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Original article

Synthesis and cytotoxicity evaluation of novel 1,4-disubstituted 1,2,3-triazoles *via* CuI catalysed 1,3-dipolar cycloaddition

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ABSTRACT

A facile and highly efficient method for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles (β-keto 1,2,3-triazoles) in good to excellent yields from *in-situ* generated β-ketoazides and terminal alkynes through Cu(I) catalyzed 1,3 dipolar cycloaddition is described. This reaction proceeds smoothly either in water or in a 1:1 mixture of water and acetone at room temperature without use of any additive. The synthesized compounds were screened for their cytotoxicity in A549 (Lung Cancer), HT-29 (Colon Cancer), He La (Cervical Cancer) using MTT assay that exhibited significant cytotoxicity at modest doses.

1. Introduction

Cycloaddition reactions involving heteroatoms, such as 1,3-dipolar cycloaddition, provides rapid access to a wide variety of interesting five- and six-membered heterocycles, which have found wide applications in medicinal chemistry and material sciences [1]. Among them, five-membered heterocycles namely, 1,4-disubstituted 1,2,3-triazoles exhibit a remarkably broad scope of selectivity, with a wide range of applications across a broad range of therapeutic areas [2]. Recently, 1,2,3-triazole fragment has attracted attention because many compounds possessing 1,2,3-triazole fragment exhibit useful biological properties [3]. Particularly 1,4-disubstituted 1,2,3-triazoles showed significant antiproliferative against a wide variety of human cancer cell lines, including those that are multidrug resistant [4].

The most widely used method for the synthesis of 1,2,3-triazoles involves the thermally driven 1,3-dipolar cycloaddition of organic azides with alkynes pioneered by Huisgen [5]. However, there are major problems commonly associated with this methodology, including the need for long reaction times and high temperatures, as well as the formation of region-isomeric mixtures of products specially when unsymmetrical alkynes are involved. Recently, Sharpless [6] and Meldal [7] groups, independently re-invigorated the Huisgen's 1,3-dipolar cycloaddition by using a sub-stoichiometric amount of Cu(I) metal source. The copper-accelerated 1,3-dipolar cycloaddition reaction of alkynes and azides not only takes place with high yield under milder conditions, but also leads to exclusively 1,4-region-isomeric products. Since then, this reaction has been used for the construction of a variety of multi-valent structures such as sugar heterodimers, glycoconjugates [8], calixsugars [9], dendritic and polymeric materials [10]. Moreover, the basic triazole ring itself is a potential pharmacophore that has gained interest over the past few years as several derivatives exhibited interesting biological activities [11].

2. Results and discussion

2.1. Chemistry

Although, organic azides are stable against most reaction conditions, compounds of low molecular weight or those containing several azides (like multi-valent scaffolds) tend to be explosive

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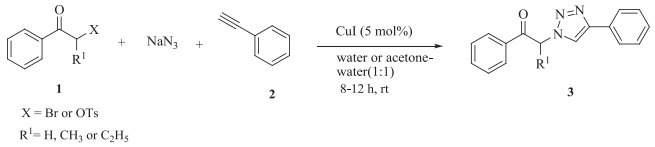


Scheme 1. Regioselective synthesis of functionalized 1,4-disubstituted-1,2,3-triazoles.

and are difficult to handle [12] and hence recently few procedures that involve the generation the azides in-situ followed by azide-alkyne cycloaddition have been reported [13]. Despite these advances, there is a need to broaden the scope of one-pot multi-step reaction in combination with "click chemistry" [14]. As part of our ongoing research program directed towards the synthesis of triazoles under various reaction conditions [15], we have studied the reactivity of α-bromo and tosyloxyketones in such reactions. Herein, we report an efficient approach for the one-pot synthesis of β-keto triazoles from α-bromo or tosyloxyketones, sodium azide, and alkynes in the presence of a catalytic amount of CuI (Scheme 1) and evaluation of their cytotoxicity. This three-component reaction, proceeds *via* the formation of β-keto azide from α-bromo or tosyloxyketones and sodium azide followed by 1,3-dipolar cycloaddition with terminal alkynes to give 1,4-disubstituted 1,2,3-triazoles in good to excellent yields.

