Highly Efficient Ultrasonic-Assisted CuCl-Catalyzed 1,3-Dipolar Cycloaddition Reactions in Water: Synthesis of Coumarin Derivatives Linked with 1,2,3-Triazole Moiety

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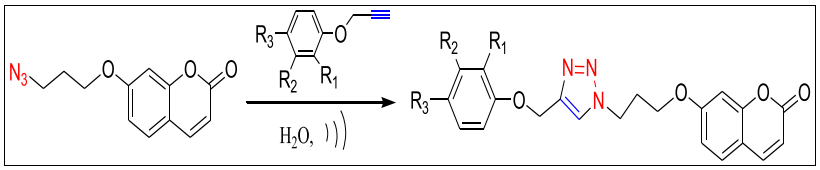

By introducing ultrasound irradiation into "on water" CuCl-catalyzed 1,3-dipolar Huisgen cycloaddition, the reaction efficiencies were notably promoted toward a wide variety of applicable azides and alkynes at room temperature, and a series of coumarin derivatives linked with 1,2,3-triazole moiety were synthesized using the optimized conditions.

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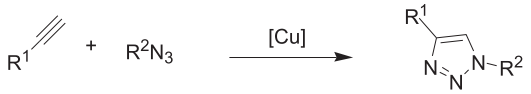
INTRODUCTION

Azole antifungals, which were discovered around 30 years ago, are currently the largest class of antifungal agents in clinical use [1]. Several 1,2,3-triazole containing compounds show diverse biological activities such as anti-HIV [2], antimicrobial [3], anti-allergic [4], and selective β_3 adrenergic receptor agonist [5]. 1,2,3-Triazole moiety does not occur in nature, although the synthetic molecules containing 1,2,3-triazole unit show diverse biological activities. 1,2,3-Triazole moieties are stable to metabolic degradation and are capable of hydrogen bonding, which can be favorable in binding of biomolecular targets and for solubility [6]. With respect to introducing 1,2,3-triazole groups into organic molecules, Huisgen's 1,3-dipolar cycloaddition of terminal acetylenes and organic azides is a useful approach. However, the regioselectivity of the cycloaddition reaction is generally low, and the reaction usually leads to a mixture of 1,4-regioisomers and 1,5-regi oisomers. In 2002, K. B. Sharpless and M. Meldal improved the regioselectivity of the reactions by introducing Cu(I) catalyst systems into the cycloaddition (click chemistry) of organic azides and terminal alkynes (Scheme 1) [7]. The Cu (I) catalyst systems not only play an important role in raising regioselectivity but also noticeably affect the conversion efficiency of a chemical process. The most common catalyst systems for copper-catalyzed azide–alkyne cycloaddition (CuAAC) employ Cu(II) salt in the presence of a reducing agent (often sodium ascorbate or metallic copper) to generate the required Cu(I) catalyst *in situ*, or sometimes directly employ copper(I) salts, such as CuCl, CuBr, and CuI, but quite often in this case need to add additional bases or ligands such as triethylamine [8], *N*,*N*-diisopropylethylamine [7c,9], and tris(benzyltriazolylmethyl)amine [10] to form stable complexes with Cu(I) ion.

Green or sustainable chemistry has now attained the status of a major scientific discipline, and the studies in this area have led to the development of cleaner and relatively benign chemical processes with many new technologies being developed each year. Green chemistry encourages the design of processes that minimize the use of hazardous substance and seeks to reduce and prevent pollution at its source. Examples of applied green chemistry are supercritical water oxidation, dry media reactions, and on water reactions. On water reactions are a group of organic reactions that take place as an emulsion in water and exhibit an unusual reaction rate acceleration compared with the same reaction in an organic solvent or compared with the corresponding dry media reaction. During the past two decades, many reactions that were conventionally believed to occur only in organic solvents have been developed to run in water. It is worth mentioning that the most commonly employed solvents for CuAAC are water/organic cosolvent mixtures, probably because general organic reactants are relatively soluble in organic solvent, whereas most of the related catalysts are relatively soluble in water. The fact that very little CuAAC work has previously been reported in pure water [11] is probably due to poor solubility of the most widely used organic reactants in water, even though organic reactions in water are of great interest in relation to today's environmental concerns.

Scheme 1. The copper-catalyzed azide–alkyne 1,3-dipolar cycloaddition.



The reportedly few CuAAC reactions carried out in aqueous reaction medium nearly unavoidably employed additional ligands for forming stable Cu(I) complex. For example, Zhao and coworkers employed water as the solvent and 10 mol% CuBr as the catalyst in the presence of 50 mol% PhSMe as the ligand to stabilize Cu(I) salt [11e,11f]. Even though the related Cu(I) complex, synthesized by Miquel A. Pericàs such as tris(triazolyl)methanol–Cu(I) complex [11g] and [(NHC)CuBr] complex (NHC═N-heterocyclic carbene) [11c], reportedly can act as the catalyst for the CuAAC reaction at very low catalyst loading in water, the less popular Cu(I) complex requires tedious and time-consuming preparation.

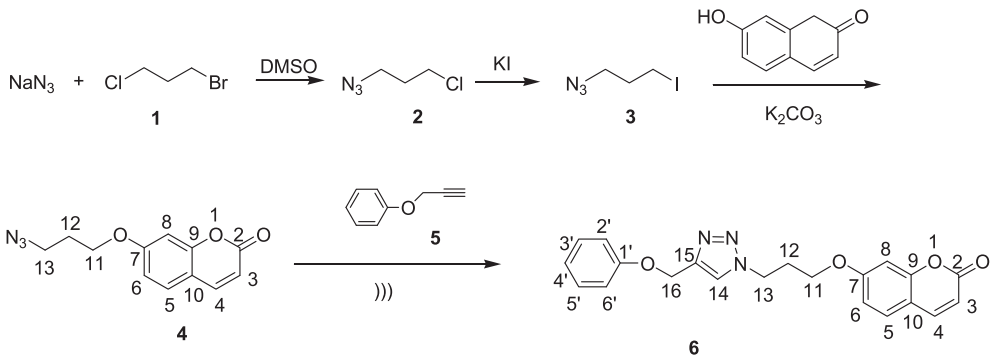
It is reported that the ultrasound (US) irradiation can lead to the apparent improvement of the reaction efficiency with increased rates and reduced reaction time [12]. Ultrasonic-assisted organic synthesis is a powerful technique that is being used more and more to accelerate organic reaction rate. The notable features of the US approach are enhanced reaction rates, formation of pure products in high yields, and easier manipulation. In the work described in this article, 7-hydroxycoumarin, a representative of natural products, initially reacted with 1-azido-3-iodiopropane through substitution reaction to form 7-(3-azidopropoxy) coumarin, which subsequently was employed as a starting reactant of Huisgen 1,3-dipolar cycloaddition to optimize the relevant reaction condition (Scheme 2). The CuAAC reaction, promoted by ultrasonic irradiation in water at room temperature, using CuCl as the catalyst, without adding any additional bases or ligands, was then applied to the syntheses of a series of triazole-containing compounds and 7-hydroxycoumarin derivatives linked with triazole moiety.

RESULTS AND DISCUSSION

The 1,3-dipolar cycloaddition reaction between 7-(3-azi dopropoxy)coumarin (**4**) and propargyl phenyl ether (**5**) was chosen as a model reaction to optimize the reaction conditions (Scheme 2). The three-step synthetic process of compound **4** is shown in Scheme 2. 1-Bromo-3-chlo ropropane (**1**) was first reacted with sodium azide in DMSO at room temperature to form 1-azido-3-chloropropane (**2**). 1-Azido-3-iodiopropane (**3**) was synthesized by treating **2** with KI in acetone under reflux [13], considering that the iodine group is a relatively good nucleophile as well as a leaving group than the chlorine group in nucleophilic substitution reaction. Then, **3** was reacted with 1 equiv of coumarin to form compound **4** using a reported procedure [14]. Azido-containing intermediate **4** was purified by column chromatography ($CHCl_3$:CH_3OH = 30:1, v/v) before it was used for the next step.

