A Short Route to [1,2,3]-Triazolyl Coumarin and Quinolone Derivatives by Cu(I) Catalyzed 1,3-Dipolar Cycloaddition and Fluorescence Studies

Krishna C. Majumdar* and Shovan Mondal

Department of Chemistry, University of Kalyani, Kalyani-741235, W.B. India

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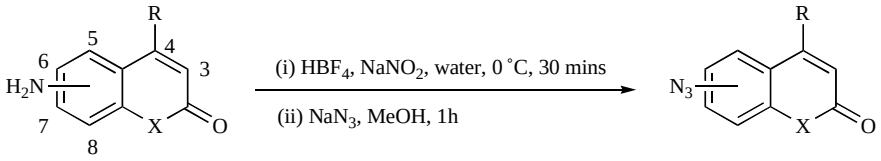
Abstract: Hitherto unreported [1,2,3]-triazolyl coumarin and quinolone derivatives in good to excellent yields have been expediently synthesized from 6- and 7-azidocoumarin and 6-azidoquinolone by copper (I) catalyzed 1,3-dipolar cycloaddition. Azidocoumarins and azidoquinolones were in turn prepared efficiently from the corresponding amines. Fluorescence studies of the newly synthesized [1,2,3]- triazolyl coumarin and quinolone derivatives are also described.

Keywords: 1,3-dipolar cycloaddition, 6 and 7-azidocoumarin, 6-azidoquinolone, [1,2,3] triazole, phenyl acetylene, fluorescence.

Nitrogen heterocycles are widely distributed in nature, including amino acids, purines, pyrimidines etc. Heterocyclic compounds such as [1,2,3]-triazoles exhibit biological activities including anti-HIV activity, [1] anti-microbial activity against Gram positive bacteria, [2] selective β_3 adrenergic receptor agonism [3]. [1,2,3]-triazoles have also found wide use in industrial applications as dyes, corrosion inhibitors, photo stabilizers, photographic materials and agrochemicals [4]. Based on the application potential of the [1,2,3]-triazole moiety, many fluorescent libraries have been developed by Cu(I)- catalyzed Huisgen 1,3-dipolar cycloaddition of azides and alkynes. Chang *et al.* recently, developed libraries of styryl dyes bearing DNA-sensitive fluorescent sensors [5] and β-amyloid sensors [6]. Subsequently, Bauerle *et al.* [7] and Wang *et al*. [8] reported coumarin libraries with diversity at the 3-position *via* Suzuki-Miyaura, Heck, Sonogashira-Hagihara or Husigen cycloaddition reactions. The compounds containing coumarin moiety showed interesting photo-physical property such as fluorescence. Therefore, in continuation to our longstanding interest in coumarin and quinolone chemistry, [9-11] we became interested to develop an efficient method for the synthesis of coumarin and quinolone containing triazolyl derivatives with diversity at the 6- and 7- positions *via* Huisgen cycloaddition reaction. Herein we report our results.

The required precursors **2**(**a-c**) were prepared by diazotization of **1(a-c)** in tetrafluoroboric acid (40% solution in water) with dropwise addition of sodium nitrite (solution in water) at 0 to -5 ˚C and stirring for 1 h. Sodium azide was added to the methanolic solution of the diazotized salt and stirred for 1 h at rt to give azido derivatives (**2a-c**) in 70-75% yields (Scheme **1**).



1 (a-c)

1a, 6-NH_2, X = O, R = H
1b, 7-NH_2, X = O, R = CH_3
1c, 6-NH_2, X = NMe, R = H

2 (a-c)

2a, 6-NH_2, X = O, R = H, 75%
2b, 7-NH_2, X = O, R = CH_3, 72%
2c, 6-NH_2, X = NMe, R = H, 70%

Scheme 1. Synthetic procedure of azido-coumarin and quinolone.