Initially, the effect of solvents on the formation of triazoles using phenacyl bromide and tosyloxy acetophenone with sodium azide and phenylacetylene in the presence of CuI (5 mol%) as the catalyst at ambient temperature was investigated and the results are illustrated in Table 1. Further, solvent effects for the formation of triazoles with phenacyl bromide have also been screened, and among the solvents tested DCM and THF required longer reaction times with 45% and 55% yields respectively. Other polar solvents like MeOH, DMF and acetonitrile gave the desired product in 59%, 62% and 65% yields, respectively, with a significant decrease in the reaction times. However, the reaction in water exhibited high catalytic activity with 81% yield of the desired product whereas a mixture of water: acetone (1:1) also gave the product in good yield (72%). Under similar conditions, when the reaction was carried out in acetone the product was obtained in moderate yield. Similarly, different solvents were tested for the synthesis of β-keto triazoles from α-tosyloxy acetophenone. The reaction in DCM, THF gave the corresponding triazoles in low yield and also required prolonged reaction times (entries 1 and 2), whereas the reaction in MeOH, DMF, acetonitrile has resulted in slightly improved yields of the product (entries 3–5). However, the reaction in acetone:water (1:1) mixture gave 76% of the corresponding triazoles in 12h. As can be seen from the Table 1, α-bromo acetophenone showed higher reactivity compared to α-tosyloxy acetophenone under similar reaction conditions.

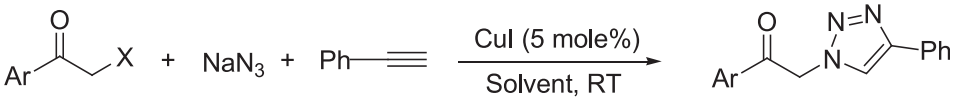
Having optimized the reaction conditions, different α-bromo and α-tosyloxyketones were reacted with sodium azide, followed by cycloaddition with phenylacetylene and the results are presented in Table 2. It is worth mentioning here that electron donating substituents like methyl, methoxy and electron withdrawing substituents such as chloro, bromo groups at para positions of both α-bromo and α-tosyloxyketones were equally effective towards the nucleophilic substitution of azide followed by 1,3-dipolar cycloaddition.

To extend the general applicability of this reaction, a wide variety of terminal alkynes were reacted with in-situ generated organic azide from α-bromo or α-tosyloxy acetophenone and sodium azide and the results are given in Table 3. *p*-Methyl-, 2, 4, 5-trimethyl- and *p*-pentyl-substituted phenylacetylenes were found to be more reactive when compared to the *m*-methoxy-substituted phenylacetylene and *p*- methoxynaphyl acetylene (Table 3, entries 1–5). The reaction with propargyl alcohol and octyne afforded the products in moderate yield (Table 3, entries 6 and 7). Among the heterocyclic terminal alkynes, 2-ethynyl pyridine was more reactive when compared with 3-ethynyl thiophene (Table 3, entries 8 and 9).

2.2. Cytotoxicity evaluation

Cytotoxicity of compounds **3a**–**p** in A549, HT-29 and HeLa cells was evaluated by MTT assay based on mitochondrial reduction of the yellow MTT tetrazolium dye to a highly colored blue formazan product [16]. This assay usually shows high correlation with number of living cells, cell proliferation and release of mitochondrial matrix enzymes [14]. The values of MTT test in A549, HT-29 and Hela cells incubated for 48 h in DMEM media with β-keto 1,2,3-triazoles are presented in Table 4. Among the compounds (1,4-disubstituted 1,2,3-triazoles, **3a-p**) tested, compound **3c** with 1-phenyl-butan-1-one at 1st position and phenyl group at 4th position exhibited the highest activity against A549, HT-29 and HeLa cells with IC_{50} values of 26 μM, 116 μM, 1550 μM, respectively [16]. Compound **3h** and **3i** with *p*-tolyl and 2,4,5-trimethyl phenyl substituents at 4th position also showed potency against A549 and HT-29 cells with IC_{50} values of 292 μM, 238 μM (**3h**) and 91 μM, 190 μM (**3i**), respectively. Compounds **3k** and **3o** with phenyl

