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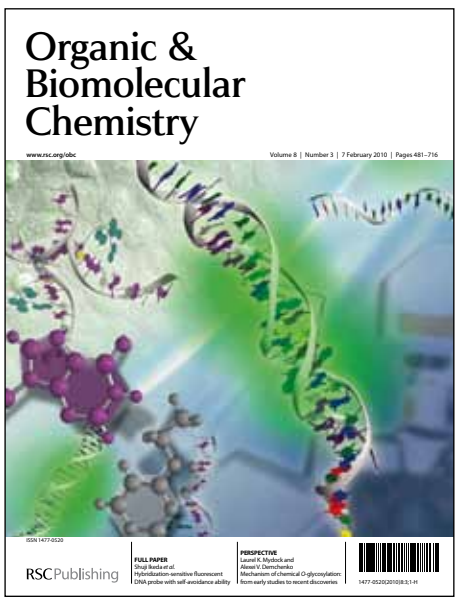

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Chemoselective Preparation of 1,2,3-triazole and Isoxazoles Bisfunctional Derivatives and Its Application in Peptidomimetic Synthesis

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A novel kind of bisfunctional nitrogen heterocycles containing both 1,2,3-triazole and isoxazole scaffolds has been prepared. The protocol utilized alkynyl substituted amines as the bifunctional linkers to conjunct a copper-free triazole synthesis with a hypervalent iodine-mediated isoxazole cycloaddition through chemoselective process. This method also been exemplified in construction of bisfunctional-modified peptidomimetics by combing of three reactions in sequential procedure. The metal free straightforward process may be of biological applications. In addition, all of the compounds were analysed by Lapinski's rule-of-five which is expected to help drug discovery.

Introduction

Nitrogen heterocycles have been received much attention for biological probes and pharmaceutical lead discovery. 1,2,3-triazole and isoxazole scaffolds form a major class of nitrogen heterocycles which have generated considerable synthetic interest due to their occurrence in diverse natural products and notable biological activity. It is reported that, 1,2,3-triazoles can act as anticancer medications[1], antibacterial[2], HIV-1 protease inhibitors[3], and ntihistaminic[4]. While, isoxazoles are core components of many natural products such as ibotenic acid[5], muscimol[6], isoxazole-4-carboxylic acid[7] and drugs like valdecoxib[8], leflunomide[9], cloxacillin[10]. Several therapeutically active compounds containing both 1,2,3-triazoles and another heterocycles such as thiazole and isoxazole have been reported.[11] The significant biological activities observed for 1,2,3-triazole and isoxazoles suggested potential bioactivity and pharmaceutically active if these two scaffolds could be combined in one molecule.

However, an efficient synthesis of such bisfunctional molecules containing 1,2,3-triazole and isoxazole scaffolds from readily accessible starting materials still remains elusive. Recently, some chemoselective sequential reactions have been developed to synthesis unsymmetrical bisfunctional molecules which could achieve complete regiochemical control of the coupling reactions in a timely and costeffective manner, while providing broad functional group tolerance.[12] These methods depend on the difference of the reactivities of bifunctional linkers such as bialkyne or biazide which leads to chemoselectivity in sequential ligation reactions. Our group also developed an efficient chemoselective method to generate alkynyl substituted 1,2,3-trazoles (Fig.1).[13] The protocol utilized alkynyl substituted amines as the bifunctional linkers reacting with azides as well as diketene which could undergo a three-component cycloaddition to form 5-methyl-1*H*-1,2,3-triazole. There were non Husigen 1,3-dipolar cycloaddition products were found, each resulting 1,2,3-trazoles scaffold contains an alkyne group that provides further opportunities to generate complex bisfunctional molecules through chemoselective sequential reactions.