The 4-chloro phenyl acetylene (**B**) and 4-nitro phenyl acetylene (**C**) were prepared from their corresponding aldehydes by portion wise addition of triphenyl phosphine to a solution of the aldehyde and carbon tetrabromide in anhydrous dichloromethane at 0 ˚C followed by stirring at rt for 1 h. The dibromoalkene was then treated with n-BuLi in anhydrous THF at –78 ˚C to give **B** and **C**. (Scheme **2**).

The final triazolyl derivatives of coumarin and quinolone (**3a-h**) were obtained in 68-80% yields by stirring azides **2a-c** (4.99 mmol) and alkynes **A-C** (5.99 mmol) in the presence of a catalytic amount (10 mol%) of CuI in DMSO at 60˚C for 1 h (Scheme **3**).

Recently, Wang *et al.* [8] have reported a coumarin library at the 3-position by [1,2,3]-triazole synthesis using $CuSO_4$ and sodium ascorbate and their protocol takes 12 to

*Address correspondence to this author at the Department of Chemistry, University of Kalyani, Kalyani 741235, west Bengal, India; Tel: +91-33-2582-7521; Fax: +91-33-25828282; E-mail: kcm_ku@yahoo.co.in

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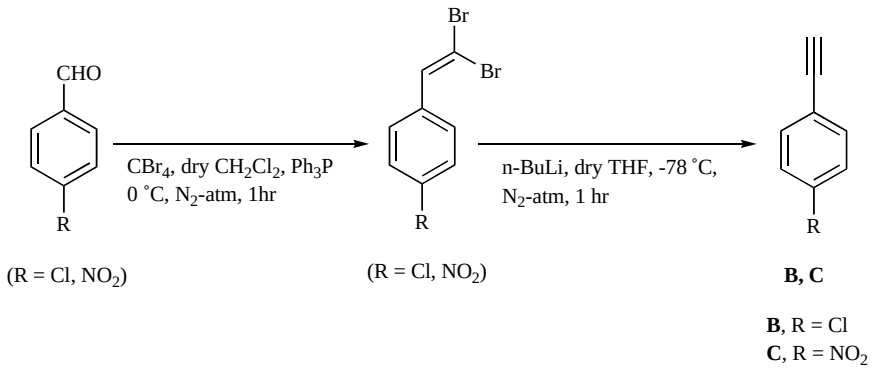
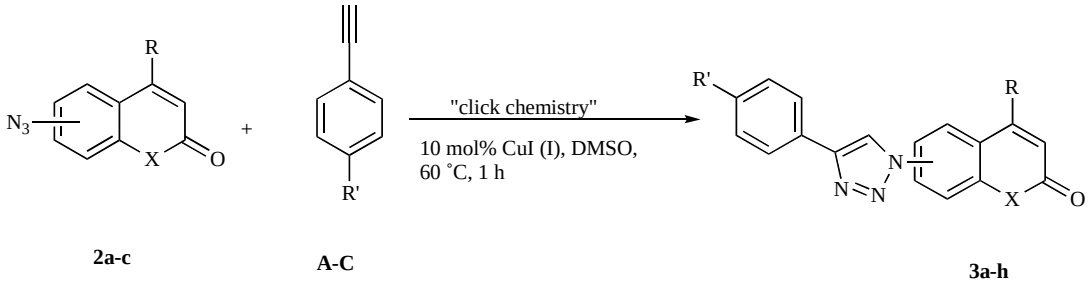


Scheme 2. Synthetic procedure of alkynes.



Scheme 3. Synthesis of [1,2,3] triazol compound.

24 h for the reaction, a lengthy method, unsuitable for construction of a library. Very recently Bertounesque and coworkers have reported triazinyl-triazole phosphate [12] using $CuSO_4$ and ascorbic acid and their protocol also took 24 h for completion of the reaction. Very recently Ackermann *et al*. also reported the synthesis of triazolyl derivatives by click reaction [13] using sodium azide. As a part of the study, we have conducted a series of experiments with the substrate **2a** where sequential changes were made to the catalyst, solvent and temperature for optimization of the reaction condition (Table **1**). Excellent result was obtained by heating the azide and the alkyne in DMSO at 60˚C. This optimized condition was applied to other substrates for the synthesis of triazole derivatives.