The experiment was initially designed to investigate how or to what extent Et_3N could promote the CuAAC model reaction efficiency under designed conditions as mentioned in the following. The cheap and easily available CuCl (10 mol%) was preferentially chosen as the catalyst. The efficiencies of the model reactions performed in water, selected organic solvents, and water/organic cosolvents (v:v = 1:1) were investigated in the presence of Et_3N or the absence of Et_3N without US irradiation at room temperature for about 45 min, respectively, as shown in Figure 1. The result shows that the model reactions carried out in the absence of Et_3N generally were less efficient in promoting the cycloaddition reactions than those in the presence of Et_3N. Different degrees of Et_3N in promoting the cycloaddition reactions were shown when different solvent systems were employed: tremendous differences were shown when pure organic solvent was employed, on the basis of the fact that only trace products were isolated in the absence of Et_3N, whereas relatively small differences were shown when water/organic cosolvent was employed and relatively big differences were shown when pure water was employed. The

Scheme 2. Synthetic routine of the coumarin linked with 1,2,3-triazoles.



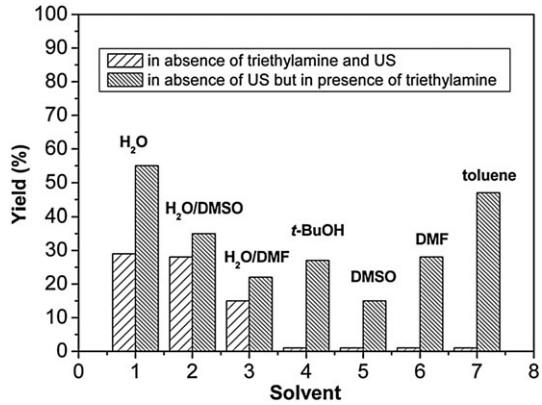


Figure 1. The yield of the model reaction in different solvents. ▨, in the absence of triethylamine and US irradiation; ▧, in the presence of triethylamine (2 equiv) without US irradiation condition. The model reaction was carried out using compound **4** (1 mmol) and propargyl phenyl ether **5** (1 mmol) in the presence of CuCl (10 mol%) in the solvent (3 mL) at room temperature for 45 min. Mixing equal volume of water and organic solvent results in the corresponding cosolvent.

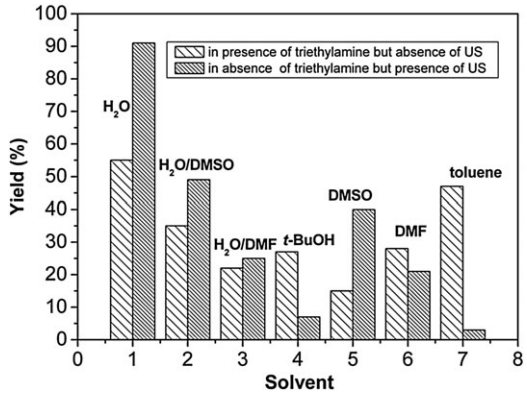


Figure 2. The yield of the model reaction in different solvents. ▨, in the presence of triethylamine (2 equiv) but without US irradiation; ▧, in the absence of triethylamine with US irradiation condition, 150 W. The model reaction was carried out using compound **4** (1 mmol) and propargyl phenyl ether **5** (1 mmol) in the presence of CuCl (10 mol%) in the solvent (3 mL) at room temperature for 45 min.

yield obtained in water in the presence of Et_3N is 55%, almost twice than that in water in the absence of Et_3N. It is especially worth mentioning that the yield obtained in water in the presence of Et_3N is the highest among the tested solvents, even though 55% is not a relatively high yield.

It seems that Et_3N was especially crucial in promoting the CuAAC reaction efficiency when CuCl was employed as the catalyst and pure water as the reaction solvent in the experiments previously shown. Is there any alternative method, for example, using US irradiation instead of using Et_3N, a compound giving off a strong fishy odor that is reminiscent of ammonia, to achieve the same or even higher yields from the model reaction? The following experiment was especially designed to investigate whether the use of US irradiation could lead to more efficient chemical reactions. Under US irradiation condition and in the absence of Et_3N, the model reaction was performed again in water, selected organic solvents, and water/organic cosolvents at room temperature for 45 min, respectively (Fig. 2). The results interestingly show that US irradiation indeed led to more efficient chemical reactions than Et_3N did when the model reactions were carried out in water or water-containing solvents, whereas US irradiation could not always achieve a better promotion efficiency than could Et_3N when the model reactions were carried out in organic solvents such as *t*-BuOH, DMF, and toluene as shown in Figure 2, even though the two reactants 7-(3-azidopropoxy)coumarin (4) and propargyl phenyl ether (5) were observed to have low aqueous solubility in water. It is especially worth mentioning that a profoundly greater conversion efficiency of CuAAC reaction in water was shown when US irradiation was employed to promote the reaction. As can be seen from the results shown in Figures 1 and 2, the model reaction carried out in water and promoted by Et_3N had only about a one-time increase in yield, from 29 to 55%, whereas the model reaction carried out in water and promoted by US irradiation had twice increases in yield, from 29 to 91%, implying an enormously promotive role of US irradiation toward the model reaction carried out in water. The influences of US power on the cycloaddition reaction were also investigated. The result showed that the yields increased along with the increased US power as shown in Figure 3.

Other Cu(I) salts and oxide such as CuBr, CuI, CuCN, and Cu_2O, respectively, were employed to compare the catalytic efficiency of the "on water" model reaction in the presence of US irradiation (150 W) at room temperature for 45 min. As it can be seen in Figure 4, CuCl showed a remarkably high catalytic efficiency among the tested catalysts. A 91% yield was obtained from CuCl catalytic

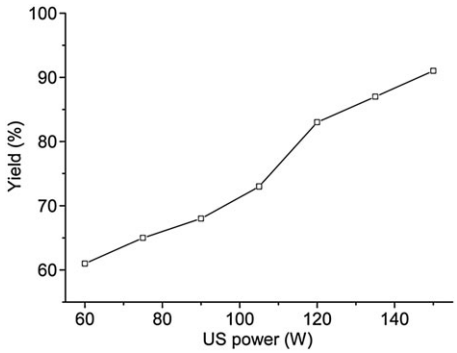


Figure 3. Yield versus US power using CuCl (10 mol%) as the catalyst and water as the reaction solvent. The model reaction was carried out using compound **4** (1 mmol) and propargyl phenyl ether **5** (1 mmol) in the presence of catalyst (10 mol%) in water (3 mL) at room temperature for 45 min.

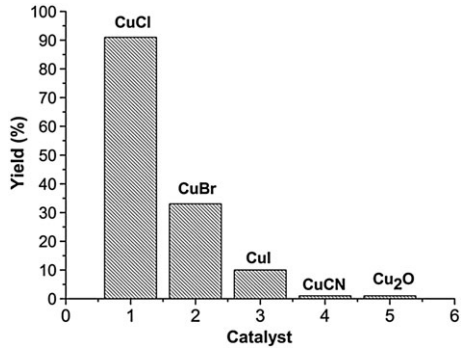


Figure 4. Screening of catalysts for the model reaction in water at room temperature under US irradiation for 45 min. The model reaction was carried out using compound **4** (1 mmol) and propargyl phenyl ether **5** (1 mmol) in the presence of catalyst (10 mol%) in water (3 mL) at room temperature for 45 min.

