38; H, 3.97; N, 19.68%; Found: C, 57.56; H, 4.07; N, 19.87%.

1-((1-(2-chloro-4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-(methylthio)-1*H*-benzo-[*d*]imidazole (7d)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.76 (s, 3H, CH_3), 5.59 (s, 2H, CH_2), 7.16-7.23 (m, 2H, ArH), 7.56-7.59 (d, 1H, *J* = 6.9 Hz, ArH), 7.65-7.68 (d, 1H, *J* = 6.9 Hz, ArH), 7.98-8.01 (d, 1H, *J* = 6.9 Hz, ArH), 8.35-8.39 (d of d, 1H, *J* = 2.3 Hz, *J* = 6.9 Hz, ArH), 8.60-8.61 (d, 1H, *J* = 2.3 Hz, ArH), 8.80 (s, 1H, CH of triazole); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 15.0, 110.3, 118.0, 122.1, 123.9, 126.2, 126.4, 129.6, 129.7, 139.4, 142.9, 143.5, 148.7; Anal. Calcd. for $C_{17}H_{13}ClN_6O_2S$: C, 50.94; H, 3.27; N, 20.97%; Found: C, 50.76; H, 3.19; N, 20.82%.

1-((1-(4-chloro-3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-2-(methylthio)-1*H*-benzo-[*d*]imidazole (7e)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.77 (s, 3H, CH_3), 5.57 (s, 2H, CH_2), 7.16-7.23 (m, 2H, ArH), 7.57-7.60 (d, 1H, *J* = 6.3 Hz, ArH), 7. 61-7.64 (d, 1H, *J* = 6.3 Hz, ArH), 7.98-8.01 (d, 1H, *J* = 8.4 Hz, ArH), 8.26-8.29 (d of d, 1H, *J* = 2.1 Hz, *J* = 8.4 Hz, ArH), 8.67-8.68 (d, 1H, *J* = 2.1 Hz, ArH), 9.01 (s, 1H, CH of triazole); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 14.9, 110.3, 118.0, 119.1, 120.3, 122.1, 122.5, 129.0, 132.0, 134.6, 137.9, 143.8; Anal. Calcd. for $C_{17}H_{13}ClN_6O_2S$: C, 50.94; H, 3.27; N, 20.97%; Found: C, 50.78; H, 3.35; N, 21.13%.

2-((1-aryl-1*H*-1,2,3-triazol-4-yl)methylthio)-1-((1-aryl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-benzo[*d*]imidazole (8a-c)

A round-bottomed flask was charged with 1-(prop-2-ynyl)-2-(prop-2-ynylthio)-1*H*-benzo[*d*]imidazole (5) (1.0 mmol, 0.22 g), an aromatic azide (6) (1.0 mmol), $Cu(OAc)_2$ (0.1 mmol, 0.18 g), sodium ascorbate (0.2 mmol, 0.4 g), and ethanol (3.0 mL). The mixture was stirred at 50°C. After completion of the reaction, the resulting mixture was washed with a (1:1) mixture of H_2O and conc. NH_3 to remove the catalyst. The residue was purified by flash column chromatography (hexane/ethyl acetate = 10:1) to give the desired product (Table 3).

2-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methylthio)-1-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-benzo[*d*]imidazole (8a)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 4.81 (s, 2H, CH_2), 5.60 (s, 2H, CH_2), 7.23-7.24 (m, 2H, ArH), 7.65-7.67 (m, 2H, ArH), 8.13-8.18 (d, 4H, *J* = 1.6 Hz, ArH), 8.38-8.41 (d, 4H, *J* = 1.6 Hz, ArH), 8.96 (s, 1H, CH of triazole), 9.03 (s, 1H, CH of triazole); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 27.3, 31.1, 110.6, 118.4, 121.0, 121.0, 122.3, 122.5, 122.7, 122.7, 125.3, 125.9, 126.7, 136.3, 141.0, 141.1, 143.4, 144.2, 145.4, 147.1, 147.1; Anal. Calcd. for $C_{25}H_{18}N_{10}O_4S$: C, 54.15; H, 3.27; N, 25.26%; Found: C, 54.35; H, 3.38; N, 25.44%.

2-((1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methylthio)-1-((1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-benzo[*d*]imidazole (8b)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 4.81 (s, 2H, CH_2), 5.50 (s, 2H, CH_2), 7.22-7.25 (m, 2H, ArH), 7.64-7.70 (m, 2H, ArH), 7.83-7.88 (t, 2H, J = 5.3 Hz, ArH), 8.29-8.38 (m, 4H, ArH), 8.65-8.68 (d, 2H, J = 5.3 Hz, ArH), 9.0 (s, 1H, CH of triazole), 9.09 (s, 1H, CH of triazole); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 27.4, 110.6, 115.2, 118.4, 122.3, 122.5, 122.7, 122.8, 123.5, 123.6, 126.5, 126.5, 131.9, 137.4, 135.7, 143.4, 144.0, 148.9; Anal. Calcd. for $C_{25}H_{18}N_{10}O_4S$: C, 54.15; H, 3.27; N, 25.26%; Found: C, 54.37; H, 3.17; N, 25.08%.