Isolation of the products is simple and straightforward as the solids precipitated after pouring the reaction mixture into water could be obtained by filtration. Simple recrystallization from ethanol gave the pure products. The results for all the new compounds are depicted in Table **2**.

Photo Physical Properties of [1,2,3]-Triazole Coumarin and Quinolone Derivatives

Coumarin and quinolone are unambiguous core moieties for the fluorogenic probes. We have utilized these moieties since they are small in size, biocompatible and easy to manipulate synthetically. In particular, coumarins are important because of their pharmacological activity [14] and photophysical properties and they have been extensively applied as laser dyes [15]. Substitution at the 3-, 6- and 7- positions of coumarin dyes are known to have a strong impact on their fluorescence properties [7, 16, 17]. Therefore we have studied the photo physical properties of the newly synthesized [1,2,3]-triazole coumarin and quinolone derivatives. A 0.5 X 10^{-6} M concentration of coumarin and quinolone derivatives (**3a-h**) in DMSO was used for photo physical property studies. The photoluminescence spectra of the compounds (**3a-h**) are shown in Fig. (**1**).

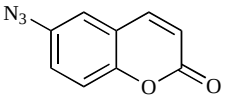
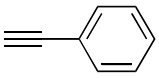
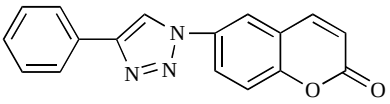
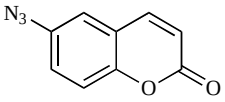
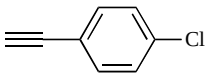
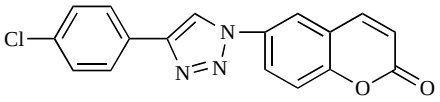
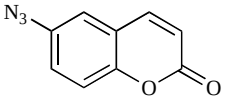
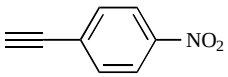
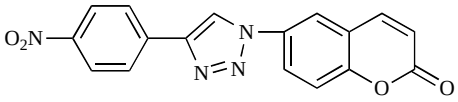
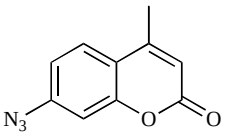
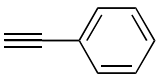
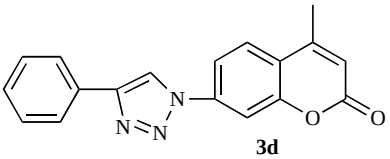
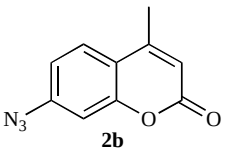
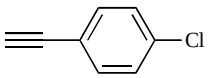
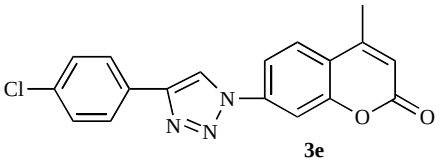
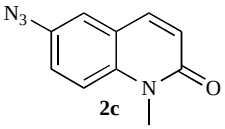
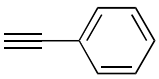
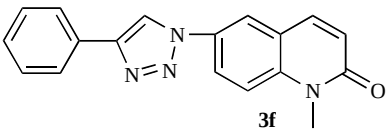
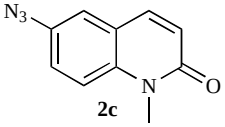
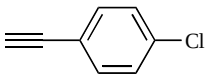
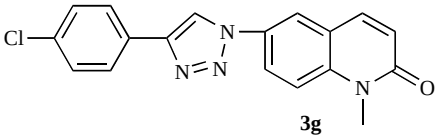
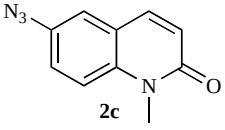
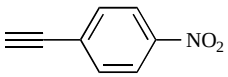
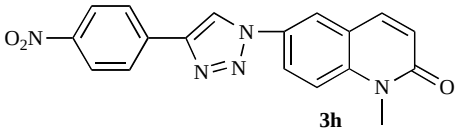
The fluorescence intensities of these compounds **3 (a-h)** in acetonitrile, methanol and DMSO were measured (Table