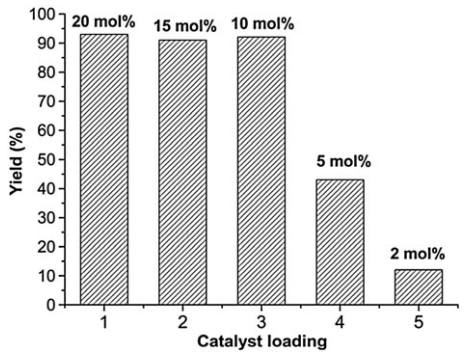


Figure 5. Catalyst loading versus the yield in 45 min under US irradiation. The model reaction was carried out using compound **4** (1 mmol) and propargyl phenyl ether **5** (1 mmol) in different catalyst loadings in water (3 mL) at room temperature for 45 min.

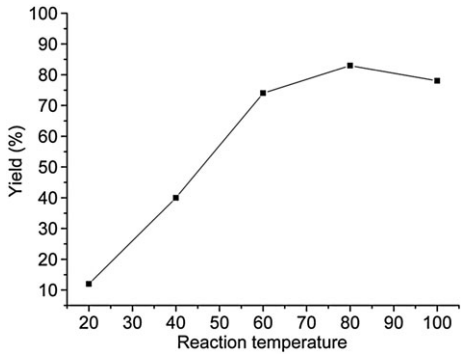


Figure 6. Yield of compound **6** versus temperature using direct heating method for 45 min. The model reaction was carried out using compound **4** (1 mmol) and propargyl phenyl ether **5** (1 mmol) in the presence of CuCl (5 mol%) in water (3 mL) using direct heating for 45 min.

reaction, whereas a 33% yield from CuBr, a 10% yield from CuI, and two trace yields were obtained from CuCN- and Cu_2O-catalytic reactions, respectively, approximately corresponding to the varying solubility of Cu(I) salt or oxide in water—the better water solubility, the higher catalytic efficiency for the "on water" model reaction in this case.

The CuCl catalyst loading on the model reaction was further investigated in water under US irradiation for 45 min, using the catalyst loadings of 20, 15, 10, 5, and 2 mol%, respectively, as shown in Figure 5. As can be seen from Figure 5, the yield increased with the increase in catalyst loading before the 10 mol% catalyst loading was reached, whereas the yields did not change a lot after the loading exceeded 10 mol%. It deserves to be pointed out that under the design condition previously mentioned, not all but few reactions could be completed within 45 min. For example, the model reactions catalyzed by 15 or 20 mol% CuCl were observably completed in less than 45 min, whereas the model reactions catalyzed by 5 or 2 mol% CuCl were observably completed in more than 45 min. A complementary experiment showed that a 91% yield could also be obtained from the model reaction when using 5 mol% CuCl not in 45 min but in about 2 h, indicating the fact that the rate of the reaction increases with the increase in the catalyst loading in this case.

It can be seen that by introducing US irradiation into the "on water" CuCl-catalyzed model reaction, the reaction efficiencies were notably promoted. The following experiment was especially carried out to discuss the impact of the ultrasonic irradiation forces on the model reaction. The influence of temperature on the model reaction was preferentially investigated by performing the model reaction in the absence of US irradiation. CuCl (5 mol%) was chosen as the catalyst to promote the model reaction for 45 min at five different temperatures, 20, 40, 60, 80, and 100°C, respectively, as shown in Figure 6. It can be seen that the yield increased quickly over the temperature range of 20 to 60°C, from 12 to 60%, and increased slightly over the range of 60 to 80°C, from 60 to 83%, and then decreased slightly over the temperature range of 80 to 100°C, from 83 to 78%, indicating that in the absence of US irradiation, the 1,3-dipolar cycloaddition reaction can be promoted by appropriately raising the temperature to a certain degree, for instance, 80°C in this case, but with the exception of relatively high temperatures. The dropping in the yield over the temperature range of 80 to 100°C was probably caused by some side reactions triggered by a relatively high temperature, such as an oxidation reaction of CuCl to $CuCl_2$ or azide thermal decomposition. As is known, US can greatly enhance chemical reactivity in a number of systems by as much as a millionfold [15], although upon irradiation with US, cavitation—the formation, growth,

Scheme 3. Syntheses of **6′a–m**.

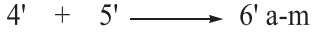
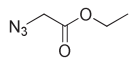
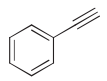
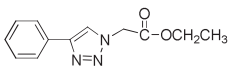
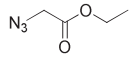
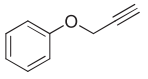
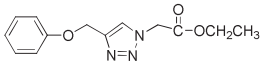
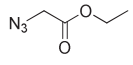
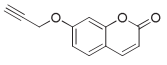
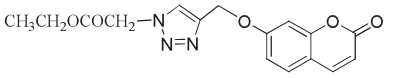
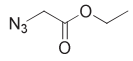
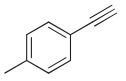
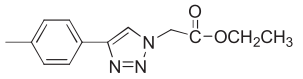
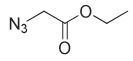
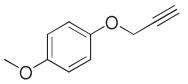
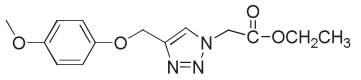
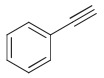
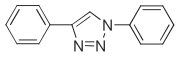
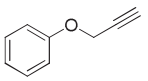
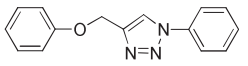
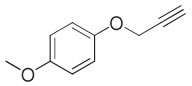
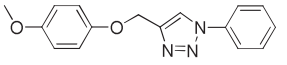
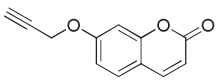
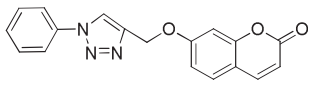
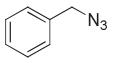
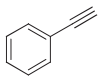
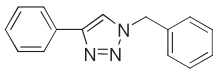
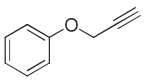
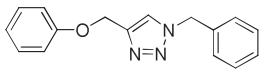
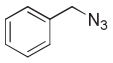
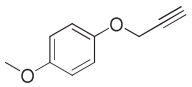
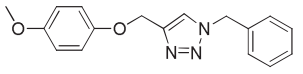
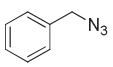
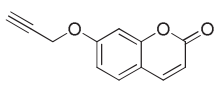
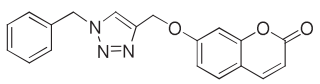


Table 1

Various terminal alkynes were investigated to be reacted with different azide.

Entry	Azide (**4′**)	Alkyne (**5′**)	Product (**6′**)	Time (min)	Yield (%)[a]
a				15	90
b				15	92
c				90	91
d				15	93
e				20	93
f				10	93
g				10	95
h				15	94
i				100	91
j				10	92
k				10	94
l				15	92
m				120	89

Condition: Alkyne (1 mmol), azide(1 mmol), and CuCl (10 mol%) as the catalyst in water (3 mL) at room temperature under ultrasonic power of 150 W.
[a]Isolated yield.

Scheme 4. Syntheses of **6a–j**.

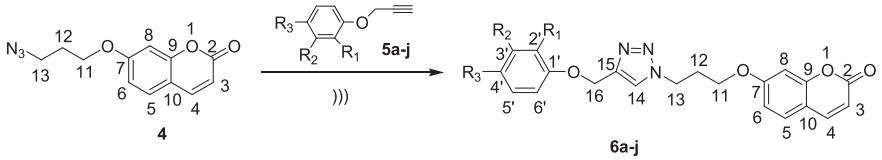


Table 2

Coumarin derivatives linked with 1,2,3-triazole moiety.