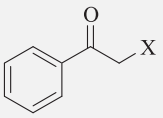
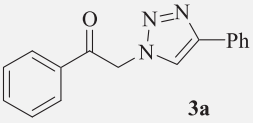
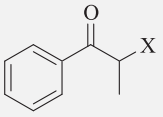
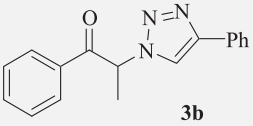
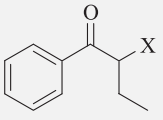
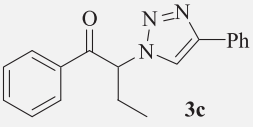
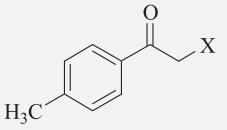
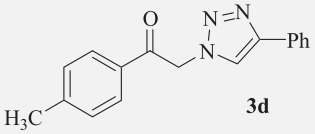
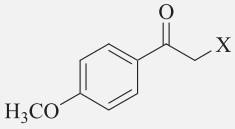
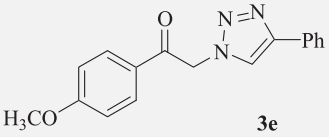
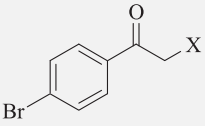
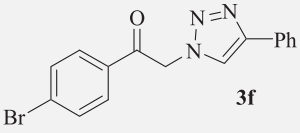
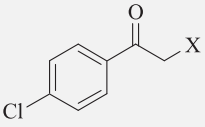
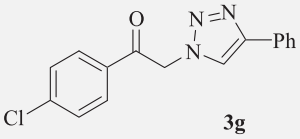
Table 1
Effect of solvent on the synthesis of -keto1,2,3-triazoles.[a]



Entry	Solvent	Br		OTs	
		Time (h)	Yield (%)	Time (h)	Yield (%)
1.	CH_2Cl_2	24	45	24	45
2.	THF	24	55	24	30
3.	MeOH	8	59	8	60
4.	DMF	8	62	12	65
5.	CH_3CN	8	65	16	62
6.	H_2O	8	81	24	57
7.	Acetone:H_2O(1:1)	8	72	12	76
8.	Acetone	8	30	12	46

[a] Reaction conditions: phenacyl bromide or -tosyloxyketone (1 mmol), sodium azide (1.5 mmol), phenylacetylene (1.2 mmol), CuI (5 mol %), solvent (6 ml).

Table 2
Synthesis of β-keto 1,2,3-triazoles using different α-tosyloxy ketones and α-bromo ketones with phenylacetylene and sodium azide.[a]

Entry	Ketone 1	Product 3[c]	X	Time (h)	Yield (%)[b]
1		 **3a**	Br OTs	8 12	81 76
2		 **3b**	Br OTs	8 12	80 71
3		 **3c**	Br OTs	8 12	85 76
4		 **3d**	Br OTs	8 12	78 65
5		 **3e**	Br OTs	8 12	80 73
6		 **3f**	Br OTs	8 12	80 71
7		 **3g**	Br OTs	8 12	76 68

[a] Reaction conditions as exemplified in the typical experimental procedure.
[b] Isolated yields.
[c] All products were characterized by IR, ^{1}H &^{13}C NMR, Mass spectroscopy and elemental analysis.

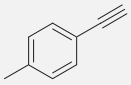
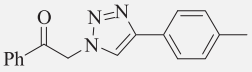
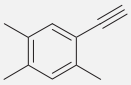
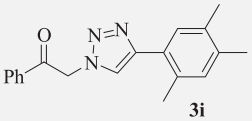
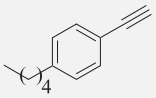
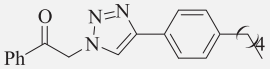
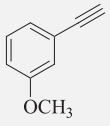
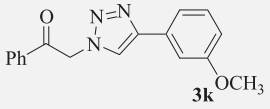
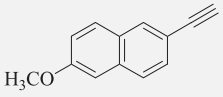
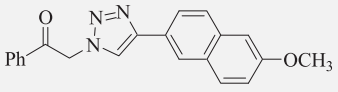
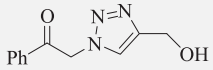
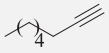
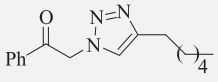
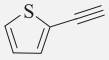
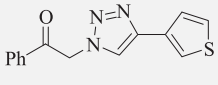
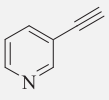
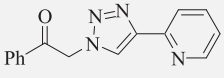
ethanone substituent at 1st position and *m*-methoxy phenyl and thiophene at position – four showed potency against only A549 cells. The remaining compounds were less potent with IC_{50} values greater than 300 μM against all cell lines tested.