2-((1-(4-chloro-3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methylthio)-1-((1-(4-chloro-3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-benzo[*d*]imidazole (8c)

^{1}H-NMR (300 MHz, DMSO-d_6): δ 4.80 (s, 2H, CH_2), 5.80 (s, 2H, CH_2), 7.22-7.24 (m, 2H, ArH), 7.63-7.65 (m, 2H, ArH), 7.96-7.99 (d, 2H, J = 5.3 Hz, ArH), 8.21-8.24 (d, 2H, J = 5.3 Hz, ArH), 8.63 (s, 2H, ArH), 8.92 (s, 1H, CH of triazole), 8.97 (s, 1H, CH of triazole); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 27.3, 110.6, 117.4, 122.3, 122.5, 122.7, 122.8, 124.9, 125.0, 125.1, 125.1, 133.5, 136.0, 136.0, 143.4, 145.4, 148.4; Anal. Calcd. for $C_{25}H_{16}Cl_2N_{10}O_4S$: C, 48.16; H, 2.59; N, 22.47%; Found: C, 48.34; H, 2.67; N, 22.62%.

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References

[1] Harkala, K. J.; Eppakayala, L.; Maringanti, T. C. Synthesis and biological evaluation of benzimidazole-linked 1, 2, 3-triazole congeners as agents. *Org. Med. Chem. Lett*. **2014**, *2*, 4-14.

[2] Naresh, G.; Kant, R.; Narender, T. Molecular iodine promoted divergent synthesis of benzimidazoles, benzothiazoles, and 2-benzyl-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazines, *J. Org. Chem*. **2014**, *79*, 3821-3829.

[3] Mann, J.; Baron, A.; Opoku-Boahen, Y.; Johansson, E.; Parkinson, G.; Kelland, L. R.; Neidle, S. A new class of symmetric bisbenzimidazole-based DNA minor groove-binding agents showing antitumor activity. *J. Med. Chem*. **2001**, *2*, 138-144.

[4] Göker, H.; Kuş, C.; Boykin, D. W.; Yildiz, S.; Altanlar, N. Synthesis of some new 2-substituted-phenyl-1*H*-benzimidazole-5-carbonitriles and their potent activity against Candida species. *Bioorg. Med. Chem*. **2002**, *10*, 2589-2596.

[5] Özden, S.; Atabey, D.; Yıldız, S.; Göker, H. Synthesis and potent antimicrobial activity of some novel methyl or ethyl 1*H*-benzimidazole-5-carboxylates derivatives carrying amide or amidine groups. *Bioorg. Med. Chem*. **2005**, *5*, 1587-1597.

[6] Tewari, A. K.; Mishra, A. Synthesis and antiviral activities of N-substituted-2-substituted-benzimidazole derivatives. *J. Org. Chem*. **2006**, *10*, 87-97.

[7] Sondhi, S. M.; Singh, N.; Kumar, A.; Lozach, O.; Meijer, L. Synthesis, anti-inflammatory, analgesic and kinase (CDK-1, CDK-5 and GSK-3) inhibition activity evaluation of benzimidazole/benzoxazole derivatives and some Schiff's bases. *Bioorg. Med. Chem*. **2006**, 11, 3758-3765.

[8] Al-Masoudim, N. A.; Al-Soud, Y. A. Synthesis of 1′-β-D-glucopyranosyl-1, 2, 3-triazole-4, 5-dimethanol-4, 5-bis (isopropylcarbamate) as potential antineoplastic agent. *Tetrahedron Lett*. **2002**, *43*, 402-4022.

[9] Tornoe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on solid phase:[1, 2, 3]-triazoles by regiospecific copper (I)-catalyzed 1, 3-dipolar cycloadditions of terminal alkynes to azides. *J. Org. Chem*. **2002**, *67*, 3057-3064.

[10] Meldal, M.; Tornøe, C. W. Cu-catalyzed azide– alkyne cycloaddition. *Chem. Rev*. **2008**, *108*, 2952-3015.

[11] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. copper (I) catalyzed regioselective "ligation" of azides and terminal alkynes. *Angew. Chem. Int. Ed*. **2002**, *114*, 2708-2711.

[12] Chan, T. R.; Robert, H.; Sharpless, K. B.; Fokin, V. V. Polytriazoles as copper (I) stabilizing ligands in catalysis. *Org. Lett*. **2004**, *6*, 2653-2656.

[13] Goodman, L. S. Goodman and Gilman's the pharmacological basis of therapeutics. *New York. McGraw-Hill*, **1996**.