Entry	R_1	R_2	R_3	Yield (%)[a]
6a	H	H	H	92
6b	NO_2	H	H	89
6c	H	H	NO_2	91
6d	OMe	H	H	88
6e	OEt	H	H	89
6f	H	H	OMe	90
6g	Me	H	H	88
6h	H	Me	H	86
6i	H	H	Cl	95
6j	Cl	H	Cl	90

Condition: Compound **4** (0.5 mmol), various substituted terminal alkynes (0.5 mmol), and CuCl (10 mol%) as the catalyst in water (3 mL) at room temperature under ultrasonic power of 150 W.
[a]Isolated yield.

and implosive collapse of bubbles irradiated with US—can create extreme physical and chemical conditions in liquids [16]. The bubbles produced by US have temperatures of around 5000 K, pressures of roughly 1000 atm, and heating and cooling rates above 10^{10} K/s [17]. The implosion of cavities reportedly established an unusual environment for reactions. The gases and vapors inside the cavity are compressed, generating intense heat that raises the temperature of the liquid immediately surrounding the cavity and creates a local hot spot. The short-lived localized hot spot produced by US irradiation can greatly accelerate the reaction rate. Even though the temperature of this region is extraordinarily high, the region itself is so small that the heat dissipates quickly. Therefore, when we mentioned the high reaction temperature, we especially refer to the temperature of the liquid surrounding the cavity, but not the temperature of the reaction solution. Of course, detection of the temperature reached in cavitation bubbles has remained a difficult experimental problem, but the temperature changes of the reaction solution during sonication inside the reaction flask can be detected directly by placing a thermometer into the reaction solution. It was found that the temperature of the reaction liquid did not exceed 30°C during sonication, a relatively mild temperature at which the side reactions could be efficiently prevented to a great extent. The model reaction, performed in water in the absence of US irradiation, using CuCl (5 mol%) as the catalyst, not for 45 min but for 2 h at 80°C, was further carried out to compare the reaction efficiency of the same reaction carried out for 2 h at room temperature, using CuCl (5 mol%) as the catalyst, in the presence of US irradiation mentioned previously. The result showed that about 83% yield was obtained at 80°C in the absence of US irradiation; however, a 91% yield was obtained from the model reaction at room temperature in the presence of US irradiation. The obvious difference in the reaction efficiencies with or without sonication suggests again that the reaction under US condition proceeded in not the same but in more efficient way than did the reaction under the heating conditions. It is known that once cavitation occurs near the solid surface, cavity collapse is nonspherical and drives high-speed jets of liquid to the solid surface [18]. These collisions break up the azide reactants into pieces in this case, which gives the azide reactants larger surface areas and increases the frequencies of collisions between azides and other reactants. It might be concluded that the US played a significant role in promoting the efficiency of the cycloaddition reaction in terms of increasing reactant contact surfaces through cavitation phenomena—the formation, growth, and implosive collapse of bubbles. With liquids containing solids, once cavitation occurs near an extended solid surface, cavity collapse drives high-speed jets of liquid to the surface [18c]. These jets and associated shock waves can damage the now highly heated surface. Liquid-powder suspensions produce high velocity interparticle collisions. The chemical enhancement of reactions by US shows an obvious beneficial result in this mixed phase synthesis.

The scope of the reactants was then enlarged to various terminal alkynes and azides as shown in Scheme 3 and Table 1. All the reactions were performed in water at room temperature using 10 mol% CuCl as the catalyst and under ultrasonic power of 150 W. The reaction completion times varied with the reactants. The reaction completion times were within 20 min when liquid reactants were employed and within longer times, some even 2 h, when solid terminal alkynes with poor water solubility were employed, but very high yields, for instance, more than 90% for each case as shown in Table 1, were achieved under the optimized reaction conditions.

The application of CuAAC reaction promoted by ultrasonic irradiation in water at room temperature then led to successful syntheses of a series of coumarin derivatives linked with triazole moiety (Scheme 4), using various

substituted terminal alkynes and **4** as reactants. As could be seen from Table 2, in all cases, coumarin derivatives linked with 1,2,3-triazoles were obtained in good yields.

CONCLUSIONS

In summary, an environmentally friendly and economically efficient method for synthesis of 1,4-disubstituted 1,2,3-triazoles was developed with the help of US irradiation in water. The model CuAAC reaction above features an enormous reaction rate acceleration in water compared with the same reaction in an organic solvent or water/organic cosolvent at room temperature. The application of CuAAC reaction promoted by ultrasonic irradiation in water finally led to successful syntheses of a series of coumarin derivatives linked with triazole moiety.

EXPERIMENTAL SECTION

General: All the chemicals were obtained from Tianjin Kermel Chemical Reagent Co., Ltd (Tianjin, China) and used as received. Melting points were recorded on an electrothermal apparatus and were uncorrected. Sonication was performed in Kunshan KQ-250B ultrasonic cleaner (Kunshan, China) with a frequency of 40 kHz and a power of 150 W. The reaction flasks were located in the maximum energy area in the cleaner, and the addition or removal of water controlled the temperature of the water bath. Infrared (IR) spectra were recorded on a Shimadazu IR-408 (Kyoto, Japan). ^{1}H and ^{13}C spectra were recorded on a Bruker Avance 400-MHz spectrometer (Billerica, MA) operating at 400.13 and 100.61 MHz, respectively. All NMR spectra were recorded in $CDCl_3$ at room temperature (20 ± 2°C). ^{1}H and ^{13}C chemical shifts are quoted in parts per million downfield from tetramethylsilane. Electrospray ionization mass spectrometry (ESI-MS) spectra were recorded on a Bruker Esquire 3000 (Billerica, MA). High-resolution mass spectrometry (HRMS) were performed on a Micromass Q-TOF MicroTM mass spectrometer with an ESI source (Waters, Manchester, UK). Substituted terminal alkynes were synthesized according to the literature [19]. Benzyl azide [20] and phenyl azide [21] were also synthesized according to previous reports.

Synthesis of 7-(3-azidopropoxy)coumarin (4). 1-Azido-3-iodopropane (35.8 mmol) and coumarin (35.8 mmol) in acetone (60 mL) with potassium carbonate (71.6 mmol) were refluxed for 28 h. Thin-layer chromatography (TLC) followed the reaction. After the completion of the reaction, the excess potassium carbonate was filtered off, and after evaporating the solvent under reduced pressure, the crude product was obtained, which was purified by column chromatography to afford **4**. White solid, mp 72–73°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 9.6 Hz, 1H, 4-H), 7.38 (d, J = 8.8 Hz, 1H, 5-H), 6.80 (dd, J = 8.4, 2.4 Hz, 1H, 6-H), 6.77 (d, J = 2.4 Hz, 1H, 8-H), 6.27 (d, J = 9.2 Hz, 1H, 3-H), 4.12 (t, J = 6.0 Hz, 2H, 13-H), 3.55 (t, J = 6.6 Hz, 2H, 11-H), 2.13–2.07 (m, 2H, 12-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.8 (C-7), 161.1 (C-2), 155.9 (C-9), 143.3 (C-4), 128.8 (C-5), 113.3 (C-3), 112.8 (C-10), 112.7 (C-6), 101.5 (C-8), 65.1 (C-11), 48.0 (C-13), 28.5 (C-12). HRMS Calcd for $C_{12}H_{12}N_3O_3$ $[M+Na]^+$: m/z 246.0873, Found 246.0877.

General procedure for the reaction between 4′ and 5′. Different azide (**4′**) (1.0 mmol) and various terminal alkynes (**5′**) (1.0 mmol) were suspended in 5 mL H_2O in a 10-mL round-bottomed flask followed by CuCl (10 mol%). The mixture was sonicated in a laboratory ultrasonic cleaning bath. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with saturated aq. NH_4Cl (20 mL) and extracted by CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and filtered. The products (**6′a–m**) were isolated by column chromatography on silica gel using C_2H_5OH:$CHCl_3$ (1:30, v/v) as eluent.

***2-(4-Phenyl-1H*-1,2,3-triazol-1-yl)ethyl acetate (6′a).** White solid, mp 97–99°C (Ref. [22], 93–95°C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.93 (s, 1H, 8-H), 7.85 (t, J = 7.6 Hz, 2H, 3, 5-H), 7.44 (t, J = 7.6 Hz, 2H, 2, 6-H), 7.35 (t, J = 7.2 Hz, 1H, 4-H), 5.21 (s, 2H, 9-H), 4.31–4.25 (q, 2H, 11-H), 1.31 (t, J = 7.2 Hz, 3H, 12-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.3 (C-10), 148.2 (C-1), 130.4 (C-7), 128.9 (C-2, 6), 128.3 (C-4), 125.8 (C-3, 5), 121.0 (C-8), 62.5 (C-11), 51.0 (C-9), 14.1 (C-12); ESI-MS m/z: 232 $[M+H]^+$.