Table 1. Optimized Conditions for 3a

Entry	Solvent	Catalyst	Temperature	Time (h)	Yielda(%)
1	Ethanol/H_2O (1 : 1)	5% $CuSO_4$ + 10% NaAsc	rt	12	63
2	DMSO/H_2O (1 :1)	5% $CuSO_4$ + 10% NaAsc	rt	12	65
3	Ethanol	10 mol% CuI	rt	5	65
4	DMSO	10 mol% CuI	rt	5	67
5	DMSO	10 mol% CuI	60 ˚C	1	80

[a]Isolated yield after recrystallisation from ethanol.

Table 2. Triazolyl-Coumarins and Quinolones

Entry	Azide	Alkyne	Product	Yield (%)
1	 **2a**	 **A**	 **3a**	80
2	 **2a**	 **B**	 **3b**	82
3	 **2a**	 **C**	 **3c**	72
4	 **2b**	 **A**	 **3d**	78
5	 **2b**	 **B**	 **3e**	73
6	 **2c**	 **A**	 **3f**	81
7	 **2c**	 **B**	 **3g**	79
8	 **2c**	 **C**	 **3h**	68

3). Compound **3 (a-c)** gave no absorption bands and compound **3 (d-e)** gave hump in methanol due to insolubility and very low solubility of these compounds respectively.

Interestingly compounds **2a-c** showed no fluorescence property due to the quenching effect from electron-rich α-nitrogen of the azide group and the compounds **3a-h** exhibited high fluorescence due to elimination of the quenching through the formation of the triazole ring. The detailed mechanistic investigations, such as measurements by single wavelength excitation, time-resolved measurement of fluorescence decays, and lifetimes, are in progress.

In conclusion, we have demonstrated a simple and short route to [1,2,3]-triazolyl coumarin and quinolone derivatives. This protocol offers several advantages such as all the reactions were completed within one hour without any undesired side products. Good yields of the products are obtained which do not need extensive purification, makes it an useful and attractive process for the construction of libraries of coumarin and quinolone possessing diversity at 6 and 7 positions by [1,2,3]-triazolyl synthesis.Coumarin and quinolone derivatives show good photo physical effects and have a stable fluorescence property.

