EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201201096

Chemoselective Preparation of Unsymmetrical Bis(1,2,3-triazole) Derivatives and Application in Bis(1,2,3-triazole)-Modified Peptidomimetic Synthesis

Teng-fei Niu,[a] Lin Gu,[a] Liang Wang,[b] Wen-bin Yi,[a] and Chun Cai*[a]

Keywords: Nitrogen heterocycles / Multicomponent reactions / Cycloaddition / Click chemistry / Chemoselectivity / Peptidomimetics

An efficient chemoselective methodology for the syntheses of unsymmetrical bis(1,2,3-triazole) derivatives has been developed. This protocol utilizes alkynyl-substituted amines as bifunctional linkers to conjoin a copper-free three-component cycloaddition with a copper(I)-catalyzed alkyne–azide cycloaddition in a one-pot procedure. In addition, we used this method for the construction of unsymmetrical bis(1,2,3-triazole)-modified peptidomimetics through a combination of multicomponent reactions taking place in a sequential process, which may be utilized in biological applications.

Introduction

Recently, new kinds of bis(triazole) derivatives have received much attention in fields as diverse as biotechnology and materials science. Various literature reports have mentioned that the bis(triazole) molecules could act as cross-linkers in the conjugation of two different ligands such as DNA,[1] RNA,[2] and peptidomimetics,[3] all of which usually have special bioactivities. In addition, metal-coordinated bis(triazoles) have shown to be efficient catalysts and form supramolecular structures.[4]

The typical approach for the construction of bis(triazole) derivatives involves a copper(I)-catalyzed 1,3-dipolar cycloaddition reaction between an acetylene and an azide (CuAAC), namely, "click chemistry".[5] However, this method is rather inefficient in its step-by-step reaction sequence, which requires many protecting groups. In most cases, only symmetrically substituted bis(1,2,3-triazoles) have been prepared. There are few reports for a flexible and efficient chemoselective protocol for the syntheses of unsymmetrical bis(1,2,3-triazole) molecules, until recently.

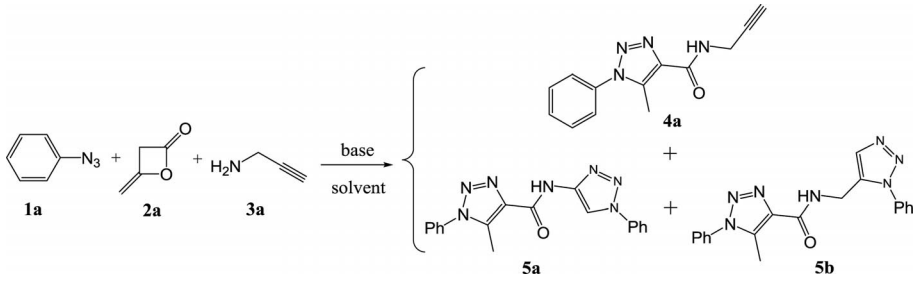
Aucagne and Leigh first reported a double-click method by using TMS (trimethylsilyl)-protected dialkynes to give the desired unsymmetrical bis(1,2,3-triazoles).[6] In a recent discovery, other kinds of dialkynes were prepared to generate these molecules by using the double-click method.[7] However, these double-click methods require a protection and deprotection sequence, which increase the workload. Recognizing the limitations associated with these processes, Girard and co-workers synthesized a new kind of dialkyne containing both activated and inactivated alkyne moieties to generate simple unsymmetrical bis(triazoles) in a one-pot process.[8] However, this method lacks regioselectivity, by affording both 1,4- and 1,5-disubstituted triazoles. Beal et al. employed a strain-promoted azide–alkyne cycloaddition (SPAAC) and CuAAC reactions in sequential biomolecular conjugations to achieve unsymmetrical bis(1,2,3-triazoles).[9] More recently, Zhu et al. introduced unsymmetrical bis(azide) compounds containing chelating and nonchelating azido groups that undergo chemoselective CuAAC reactions with two different alkyne molecules.[10] However, because they are potentially explosive, these bis(azide) compounds are very dangerous. Although these approaches are available for various degrees of chemoselective syntheses, they suffer from the limitations mentioned above. More importantly, these bifunctional molecules are not commercially available and not so convenient to prepare in house. Herein, we report an efficient procedure for the successive copper-free and copper-mediated chemoselective formation of two distinct triazole linkages using commercially available alkynyl-substituted amines as bifunctional linkers. In addition, to verify its possible biological applications, we utilized and took advantage of this chemoselective reaction to access bis(1,2,3-triazole)-modified peptidomimetics by tandem multicomponent reactions.

Results and Discussion

Taking into account recent reports of triazole syntheses, it is known that azides easily and regioselectively react with acetoacetic acids esters as well as amides to undergo a three-component cycloaddition and form 5-methyl-1*H*-

[a] Chemical Engineering College, Nanjing University of Science and Technology,
Nanjing, 210094, P. R. China
Fax: +86-25-84315030
E-mail: c.cai@mail.njust.edu.cn
Homepage: http://sce.njust.edu.cn
[b] Jiangsu Province Key Laboratory of Fine Petrochemical Engineering, Changzhou University,
Changzhou 213164, P. R. China

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201096.



Scheme 1. Chemoselective synthesis of monotriazole by a three-component reaction.

1,2,3-triazole.[11] We wondered whether alkynyl-substituted amines could regioselectively be used for the formation of a monotriazole, leaving the alkynyl group available for a CuAAC reaction with another azide. In our initial experiment (see Scheme 1), 2-propynylamine (**3a**) was chosen as a bifunctional linker and was combined with 1 equiv. of azide **1a** and 1 equiv. of diketene **2a** in MeCN under base-catalyzed (1 equiv. of Et_3N) conditions at reflux. To our delight, the resulting monotriazole **4a** was obtained in 37% yield. However, a mixtures of the 1,4 and 1,5 isomers, bis-(triazoles) **5a** and **5b**, also formed with as selectivity toward **4a** [**4a**/(**5a** + **5b**), 59:41].

To optimize the reaction, we screened a number of experimental conditions to facilitate the cyclization. The results of our optimization studies are summarized in Table 1. Both organic and inorganic bases catalyzed the formation of the monotriazole. Although strong bases such as NaOH and *t*BuOK resulted in a short reaction time (see Table 1, Entries 6 and 7), using DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) afforded an excellent yield with a higher selectivity (see Table 1, Entry 4). However, if no base was added, no conversion was observed (see Table 1, Entry 8). The effect of solvent was also examined, and from Table 1, Entries 9–12, we can see that highly polar solvents such as MeOH resulted in a higher yield and selectivity of the product within a shorter reaction period. In addition, a long reaction time was needed or a lower yield resulted when a lower temperature (see Table 1, Entry 15) or solvent-free condition (see Table 1, Entry 16) was applied. Gratifyingly, the best result was obtained with 1.1 equiv. of diketene **2a**, 1.1 equiv. of 2-propynylamine **3a**, 1.1 equiv. of DBU as the catalyst, and MeOH as the solvent (see Table 1, Entry 13).

Table 1. Optimization of conditions for the first cycloaddition.

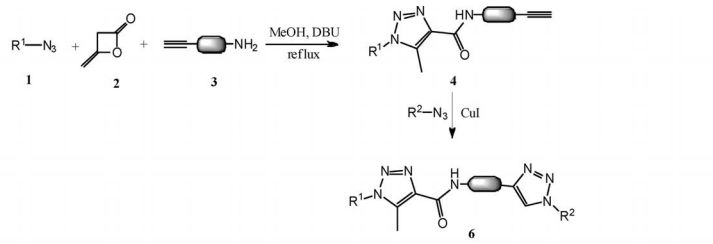
Entry	Conditions[a]				**4a**/(**5a** + **5b**)	% Yield **4a**[b]
	Catalyst	Solvent	*T* [h]	*T* [°C]		
1	Et_3N	MeCN	8	80	59:41	37
2	DIPEA[c]	MeCN	8	80	61:39	35
3	DMAP[c]	MeCN	8	80	65:35	47
4	DBU	MeCN	8	80	85:15	60
5	DABCO[c]	MeCN	8	80	73:27	53
6	NaOH	MeCN	4	80	81:19	22
7	*t*BuOK	MeCN	4	80	85:15	19
8	–	MeCN	24	80	–	trace
9	DBU	DMF[c]	12	100	83:17	55
10	DBU	MeOH	8	70	90:10	64
11	DBU	THF[c]	12	70	65:35	35
12	DBU	toluene	12	100	51:49	27
13	DBU[d]	MeOH	8	70	>95	71
14	DBU[e]	MeOH	8	70	>95	71
15	DBU[d]	MeOH	24	50	90:10	52
16	DBU[d]	–	6	70	83:17	53

[a] **1a** (1 equiv.), **2a** (1 equiv.), **3a** (1 equiv.), and catalyst (1 equiv.). [b] Isolated yield. [c] DIPEA = *N*,*N*-diisopropylethylamine, DMAP = 4-(dimethylamino)pyridine, DABCO = 1,4-diazabicyclo[2.2.2]octane, DMF = *N*,*N*-dimethylformamide , THF = tetrahydrofuran. [d] **1a** (1 equiv.), **2a** (1.1 equiv.), **3a** (1.1 equiv.), and catalyst (1.1 equiv.). [e] **1a** (1 equiv.), **2a** (1.2 equiv.), **3a** (1.2 equiv.), and catalyst (1.2 equiv.).