Herein, we demonstrated an efficient chemoselective synthesis of complex nitrogen heterocycles containing both 1,2,3-triazole and isoxazoles motifs. In addition, we also explored and took advantage of this chemoselective reaction in order to access bisfunctional modified peptidomimetics by tandem multicomponent reactions (MCRs). Peptidomimetics are of primordial importance for the study of functions and structures of proteins in chemical biology and can in many cases be used as drug molecules.[3,14] However, this synthesis is traditionally attained through a inefficient reaction , requiring many protecting groups. In modern therapeutic discovery, the rapid assembly of drug without protecting groups is gaining considerable interest. Tandem multicomponent reactions are one type of the approaches to address this challenge.[15]

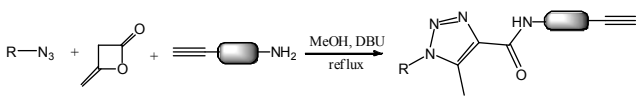
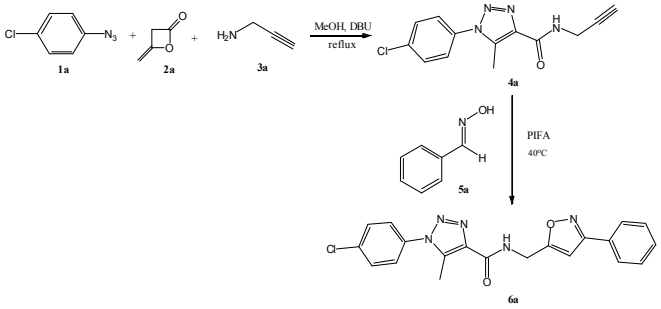


Fig.1 Chemoselective synthesis of monotriazoles

Results and Discussion

The key feature in this strategy is to find a suitable method for the construction of isoxazoles building blocks. Taking into account recent reports of on the isoxazoles synthesis, we focused on the

synthesis of the isoxazoles structure by hypervalent iodine-mediated cycloaddition of nitrile oxides to alkynes (scheme 1).[16] Although many transition metals mediated isoxazoles syntheses have been reported[17] not all are viable in such a combination since the residual metal catalysts could be toxic to both bacterial and mammalian cells.[18] Therefore from a biological perspective the transition metals approach is not a preferred catalytic method favored. In our initial experiment, we synthesized alkynyl substituted 1,2,3-trazoles **4a** by using 2-propynylamine **3a** (all components see Figure 2) as bisfunctional linkers which mixed with 1.1 equiv azides **1a** and 1.1 equiv diketene **2a** under base catalyst (1.1 equiv DBU) conditions in MeOH at reflux. Subsequently, according to the report of Delft group, we employed phenyliodine bis(trifluoroacetate) (PIFA, 1.5 equiv) as catalyst to react with benzaldoxime **5a** (1.5 equiv) led to the isolation of bisfunctional molecule **6a** in 83% yield after 1.5 h at 40°C (71% total yield). However, the alkyl azides can not work in this reaction.



Scheme 1. Chemoselective synthesis of 1,2,3-triazole and isoxazoles containing bisfunctional molecule

Transparent plate crystals of **6a** were obtained. A small single crystal was measured by X-ray crystallography (Figure 3). The crystal structure clearly shows compound **6a** with both 1,2,3-triazole and isoxazoles scaffolds.

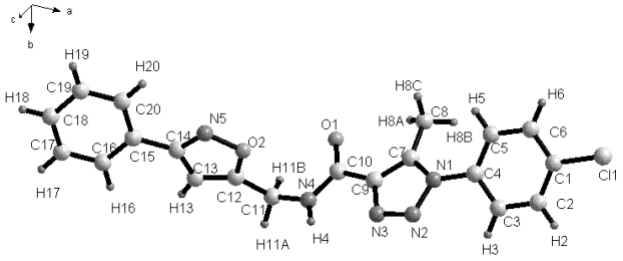
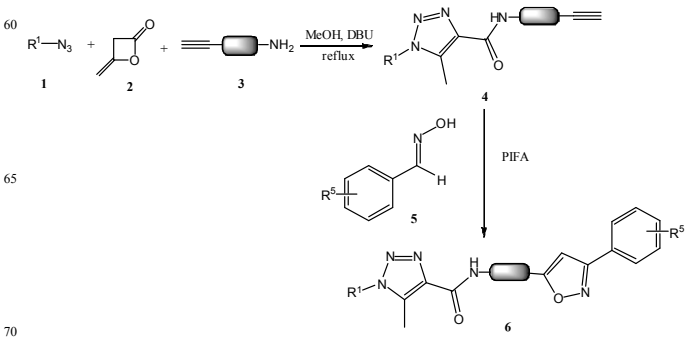
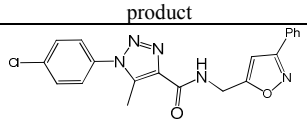
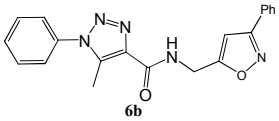
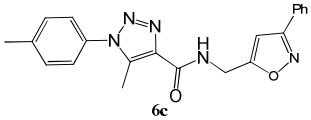
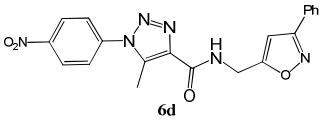
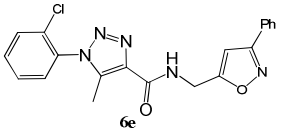
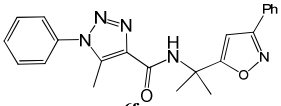
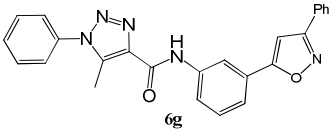
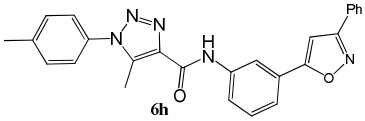
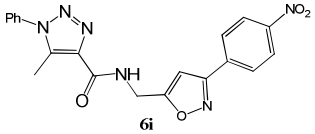
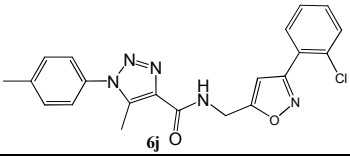