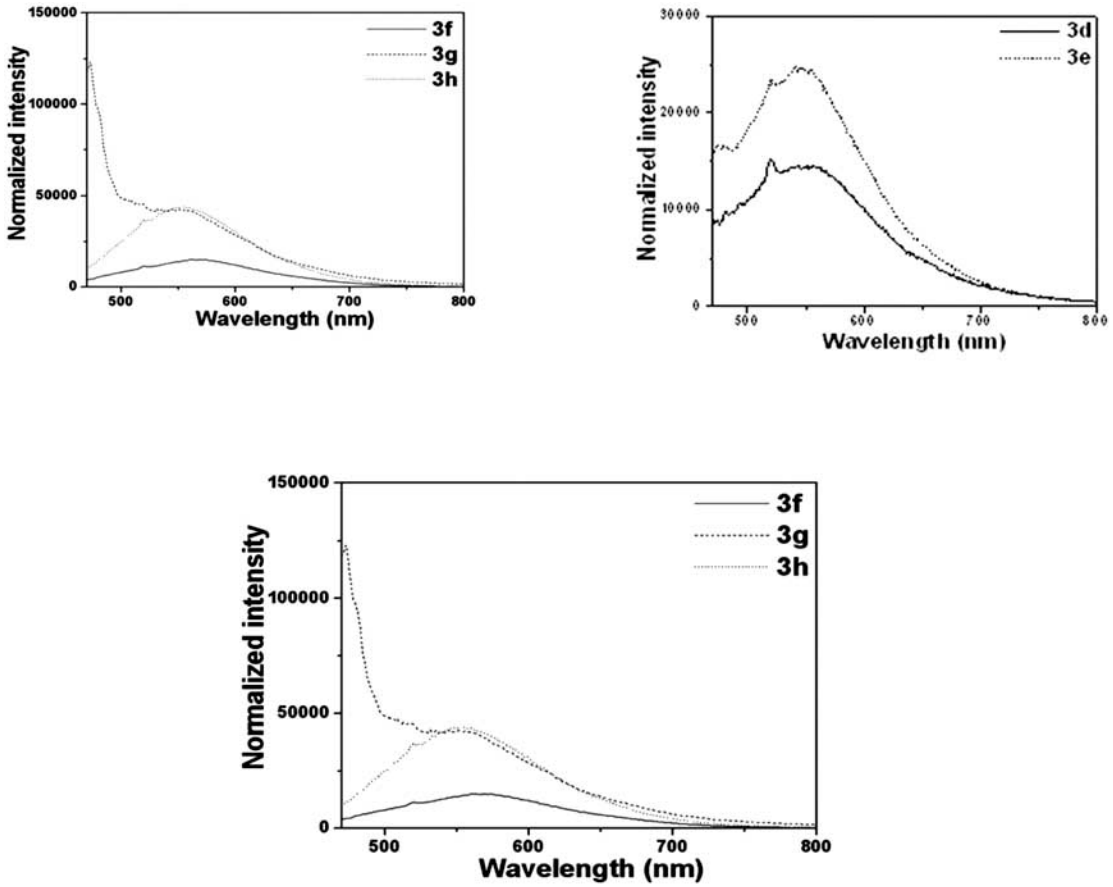


Fig. (1). Fluorescence spectra of triazolyl-coumarin and quinolone dyes. Each compound were measured in 0.5 X 10^{-6} M solution in DMSO.

Table 3. Fluorescence Intensity of Triazolyl-Coumarin and Quinolone Dyes

Compound	DMSO		CH_3CN[a]		CH_3OH[a]		UV (nm) (in DMSO)
	Peak (nm)	Intensity	Peak (nm)	Intensity	Peak (nm)	Intensity	
3a	565	5581	566	16166	-	-	895, 263, 204
3b	562	8607	531	8793	-	-	890, 266, 217
3c	560	13435	531	11529	-	-	895, 888, 321
3d	557	14470	548	14090	576(h)	21452	861, 326, 284
3e	548	24492	543	16122	576 (h)	21583	861, 491, 326
3f	571	14707	570	16302	574	17118	891, 456, 344
3g	561	41945	554	30611	556	31294	895, 457, 338
3h	554	43595	542	48552	546	33260	883, 332, 260

[a]Containing 0.5% DMSO as cosolvent, h = hump.

EXPERIMENTAL SECTION

General

Melting points were determined in open capillaries and are uncorrected. IR spectra were run on KBr pellets on a Perkin-Elmer 120-000A apparatus (ν_{max} in cm^{-1}) and ^{1}H-NMR spectra were determined for solutions in $CDCl_3$ with TMS as internal standard on a Bruker DPX-400. ^{13}C-NMR spectra were determined for solutions in $CDCl_3$ on a Bruker DPX-125. The photoluminescence experiments of the compounds were performed on a Fluoro Max-3 (HORIBA JOBIN YVON luminescence spectrometer). Silica gel (60-120 mesh) was used for chromatographic separation. Silica gel-G [E-Mark (India)] was used for TLC. Petroleum-ether refers to the fraction between 60 and 80 ˚C.