***2-(4-(Phenoxymethyl)-1H*-1,2,3-triazol-1-yl)ethyl acetate (6′b).** Pale yellow solid, mp 67–68°C (Ref. [23], 116–118°C; Ref. [24], pale yellow oil). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.74 (s, 1H, 9-H), 7.30–7.26 (m, 2H, 3, 5-H), 6.99–6.94 (m, 3H, 2, 4, 6-H), 5.21 (s, 2H, 7-H), 5.13 (s, 2H, 10-H), 4.26–4.21 (q, 2H, 12-H), 1.27 (t, J = 7.2 Hz, 3H, 13-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.3 (C-11), 158.2 (C-1), 144.6 (C-8), 129.5 (C-3, 5), 124.2 (C-9), 121.2 (C-4), 114.8 (C-2, 6), 62.4 (C-12), 61.8 (C-7), 50.9 (C-10), 14.0 (C-13). ESI-MS m/z: 262 $[M+H]^+$.

***2-(4-(7-Coumarinoxymethyl)-1H*-1,2,3-triazol-1-yl)ethyl acetate (6′c).** Pale yellow solid, mp 104–106°C. IR (KBr) ν: 3150, 3084, 3068, 2995, 2958, 1715, 1743 1613, 1378, 1275, 1231, 1126, 1052, 1012 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.83 (s, 1H, 13-H), 7.64 (d, J = 9.6 Hz, 1H, 4-H), 7.39 (d, J = 9.6 Hz, 1H, 5-H), 6.95–6.93 (m, 2H, 6, 8-H), 6.26 (d, J = 9.2 Hz, 1H, 3-H), 5.29 (s, 2H, 11-H), 5.19 (s, 2H, 14-H), 4.31–4.26 (m, 2H, 16-H), 1.31 (t, J = 7.0 Hz, 1H, 17-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.1 (C-15), 161.3 (C-7), 161.0 (C-2), 155.7 (C-9), 143.4 (C-12), 143.3 (C-4), 128.9 (C-5), 124.4 (C-13), 113.5 (C-3), 113.0 (C-10), 112.8 (C-6), 102.1 (C-8), 62.6 (C-16), 62.3 (C-11), 50.9 (C-14), 14.0 (C-17). HRMS Calcd for $C_{16}H_{15}N_3NaO_5$ $[M+Na]^+$: m/z 352.0909, Found 352.0918.

***2-(4-p*-Tolyl-1*H*-1,2,3-triazol-1-yl) ethyl acetate (6′d).** White solid, mp 100–102°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1H, 5-H), 7.75 (d, J = 8.0 Hz, 2H, 2′, 6′-H), 7.26 (d, J = 8.0 Hz, 2H, 3′, 5′-H), 5.20 (s, 2H, 4-H), 4.32–4.26 (q, 2H, 2-H), 2.39 (s, 3H, 7-H), 1.32 (t, J = 7.2 Hz, 3H, 1-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.3 (C-3), 148.4 (C-6), 138.1 (C-4′), 129.5 (C-3′, 5′), 127.6 (C-1′), 125.7 (C-2′, 6′), 120.6 (C-5), 62.5 (C-2), 50.9 (C-4), 21.3 (C-7), 14.1 (C-1). ESI-MS m/z: 246 $[M+H]^+$.

***2-(4-((4-Methoxyphenoxy)methyl)-1H*-1,2,3-triazol-1-yl)ethyl acetate (6′e).** White solid, mp 103–104°C (Ref. [25], 103–104°C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1H, 9-H), 6.95–6.92 (m, 2H, 2, 6-H), 6.87–6.83 (m, 2H, 3, 5-H), 5.21 (s, 2H, 7-H), 5.17 (s, 2H, 10-H), 4.31–4.26 (q, 2H, 12-H), 3.78 (s, 3H, —OC<u>H</u>$_3$), 1.31 (t, J = 7.2 Hz, 3H, 13-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.4 (C-11), 154.1 (C-4), 152.3 (C-1), 144.5 (C-8), 124.5 (C-9), 115.8 (C-2, 6), 114.6 (C-3, 5), 62.4 (C-10), 62.3 (C-12), 55.6 (—O<u>C</u>H$_3$), 50.8 (C-7), 14.0 (C-13). ESI-MS m/z: 314 $[M+Na]^+$.

***1,4-Diphenyl-1H*-1,2,3-triazole (6′f).** White solid, mp 180–182°C (Ref. [22], 183–184°C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.22 (s, 1H, 8-H), 7.93 (d, J = 7.6 Hz, 2H, 3, 5-H), 7.82 (d, J = 7.6 Hz, 2H, 10, 14-H), 7.57 (t, J = 8.0 Hz, 2H, 11, 13-H), 7.50–7.47 (m, 3H, 2, 4, 6-H),

7.39 (t, J = 7.4 Hz, 1H, 12-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.4 (C-1), 137.1 (C-9), 130.2 (C-7), 129.8 (C-11, 12), 129.0 (C-2, 6), 128.8 (C-12), 128.5 (C-4), 125.9 (C-3, 5), 120.5 (C-10, 14), 117.6 (C-8). ESI-MS m/z: 222 $[M + H]^+$.

***4-(Phenoxymethyl)-1-phenyl-1H*-1,2,3-triazol (6′g).** White solid, mp 80–81°C (Ref. [26], 89.5–90.5°C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1H, 9-H), 7.76 (d, J = 8.0 Hz, 2H, 11, 15-H), 7.54 (t, J = 3.6, 2H, 12, 14-H), 7.47 (t, J = 3.1 Hz, 1H, 13-H), 7.33 (t, J = 3.7 Hz, 2H, 3, 5-H), 7.06–6.99 (m, 3H, 2, 4, 6-H), 5.33 (s, 2H, 7-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 158.2 (C-1), 145.0 (C-8), 137.0 (C-10), 129.8 (C-12, 14), 129.63 (C-3, 5), 128.9 (C-13), 121.4 (C-4), 121.0 (C-9), 120.6 (C-11, 15), 114.7 (C-2, 6), 61.9 (C-7). ESI-MS m/z: 252 $[M + H]^+$.

***4-((4-Methoxyphenoxy)methyl)-1-phenyl-1H*-1,2,3-triazole (6′h).** White solid, mp 102–104°C (Ref. [27], 97–99°C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.06 (s, 1H, 9-H), 7.75 (d, J = 8.0 Hz, 2H, 11, 15-H), 7.55 (t, J = 8.0 Hz, 2H, 12, 14-H), 7.46 (t, J = 8.0 Hz, 1H, 13-H), 6.97 (m, 2H, 2, 6-H), 6.88 (m, 2H, 3, 5-H), 5.27 (s, 2H, 7-H), 3.80 (s, 3H, —OC<u>H</u>$_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 154.2 (C-4), 152.3 (C-1), 145.1 (C-8), 136.9 (C-10), 129.8 (C-12, 14), 128.9 (C-13), 121.0 (C-9), 120.5 (C-11, 15), 115.8 (C-2, 6), 114.7 (C-3, 5), 62.6 (C-7), 55.7 (—O<u>C</u>H$_3$). ESI-MS m/z: 282 $[M + H]^+$.