Cell viability assay revealed that compounds **3c**, **3e**, **3h** and **3i** exhibited cytotoxic activity against cell lines of various origins. To investigate whether the antiprolifirative activities of these compounds derived from the interaction of tubulin, they were evaluated for their inhibition of tubulin polymerization at 30 μM. For comparison, colchicine and Podophyllotoxin were examined in contemporaneous experiments. Interestingly, compounds **3c**, **3e**, **3h** and **3i** showed inhibition of tubulin polymerization. Interestingly compounds **3c** and **3e** showed inhibition of tubulin polymerization. However compounds **3h** and **3i** less effective as tubulin polymerization inhibitors. In contrast, Podophyllotoxin and colchicine demonstrated an inhibition of tubulin assembly at 53% and 59% respectively (Table 5).

2.3. Conclusion

In conclusion, 1,4-disubstituted 1,2,3-triazoles (β-keto1,2,3-triazoles) have been synthesized directly from a variety of α-bromo or tosyloxyketones, terminal alkynes and sodium azide using CuI as catalyst at room temperature *via* a sequence of nucleophilic displacement and 1,3-dipolar cycloadditions either in water or in a 1:1 mixture of water and acetone at room temperature. The advantage of the present method described here is very simple and facile and can be applicable to a wide range of substrates with high functional group tolerance. The synthesized triazoles exhibited significant cytotoxicity against A549, HT-29 and HeLa cells at

Table 3
Synthesis of β-keto 1,2,3-triazoles using different α-tosyloxyketones and α-bromo ketones with substituted phenylacetylenes and sodium azide.[a]

Entry	Terminal alkyne 2	Product 3[c]	Ph(C=O)CH$_2$X	Time (h)	Yield (%)[b]
1		 **3h**	Br OTs	8 12	86 80
2		 **3i**	Br OTs	8 12	80 74
3		 **3j**	Br OTs	8 12	85 81
4		 **3k**	Br OTs	8 12	74 68
5		 **3l**	Br OTs	24 24	61 45
6		 **3m**	Br OTs	12 16	75 62
7		 **3n**	Br OTs	12 16	79 63
8		 **3o**	Br OTs	12 16	77 58
9		 **3p**	Br OTs	12 16	86 78

[a] Reaction conditions as exemplified in the typical experimental procedure.
[b] Isolated yields.
[c] All products were characterized by IR, ^{1}H &^{13}C NMR.

Table 4
In vitro cytotoxic activities of compounds **3a**–**p** against human cancer cell lines – A549, HT-29 and HeLa.

Entry	Compound	IC_{50} μM[a]		
		A549	HT-29	HeLa
1	**3a**	>300	>300	>300
2	**3b**	>300	>300	>300
3	**3c**	26	116	155
4	**3d**	>300	>300	>300
5	**3e**	>300	49	>300
6	**3f**	>300	>300	>300
7	**3g**	>300	>300	>300
8	**3h**	292	238	>300
9	**3i**	91	190	>300
10	**3j**	>300	>300	>300
11	**3k**	187	>300	>300
12	**3l**	>300	>300	>300
13	**3m**	>300	>300	>300
14	**3n**	>300	>300	>300
15	**3o**	260	>300	>300
16	**3p**	>300	>300	>300
	Colchicine	<1.0	<1.0	<1.0

[a] IC_{50}, compound concentration required to inhibit tumor cell proliferation by 50%.

modest doses mechanestic studies indicate that these compounds inhibits tubulin polymerixation in vitro.