General Procedure for the Synthesis of Azido-Coumarins and Quinolone

To a magnetically well-stirred mixture of the amines **1a-c** (12.41 mmol) in tetrafluoroboric acid (40% solution in water, 6.8 mL), a solution of $NaNO_2$ (1.28g, 18.6 mmol) in wa-

ter (2 mL) was added drop wise at 0 to -5 ˚C and stirring was continued for 1 h. The solid diazonium salt was filtered and dried. The solid salt was then taken in dry MeOH (10 mL) and sodium azide (0.887g, 13.7 mmol) was added all at once at ice cool condition. After stirring for 1 h at rt, the solvent was removed in *vacuo* and the residue was extracted with Et_2O (3 X 30 mL) and the ether extract was washed with water (20 mL). The ether extract was dried (Na_2SO_4) and concentrated to afford the desired products **2a-c** in 70-75% yield.

6-azido-2H-chromen-2-one (2a)

White solid, mp 158-160 ˚C, yield 75%. IR (KBr, cm^{-1}) ν_{max}: 2108, 1713; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.56 (d, 1H, *J* = 9.6 Hz), 7.34 (dd, 1H, *J* = 8.4, 1.6 Hz), 7.44 (d, 1H, *J* = 8.8 Hz), 7.58 (d, 1H, *J* = 1.8 Hz), 8.05 (d, 1H, *J* = 9.5 Hz); LCMS: *m/z* $[M + H]^+$ 188.2. Anal. Calcd. for $C_9H_5N_3O_2$: C, 57.76; H, 2.69; N, 22.45 %. Found: C, 57.85; H, 2.74; N, 22.54 %.

7-azido-4-methyl-2H-chromen-2-one (2b)

White solid, mp 100-102 ˚C, yield 72%. IR (KBr, cm^{-1}) ν_{max}: 2118, 1722; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.41 (s, 3H), 6.33 (s, 1H), 7.12 (d, 1H, *J* = 8.5 Hz), 7.15 (s, 1H), 7.77 (d, 1H, *J* = 8.4 Hz); LCMS: *m/z* $[M + H]^+$ 202.3. Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89 %. Found: C, 59.84; H, 3.63; N, 20.82 %.

6-azido-1-methylquinoline-2-(1H)-one (2c)

Off-white solid, mp 80-82 ˚C, yield 70%. IR (KBr, cm^{-1}) ν_{max}: 2098, 1651; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.58 (s, 3H), 6.64 (d, 1H, *J* = 9.5 Hz), 7.34 (dd, 1H, *J* = 8.9, 2.3 Hz), 7.52 (d, 1H, *J* = 2.5 Hz), 7.54 (d, 1H, *J* = 9.1 Hz), 7.88 (d, 1H, *J* = 9.5 Hz); LCMS: *m/z* $[M + H]^+$ 201.3. Anal. Calcd. for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99 %. Found: C, 59.91; H, 4.11; N, 27.92 %.

General Procedure for the Synthesis of Alkynes from Aldehydes

To a well-stirred solution of aldehyde (11.5 mmol) and CBr_4 (5.74g, 17.25 mmol) in dry CH_2Cl_2 (25 mL), Ph_3P (6.31g, 24.05 mmol) was added in four portions at 3 min interval at 0 ˚C. Stirring was continued for 1 h at rt and diluted with petroleum ether (60-80 ˚C). The phosphine oxide was removed by column chromatography over silica gel using (1:1) ethyl acetate : pet ether as eluent.

A solution of dibromoalkene (14.20 mmol) in dry THF (40 mL) at -78 ˚C under nitrogen atmosphere was stirred with n-BuLi in hexane (29.82 mmol) for 1 h at -78 ˚C. The reaction mixture was warmed to -25 ˚C and was stirred at that temperature for further 1 h. The reaction mixture was quenched with water (20 mL) and extracted with ethylacetate (3 X 30 mL). Removal of the solvent and flash chromatography with (1:9) ethyl acetate : pet ether as eluent gave the desired alkynes (**B, C**).