***4-(7-Coumarinoxymethyl)-1-phenyl-1H*-1,2,3-triazol (6′i).** Pale yellow solid, mp 160–162°C. IR (KBr) v: 3141, 3075, 2930, 2879, 1724, 1614, 1344, 1278, 1228, 1121, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1H, 13-H), 7.76–7.74 (m, 2H, 2′, 6′-H), 7.65 (d, J = 9.2 Hz, 1H, 4-H), 7.56–7.52 (m, 2H, 3′, 5′-H), 7.48–7.45 (m, 1H, 4′-H), 7.41 (d, J = 9.2 Hz, 1H, 5-H), 6.99–6.96 (m, 2H, 6, 8-H), 6.27 (d, J = 9.2 Hz, 1H, 3-H), 5.36 (s, 2H, 11-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.2 (C-7), 161.1 (C-2), 155.7 (C-9), 143.7 (C-12), 143.3 (C-4), 136.8 (C-1′), 129.8 (C-3′, 5′), 129.1 (C-4′), 129.0 (C-5), 121.30 (C-13), 120.6 (C-2′, 6′), 113.5 (C-3), 113.1 (C-10), 112.7 (C-6), 102.1 (C-8), 62.3 (C-11). HRMS Calcd for $C_{18}H_{13}N_3NaO_3$ $[M + Na]^+$: m/z 342.0855, Found 342.0835.

***1-Benzyl-4-phenyl-1H*-1,2,3-triazole (6′j).** White solid, mp 131–133°C (Ref. [22], 130–132°C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 7.2 Hz, 2H, 3, 5-H), 7.68 (s, 1H, 8-H), 7.43–7.38 (m, 5H, 2, 4, 6, 12, 14-H), 7.35–7.31 (m, 3H, 11, 13, 15-H), 5.60 (s, 2H, 9-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.1 (C-1), 134.8 (C-10), 130.6 (C-7), 129.1 (C-12, 14), 128.9 (C-2, 6), 128.7 (C-4), 128.2 (C-13), 128.0 (C-11, 15), 125.7 (C-3, 5), 119.8 (C-8), 54.1 (C-9). ESI-MS m/z: 236 $[M + H]^+$.

***1-Benzyl-4-(phenoxymethyl)-1H*-1,2,3-triazole (6′k).** Pale yellow solid, mp 120–121°C (Ref. [24], 119–121°C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.55 (s, 1H, 9-H), 7.41–7.38 (m, 3H 13, 14, 15-H), 7.32–7.27 (m, 4H, 3, 5, 12, 16-H), 6.98 (m, 3H, 2, 4, 6-H), 5.55 (s, 2H, 10-H), 5.20 (s, 2H, 7-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 158.2 (C-1), 144.6 (C-8), 134.6 (C-11), 129.6 (C-3, 5), 129.2 (C-13, 15), 128.8 (C-14), 128.1 (C-12, 16), 122.8 (C-9), 121.3 (C-4), 114.8 (C-2, 6), 62.0 (C-7), 54.2 (C-10). ESI-MS m/z: 266 $[M + H]^+$.

***1-Benzyl-4-((4-methoxyphenoxy)methyl)-1H*-1,2,3-triazole (6′l).** Pale yellow solid, mp 86–88°C (Ref. [28], 86–88°C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.52 (s, 1H, 9-H), 7.40–7.37 (m, 3H, 13, 14, 15-H), 7.29–7.26 (m, 2H, 12, 16-H), 6.92–6.89 (m, 2H, 2, 6-H), 6.85–6.82 (m, 2H, 3, 5-H), 5.54 (s, 2H, 10-H), 5.15 (s, 2H, 7-H), 3.77 (s, 3H, —OC<u>H</u>$_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 154.2 (C-4), 152.3 (C-1), 144.7 (C-8), 134.6 (C-11), 129.1 (C-13, 15), 128.7 (C-14), 128.1 (C-12, 16), 122.8 (C-9), 115.9 (C-2, 6), 114.6 (C-3, 5), 62.7 (C-7), 55.6 (—O<u>C</u>H$_3$), 54.1 (C-10). ESI-MS m/z: 296 $[M + H]^+$.

***1-Benzyl-4-(7-coumarinoxymethyl)-1H*-1,2,3-triazole (6′m).** Pink solid, mp 153–155°C. IR (KBr) v: 3141, 3079, 2926, 1711, 1614, 1278, 1231, 1204, 1128, 1055, 1032 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 9.6 Hz, 1H, 4–H), 7.57 (s, 1H, 13-H), 7.42–7.36 (m, 4H, 3′, 4′, 5′, 5-H), 7.32–7.27 (m, 2H, 2′, 6′-H), 6.93–6.90 (m, 2H, 6, 8-H), 6.26 (d, J = 9.2 Hz, 1H, 3-H), 5.55 (s, 2H, 14-H), 5.23 (s, 2H, 11-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.3 (C-7), 161.0 (C-2), 155.7 (C-9), 143.3 (C-4), 143.3 (C-12), 134.3 (C-1′), 129.2 (C-3′, 5′), 128.9 (C-4′, 5), 128.2 (C-2′, 6′), 122.9 (C-13), 113.4 (C-3), 113.0 (C-10), 112.7 (C-6), 102.1 (C-8), 62.3 (C-11), 54.3 (C-14). HRMS Calcd for $C_{19}H_{15}N_3NaO_3$ $[M + Na]^+$: m/z 356.1011, Found 356.1020.

General procedure for the synthesis of the target molecules (6a–j). Substituted terminal alkyne (5.0 mmol) and **4** (4.0 mmol) were suspended in 30 mL H_2O in a 50-mL round-bottomed flask followed by CuCl (10 mol%). The mixture was sonicated for 2 h in a laboratory ultrasonic cleaning bath. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with 20 mL water, and the precipitate was collected and washed with cold water and saturated ammonium chloride. The crude product was purified by column chromatography on silica gel using CH_3OH:$CHCl_3$ (1:30, v/v) as eluent.

***7-(3-(4-(Phenoxymethyl)-1,2,3-triazol-1-yl)propoxy)coumarin (6a).** White solid, mp 104–106°C. IR (KBr) v: 3133, 3093, 2927, 2880, 1729, 1617, 1296, 1241, 1133, 1047 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 9.2 Hz, 1H, 4-H), 7.63 (s, 1H, 14-H), 7.37 (d, J = 8.8 Hz, 1H, 5-H), 7.30–7.28 (m, 2H, 2′, 6′-H), 6.98–6.95 (m, 3H, 3′, 4′, 5′-H), 6.81 (dd, J = 8.8, 2.4 Hz, 1H, 6-H), 6.77 (d, J = 2.4 Hz, 1H, 8-H), 6.27 (d, J = 9.6 Hz, 1H, 3-H), 5.22 (s, 2H, 16-H), 4.61 (t, J = 6.8 Hz, 2H, 13-H), 4.04 (t, J = 5.8 Hz, 2H, 11-H), 2.49–2.43 (m, 2H, 12-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.5 (C-7), 161.0 (C-2), 158.1 (C-1′), 155.8 (C-9), 144.4 (C-15), 143.3 (C-4), 129.5 (C-2′, 6′), 128.9 (C-5), 123.1 (C-14), 121.3 (C-4′), 114.7 (C-3′, 5′), 113.4 (C-3), 112.9 (C-10), 112.5 (C-6), 101.6 (C-8), 64.7 (C-11), 62.9 (C-16), 47.0 (C-13), 29.7 (C-12). HRMS Calcd for $C_{21}H_{19}N_3NaO_4$ $[M + Na]^+$: m/z 400.1273, Found 400.1291.