3. Experimental section

3.1. Materials and methods

All chemicals were purchased from Aldrich and S.D Fine Chemicals Pvt. Ltd. India and were used as received. All the solvents used were of LR grade from Merck India Pvt. Ltd. α-bromo and α-tosyloxyketones were prepared according to reported literature methods [17]. HT-29 (Colon cancer), A549 (Lung cancer), HeLa (Cervical cancer) cell line was obtained from National Center for Cell Science (NCCS), Pune, India. DMEM (Dulbeccos Modified Eagles Medium), MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide], Trypsin, EDTA were purchased from Sigma Chemicals Co (St.Louis, MO, USA), Fetal bovine serum were purchased from Gibco. Tubulin polymerization is temperature and light sensitive, pure un-polymerized tubulin was obtained from Cytoskeliton, USA. In the presence of GTP it polymerizes and polymerized tubulin gives fluorescence in a linear fashion. Fluorescence can be used for estimation of tubulin polymerization. Set of compounds are tested for their tubulin polymerization inhibition activity. The assay was carried out in a 384 well plate in PEM buffer [80 mM PIPES (pH-6.9), 1 mM MgCl2, 1 mM EGTA, 10% glycerol]. Briefly, the reaction mixture in a total volume of 10 μl contained PEM buffer, GTP (1 mM) in the presence or absence of test compound (30 μM). The reaction was initiated by the addition of GTP to all the wells. Since polymerization of tubulin is light sensitive entire reaction was carried out in the absence of light. Polymerization reaction was monitored by the increase in fluoroscence at 360/420 nm excitation/emission wavelength using VARIOSCAN multimode plate reader at 37 °C. fluoroscence was recorded at every 60 s intervals for up to 1 h. TLC analyses was performed on Merck precoated silica gel 60-F254 plates. Melting points were measured in open capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer, SpectrumGX FT-IR spectrometer as KBr pellets. The ^1H & ^{13}C NMR spectra were recorded on a Varian-Gemini 200 MHz and Bruker-Avance 300 MHz Spectrometers. Chemical shifts (δ) are reported in ppm, using TMS ($\delta = 0$) as an internal standard in $CDCl_3$. ESI mass spectra were recorded on a Finnigan Finnigan LCQ Advantagemax spectrometer and EI mass spectra were recorded on a GC-MS QP2010 Plus (Shimadzu).

Table 5
Effect of β-keto 1,2,3-triazoles on *in vitro* tubulin polymerization.[a]

Compounds	Fluoroscence	% Polymerization	% Inhibition
Control	9.7	100	0.0
Podophyllotoxin	4.5	46.2	53.8
Colchicine	4.1	41.9	58.1
3c	7.8	80.7	19.3
3e	8.6	85.9	14.1
3h	9.4	97.2	2.8
3i	9.1	93.4	6.6

[a] All compounds were tested at concentration of 30 μM, colchicine and Podophyllotoxin were tested at 3 μM and assay is performed in 384 well plate at 360–420 nm.

3.2. General procedure for the synthesis of 1,2,3-triazoles(*3a*–*p*)

A mixture of α-bromo or tosyloxy ketone **1** (1 mmol) sodium azide **2** (1.5 mmol), phenylacetylene **3** (1.2 mmol), and CuI (5 mol %) in water (6 mL) or water/acetone (1:1) was stirred at ambient temperature for 8–12 h. After completion of the reaction (as monitored by TLC), the catalyst was filtered through Celite and the product was extracted with ether (3 × 10 mL). After removing the solvent under vacuum, the crude product was purified by column chromatography on silica gel using hexane-ethyl acetate mixture (7:3) as eluent.

3.2.1. 1-Phenyl-2-(4-phenyl-[1,2,3]triazol-1-yl)-ethanone (*3a*)

White solid; mp 172–175 °C; R_f (30% EtOAc/Hexane) = 0.34; IR (KBr): 3087, 2929, 1700, 1586, 1443, 1223, 982, 761, 688 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 5.85 (s, 2H), 7.29–7.42 (m, 3H), 7.52–7.69 (m, 3H), 7.84 (d, 2H, $J = 7.6$ Hz), 7.91 (s, 1H), 8.04 (d, 2H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.48, 121.37, 125.85, 127.31, 128.24, 128.87, 129.17, 132.18,133.97, 194.71. ESI MS (*m/z*): 264 $(M+H)^+$. Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.58; H, 4.84; N, 15.92.

3.2.2. 1-Phenyl-2-(4-phenyl-[1,2,3]triazol-1-yl)-propan-1-one (*3b*)

White solid; mp 122–125 °C; R_f (40% EtOAc/Hexane) = 0.42; IR (KBr): 3137, 2924, 1694, 1588, 1463, 1218, 1090, 971, 963 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.83 (d, 3H, $J = 7.3$ Hz), 6.47 (q, 1H, $J = 7.3$ Hz), 7.26–7.49 (m, 6H), 7.80 (d, 2H, $J = 7.8$ Hz), 7.88 (s, 1H), 8.01 (d, 2H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.39, 59.29, 118.59, 125.9, 128.30, 128.85, 129.49, 129.55, 130.22, 132.14, 192.94. ESI MS (*m/z*): 279 $(M)^{2+}$. Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.84; H, 5.60; N, 14.97.