[14] Harkala, K. J.; Eppakayala, L.; Maringanti, T. C. Synthesis and biological evaluation of benzimidazole-linked 1, 2, 3-triazole congeners as agents. *Org. Med. Chem. Lett*. **2014**, *4*, 14-17.

[15] Ammermann, E.; Loecher, F.; Lorenz, G.; Janseen, B.; Karbach, S.; Meyer, N. The science and practice of pharmacy. *Int. Crop. Prot. Conf*. **1990**, *2*, 407-414.

[16] Ammermann, E.; Loecher, F.; Lorenz, G.; Janseen, B.; Karbach, S. The science and practice of pharmacy. *Chem. Abstr.* **1991**, *114*, 223-225.

[17] Sommer, S.; Weikart, N. D.; Brockmeyer, A.; Janning, P.; Mootz, H. D. Expanded click conjugation of recombinant proteins with ubiquitin like modifiers reveals altered substrate preference of SUMO$_2$ modified Ubc9. *Angew. Chem. Int. Ed*. **2011,** *50*, 9888-9892.

[18] Lallana, E.; Riguera, R.; Fernandez Megia, E. Reliable and efficient procedures for the conjugation of biomolecules through Huisgen azide–alkyne cycloadditions. *Angew. Chem. Int. Ed*. **2011**, *12*, 8794-8804.

[19] Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. Copper-catalysed multicomponent click synthesis of 5-alkynyl 1, 2, 3-triazoles under ambient conditions. *Org. Lett.* **2006**, *13*, 2761-2763.

[20] Molander, G. A.; Ham, J. Synthesis of functionalized organotrifluoroborates via the 1, 3-dipolar cycloaddition of azides. *Org. Lett*. **2006**, *13*, 2767-2770.

[21] Ilgen, F.; König, B. Organic reactions in low melting mixtures based on carbohydrates and L-carnitine a comparison. *Green Chem*. **2009**,*11*, 848-8454.

[22] Mukherjee, N.; Ahammed, S.; Bhadra, S.; Ranu, B. C. Solvent-free one-pot synthesis of 1, 2, 3-triazole derivatives by the 'Click'reaction of alkyl halides or aryl boronic acids, sodium azide and terminal alkynes over a Cu/Al_2O_3 surface under ball-milling. *Green Chem*. **2013**, *15*, 389-397.

[23] Feldman, A. K.; Colasson, B.; Fokin, V. V. One-pot synthesis of 1, 4-disubstituted 1, 2, 3-triazoles from in situ generated azides. *Org. Lett*. **2004**, *8*, 3897-3899.

[24] Molteni, G.; Bianchi, C. L.; Marinoni, G.; Santo, N.; Ponti, A. Cu/Cu-oxide nanoparticles as catalyst in the "click" azide–alkyne cycloaddition. *New J. Chem*. **2006**, *30*, 1137-1139.

[25] Lipshutz, B. H.; Taft, B. R. Heterogeneous copper in charcoal catalyzed click chemistry. *Angew. Chem. Int. Ed*. **2006**, *45*, 8235-8238.

[26] Pachon, L. D.; Van Maarseveen, J. H.; Rothenberg, G. Click chemistry: Copper clusters catalyse the cycloaddition of azides with terminal alkynes. *Adv. Synth. Catal*. **2005**, *347*, 811-815.

[27] Anand, A.; Kulkarni, M. V.; Joshi, S. D.; Dixit, S. R. One pot Click chemistry: A three component reaction for the synthesis of 2-mercaptobenzimidazole linked coumarinyl triazoles as anti-tubercular agents. *Bioorg. Med. chem. Lett*. **2016**, *6*, 4709-4713.

[28] Pathak, R. K.; Hinge, V. K.; Mondal, P.; Rao, C. P. Ratiometric fluorescence off-on-off sensor for Cu^{2+} in aqueous buffer by a lower rim triazole linked benzimidazole conjugate of calix [4] arene. *Dalton. Trans*. **2012**, *35*, 10652-10660.

[29] Bakherad, M.; Karami, S.; Keivanloo, A.; Sepehri, S. Synthesis of New Derivatives of 1, 2, 3 Triazole Linked Phthalazine 1,4 dione in Water: Experimental Aspects and Molecular Docking Calculations. *Chem. Select* **2018**, 24, 11042-11047.

[30] Bakherad, M.; Rezaeimanesh, F.; Nasr Isfahani, H. Copper Catalyzed Click Synthesis of Novel 1, 2, 3 Triazole Linked Pyrimidines. *Chem. Select* **2018,** *7*, 2594-2598.

[31] Keivanloo, A.; Bakherad, M.; Lotfi, M. Use of ligand-assisted click reactions for the rapid synthesis of novel 1, 2, 3-triazole pharmacophore-based 1, 2, 4-triazines and their benzo-fused analogues. *Tetrahedron* **2017**, *40*, 5872-5882.