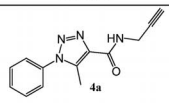
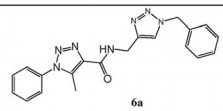
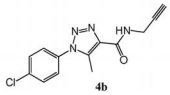
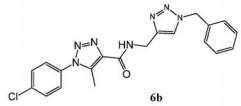
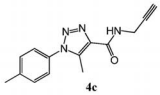
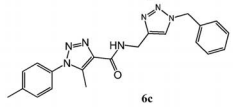
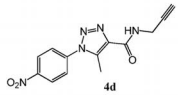
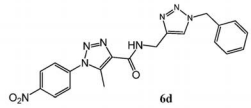
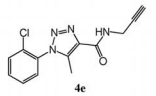
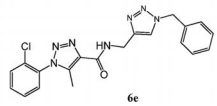
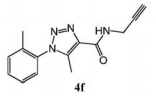
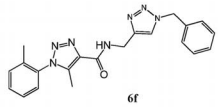
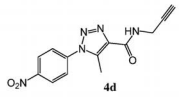
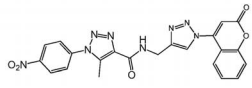
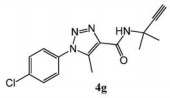
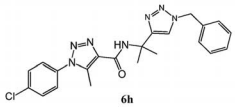
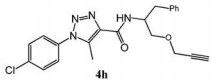
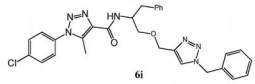
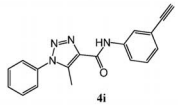
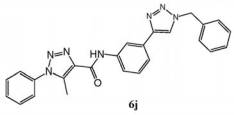
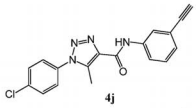
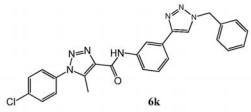
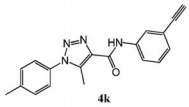
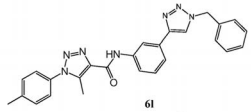
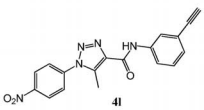
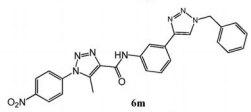
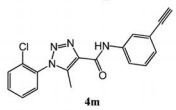
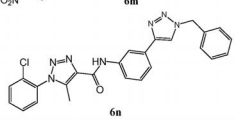
Using these optimized conditions, the scope of the reaction is illustrated by the examples in Table 2. To our delight, both aromatic and aliphatic alkynyl-substituted amines (see Figure 1) were used and gave satisfactory yields and selectivities. The type of the alkynyl-substituted amine was important, as *meta*-substituted ethynylaniline (**3c**) gave a significantly higher yield than alkynylamines **3a**, **3b**, or **3d**, presumably because of electronic effects. However, *para*-substituted ethynylaniline was not tolerated, and the desired product was not formed. Moreover, it was previously shown that different azides have various reactivities. Both electron-donating and electron-withdrawing groups on the aromatic ring of the azide were tolerated, and the electronic properties of the substituted azides had a slight influence on the yields of the reaction (see Table 2, Entries 2–4 and 11–13). However, the steric effects of the substituted azides had a significant influence on the yields of the reaction (see Table 2, Entries 5, 6, and 14). In addition, compounds **3a**, **3b**, and **3c** were commercially available, and **3d** can also be prepared easily.[12]

Benzyl azide and 3-azidocoumarin were then employed in the second triazole synthesis. The addition of the second azide (1.0 equiv.) with a catalytic amount of CuI (20 mol-%) and Et_3N (1.0 equiv.) to the solution of the purified monotriazoles **4** (1.0 equiv.) in CH_2Cl_2/MeOH gave the expected unsymmetrical bis(1,2,3-triazoles) **6** in good yields (see Table 2). It is noteworthy that the three-component cycloaddition and subsequent CuAAC can be performed as a "one-pot" tandem reaction. The first 3CR (three-component reaction) for the cyclization step was performed in MeOH. After the reaction was complete, without separating the intermediate monotriazoles **4**, the second azide (1.0 equiv.) and CuI (20 mol-%) were added (for **6k**, **6l**, and **6m**, additional CH_2Cl_2 was added). The reaction was stirred

Table 2. Chemoselective formation of mono- and bis(triazoles).



1 2 3 4 6

Entry	Product	Selectivity [%]	Yield [%]	Product	Yield [%]
1	 4a	>95	71	 6a	88
2	 4b	>95	85	 6b	88
3	 4c	>95	83	 6c	87
4	 4d	>95	86	 6d	84
5	 4e	>95	74	 6e	88
6	 4f	>95	70	 6f	86
7	 4d	>95	86	 6g	81
8	 4g	>95	88	 6h	87
9	 4h	>95	73	 6i	85
10	 4i	>95	76	 6j	85
11	 4j	>95	88	 6k	82
12	 4k	>95	85	 6l	83
13	 4l	>95	87	 6m	80
14	 4m	>95	76	 6n	85

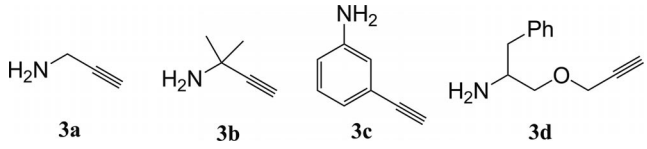
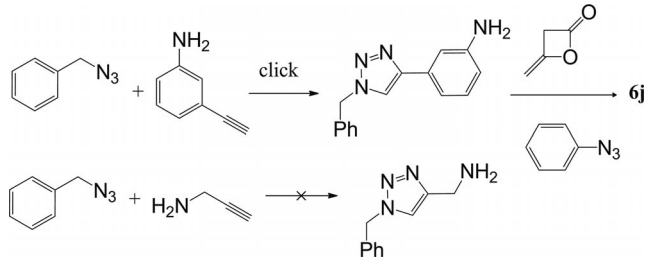


Figure 1. Alkynyl-substituted amines.

at 40 °C for an additional 6 h. The one-pot sequence process did not decrease the yields (e.g., **6a** was obtained in 60% yield). Consequently, we developed an efficient one-pot strategy for the syntheses of unsymmetrical bis(1,2,3-triazole) molecules without the use of protecting groups.

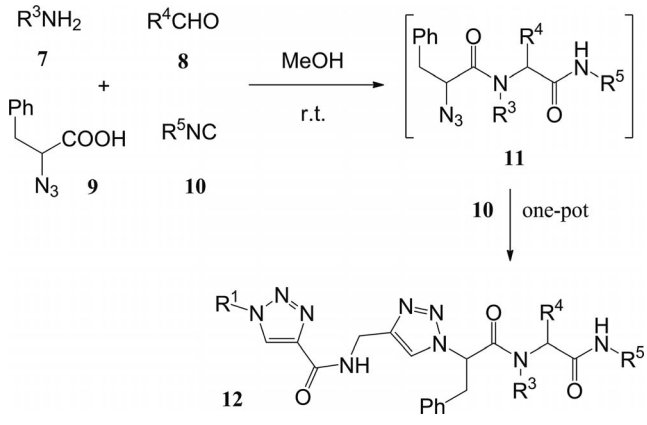
We subsequently investigated the possibility of the CuAAC triazole synthesis as the first reaction. An alternative route to the unsymmetrical bis(1,2,3-triazole) molecules is presented in Scheme 2. However, the typical catalytic systems such as CuI/Et_3N and $CuSO_4$/sodium ascorbate/Et_3N could not catalyze the first "click reaction" when using aliphatic alkynyl-substituted amines, and no desired product was found. Although aromatic alkynyl-substituted amines could undergo this process, lower yields were obtained (32% yield for **6j**). Apparently, the chosen 3CR for the cycloaddition in the first reaction was the best choice for this combination.



Scheme 2. An alternative route for unsymmetrical bis(1,2,3-triazoles).

To further expand the scope of this combination of reactions, we decided to focus on bis(1,2,3-triazole)-modified peptidomimetic syntheses.[13] It is noteworthy that there is an amido bond in the bis(triazole) structure, which is suitable for bis(1,2,3-triazole)-modified peptidomimetic syntheses. Monotriazoles **4** were effective for the conjugation of a peptide fragment that contains an azide group. In our recent study, we found that the Ugi reaction was an efficient method for the construction of peptide building blocks and peptoid molecules in one step.[14] Azido acid was chosen as the "bridge molecule" to combine a Ugi 4CR (four-component reaction) with the 3CR used in the monotriazole synthesis. The Ugi reaction was preferred as the first step for the MCRs. On the basis of classic reports on the Ugi 4CR, **9** was treated with **7**, **8**, and **10** in MeOH at room temperature to form intermediate **11**. Then, without isolation of the intermediate, a one-pot combination with monotriazoles **4** led to the desired unsymmetrical bis(1,3-triazole)-modified peptidomimetics **12** (see Table 3).

Table 3. One-pot combination of two MCRs (multicomponent reaction) to generate unsymmetrical bis(1,2,3-triazole)-modified peptidomimetics.