3.2.3. 1-Phenyl-2-(4-phenyl-[1,2,3]triazol-1-yl)-butan-1-one (*3c*)

White solid; mp 114–116 °C; R_f (40% EtOAc/Hexane) = 0.5; IR (KBr): 3119, 2963, 1697, 1596, 1383, 1223, 1077, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (t, 3H, $J = 7.6$ Hz), 2.07–2.19 (m, 1H), 2.23–2.35 (m, 1H), 6.31 (dd, 1H, $J = 6.0$, 9.8 Hz), 7.28–7.64 (m, 6H), 7.82 (d, 2H, $J = 7.0$ Hz), 7.99 (s, 1H), 8.07 (d, 2H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.39, 26.80, 65.08, 118.85, 125.74, 128.21, 128.80, 129.14, 130.57, 134.44, 194.22. ESI MS (*m/z*): 292 $(M+H)^+$. Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.24; H, 5.69; N, 14.57.

3.2.4. 2-(4-Phenyl-[1,2,3]triazol-1-yl)-1-p-tolyl-ethanone (*3d*)

White solid; mp 158–160 °C; R_f (30% EtOAc/Hexane) = 0.27; IR (KBr): 2832, 1700, 1598, 1385, 1223, 1074, 814 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H), 5.81 (s, 2H), 7.12 (d, 2H, $J = 8.0$ Hz), 7.41–7.69 (m, 5H), 7.81 (s, 1H), 7.92 (d, 2H, $J = 8.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.20, 55.32, 120.18, 125.59, 126.36, 127.91,

128.53, 129.09, 131.43, 134.76, 140.02, 146.91, 190.85. EI MS (*m/z*): 277 $(M)^+$. Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.51; H, 5.34; N, 15.22.

3.2.5. 2-[4-(4-Methoxy-phenyl)-[1,2,3]triazol-1-yl]-1-phenyl-ethanone (**3e**)

White solid; mp 106–109 °C; R_f (30% EtOAc/Hexane) = 0.33; IR (KBr): 3093, 1703, 2840, 1498, 1450, 1247, 1220, 1026, 823 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 3H), 5.85 (s, 2H), 6.92 (d, 2H, J = 8.7 Hz), 7.44–7.66 (m, 3H), 7.74 (s, 1H), 7.80 (d, 2H, J = 8.0 Hz), 8.04 (d, 2H, J = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.30, 55.45, 114.19, 120.50, 127.10, 127.31, 127.95, 128.21, 129.20, 131.99, 134.61, 140.43, 161.58, 188.14. EI MS (*m/z*): 293 (M^+). Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.42; H, 5.09; N, 14.51.

3.2.6. 1-(4-Bromo-phenyl)-2-(4-phenyl-[1,2,3]triazol-1-yl)-ethanone (**3f**)

Pale yellow colour solid; mp 115–118 °C; R_f (30% EtOAc/Hexane) = 0.37; IR (KBr): 3083, 2925, 1696, 1484, 1231, 1078, 762, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.81 (s, 2H), 7.29–7.44 (m, 3H), 7.52–7.63 (m, 2H), 7.71 (s, 1H), 7.83 (d, 2H, J = 7.3 Hz), 7.99 (d, 2H, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.30, 121.31, 125.79, 128.27, 128.24, 128.88, 129.60, 129.75, 132.54, 134.75, 136.18, 189.51. ESI MS (*m/z*): 343 $(M + H)^+$. Anal. Calcd for $C_{16}H_{12}BrN_3O$: C, 56.16; H, 3.53; N, 12.28. Found: C, 56.05; H, 3.62; N, 12.35.