General Procedure for [1,2,3] Triazole Synthesis (3a-h)

To a well-stirred solution of the azides **2a-c** (4.99 mmol) and alkynes **A-C** (5.99 mmol) in DMSO (10 mL), catalytic amount (10 mol%) of CuI (I) was added and stirred for 1 h at 60 ˚C. After cooling, the reaction mixture was poured into water (100 mL). The solid was filtered and crystallized from ethanol (100 mL) to give the desired products.

6-(4-phenyl-1H-1,2,3-triazol-1-yl)-2H-chromen-2-one (3a)

Green solid, mp above 260˚C, yield 80%. IR (KBr, cm^{-1}) ν_{max}: 1735; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.65 (d, 1H, *J* = 9.7 Hz), 7.41 (d, 1H, *J* = 6.1 Hz), 7.50 (d, 2H, *J* = 7.1 Hz), 7.68 (d, 1H, *J* = 8.3 Hz), 7.95 (d, 2H, *J* = 7.0 Hz), 8.18 (t, 2H, *J* = 9.8 Hz), 8.39 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 117.6, 117.8, 119.4, 119.5, 119.7, 123.4, 125.2, 128.2, 128.7, 128.9, 129.9, 132.2, 132.7, 143.4, 147.3, 152.8, 159.3; LCMS: *m/z* $[M + H]^+$ 290.2. Anal. Calcd. for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53 %. Found: C, 70.74; H, 3.68; N, 14.66 %.

6-(4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl)-2H-chromen-2-one (3b)

Yellow solid, mp above 230˚C, yield 82%. IR (KBr, cm^{-1}) ν_{max}: 1725; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.65 (d, 1H, *J* = 9.6 Hz), 7.59 (d, 2H, *J* = 8.5 Hz), 7.69 (d, 1H, *J* = 9.0 Hz), 7.96 (d, 2H, *J* = 8.5 Hz), 8.15 (dd, 1H, *J* = 8.9, 2.5 Hz), 8.19 (d, 1H, *J* = 9.7 Hz), 8.37 (d, 1H, *J* = 2.5 Hz); LCMS: *m/z* $[M + H]^+$ 324.3. Anal. Calcd. for $C_{17}H_{1^{\circ}C}lN_3O_2$: C, 63.07; H, 3.11; N, 12.98 %. Found: C, 62.88; H, 3.12; N, 12.90 %.

6-(4-(4-nitrophenyl)-1H-1,2,3-triazol-1-yl)-2H-chromen-2-one (3c)

Yellow solid, mp 180-182˚C, yield 72%. IR (KBr, cm^{-1}) ν_{max}: 1729, 1343; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.66 (d, 1H, *J* = 9.6 Hz), 7.70 (d, 1H, *J* = 8.8 Hz), 8.01 (dd, 1H, *J* = 8.4, 1.6 Hz), 8.10 (dd, 1H, *J* = 8.5, 1.7 Hz), 8.15 (d, 1H, *J* = 8.6 Hz), 8.17 - 8.22 (m, 2H), 8.39-8.41 (m, 2H), 9.6 (d, 1H, *J* = 9.6 Hz); LCMS: *m/z* $[M + H]^+$ 335.1. Anal. Calcd. for $C_{17}H_{10}N_4O_4$: C, 61.08; H, 3.02; N, 16.76 %. Found: C, 61.2; H, 3.2; N, 16.86 %.

4-methyl-7-(4-phenyl-1H-1,2,3-triazol-1-yl)-2H-chromen-2-one (3d)

Yellow solid, mp above 230˚C, yield 78%. IR (KBr, cm^{-1}) ν_{max}: 1712, 1622; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.38 (s, 3H), 6.50 (s, 1H), 7.41 (t, 1H, *J* = 7.3 Hz), 7.52 (t, 2H, *J* = 7.5 Hz), 7.95 (d, 1H, *J* = 7.4 Hz), 8.0 (s, 3H), 9.48 (s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 18, 107.3, 114.6, 115.3, 119.4, 119.7, 125.3, 127.2, 128.4, 129, 129.8, 138.4, 147.5, 152.6, 153.7, 159.3; LCMS: *m/z* $[M + H]^+$ 304.3. Anal. Calcd. for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85 %. Found: C, 71.39; H, 4.28; N, 13.96 %.