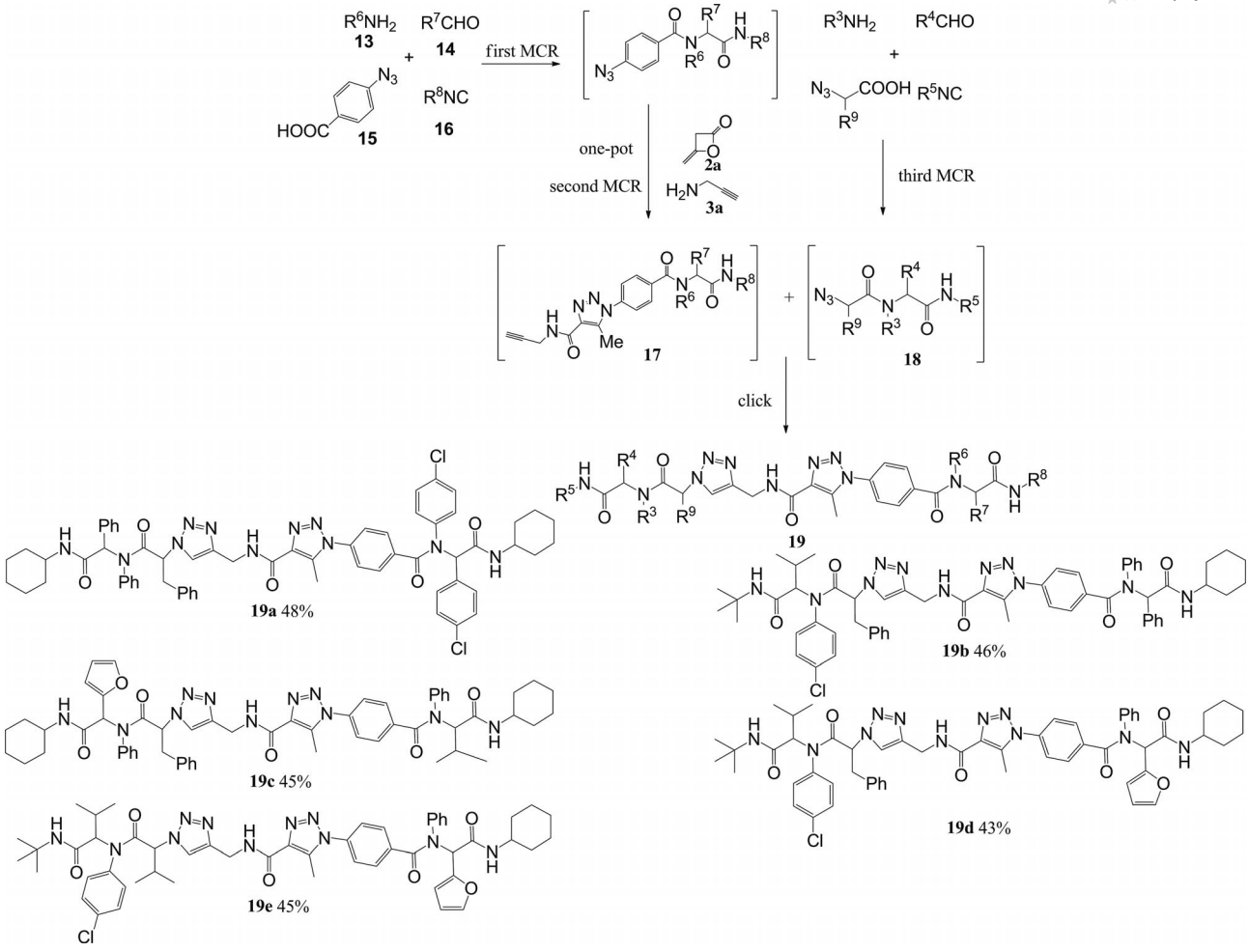


Entry	R^3	R^4	R^5	**4**	Product	% Yield
1	*n*-butyl	4-ClC_6H_4	*c*-hex	**4a**	**12a**	56
2	4-ClC_6H_4	furan-2-yl	*c*-hex	**4c**	**12b**	73
3	Bn	*i*Pr	*c*-hex	**4b**	**12c**	76
4	*n*-butyl	4-ClC_6H_4	*c*-hex	**4b**	**12d**	72

Recently, our group discovered a six-component reaction to generate 1,2,3-triazole-modified peptidomimetics by conjugating two MCRs in one pot.[15] The chemoselective bis(triazole) syntheses provide an opportunity to introduce a six-component reaction to generate complex bis(1,2,3-triazole)-modified peptidomimetics by combining three MCRs in a sequential process. First, the Ugi 4CR was performed by using *para*-azidobenzoic acid as the "bridge molecule". After the reaction was complete, for the second MCR, a one-pot combination with 1.1 equiv. of **3a**, 1.1 equiv. of diketene **2a**, and 1.1 equiv. of DBU at reflux led to the intermediate monotriazole-modified peptidomimetics **17**. No symmetrical bis(triazoles) were observed. Then, a subsequent CuAAC reaction with another Ugi 4CR product, which contained an azide group, gave unsymmetrical bis(1,2,3-triazole)-modified peptidomimetics in good yields (see Scheme 3). In addition, an α,β-unsaturated functional group, such as furaldehyde, was tolerated in the process. These tandem multicomponent reactions provide an opportunity to generate unsymmetrical bis(1,2,3-triazole)-modified peptidomimetics in a rapid and efficient process, which fully lives up to the principle of "green chemistry" and atom economy.

Conclusions

We have described an efficient approach to the chemoselective syntheses of unsymmetrical bis(1,2,3-trazoles). This strategy employed alkynyl-substituted amines as bifunctional linkers, which could generate 1,2,3-trazoles by undergoing a copper-free cycloaddition and CuAAC reactions, respectively. The commercially available bifunctional linkers suggest this chemoselective ligation strategy could have wide potential. In particular, this methodology is suitable



Scheme 3. Unsymmetrical bis(1,2,3-triazole)-modified peptidomimetic syntheses by combining three MCRs in a sequential process.

for the syntheses of unsymmetrical bis(1,2,3-trazoles)-modified peptidomimetics by combining the multicomponent reactions in a sequential process. This strategy allows direct access to complex structures from simple building blocks and fully lives up to the principle of "green chemistry" and atom economy. We anticipate that this method could be a useful protocol for biochemistry.

Experimental Section

General Methods: All of the chemicals were commercially available and used without further purification. Analytical thin layer chromatography was performed with glass plates that were precoated with silica gel, which was impregnated with a fluorescent indicator (254 nm). The plates were visualized by exposure to ultraviolet light. The ^{1}H NMR spectroscopic data were recorded with a Bruker DRX500 (500 MHz) spectrometer, and the ^{13}C NMR spectroscopic data were recorded with a Bruker DRX500 (125 MHz) spectrometer. Mass spectra were recorded with a Finnigan TSQ Quantum-MS instrument in the electrospray ionization (ESI) mode. Elemental analyses were performed with a Yanagimoto MT3CHN recorder.

Preparation of Monotriazoles 4: The azide (2.0 mmol), diketene (2.2 mmol), alkynyl-substituted amine (2.2 mmol), and DBU (2.2 mmol) were placed in a sealed tube with MeOH (4 mL), and the resulting mixture was stirred and heated at reflux for 8 h. Then, the solvent was removed in vacuo, and the residue was purified by column chromatography (hexanes/ethyl acetate, 2:1) to afford monotriazole **4**.

5-Methyl-1-phenyl-*N*-(prop-2-ynyl)-1*H*-1,2,3-triazole-4-carboxamide (4a): White solid (0.34 g, 71%); m.p. 86–88 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.00–8.97 (t, J = 6 Hz, 1 H), 7.66–7.61 (m, 5 H), 4.06–4.04 (m, 2 H), 3.08–3.07 (t, J = 2.5 Hz, 1 H), 2.53 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.1, 137.3, 136.4, 134.8, 129.5, 129.2, 124.9, 80.9, 71.9, 39.5, 39.4, 39.2, 39.0, 38.8, 38.7, 38.5, 27.3, 8.8 ppm. MS (ESI): m/z = 241 [M + 1]$^+$. $C_{13}H_{12}N_4O$ (240.26): calcd. C 64.99, H 5.03, N 23.32; found C 64.86, H 4.95, N 23.22.

1-(4-Chlorophenyl)-5-methyl-*N*-(prop-2-ynyl)-1*H*-1,2,3-triazole-4-carboxamide (4b): White solid (0.46 g, 85%); m.p. 156–158 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.02–8.99 (t, J = 6 Hz, 1 H), 7.73–7.68 (m, 4 H), 4.05–4.03 (m, 2 H), 3.08–3.07 (t, J = 2.5 Hz, 1 H), 2.54 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.0, 137.4, 136.6, 134.1, 133.6, 129.2, 126.7, 80.8, 71.8, 39.5, 39.4, 39.2, 39.0, 38.9, 38.7, 38.5, 27.3, 8.7 ppm. MS (ESI): m/z = 275 [M + 1]$^+$. $C_{13}H_{11}ClN_4O$ (274.71): calcd. C 56.84, H 4.04, N 20.40; found C 56.71, H 4.11, N 20.31.

5-Methyl-*N*-(prop-2-ynyl)-1-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide (4c): White solid (0.29 g, 83%); m.p. 136–138 °C. ^{1}H NMR

(500 MHz, [D$_6$]DMSO): δ = 8.99–8.96 (t, J = 6 Hz, 1 H), 7.50 (d, J = 8.5 Hz, 2 H), 7.44 (d, J = 8 Hz, 2 H), 4.05–4.03 (m, 2 H), 3.08–3.07 (t, J = 2.5 Hz, 1 H), 2.51 (s, 3 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.1, 139.3, 137.2, 136.3, 132.3, 129.5, 124.7, 80.9, 71.8, 27.3, 20.2, 8.7 ppm. MS (ESI): m/z = 255 [M + 1]$^+$. $C_{14}H_{14}N_4O$ (254.29): calcd. C 66.13, H 5.55, N 22.03; found C 66.30, H 5.63, N 22.15.

5-Methyl-1-(4-nitrophenyl)-*N*-(prop-2-ynyl)-1*H*-1,2,3-triazole-4-carboxamide (4d): White solid (0.49 g, 86%); m.p. 112–114 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.07–9.05 (t, J = 6 Hz, 1 H), 8.49 (d, J = 9 Hz, 2 H), 8.00 (d, J = 9 Hz, 2 H), 4.05–4.04 (m, 2 H), 3.09–3.08 (t, J = 2 Hz, 1 H), 2.62 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.8, 147.3, 139.6, 137.7, 137.0, 125.9, 124.6, 80.8, 71.9, 27.3, 8.9 ppm. MS (ESI): m/z = 286 [M + 1]$^+$. $C_{13}H_{11}N_5O_3$ (285.26): calcd. C 54.74, H 3.89, N 24.55; found C 54.53, H 3.97, N 24.41.