3.2.7. 1-(4-Chloro-phenyl)-2-(4-phenyl-[1,2,3]triazol-1-yl)-ethanone (**3g**)

White solid; mp 106–109 °C; R_f (30% EtOAc/Hexane) = 0.35; IR (KBr): 3122, 2987, 1706, 1456, 1352, 1223, 1076, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.83 (s, 2H), 7.23–7.59 (m, 7H), 7.75 (s, 1H), 7.98 (d, 2H, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.34, 125.92, 128.32, 129.13, 129.72, 130.61, 134.43, 135.54, 139.44, 190.11. ESI MS (*m/z*): 265 $(M + 1)^+$. Anal. Calcd for $C_{16}H_{12}N_3O$: C, 64.54; H, 4.06; N, 14.11. Found: C, 64.42; H, 4.12; N, 41.14.

3.2.8. 1-Phenyl-2-(4-p-tolyl-[1,2,3]triazol-1-yl)-ethanone (**3h**)

White solid; mp 158–160 °C; R_f (30% EtOAc/Hexane) = 0.28; IR (KBr): 2930, 1700, 1448, 1347, 1223, 976, 817 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H), 5.83 (s, 2H), 7.19 (d, 2H, J = 8.1 Hz), 7.38–7.73 (m, 5H), 7.86 (s, 1H), 8.03 (d, 2H, J = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.24, 55.36, 125.71, 128.18, 128.79, 129.14, 129.40, 129.84, 134.49, 137.95, 139.06, 190.36. EI MS (*m/z*): 277 $(M)^+$. Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.45; H, 5.31; N, 14.95.

3.2.9. 1-Phenyl-2-[4-(2,4,5-trimethyl-phenyl)-[1,2,3]triazol-1-yl]-ethanone (**3i**)

White solid; mp 165–167 °C; R_f (30% EtOAc/Hexane) = 0.32; IR (KBr): 2951, 1712, 1447, 1221, 1601, 994, 753 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.28 (s, 2H), 2.43 (s, 3H), 5.87 (s, 2H), 7.00 (s, 1H), 7.44–7.67 (m, 3H), 7.76 (s, 1H), 8.04 (d, 2H, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.06, 19.38, 20.68, 55.36, 123.20, 127.16, 128.15, 129.14, 130.01, 132.17, 132.66, 134.09, 134.20, 134.55, 136.59, 190.35. EI MS (*m/z*): 305 (M^+). Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.15; H, 5.87; N, 13.82.

3.2.10. 2-[4-(4-Pentyl-phenyl)-[1,2,3]triazol-1-yl]-1-phenyl-ethanone (**3j**)

White solid; mp 172–175 °C; R_f (30% EtOAc/Hexane) = 0.39; IR (KBr): 3086, 2925, 2854, 1704, 1451, 1346, 1221, 981, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 6.8 Hz), 1.30–1.39 (m, 4H), 1.58–1.69 (m, 2H), 2.62 (t, 2H, J = 7.5 Hz), 5.83 (s, 2H), 7.19 (d, 2H, J = 7.6 Hz), 7.50–7.68 (m, 3H), 7.73 (d, 2H, J = 8.3 Hz), 7.86 (s, 1H), 8.03 (d, 2H, J = 7.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.02, 22.52, 31.04, 31.48, 35.70, 55.45, 121.05, 125.74, 127.89, 128.18, 128.85, 129.14, 134.03, 134.55, 143.13, 148.34, 190.29. EI MS (*m/z*): 333 $(M)^+$. Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 74.92; H, 7.11; N, 12.69.

3.2.11. 2-[4-(3-Methoxy-phenyl)-[1,2,3]triazol-1-yl]-1-phenyl-ethanone (**3k**)

White solid; mp 167–170 °C; R_f (30% EtOAc/Hexane) = 0.31; IR (KBr): 3438, 2956, 2361, 1701, 1496, 1249, 1223, 1030, 824 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 3H), 5.86 (s, 2H), 7.28–7.42 (m, 8H), 7.74 (s, 1H), 8.01 (d, 2H, J = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.32, 55.38, 112.05, 121.35, 126.95, 127.12, 127.56, 127.98, 128.31, 128.93, 130.05, 134.01, 137.89, 160.20, 190.21. ESI MS (*m/z*): 294 $(M+H)^+$. Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.42; H, 5.09; N, 14.51.