***7-(3-(4-((2-Nitrophenoxy)methyl)-1,2,3-triazol-1-yl)propoxy) coumarin (6b).** Yellow solid, mp 135–137°C. IR (KBr) v: 3154, 3078, 2917, 2839, 1724, 1617, 1345, 1277, 1124, 1044 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.83 (dd, J = 8.0, 1.2 Hz, 1H, 3′-H), 7.51 (s, 1H, 14-H), 7.64 (d, J = 9.2 Hz, 1H, 4-H), 7.57–7.53 (m, 1H, 5′-H), 7.38 (d, J = 8.8 Hz, 1H, 5-H), 7.29 (dd, J = 8.4, 0.8 Hz, 1H, 6′-H), 7.09–7.05 (m, 1H, 4′-H), 6.82 (dd, J = 8.8, 2.4 Hz, 1H, 6-H), 6.74 (d, J = 2.4 Hz, 1H, 8-H), 6.26 (d, J = 9.6 Hz, 1H, 3-H), 5.37 (s, 2H, 16-H), 4.63 (t, J = 6.8 Hz, 2H, 13-H), 4.03 (t, J = 5.6 Hz, 2H, 11-H), 2.50–2.44 (m, 2H, 12-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.5 (C-7), 161.1 (C-2), 155.8 (C-9), 151.4 (C-1′), 143.4 (C-15), 143.3 (C-4), 140.1 (C-2′), 134.3 (C-5′), 129.0 (C-5), 125.7 (C-3′), 123.5 (C-14), 121.1 (C-4′), 115.3 (C-6′), 113.4 (C-3), 112.9 (C-10), 112.7 (C-6), 101.5 (C-8), 64.6 (C-11), 63.8 (C-16), 47.1 (C-13), 29.6 (C-12). HRMS Calcd for $C_{21}H_{18}N_4NaO_6$ $[M + Na]^+$: m/z 445.1124, Found 445.1139.

***7-(3-(4-((4-Nitrophenoxy)methyl)-1,2,3-triazol-1-yl)propoxy) coumarin (6c).** Yellow solid, mp 150–152°C. IR (KBr) v: 3150, 3074, 2939, 2884, 1707, 1610, 1338, 1254, 1125, 1048 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.20–8.17 (m, 2H, 3′, 5′-H), 7.70 (s, 1H, 14-H), 7.64 (d, J = 9.6 Hz, 1H, 4-H), 7.38 (d, J = 8.4 Hz, 1H, 5-H), 7.10–7.04 (m, 2H, 2′, 6′-H), 6.80 (dd, J = 8.4, 2.4 Hz, 1H, 6-H), 6.76 (d, J = 2.4 Hz, 1H, 8-H), 6.27 (d, J = 9.2 Hz, 1H, 3-H), 5.31 (s, 2H, 16-H), 4.65

(t, J = 6.8 Hz, 2H, 13-H), 4.05 (t, J = 5.6 Hz, 2H, 11-H), 2.51–2.45 (m, 2H, 12-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.1 (C-1′), 161.4 (C-7), 161.0 (C-2), 155.8 (C-9), 143.3 (C-4), 142.9 (C-15), 141.9 (C-4′), 129.0 (C-5), 125.9 (C-3′, 5′), 123.5 (C-14), 114.8 (C-2′, 6′), 113.5 (C-3), 113.0 (C-10), 112.4 (C-6), 101.6 (C-8), 64.7 (C-11), 62.4 (C-16), 47.2 (C-13), 29.6 (C-12). HRMS Calcd for $C_{21}H_{18}N_4NaO_6$ $[M+Na]^+$: m/z 445.1124, Found 445.1139.

7-(3-(4-((2-Methoxyphenoxy)methyl)-1,2,3-triazol-1-yl) propoxy)coumarin (6d). White solid, mp 113–115°C. IR (KBr) v: 3129, 3083, 2988, 2951, 2834, 1727, 1626, 1404, 1298, 1251, 1135, 1047 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 1H, 14-H), 7.64 (d, J = 9.6 Hz, 1H, 4-H), 7.37 (d, J = 8.4Hz, 1H, 5-H), 7.03 (dd, J = 8.0, 1.6 Hz, 1H, 6′-H), 6.97–6.93 (m, 1H, 4′-H), 6.90–6.85 (m, 2H, 3′, 5′-H), 6.80 (dd, J = 8.4, 2.4 Hz, 1H, 6-H), 6.77 (d, J = 2.4Hz, 1H, 8-H), 6.27 (d, J = 9.6 Hz, 1H, 3-H), 5.30 (s, 2H, 16-H), 4.59 (t, J = 7.0 Hz, 2H, 13-H), 4.03 (t, J = 5.8 Hz, 2H, 11-H), 3.85 (s, 3H, —OCH_3), 2.48–2.41 (m, 2H, 12-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.5 (C-7), 161.0 (C-2), 155.8 (C-9), 149.5 (C-2′), 147.5 (C-1′), 144.6 (C-15), 143.3 (C-4), 128.9 (C-5), 123.2 (C-14), 121.9 (C-4′), 120.9 (C-5′), 114.2 (C-6′), 113.5 (C-3), 112.9 (C-10), 112.5 (C-6), 111.8 (C-3′), 101.6 (C-8), 64.7 (C-11), 63.2 (C-16), 55.9 (—OCH3), 47.0 (C-13), 29.6 (C-12). HRMS Calcd for $C_{22}H_{21}N_3NaO_5$ $[M+Na]^+$: m/z 430.1379, Found 430.1397.

7-(3-(4-((2-Ethyoxyphenoxy)methyl)-1,2,3-triazol-1-yl)propoxy) coumarin (6e). White solid, mp 93–95°C. IR (KBr) v: 3142, 3083, 2978, 2935, 2872, 1733, 1614, 1394, 1328, 1283, 1123, 1046, 1030 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1H, 14-H), 7.63 (d, J = 9.6 Hz, 1H, 4-H), 7.36 (d, J = 8.8Hz, 1H, 5-H), 7.00 (dd, J = 8.0, 1.6 Hz, 1H, 6′-H), 6.94–6.82 (m, 3H, 3′, 4′, 5′-H), 6.79 (dd, J = 8.8, 2.4 Hz, 1H, 6-H), 6.74 (d, J = 2.4Hz, 1H, 8-H), 6.24 (d, J = 9.6 Hz, 1H, 3-H), 5.27 (s, 2H, 16-H), 4.59 (t, J = 6.8 Hz, 2H, 13-H), 4.09–4.03 (m, 2H, —$O\underline{CH_2}CH_3$), 4.01 (t, J = 5.8 Hz, 2H, 11-H), 2.46–2.39 (m, 2H, 12-H), 1.40 (t, J = 7.0 Hz, 3H, —$OCH_2\underline{CH_3}$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.5 (C-7), 161.0 (C-2), 155.7 (C-9), 149.1 (C-2′), 147.9 (C-1′), 144.7 (C-15), 143.4 (C-4), 128.9 (C-5), 123.2 (C-14), 122.1 (C-4′), 120.9 (C-5′), 115.3 (C-6′), 113.6 (C-3′), 113.3 (C-3), 112.9 (C-10), 112.5 (C-6), 101.5 (C-8), 64.7 (C-11), 64.4 (—$O\underline{CH_2}CH_3$), 63.5 (C-16), 47.0 (C-13), 29.6 (C-12), 14.9 (—$OCH_2\underline{CH_3}$). HRMS Calcd for $C_{23}H_{23}N_3NaO_5$ $[M+Na]^+$: m/z 444.1535, Found 444.1550.