1-(2-Chlorophenyl)-5-methyl-*N*-(prop-2-ynyl)-1*H*-1,2,3-triazole-4-carboxamide (4e): White solid (0.40 g, 74%); m.p. 106–108 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.07 (s, 1 H), 7.57–7.56 (m, 1 H), 7.52–7.49 (m, 1 H), 7.45–7.42 (m, 1 H), 7.38–7.37 (m, 1 H), 4.23–4.23 (m, 2 H), 2.42 (s, 3 H), 2.24 (s, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.9, 136.6, 132.0, 131.1, 130.7, 129.7, 128.1, 127.1, 79.6, 70.4, 27.6, 8.0 ppm. MS (ESI): m/z = 275 [M + 1]$^+$. $C_{13}H_{11}ClN_4O$ (274.71): calcd. C 56.84, H 4.04, N 20.40; found C 56.75, H 4.11, N 20.32.

5-Methyl-*N*-(prop-2-ynyl)-1-*o*-tolyl-1*H*-1,2,3-triazole-4-carboxamide (4f): White solid (0.36 g, 70%); m.p. 108–110 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.01–9.00 (t, J = 6 Hz, 1 H), 7.58–7.52 (m, 2 H), 7.47–7.42 (m, 2 H), 4.06–4.04 (m, 2 H), 3.08–3.07 (t, J = 2.5 Hz, 1 H), 2.34 (s, 3 H), 1.98 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.1, 137.1, 136.8, 134.5, 133.6, 130.8, 130.3, 126.8, 126.7, 80.9, 71.9, 27.2, 16.1, 8.2 ppm. MS (ESI): m/z = 255 [M + 1]$^+$. $C_{14}H_{14}N_4O$ (254.29): calcd. C 66.13, H 5.55, N 22.03; found C 66.21, H 5.66, N 21.89.

1-(4-Chlorophenyl)-5-methyl-*N*-(2-methylbut-3-yn-2-yl)-1*H*-1,2,3-triazole-4-carboxamide (4g): White solid (0.53 g, 88%); m.p. 116–118 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.14 (s, 1 H), 7.73–7.67 (m, 4 H), 3.16 (s, 1 H), 2.53 (s, 3 H), 1.64 (s, 6 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.5, 136.7, 134.1, 133.6, 129.2, 126.7, 130.3, 126.8, 126.7, 87.2, 70.6, 46.0, 28.6, 8.7 ppm. MS (ESI): m/z = 303 [M + 1]$^+$. $C_{15}H_{15}ClN_4O$ (302.76): calcd. C 59.51, H 4.99, N 18.51; found C 59.43, H 5.06, N 18.43.

1-(4-Chlorophenyl)-5-methyl-*N*-[1-phenyl-3-(prop-2-ynyloxy)propan-2-yl]-1*H*-1,2,3-triazole-4-carboxamide (4h): White solid (0.59 g, 73%); m.p. 102–104 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.58–7.55 (m, 3 H), 7.44–7.41 (m, 2 H), 7.34–7.30 (m, 4 H), 7.26–7.23 (m, 1 H), 4.54 (d, J = 9 Hz, 1 H), 4.27–4.18 (m, 2 H), 3.63–3.56 (m, 2 H), 3.03 (d, J = 7 Hz, 2 H), 2.64 (s, 3 H), 2.46–2.45 (t, J = 2.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.7, 137.7, 136.8, 135.7, 135.1, 133.1, 129.0, 128.5, 127.5, 125.5, 78.4, 73.0, 68.6, 57.5, 49.0, 36.6, 8.7 ppm. MS (ESI): m/z = 409 [M + 1]$^+$. $C_{22}H_{21}ClN_4O_2$ (408.89): calcd. C 64.62, H 5.18, N 13.70; found C 64.75, H 5.27, N 13.59.

***N*-(3-Ethynylphenyl)-5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxamide (4i):** White solid (0.46 g, 76%); m.p. 160–162 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.65 (s, 1 H), 8.07 (s, 1 H), 7.90 (d, J = 6 Hz, 1 H), 7.67 (m, 5 H), 7.39–7.36 (t, J = 7.5 Hz, 1 H), 7.22 (d, J = 5.5 Hz, 1 H), 4.19 (s, 1 H), 2.58 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 138.4, 137.6, 137.4, 134.8, 129.6, 129.2, 128.5, 126.4, 125.0, 122.8, 121.4, 120.6, 82.9, 80.0, 8.9 ppm. MS (ESI): m/z = 303 [M + 1]$^+$. $C_{18}H_{14}N_4O$ (302.33): calcd. C 71.51, H 4.67, N 18.53; found C 71.44, H 4.59, N 18.41.

1-(4-Chlorophenyl)-*N*-(3-ethynylphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide (4j): White solid (0.59 g, 88%); m.p. 136–138 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.67 (s, 1 H), 8.07 (s, 1 H), 7.90 (d, J = 8.5 Hz, 1 H), 7.75–7.71 (m, 4 H), 7.38–7.35 (t, J = 8 Hz, 1 H), 7.22 (d, J = 7.5 Hz, 1 H), 4.19 (s, 1 H), 2.59 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.1, 138.3, 137.6, 134.3, 133.5, 129.3, 128.5, 126.8, 126.4, 122.8, 121.4, 120.6, 82.9, 80.0, 8.9 ppm. MS (ESI): m/z = 338 [M + 1]$^+$. $C_{18}H_{13}ClN_4O$ (336.78): calcd. C 64.19, H 3.89, N 16.64; found C 64.08, H 3.98, N 16.55.

***N*-(3-Ethynylphenyl)-5-methyl-1-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide (4k):** White solid (0.54 g, 85%); m.p. 144–146 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.64 (s, 1 H), 8.06 (s, 1 H), 7.90–7.88 (m, 1 H), 7.54 (d, J = 8.5 Hz, 2 H), 7.47 (d, J = 8 Hz, 2 H), 7.38–7.22 (t, J = 8 Hz, 1 H), 7.22 (d, J = 7.5 Hz, 1 H), 4.19 (s, 1 H), 2.56 (s, 3 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 139.4, 138.4, 137.5, 137.3, 132.3, 129.6, 128.5, 126.4, 124.7, 122.7,121.4, 120.5, 82.9, 80.0, 20.2, 8.9 ppm. MS (ESI): m/z = 317 [M + 1]$^+$. $C_{19}H_{16}N_4O$ (316.36): calcd. C 72.13, H 5.10, N 17.71; found C 72.05, H 5.167, N 17.53.

***N*-(3-Ethynylphenyl)-5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxamide (4l):** White solid (0.60 g, 87%); m.p. 116–118 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.72 (s, 1 H), 8.51–8.49 (s, 2 H), 8.07–8.06 (t, J = 2 Hz, 1 H), 8.03–8.02 (m, 2 H), 7.90–7.88 (m, 1 H), 7.39–7.36 (t, J = 8 Hz, 1 H), 7.24–7.22 (m, 1 H), 4.20 (s, 1 H), 2.67 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.0, 147.4, 139.5, 138.3, 137.9, 128.5, 126.5, 126.0, 124.6, 122.8, 121.4, 120.6, 82.9, 80.0, 9.1 ppm. MS (ESI): m/z = 348 [M + 1]$^+$. $C_{18}H_{13}N_5O_3$ (347.33): calcd. C 62.24, H 3.77, N 20.16; found C 62.45, H 3.86, N 20.05.

1-(2-Chlorophenyl)-*N*-(3-ethynylphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide (4m): White solid (0.53 g, 76%); m.p. 112–114 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.70 (s, 1 H), 7.57–7.56 (m, 1 H), 7.52–7.49 (m, 1 H), 7.45–7.42 (m, 1 H), 7.38–7.37 (m, 1 H), 4.24–4.22 (m, 2 H), 2.43 (s, 3 H), 2.24 (s, 1 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.9, 147.4, 137.8, 138.3, 136.6, 132.0, 131.1, 130.7, 129.7, 128.1, 127.1, 78.6, 70.4, 27.6, 8.0 ppm. MS (ESI): m/z = 348 [M + 1]$^+$. $C_{18}H_{13}N_5O_3$ (347.33): calcd. C 62.24, H 3.77, N 20.16; found C 62.35, H 3.69, N 20.24.

Bis(triazoles) 6: To a solution of compound **4** (0.5 mmol) and the azide (0.5 mmol) in CH_2Cl_2/MeOH (50:50, 3 mL) were added Et_3N (0.5 mmol) and CuI (0.1 mmol). The reaction mixture was stirred at room temperature for 8 h. Then, the solvent was removed in vacuo, and the residue was purified by column chromatography (hexanes/ethyl acetate, 2:1) to afford bis(triazole) **6**.

One-Pot Process for Bis(triazoles) 6: The azide (2.0 mmol), diketene (2.2 mmol), alkynyl-substituted amine (2.2 mmol), and DBU (2.2 mmol) were placed in a sealed tube with MeOH (4 mL), and the resulting mixture was stirred and heated at reflux for 8 h. After the reaction was complete, without separating the intermediate monotriazole **4**, the second azide (1.0 equiv.) and CuI (20 mol-%) were added (for **6k**, **6l**, **6m** additional CH_2Cl_2 was added). The reaction mixture was then stirred at 40 °C for another 6 h.