7-(4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl)-4-methyl-2H-chromen-2-one (3e)

Yellow solid, mp above 230˚C, yield 73%. IR (KBr, cm^{-1}) ν_{max}: 1706, 1621; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.38 (s, 3H), 6.50 (s, 1H), 7.60 (d, 2H, *J* = 8.6 Hz), 7.97 (d, 2H, *J* = 8.6 Hz), 7.99-8.03 (m, 3H), 9.52 (s, 1H); LCMS: *m/z* $[M + H]^+$ 338.2. Anal. Calcd. for $C_{18}H_{12}ClN_3O_2$: C, 64.01; H, 3.58; N, 12.44 %. Found: C, 63.91; H, 3.42; N, 12.31 %.

1-methyl-6-(4-phenyl-1H-1,2,3-triazol-1-yl)quinolin-2(1H)-one (3f)

Yellow solid, mp 212-214˚C, yield 81%. IR (KBr, cm^{-1}) ν_{max}: 1735; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.68 (s, 3H), 6.76

(d, 1H, *J* = 9.5 Hz), 7.39 (t, 1H, *J* = 7.4 Hz), 7.51 (t, 2H, *J* = 7.5 Hz), 7.78 (d, 1H, *J* = 9.2 Hz), 7.95 (d, 2H, *J* = 8.3 Hz), 8.04 (d, 1H, *J* = 9.6 Hz), 8.18 (dd, 1H, *J* = 9.1, 2.44 Hz), 8.36 (d, 1H, *J* = 2.4 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ: 29.2, 116, 119.3, 119.4, 120.4, 122.1, 122.5, 125.2, 128.1, 128.8, 130.1, 130.8, 138.6, 139.3, 147.2, 160.8; LCMS: *m/z* $[M + H]^+$ 303.1. Anal. Calcd. for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53 %. Found: C, 71.62; H, 4.64; N, 18.64 %.

6-(4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl)-1-methylquinolin-2(1H)-one (3g)

Green solid, mp 260-262˚C, yield 79%. IR (KBr, cm^{-1}) ν_{max}: 1643; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.68 (s, 3H), 6.76 (d, 1H, *J* = 11.2 Hz), 7.61 (d, 2H, *J* = 10.0 Hz), 7.79 (d, 1H, *J* = 10 Hz), 7.97 (d, 2H, *J* = 9.6 Hz), 8.04 (d, 1H, *J* = 10.7 Hz), 8.16 (d, 1H, *J* = 10.6 Hz), 8.31 (s, 1H), 9.39 (s, 1H); LCMS: *m/z* $[M + H]^+$ 337.2. Anal. Calcd. for $C_{18}H_{13}ClN_4O$: C, 64.19; H, 3.89; N, 16.64 %. Found: C, 64.33; H, 3.88; N, 16.5 %.

1-methyl-6-(4-(4-nitrophenyl)-1H-1,2,3-triazol-1-yl)quinolin-2(1H)-one (3h)

Yellow solid, mp 160-162˚C, yield 68%. IR (KBr, cm^{-1}) ν_{max}: 1651, 1343; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 3.69 (s, 3H), 7.80 (d, 1H, *J* = 9.2 Hz), 8.02 – 8.11 (m, 2H), 8.16-8.23 (m, 3H), 8.39 (d, 2H, *J* = 8.9 Hz), 9.6 (d, 1H, *J* = 8.9 Hz); LCMS: *m/z* $[M + H]^+$ 348.4. Anal. Calcd. for $C_{18}H_{13}N_5O_3$: C, 62.24; H, 3.77; N, 20.16 %. Found: C, 62.1; H, 3.88; N, 20.35 %.

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