3.2.12. 2-[4-(6-Methoxy-naphthalen-2-yl)-[1,2,3]triazol-1-yl]-1-phenyl-ethanone (**3l**)

White solid; mp 160–163 °C; R_f (40% EtOAc/Hexane) = 0.32; IR (KBr): 3446, 2923, 2852, 2362, 1702, 1456, 1218, 1026, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.93 (s, 3H), 5.86 (s, 2H), 7.43–7.64 (m, 9H), 7.99 (s, 1H), 8.08 (d, 2H, J = 8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.29, 59.92, 105.82, 118.18, 124.16, 124.43, 126.51, 127.24, 128.49, 129.03, 129.60, 134.28, 139.92, 148.19, 156.79, 190.56. ESI MS (*m/z*): 344 $(M + H)^+$. Anal. Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.21; H, 4.81; N, 12.32.

3.2.13. 2-(4-Hydroxymethyl-[1,2,3]triazol-1-yl)-1-phenyl-ethanone (**3m**)

White solid; mp 115–118 °C; R_f (10% CH_3OH/CH_2Cl_2) = 0.29; IR (KBr): 3306, 1690, 1443, 1225, 933, 755 cm^{-1}. ^1H NMR (200 MHz, DMSO d_6): δ 4.67 (d, 2H, J = 5.9 Hz), 4.85 (t, 1H, J = 5.9 Hz), 5.96 (s, 2H), 7.50–7.66 (m, 3H), 7.77 (s, 1H), 8.04 (d, 2H, J = 8.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.36, 56.70, 123.50, 128.12, 128.24, 129.17, 134.67, 148.02, 190.02. ESI MS (*m/z*): 218 $(M + 1)^+$. Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.30; H, 4.96; N, 19.42.

3.2.14. 2-(4-Hexyl-[1,2,3]triazol-1-yl)-1-phenyl ethanone (**3n**)

White solid; mp 106–108 °C; R_f (30% EtOAc/Hexane) = 0.26; IR (KBr): 3396, 3062, 2926, 2852, 1594, 1706, 1447, 1220, 1057, 985, 756 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, 3H, J = 6.6 Hz), 1.27–1.41 (m, 6H), 1.63–1.77 (m, 2H), 2.75 (t, 2H, J = 7.3 Hz), 5.76 (s, 2H), 7.40 (s, 1H), 7.48–7.65 (m, 3H), 8.01 (d, 2H, J = 8.03 Hz).^{13}C NMR (75 MHz, $CDCl_3$): δ 14.02, 22.52, 25.66, 28.92, 29.24, 31.58, 55.36, 125.08, 128.15, 134.03, 134.46, 190.61. ESI MS (*m/z*): 272 $(M + 1)^+$. Anal. Calcd for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.49. Found: C, 69.98; H, 7.61; N, 15.69.

3.2.15. 1-Phenyl-2-(4-thiophen-3-yl-[1,2,3]triazol-1-yl)-ethanone (**3o**)

White solid; mp 167–170 °C; R_f (40% EtOAc/Hexane) = 0.31; IR (KBr): 2988, 1703, 1595, 1448, 1321, 1222, 943 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.84 (s, 2H), 7.21 (d, 1H, J = 6.2 Hz), 7.32–7.43 (m, 5H), 7.81 (s, 1H), 8.03 (d, 2H, J = 7.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.99, 121.26, 122.91, 125.47, 125.88, 126.93, 128.06, 128.88, 129.23, 134.55, 147.41,189.88. EI MS (*m/z*): 269 $(M)^+$. Anal. Calcd for $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60; S, 11.91. Found: C, 62.62; H, 3.98; N, 15.74; S, 11.87.

3.2.16. 1-Phenyl-2-(4-pyridin-2-yl-[1,2,3]triazol-1-yl)-ethanone (**3p**)

Yellowish green solid; mp 173–175 °C; R_f (50% EtOAc/Hexane) = 0.35; IR (KBr): 3065, 2936, 1705, 1593, 1561, 1443, 1350,

1225, 1049, 993, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.88 (s, 2H), 7.17–7.23 (m, 1H), 7.51–7.81 (m, 3H), 8.05 (d, 2H, $J = 7.5$ Hz), 8.27 (s, 2H), 8.54 (d, 1H $J = 6.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.57, 120.32, 122.86, 123.93, 128.18, 129.14, 134.58, 136.82, 149.42, 189.85. ESI MS (*m/z*): 265 $(M + H)^+$. Anal. Calcd for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.02; H, 4.32; N, 21.44.

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