***N*-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxamide (6a):** White solid (0.16 g, 88%); m.p. 122–124 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.13–9.10 (t, J = 6 Hz, 1 H), 8.65 (s, 2 H), 7.92–7.90 (d, J = 8 Hz, 2 H), 7.67–7.60 (m, 5 H), 7.60–7.57 (t, J = 7.5 Hz, 2 H), 7.49–7.46 (t, J = 7.5 Hz, 1 H), 4.66–4.64 (d, J = 6 Hz, 2 H), 2.55–2.50 (m, 3 H) ppm ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.4, 145.8, 137.6, 136.2, 134.8, 129.4, 129.3, 129.2, 128.0, 124.8, 120.6, 119.5, 33.6, 8.8 ppm.

MS (ESI): m/z = 374 $[M + 1]^+$. $C_{20}H_{19}N_7O$ (373.42): calcd. C 64.33, H 5.13, N 26.26; found C 64.25, H 5.18, N 26.18.

***N*-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-1-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide (6b):** White solid (0.18 g, 88%); m.p. 112–114 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.11–9.08 (t, J = 6 Hz, 1 H), 8.00 (s, 1 H), 7.73–7.67 (m, 4 H),7.39–7.31 (m, 5 H), 5.57 (s, 2 H), 4.53 (d, J = 6 Hz, 2 H), 2.53 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.3, 146.0, 137.6, 136.5, 135.0, 134.1, 133.6, 132.2, 129.3, 126.7, 121.1, 120.7, 55.5, 33.6, 30.2, 18.0, 8.8 ppm. MS (ESI): m/z = 408 $[M + 1]^+$. $C_{20}H_{18}ClN_7O$ (407.86): calcd. C 58.90, H 4.45, N 24.04; found C 58.77, H 4.52, N 23.93.

***N*-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-5-methyl-1-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide (6c):** White solid (0.17 g, 87%); m.p. 126–130 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.09–9.07 (t, J = 6 Hz, 1 H), 8.02 (s, 1 H), 7.49 (d, J = 8.5 Hz, 1 H), 7.44–7.42 (d, J = 8 Hz, 2 H), 7.38–7.32 (m, 5 H), 5.58 (s, 2 H), 4.55 (d, J = 5.5 Hz, 2 H), 2.50 (s, 3 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.3, 145.1, 139.3, 137.4, 136.2, 135.6, 132.4, 130.0, 128.2, 127.6, 127.5, 124.6, 122.5, 52.2, 33.6, 20.2, 8.7 ppm. MS (ESI): m/z = 388 $[M + 1]^+$. $C_{21}H_{21}N_7O$ (387.44): calcd. C 65.10, H 5.46, N 25.31; found C 65.02, H 5.38, N 25.40.

***N*-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxamide (6d):** White solid (0.17 g, 84%); m.p. 142–146 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.15–9.13 (t, J = 5 Hz, 1 H), 8.48 (d, J = 5 Hz, 2 H), 8.01–7.97 (t, J = 10 Hz, 3 H), 7.38–7.32 (m, 5 H), 5.58 (s, 2 H), 4.54 (d, J = 5 Hz, 2 H), 2.61 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.0, 147.3, 139.6, 137.9, 136.8, 135.6, 128.2, 127.6, 127.5, 125.8, 124.6, 122.5, 52.2, 33.7, 8.9 ppm. MS (ESI): m/z = 419 $[M + 1]^+$. $C_{20}H_{18}N_8O_3$ (418.41): calcd. C 57.41, H 4.34, N 26.78; found C 57.18, H 4.46, N 26.65.

***N*-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-1-(2-chlorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide (6e):** White solid (0.18 g, 88%); m.p. 134–136 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.53 (s, 1 H), 8.00 (s, 1 H), 7.39–7.36 (t, J = 6.5 Hz, 3 H), 7.34–7.30 (m, 3 H), 5.58 (s, 2 H), 4.31 (d, J = 5.5 Hz, 2 H), 3.32 (s, 2 H), 2.11 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 202.4, 165.5, 144.4, 135.6, 128.2, 127.6, 127.4, 122.5, 52.5, 50.6, 33.8, 29.4 ppm. MS (ESI): m/z = 408 $[M + 1]^+$. $C_{20}H_{18}ClN_7O$ (407.86): calcd. C 58.90, H 4.45, N 24.04; found C 58.84, H 4.53, N 23.97.

***N*-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-5-methyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide (6f):** White solid (0.17 g, 86%); m.p. 146–148 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.10–9.08 (t, J = 6 Hz, 1 H), 8.03 (s, 1 H), 7.58–7.52 (m, 2 H), 7.47–7.41 (m, 2 H), 7.39–7.36 (m, 2 H), 7.34–7.31 (m, 3 H), 5.58 (s, 2 H), 4.69 (d, J = 5.5 Hz, 2 H), 2.64 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.2, 160.0, 153.1, 147.3, 143.4, 139.6, 137.9, 136.9, 132.9, 125.8, 125.0, 124.6, 124.4, 124.3, 116.7, 113.9, 109.8, 33.5, 8.9 ppm. MS (ESI): m/z = 388 $[M + 1]^+$. $C_{21}H_{21}N_7O$ (387.44): calcd. C 65.10, H 5.46, N 25.31; found C 64.96, H 5.55, N 25.24.

5-Methyl-1-(4-nitrophenyl)-*N*-{[1-(2-oxo-2*H*-chromen-4-yl)-1*H*-1,2,3-triazol-4-yl]methyl}-1*H*-1,2,3-triazole-4-carboxamide (6g): White solid (0.31 g, 81%); m.p. 116–118 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.6 (d, J = 6 Hz, 1 H), 8.68 (s, 1 H), 8.48 (d, J = 9 Hz, 2 H), 7.99 (d, J = 9 Hz, 2 H), 7.87 (d, J = 8 Hz, 1 H), 7.79–7.76 (t, J = 7.5 Hz, 1 H), 7.58 (d, J = 8 Hz, 1 H), 7.47–44 (t, J = 7.5 Hz, 1 H), 6.93 (s, 1 H), 4.54–4.53 (d, J = 6 Hz, 2 H), 2.33 (s, 3 H), 1.97 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.2, 144.9, 137.1, 136.9, 135.6, 134.5, 133.7, 130.8, 130.2, 128.2, 127.6, 127.5, 126.8, 126.6, 122.5, 52.2, 33.6, 16.2, 8.2 ppm. MS (ESI): m/z = 797 $[M + 23]^+$. $C_{22}H_{16}N_8O_5$ (472.42): calcd. C 55.93, H 3.41, N 23.72; found C 55.80, H 3.33, N 23.84.

***N*-[2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-1-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide (6h):** White solid (0.18 g, 87%); m.p. 108–110 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.72 (s, 1 H), 7.55 (d, J = 8 Hz, 2 H), 7.49 (s, 1 H), 7.40–7.36 (m, 5 H), 7.28 (d, J = 6 Hz, 1 H), 5.52 (s, 2 H), 2.56 (s, 3 H), 1.88 (s, 6 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 159.5, 152.6, 138.0, 135.5, 135.1, 133.9, 133.1, 128.9, 128.1, 127.6, 127.0, 125.5, 119.4, 53.1, 50.5, 27.3, 8.7 ppm. MS (ESI): m/z = 436 $[M + 1]^+$. $C_{22}H_{22}ClN_7O$ (435.92): calcd. C 60.62, H 5.09, N 22.49; found C 60.49, H 5.17, N 22.37.

***N*-{1-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-3-phenylpropan-2-yl}-1-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide (6i):** White solid (0.23 g, 85%); m.p. 106–108 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.58–7.50 (m, 3 H), 9.28 (s, 1 H), 7.43–7.42 (t, J = 2 Hz, 1 H), 7.41–7.40 (t, J = 3 Hz, 5 H), 7.39 (s, 2 H), 7.38–7.36 (t, J = 4 Hz, 8 H), 7.31–7.22 (m, 4 H), 5.55 (s, 2 H), 4.68–4.50 (t, J = 2.5 Hz, 2 H), 4.50–4.49 (m, 1 H), 3.56–3.55 (d, J = 4 Hz, 2 H), 3.01–2.98 (t, J = 7.5 Hz, 2 H), 2.62 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.6, 144.4, 137.7, 136.8, 135.7, 135.2, 133.7, 133.1, 129.0, 128.4, 128.1, 127.7, 127.5, 127.1, 125.5, 121.5, 69.2, 63.8, 53.2, 49.0, 36.6, 8.7 ppm. MS (ESI): m/z = 543 $[M + 1]^+$. $C_{29}H_{28}ClN_7O_2$ (542.04): calcd. C 64.26, H 5.21, N 18.09; found C 64.12, H 5.33, N 18.17.

***N*-[3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)phenyl]-5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxamide (6j):** White solid (0.18 g, 85%); m.p. 182–186 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.63 (s, 1 H), 9.28 (s, 1 H), 8.59 (s, 1 H), 8.00 (d, J = 8 Hz, 2 H), 7.82 (d, J = 8 Hz, 1 H), 7.68–7.63 (m, 8 H), 7.54–7.47 (m, 2 H), 2.61 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.1, 147.0, 138.7, 137.7, 137.2, 136.2, 134.8, 130.2, 129.6, 129.4, 129.2, 128.7, 128.2, 125.0, 120.5, 119.9, 119.6, 119.2, 117.0, 9.0 ppm. MS (ESI): m/z = 436 $[M + 1]^+$. $C_{25}H_{21}N_7O$ (435.49): calcd. C 68.95, H 4.86, N 22.51; found C 69.08, H 4.98, N 22.39.