7-(3-(4-((4-Methoxyphenoxy)methyl)-1,2,3-triazol-1-yl)propoxy) coumarin (6f). Pale yellow solid, mp 138–140°C. IR (KBr) v: 3141, 3087, 2996, 2958, 2922, 2888, 1729, 1629, 1386, 1300, 1234, 1140, 1106, 1033 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.66 (s, 1H, 14-H), 7.59 (d, J = 9.6 Hz, 1H, 4-H), 7.32 (d, J = 8.8 Hz, 1H, 5-H), 7.13 (t, J = 7.8 Hz, 1H, 5′-H), 6.76 (dd, J = 5.6, 2.4 Hz, 1H, 6-H), 6.70 (d, J = 2.4 Hz, 1H, 8-H), 6.54–6.47 (m, 3H, 2′, 4′, 6′-H), 6.19 (d, J = 9.2 Hz, 1H, 3-H), 5.13 (s, 2H, 16-H), 4.57 (t, J = 6.8 Hz, 2H, 13-H), 3.99 (t, J = 5.8 Hz, 2H, 11-H), 3.72 (s, 3H, $O\underline{CH_3}$), 2.44–2.38 (m, 2H, 12-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.5 (C-7), 161.0 (C-2), 160.8 (C-3′), 155.7 (C-1′), 155.7 (C-9), 144.1 (C-15), 143.4 (C-4), 129.8 (C-5′), 129.0 (C-5), 123.3 (C-14), 113.2 (C-3), 112.8 (C-10), 112.5 (C-6), 106.8 (C-6′), 106.7 (C-4′), 101.5 (C-8), 101.3 (C-2′), 64.8 (C-11), 61.9 (C-16), 55.3 (—$O\underline{CH_3}$), 47.0 (C-13), 29.6 (C-12). HRMS Calcd for $C_{22}H_{21}N_3NaO_5$ $[M+Na]^+$: m/z 430.1379, Found 430.1391.

***7-(3-(4-(o-*Tolyloxymethyl)-1,2,3-triazol-1-yl)propoxy)coumarin (6g).** Pink solid, mp 95–97°C. IR (KBr) v: 3140, 3065, 2926, 2855, 1713, 1616, 1400, 1284, 1237, 1160, 1127, 1052 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 9.6 Hz, 1H, 4-H), 7.59 (s, 1H, 14-H), 7.37 (d, J = 8.8 Hz, 1H, 5-H), 7.16–7.12 (m, 2H, 3′, 5′-H), 6.93 (d, J = 8.0 Hz, 1H, 6′-H), 6.86 (t, J = 7.2 Hz, 2H, 4′-H), 6.27 (d, J = 9.6 Hz, 1H, 3-H), 5.22 (s, 2H, 16-H), 4.62 (t, J = 6.8 Hz, 2H, 13-H), 4.03 (t, J = 5.8 Hz, 2H, 11-H), 2.50–2.43 (m, 2H, 12-H), 2.18 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.5 (C-7), 161.0 (C-2), 156.3 (C-1′), 155.8 (C-9), 144.9 (C-15), 143.3 (C-4), 130.8 (C-3′), 128.9 (C-5), 126.9 (C-2′), 126.9 (C-5′), 122.8 (C-14), 121.0 (C-4′), 115.6 (C-2′), 113.5 (C-3), 112.9 (C-10), 112.5 (C-6), 111.5 (C-6′), 101.6 (C-8), 64.7 (C-11), 62.3 (C-16), 47.0 (C-13), 29.6 (C-12), 16.2 (CH_3). HRMS Calcd for $C_{22}H_{21}N_3NaO_4$ $[M+Na]^+$: m/z 414.1430, Found 414.1446.

***7-(3-(4-(m-*Tolyloxymethyl)-1,2,3-triazol-1-yl)propoxy coumarin (6h).** Pale yellow solid, mp 102–104°C. IR (KBr) v: 3146, 3088, 2942, 2913, 2868, 1723, 1614, 1395, 1282, 1263, 1170, 1122, 1050 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 9.6 Hz, 1H, 4-H), 7.63 (s, 1H, 14-H), 7.37 (d, J = 8.4 Hz, 1H, 5-H), 7.16 (t, J = 7.8 Hz, 1H, 5′-H), 6.82–6.76 (m, 5H, 6, 8, 2′, 4′, 6′-H), 6.25 (d, J = 9.6 Hz, 1H, 3-H), 5.19 (s, 2H, 16-H), 4.61 (t, J = 6.8 Hz, 2H, 13-H), 4.03 (t, J = 5.8 Hz, 2H, 11-H), 2.49–2.42 (m, 2H, 12-H), 2.31 (s, 3H, CH3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.5 (C-7), 161.0 (C-2), 158.2 (C-1′), 155.8 (C-9), 144.5 (C-15), 143.3 (C-4), 139.6 (C-3′), 129.3 (C-5′), 128.9 (C-5), 123.0 (C-14), 122.1 (C-4′), 115.6 (C-2′), 113.4 (C-3), 112.9 (C-10), 112.5 (C-6), 111.5 (C-6′), 101.6 (C-8), 64.7 (C-11), 61.9 (C-16), 47.0 (C-13), 29.7 (C-12), 21.5 ($\underline{C}H_3$). HRMS Calcd for $C_{22}H_{21}N_3NaO_4$ $[M+Na]^+$: m/z 414.1430, Found 414.1443.

7-(3-(4-((4-Chlorophenoxy)methyl)-1,2,3-triazol-1-yl)propoxy) coumarin (6i). Pale yellow solid, mp 147–149°C. IR (KBr) v: 3142, 3067, 2930, 2876, 1725, 1614, 1282, 1244, 1127, 1097, 1026 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 9.6 Hz, 1H, 4-H), 7.62 (s, 1H, 14-H), 7.38 (d, J = 9.6 Hz, 1H, 5-H), 7.22 (m, 2H, 3′, 5′-H), 6.90 (m, 2H, 2′, 6′-H), 6.81–6.77 (m, 2H, 6, 8-H), 6.27 (d, J = 9.6 Hz, 1H, 3-H), 5.18 (s, 2H, 16-H), 4.62 (t, J = 6.8 Hz, 2H, 13-H), 4.04 (t, J = 5.6 Hz, 2H, 11-H), 2.49–2.43 (m, 2H, 12-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.4 (C-7), 161.0 (C-2), 156.7 (C-1′), 155.8 (C-9), 144.0 (C-15), 143.2 (C-4), 129.4 (C-3′, 5′), 128.9 (C-5), 126.2 (C-4′), 123.1 (C-14), 116.1 (C- 2′, 6′), 113.5 (C-3), 113.0 (C-10), 112.4 (C-6), 101.6 (C-8), 64.9 (C-11), 62.2 (C-16), 47.1 (C-13), 29.6 (C-12). HRMS Calcd for $C_{21}H_{18}ClN_3NaO_4$ $[M+Na]^+$: m/z 434.0884, Found 434.0883.

7-(3-(4-((2,4-Dichlorophenoxy)methyl)-1,2,3-triazol-1-yl)propoxy) coumarin (6j). White solid, mp 124–126°C. IR (KBr) v: 3100, 3075, 2938, 2876, 1739, 1614, 1285, 1230, 1124, 1050, 1032 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1H, 14-H), 7.65 (d, J = 9.6 Hz, 1H, 4-H), 7.38 (d, J = 8.8 Hz, 1H, 5-H), 7.34 (d, J = 2.4 Hz, 1H, 3′-H), 7.17 (dd, J = 8.8, 2.4 Hz, 1H, 5′-H), 7.04 (d, J = 8.8 Hz, 1H, 6′-H), 6.80 (dd, J = 8.4, 2.4 Hz, 1H, 6-H), 6.77 (d, J = 2.0 Hz, 1H, 8-H), 6.27 (d, J = 9.6 Hz, 1H, 3-H), 5.27 (s, 2H, 16-H), 4.63 (t, J = 6.6 Hz, 2H, 13-H), 4.03 (t, J = 5.6 Hz, 2H, 11-H), 2.50–2.44 (m, 2H, 12-H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 161.4 (C-7), 161.0 (C-2), 155.8 (C-9), 152.5 (C-1′), 143.7 (C-15), 143.3 (C-4), 130.1 (C-3′), 128.9 (C-5), 127.7 (C-5′), 126.5 (C-4′), 123.9 (C-2′), 123.3 (C-14), 115.0 (C-6′), 113.5 (C-3), 113.0 (C-10), 112.5 (C-6), 101.6 (C-8), 64.6 (C-11), 63.5 (C-16), 47.1 (C-13), 29.6 (C-12). HRMS Calcd for $C_{21}H_{17}Cl_2N_3NaO_4$ $[M+Na]^+$: m/z 468.0494, Found 468.0496.

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