***N*-[3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)phenyl]-1-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide (6k):** White solid (0.19 g, 82%); m.p. 152–156 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 10.65 (s, 1 H), 8.61 (s, 1 H), 8.46 (s, 1 H), 7.87–7.75 (m, 1 H), 7.75–7.73 (m, 3 H), 7.69–7.67 (m, 1 H), 7.59 (d, J = 8 Hz, 1 H), 7.43–7.35 (m, 6 H), 5.67 (s, 2 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.0, 146.1, 138.6, 137.8, 137.5, 135.5, 134.2, 133.6, 130.5, 129.3, 128.6, 128.3, 127.7, 127.4, 126.8, 121.1, 120.2, 119.5, 116.7, 52.5, 8.9 ppm. MS (ESI): m/z = 470 $[M + 1]^+$. $C_{25}H_{20}ClN_7O$ (469.93): calcd. C 63.90, H 4.29, N 20.86; found C 63.83, H 4.35, N 20.75.

***N*-[3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)phenyl]-5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazole-4-carboxamide (6l):** White solid (0.18 g, 83%); m.p. 200–204 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.56 (s, 1 H), 8.61 (s, 1 H), 8.46 (s, 1 H), 7.78 (d, J = 7.5 Hz, 1 H), 7.58–7.54 (t, J = 8 Hz, 3 H), 7.47 (d, J = 8 Hz, 2 H), 7.42–7.35 (m, 6 H), 5.66 (s, 2 H), 2.57 (s, 3 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.1, 146.1, 139.4, 138.6, 137.6, 137.2, 135.5, 132.3, 130.5, 129.6, 128.6, 128.3, 127.7, 127.4, 124.8, 121.1, 120.1, 119.4, 116.7, 52.5, 20.2, 8.9 ppm. MS (ESI): m/z = 450 $[M + 1]^+$. $C_{26}H_{23}N_7O$ (449.51): calcd. C 69.47, H 5.16, N 21.81; found C 69.34, H 5.23, N 21.63.

***N*-[3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)phenyl]-5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxamide (6m):** White solid (0.19 g, 80%); m.p. 182–184 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.66 (s, 1 H), 8.62 (s, 1 H), 8.52–8.48 (t, J = 10 Hz, 3 H), 8.04 (d,

J = 5 Hz, 2 H), 7.79 (d, *J* = 10 Hz, 1 H), 7.59 (d, *J* = 10 Hz, 1 H), 7.44–7.35 (m, 6 H), 5.67 (s, 2 H), 2.68 (s, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 158.8, 147.4, 146.1, 139.6, 138.5, 138.1, 137.8, 135.5, 130.5, 128.7, 128.3, 127.7, 127.4, 126.0, 124.6, 124.2, 121.1, 120.3, 119.5, 116.7, 52.5, 9.1 ppm. MS (ESI): *m*/*z* = 481 [M + 1]$^+$. $C_{25}H_{20}N_8O_3$ (480.48): calcd. C 62.49, H 4.20, N 23.32; found C 62.65, H 4.33, N 23.16.

***N*-[3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)phenyl]-1-(2-chlorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide (6n):** White solid (0.20 g, 85%); m.p. 158–162 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.65 (s, 1 H), 8.61 (s, 1 H), 8.46 (s, 1 H), 7.87–7.78 (m, 1 H), 7.78–7.73 (m, 3 H), 7.69–7.67 (m, 1 H), 7.59–7.57 (m, 1 H), 7.43–7.35 (m, 6 H), 5.67 (s, 2 H), 2.43 (s, 2 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 202.3, 164.7, 146.0, 138.9, 135.5, 130.6, 128.9, 128.3, 127.7, 127.4, 121.1, 120.0, 118.1, 115.2, 52.5, 51.8, 29.7 ppm. MS (ESI): *m*/*z* = 470 [M + 1]$^+$. $C_{25}H_{20}ClN_7O$ (469.93): calcd. C 63.90, H 4.29, N 20.86; found C 63.93, H 4.27, N 20.84.

Unsymmetrical Bis(1,2,3-triazole)-Modified Peptidomimetics 12: The amine (0.5 mmol) and aldehyde (0.5 mmol) were dissolved in a sealed tube with MeOH (2 mL), and the resulting mixture was stirred at room temperature for 30 min. Then, 2-azido-3-phenylpropanoic acid (0.5 mmol) and isocyanide (0.5 mmol) were added, and the mixture was stirred for 24 h. Then, monotriazole **4** (0.5 mmol), Et$_3$N (0.5 mmol), and CuI (0.1 mmol) were added to the sealed tube, and the reaction mixture was stirred for another 8 h. The solvent was removed in vacuo, and the residue was purified by column chromatography (hexanes/ethyl acetate, 2:1).

***N*-{[1-(1-{Butyl[1-(4-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl]-amino}-1-oxo-3-phenylpropan-2-yl)-1*H*-1,2,3-triazol-4-yl]methyl}-1-phenyl-1*H*-1,2,3-triazole-4-carboxamide (12a):** White solid (0.20 g, 56%); m.p. 94–96 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.72–7.70 (t, *J* = 5.5 Hz, 1 H), 7.69 (s, 1 H), 7.60–7.56 (m, 3 H), 7.46–7.44 (m, 7 H), 7.37 (s, 3 H), 7.28 (s, 1 H), 6.83 (s, 1 H), 5.92 (s, 1 H), 5.72 (d, *J* = 7 Hz, 1 H), 4.75 (d, *J* = 7 Hz, 1 H), 3.84–3.80 (m, 1 H), 3.32–3.19 (m, 1 H), 2.62 (s, 3 H), 1.94–1.88 (m, 2 H), 1.52 (s, 4 H), 1.71–1.53 (m, 4 H), 1.39–1.36 (m, 2 H), 1.16–1.06 (m, 3 H), 1.02–0.96 (m, 1 H), 0.71–0.68 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 166.7, 160.2, 143.4, 137.3, 135.8, 134.6, 134.1, 132.0, 131.8, 130.4, 129.0, 128.7, 128.1, 127.3, 124.3, 122.1, 63.8, 60.9, 47.7, 45.2, 33.6, 31.8, 31.1, 24.4, 23.7, 19.0, 12.3, 8.7 ppm. MS (ESI): *m*/*z* = 744 [M + 23]$^+$. $C_{39}H_{44}ClN_9O_3$ (722.29): calcd. C 64.85, H 6.14, N 17.45; found C 64.78, H 6.21, N 17.53.

***N*-{[1-(1-{(4-Chlorophenyl)[2-(cyclohexylamino)-1-(furan-2-yl)-2-oxoethyl]amino}-1-oxo-3-phenylpropan-2-yl)-1*H*-1,2,3-triazol-4-yl]methyl}-1-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide (12b):** White solid (0.27 g, 73%); m.p. 102–104 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.67–7.64 (m, 2 H), 7.39–7.34 (m, 5 H), 7.31 (d, *J* = 8.5 Hz, 2 H), 7.28 (d, *J* = 2 Hz, 2 H), 7.25–7.23 (m, 2 H), 7.21 (d, *J* = 7.5 Hz, 2 H), 7.05 (s, 1 H), 6.98 (s, 1 H), 6.91 (s, 1 H), 6.43 (s, 1 H), 6.20–6.18 (m, 1 H), 5.71 (d, *J* = 8 Hz, 1 H), 4.74–4.73 (m, 2 H), 3.85–3.82 (m, 1 H), 2.59 (s, 3 H), 2.47 (s, 3 H), 1.99 (d, *J* = 10.5 Hz, 1 H), 1.88 (d, *J* = 10.5 Hz, 1 H), 1.65–1.61 (m, 3 H), 1.41–1.34 (m, 2 H), 1.19–1.16 (m, 2 H), 1.12–1.05 (m, 1 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 166.0, 164.8, 160.2, 145.4, 143.3, 142.5, 139.2, 137.2, 135.8, 134.9, 134.1, 132.1, 131.9, 131.4, 130.0, 129.2, 128.6, 128.3, 128.0, 127.6, 124.1, 121.8, 112.0, 109.8, 63.8, 57.7, 48.0, 33.5, 31.8, 24.4, 23.8, 23.7, 20.3, 8.7 ppm. MS (ESI): *m*/*z* = 768 [M + 23]$^+$. $C_{40}H_{40}ClN_9O_4$ (746.27): calcd. C 64.38, H 5.40, N 16.89; found C 64.31, H 5.19, N 16.97.

***N*-{[1-(1-{Benzyl[1-(cyclohexylamino)-3-methyl-1-oxobutan-2-yl]amino}-1-oxo-3-phenylpropan-2-yl)-1*H*-1,2,3-triazol-4-yl]methyl}-1-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-carboxamide (12c):** White solid (0.27 g, 76%); m.p. 100–104 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.75–7.70 (m, 1 H), 7.62 (d, *J* = 6 Hz, 1 H), 7.56–7.55 (m, 3 H), 7.44–7.43 (m, 3 H), 7.42–7.39 (m, 3 H), 7.34–7.30 (m, 2 H), 7.28–7.26 (m, 2 H), 7.23–7.21 (m, 2 H), 6.75–6.59 (m, 1 H), 6.61 (d, *J* = 5.5 Hz, 3 H), 2.88 (d, *J* = 8 Hz, 1 H), 1.86–1.84 (m, 2 H), 1.71–1.68 (m, 2 H), 1.60–1.58 (m, 1 H), 1.39–1.30 (m, 2 H), 1.20–1.14 (m, 3 H), 0.93–0.90 (m, 3 H), 0.75–0.69 (m, 3 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 168.3, 168.0, 167.4, 166.9, 160.0, 143.2, 142.9, 137.5, 135.8, 135.1, 134.8, 133.1, 131.4, 131.2, 129.5, 129.3, 129.0, 128.7, 128.4, 128.1, 128.0, 127.9, 127.5, 127.3, 127.1, 127.0, 126.9, 125.7, 125.5, 125.1, 121.7, 121.6, 65.7, 64.6, 63.6, 48.1, 47.4, 47.1, 33.5, 32.0, 31.9, 31.6, 26.6, 26.2, 24.5, 23.8, 18.7, 18.5, 17.9, 8.7 ppm. MS (ESI): *m*/*z* = 744 [M + 23]$^+$. $C_{39}H_{44}ClN_9O_3$ (722.29): calcd. C 64.85, H 6.14, N 17.45; found C 64.72, H 6.08, N 17.36.

***N*-{[1-(1-{Butyl[1-(4-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl]-amino}-1-oxo-3-phenylpropan-2-yl)-1*H*-1,2,3-triazol-4-yl]methyl}-1-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-carboxamide (12d):** White solid (0.27 g, 72%); m.p. 98–100 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.77–7.73 (m, 1 H), 7.68 (d, *J* = 9.5 Hz, 1 H), 7.55–7.53 (m, 2 H), 7.48–7.46 (m, 2 H), 7.44–7.43 (m, 4 H), 7.41–7.39 (m, 2 H), 7.33 (s, 1 H), 7.27 (d, *J* = 8 Hz, 1 H), 7.21 (d, *J* = 8.5 Hz, 1 H), 6.82 (d, *J* = 9.5 Hz, 1 H), 6.18 (d, *J* = 8 Hz, 0.5 H), 5.94 (s, 0.5 H), 5.91 (d, *J* = 8 Hz, 0.5 H), 5.54 (s, 0.5 H), 4.71–4.70 (m, 2 H), 3.79–3.77 (m, 1 H), 3.34–3.25 (m, 1 H), 2.58–2.57 (m, 3 H), 2.15 (s, 1 H), 1.87–1.83 (m, 2 H), 1.66–1.64 (m, 2 H), 1.59–1.56 (m, 2 H), 1.46–1.43 (m, 1 H), 1.35–1.29 (m, 2 H), 1.16–1.03 (m, 5 H), 0.80–0.77 (m, 2 H), 0.68–0.65 (m, 2 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 166.7, 166.6, 166.4, 166.3, 160.0, 143.4, 137.5, 135.8, 135.1, 134.0, 133.4, 133.1, 132.7, 132.1, 131.9, 130.4, 129.0, 128.9, 128.7, 128.0, 127.7, 127.5, 127.3, 125.5, 122.1, 122.0, 63.8, 63.6, 62.9, 60.8, 47.7, 47.0, 45.1, 33.6, 31.7, 31.1, 30.6, 24.4, 23.7, 19.0, 18.9, 12.5, 12.3, 8.7 ppm. MS (ESI): *m*/*z* = 778 [M + 23]$^+$. $C_{39}H_{43}Cl_2N_9O_3$ (756.73): calcd. C 61.90, H 5.73, N 16.66; found C 61.84, H 5.67, N 16.58.

Unsymmetrical Bis(1,2,3-triazole)-Modified Peptidomimetics 19: The amine (0.5 mmol) and aldehyde (0.5 mmol) were dissolved in MeOH (3 mL) and placed in a sealed tube. The resulting mixture was stirred at room temperature for 30 min. Then, *para*-azidobenzoic acid (0.5 mmol) and isocyanide (0.5 mmol) were added, and the mixture was stirred for 24 h. Then, the corresponding aniline (0.55 mmol), diketene (0.55 mmol), and DBU (0.55 mmol) were added to the seal tube, and the reaction temperature was raised to 80 °C for 24 h. The solvent was removed in vacuo, and the residue was purified by column chromatography (hexanes/ethyl acetate, 3:1) to give intermediate **17**. To a solution of compound **17** (0.5 mmol) and Ugi products **18** (0.5 mmol) in MeOH (2 mL) were added Et$_3$N (0.5 mmol) and CuI (0.1 mmol). The reaction mixture was stirred at 40 °C for 8 h. The solvent was removed in vacuo, and the residue was purified by column chromatography (hexanes/ethyl acetate, 2:1).

1-(4-{(4-Chlorophenyl)-[(4-chlorophenyl)cyclohexylcarbamoylmethyl]carbamoyl}phenyl)-*N*-(1-{1-[(cyclohexylcarbamoylphenylmethyl)-phenylcarbamoyl]-2-phenylethyl}-1*H*-1,2,3-triazol-4-ylmethyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide (19a): White solid (0.27 g, 48%); m.p. 142–146 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 9.12 (s, 1 H), 8.08 (s, 1 H), 7.93 (s, 1 H), 7.73 (d, *J* = 9 Hz, 1 H), 7.64 (d, *J* = 7.5 Hz, 1 H), 7.43–7.37 (m, 6 H), 7.32–7.25 (m, 7 H), 7.17–7.13 (m, 3 H), 7.01 (d, *J* = 8 Hz, 3 H), 6.66 (d, *J* = 7.5 Hz, 1 H), 6.44 (s, 1 H), 6.15 (s, 1 H), 5.48 (d, *J* = 8.5 Hz, 1 H), 3.88–3.85 (m, 1 H), 2.68 (s, 3 H), 2.50 (s, 2 H), 2.15 (d, *J* = 7.5 Hz, 1 H), 1.84 (d, *J* = 7.5 Hz, 1 H), 1.65 (d, *J* = 8.5 Hz, 1 H), 1.63–1.57 (m, 4 H),

1.40–1.35 (m, 4 H), 1.27 (s, 2 H), 1.20–1.16 (m, 3 H), 1.06–1.03 (m, 2 H), 0.92–0.87 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6, 165.1, 158.4, 146.2, 139.4, 137.1, 134.5, 132.0, 130.9, 129.3, 128.5, 128.4, 127.9, 127.6, 124.1, 120.8, 120.0, 118.4, 115.9, 63.9, 63.0, 48.1, 31.8, 28.7, 24.4, 23.7, 20.3, 8.8 ppm. MS (ESI): *m*/*z* = 1146 $[M + 23]^+$. $C_{63}H_{63}Cl_2N_{11}O_5$ (1125.17): calcd. C 67.25, H 5.64, N 13.69; found C 67.08, H 5.56, N 13.60.

***N*-{[1-(1-{[1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl](4-chlorophenyl)amino}-1-oxo-3-phenylpropan-2-yl)-1*H*-1,2,3-triazol-4-yl]methyl}-1-(4-{[2-(cyclohexylamino)-2-oxo-1-phenylethyl](phenyl)carbamoyl}phenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide (19b):** White solid (0.24 g, 46%); m.p. 136–140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64–7.61 (m, 2 H), 7.52 (d, *J* = 8.5 Hz, 2 H), 7.45 (s, 2 H), 7.39–7.37 (t, *J* = 7 Hz, 1 H), 7.32–7.22 (m, 9 H), 7.11 (d, *J* = 7.5 Hz, 3 H), 7.04 (s, 4 H), 6.92 (d, *J* = 7.5 Hz, 1 H), 6.46 (s, 1 H), 6.26 (s, 1 H), 6.21 (s, 1 H), 5.67 (d, *J* = 8 Hz, 1 H), 4.72–4.68 (m, 2 H), 4.35 (d, *J* = 11 Hz, 1 H), 3.92–3.86 (m, 1 H), 2.49 (s, 3 H), 1.99–1.84 (m, 4 H), 1.69–1.59 (m, 3 H), 1.36 (s, 9 H), 1.17–1.09 (m, 3 H), 0.91–0.90 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 167.5, 167.2, 160.0, 143.1, 139.6, 137.4, 136.9,135.7, 135.1, 134.9, 134.2, 133.5, 131.4, 130.8, 129.9, 129.4, 129.3, 128.9, 128.3, 127.6, 127.4, 126.6, 123.3, 121.7, 67.9, 65.7, 63.8, 50.5, 48.0, 33.5, 31.8, 28.7, 27.6, 25.5, 24.5, 23.8, 23.7, 19.1, 18.4, 8.7 ppm. MS (ESI): *m*/*z* = 1052 $[M + 23]^+$. $C_{58}H_{64}ClN_{11}O_5$ (1030.67): calcd. C 67.59, H 6.26, N 14.95; found C 67.67, H 6.32, N 14.83.

***N*-{[1-(1-{[2-(Cyclohexylamino)-1-(furan-2-yl)-2-oxoethyl](phenyl)amino}-1-oxo-3-phenylpropan-2-yl)-1*H*-1,2,3-triazol-4-yl]methyl}-1-(4-{[1-(cyclohexylamino)-3-methyl-1-oxobutan-2-yl](phenyl)carbamoyl}phenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide (19c):** White solid (0.23 g, 45%); m.p. 110–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65–7.63 (m, 2 H), 7.43–7.36 (m, 4 H), 7.32–7.28 (m, 5 H), 7.24–7.23 (m, 2 H), 7.21–7.20 (m, 5 H), 7.04 (d, *J* = 7.5 Hz, 1 H), 6.77 (d, *J* = 7.5 Hz, 1 H), 6.89 (d, *J* = 7.5 Hz, 1 H), 6.75 (s, 1 H), 6.43 (s, 1 H), 6.26 (s, 1 H), 6.18 (d, *J* = 1 Hz, 2 H), 5.68 (d, *J* = 8 Hz, 1 H), 4.71 (d, *J* = 5.5 Hz, 2 H), 4.57 (d, *J* = 5.5 Hz, 1 H), 3.84–3.82 (m, 1 H), 2.57 (s, 3 H), 2.42–2.41 (m, 1 H), 1.97–1.89 (m, 4 H), 1.73–1.61 (m, 5 H), 1.41–1.36 (m, 4 H), 1.28–1.21 (m, 7 H), 1.05–1.01 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.4, 167.9, 165.9, 164.4, 159.9, 145.4, 143.2, 142.5, 138.5, 137.6, 136.6, 135.7, 135.4, 134.9, 134.1, 132.7, 131.9, 131.4, 129.9, 129.1, 128.7, 128.3, 128.0, 127.6, 123.7, 121.8, 120.0, 109.8, 76.3, 76.0, 75.8, 69.2, 63.8, 57.7, 48.0, 47.2, 33.5, 32.0, 31.8, 25.8, 24.5, 23.7, 18.9, 18.8, 8.7 ppm. MS (ESI): *m*/*z* = 1034 $[M + 23]^+$. $C_{58}H_{65}N_{11}O_6$ (1012.22): calcd. C 68.82, H 6.47, N 15.22; found C 68.91, H 6.53, N 15.10.

***N*-{[1-(1-{[1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl](4-chlorophenyl)amino}-1-oxo-3-phenylpropan-2-yl)-1*H*-1,2,3-triazol-4-yl]methyl}-1-(4-{[2-(cyclohexylamino)-1-(furan-2-yl)-2-oxoethyl](phenyl)carbamoyl}phenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide (19d):** White solid (0.22 g, 43%); m.p. 140–144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63–7.62 (m, 2 H), 7.53–7.46 (m, 2 H), 7.38–7.37 (m, 2 H), 7.33–7.28 (m, 8 H), 7.12–7.08 (m, 4 H), 7.03 (s, 2 H), 6.92 (d, *J* = 8 Hz, 1 H), 6.47 (s, 1 H), 6.39 (d, *J* = 3.5 Hz, 1 H), 6.35 (s, 1 H), 6.31–6.30 (m, 1 H), 6.25 (s, 1 H), 5.90 (d, *J* = 7.5 Hz, 1 H), 4.74–4.70 (m, 2 H), 4.35 (d, *J* = 11 Hz, 1 H), 3.89–3.86 (m, 1 H), 2.54 (s, 3 H), 1.95–1.92 (m, 3 H), 1.72–1.62 (m, 9 H), 1.37 (s, 9 H), 1.20–1.17 (m, 3 H), 0.93–0.91 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 167.5, 167.2, 164.9, 160.0, 146.4, 143.0, 142.3, 137.9,137.5, 136.0, 135.7, 135.3, 135.0, 134.2, 132.8, 131.3, 130.8, 130.0, 128.9, 128.4, 128.0, 127.4, 123.5, 121.7, 111.8, 110.0, 63.8, 58.7, 50.5, 48.1, 33.5, 31.8, 27.6, 25.5, 24.5, 23.8, 19.1, 18.4, 8.7 ppm. MS (ESI): *m*/*z* = 1042 $[M + 23]^+$. $C_{56}H_{62}ClN_{11}O_6$ (1020.63): calcd. C 65.90, H 6.12, N 15.10; found C 65.83, H 6.05, N 15.22.

***N*-{[1-(1-{[1-(*tert*-Butylamino)-3-methyl-1-oxobutan-2-yl](4-chlorophenyl)amino}-3-methyl-1-oxobutan-2-yl)-1*H*-1,2,3-triazol-4-yl]methyl}-1-(4-{[2-(cyclohexylamino)-1-(furan-2-yl)-2-oxoethyl](phenyl)carbamoyl}phenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide (19e):** White solid (0.22 g, 45%); m.p. 120–124 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.93 (s, 1 H), 7.76–7.70 (m, 2 H), 7.55–7.53 (m, 2 H), 7.45–7.42 (t, *J* = 8.5 Hz, 2 H), 7.28–7.24 (m, 8 H), 7.12–7.10 (m, 4 H), 7.05 (s, 5 H), 6.21 (s, 2 H), 5.68 (s, 1 H), 4.95 (d, *J* = 10.5 Hz, 1 H), 4.76 (d, *J* = 6 Hz, 2 H), 4.31 (d, *J* = 11 Hz, 1 H), 3.91–3.87 (m, 1 H), 2.56 (s, 3 H), 2.48–2.43 (m, 1 H), 2.00–1.82 (m, 6 H), 1.71–1.59 (m, 3 H), 1.36 (s, 10 H), 1.17–1.09 (m, 3 H), 0.891 (d, *J* = 6.5 Hz, 6 H), 0.73 (d, *J* = 6 Hz, 3 H), 0.56 (d, *J* = 6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.7, 168.6, 167.9, 167.3, 160.1, 143.9, 139.6, 137.4, 137.0, 135.8, 135.3, 134.9, 134.1, 133.5, 130.7, 130.0, 129.4, 129.3, 128.9, 128.7, 128.6, 127.6, 126.6, 123.3, 119.9, 67.4, 65.7, 65.2, 50.5, 48.0, 33.6, 32.3, 31.8, 27.6, 25.7, 24.5, 23.8, 23.7, 19.1, 18.5, 17.9, 17.4, 8.7 ppm. MS (ESI): *m*/*z* = 994 $[M + 23]^+$. $C_{52}H_{62}ClN_{11}O_6$ (972.59): calcd. C 64.22, H 6.43, N 15.84; found C 64.16, H 6.52, N 15.75.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra.

Acknowledgments

We thank Nanjing University of Science and Technology (NUST) research funding (grant number 2011ZDJH07) and the Jiangsu Province Key Laboratory of Fine Petrochemical Engineering (KF1101) for their financial support. We also thank the Analysis and Testing Center of Nanjing University of Science and Technology for assistance with the NMR spectroscopic analysis.

[1] a) S. S. Pujari, F. Seela, *J. Org. Chem.* **2012**, *77*, 4460–4465; b) S. S. Pujari, H. Xiong, F. Seela, *J. Org. Chem.* **2010**, *75*, 8693–8696; c) H. Xiong, F. Seela, *J. Org. Chem.* **2011**, *76*, 5584–5597.

[2] J. Guiard, B. Fiege, P. I. Kitov, T. Peters, D. R. Bundle, *Chem. Eur. J.* **2011**, *17*, 7438–7441.

[3] a) A. Ghorai, A. Gayen, G. Kulsi, E. Padmanaban, A. Laskar, B. Achari, C. Mukhopadhyay, P. Chattopadhyay, *Org. Lett.* **2011**, *13*, 5512–5515; b) Z. Ke, H.-F. Chow, M.-C. Chan, Z. Liu, K.-H. Sze, *Org. Lett.* **2012**, *14*, 394–397.

[4] a) N. Wang, Y. C. Feng, W. Shi, B. Zhao, P. Cheng, D. Z. Liao, S. P. Yan, *CrystEngComm* **2012**, *14*, 2769–2778; b) L. Tian, Z. Chen, A. Yu, H. B. Song, P. Cheng, *CrystEngComm* **2012**, *14*, 2032–2039; c) A. Kumar, K. Lib, C. Z. Cai, *Chem. Commun.* **2011**, *47*, 3186–3188; d) S. Warsink, R. M. Drost, M. Lutz, A. L. Spek, C. J. Elsevier, *Organometallics* **2010**, *29*, 3109–3116; e) E. M. Schuster, M. Botoshansky, M. Gandelman, *Angew. Chem.* **2008**, *120*, 4631; *Angew. Chem. Int. Ed.* **2008**, *47*, 4555–4558.

[5] a) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599.

[6] V. Aucagn, D. A. Leigh, *Org. Lett.* **2006**, *8*, 4505–4507.

[7] a) J. M. Aizpurua, I. Azcune, R. M. Fratila, E. Balentova, M. S. Aizpurua, J. I. Miranda, *Org. Lett.* **2010**, *12*, 1584–1587; b) B. C. Doak, M. J. Scanlon, J. S. Simpson, *Org. Lett.* **2011**, *13*, 537–539.

[8] H. Elamari, F. Meganem, J. Herscovici, C. Girard, *Tetrahedron Lett.* **2011**, *52*, 658–660.

[9] D. M. Beal, V. E. Albrow, G. Burslem, L. Hitchen, C. Fernandes, C. Lapthorn, L. R. Roberts, M. D. Selby, L. H. Jones, *Org. Biomol. Chem.* **2012**, *10*, 548–554.

[10] Z. Yuan, G. C. Kuang, R. J. Clark, L. Zhu, *Org. Lett.* **2012**, *14*, 2590–2593.
[11] a) V. P. Krivopalov, O. P. Shkurko, *Russ. Chem. Rev.* **2005**, *74*, 339–379; b) N. T. Pokhodylo, V. S. Matiychuk, M. D. Obushak, *J. Comb. Chem.* **2009**, *11*, 481–485.
[12] S. E. Howson, L. E. N. Allan, N. P. Chmel, G. J. Clarkson, R. Gorkum, P. Scott, *Chem. Commun.* **2009**, *13*, 1727–1729.
[13] a) W. S. Horne, M. K. Yadav, C. D. Stout, M. R. Ghadiri, *J. Am. Chem. Soc.* **2004**, *126*, 15366–15367; b) Y. L. Angell, K. Burgess, *Chem. Soc. Rev.* **2007**, *36*, 1674–1689; c) S. Beraa, G. G. Zhanel, F. Schweizera, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3031–3035; d) D. S. Pedersen, A. Abell, *Eur. J. Org. Chem.* **2011**, 2399–2411.
[14] a) V. G. Nenajdenko, A. V. Gulevich, N. V. Sokolova, A. V. Mironov, E. S. Balenkova, *Eur. J. Org. Chem.* **2010**, 1445–1449; b) N. V. Sokolova, G. V. Latyshev, N. V. Lukashev, V. G. Nenajdenko, *Org. Biomol. Chem.* **2011**, *9*, 4921–4926; c) T. F. Niu, C. Cai, L. Yi, *Helv. Chim. Acta* **2012**, *95*, 87–99.
[15] T. F. Niu, L. Gu, W. B. Yi, C. Cai, *ACS Comb. Sci.* **2012**, *14*, 309–315.

Received: August 13, 2012
Published Online: October 22, 2012