Figure 3. X-ray diffraction measurement of **6a**.

It is noteworthy that, our system for isoxazoles synthesis is more convenient than that literature reported. For example, in our process only MeOH was used as solvent, there is no addition was added. However, according to the report of Delft group[16(a)] and Ciufolini group[20], another amount of water or TFA was needed. In addition, the reaction consumes shorter time and less catalyst. That means the 1,2,3-trazoles modified alkynyl **4a** is more active than normal alkynyl for the isoxazoles synthesis. It is presumably because of the electronic effects. For electron-withdrawing alkynyl will give significant high yields. There is an amido bond in triazole modified alkyne, which may have electron-withdrawing effect.

Table 1. Scope of chemoselective sequential reaction for the synthesis of bisfunctional nitrogen heterocycles combining both 1,2,3-triazole and isoxazoles motifs.



Entry	product	Yield[a]	Yield[b]
1	 **6a**	83	71
2	 **6b**	82	58
3	 **6c**	82	70
4	 **6d**	84	71
5	 **6e**	83	61
6	 **6f**	76	65
7	 **6g**	85	65
8	 **6h**	84	71
9	 **6i**	89	65
10	 **6j**	80	66

[a] The second step isolated yield [b] The total isolated yield

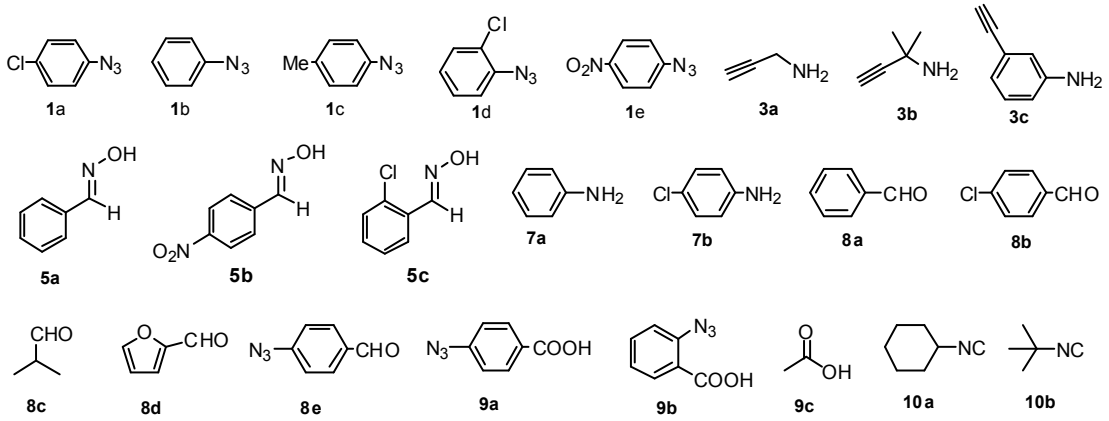
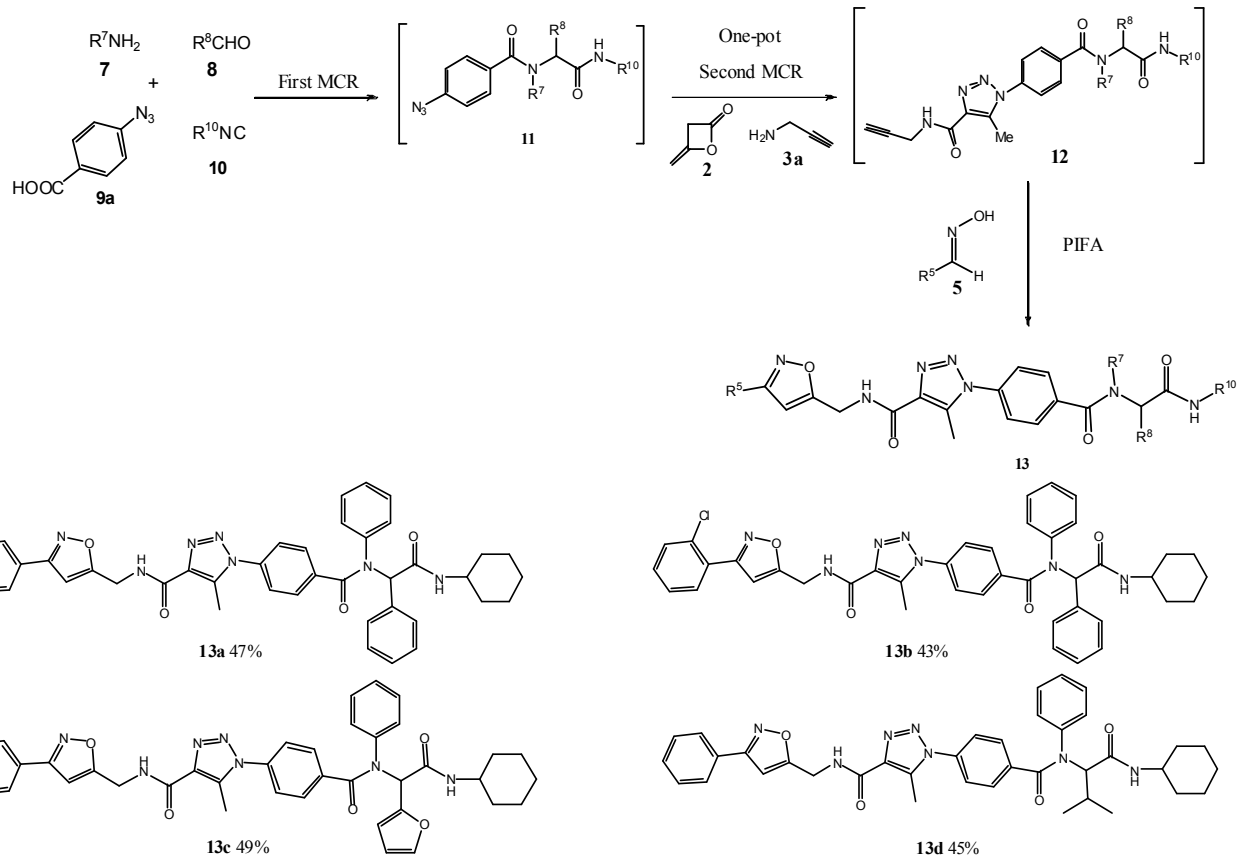


Figure 2. Components involved in the described chemoselective sequential reactions.

With these optimized conditions in hand, the scope of the reaction is illustrated by the examples in Table 1. To our delight, both aromatic and aliphatic alkynyl substituted amines were used and gave satisfactory yields. However, the electronic properties of the alkynyl substituted anilines for the second step had a significant influence on the yield of the reaction. The electron-donating 2- methylbut-3-yn-2-amine **3b** gave lower yield than 2-propynylamine **3a** (table 1, entries 2, 6). Moreover, it was shown previously that different oximes have various reactivities. The electron-deficient 4-nitro- benzaldoxime **5b** gave higher yield than others for the isoxazoles synthesis (table 1, entries 2, 9, 10). The steric effects also had a significant influence on the yields of both first and second cycloadditions (Table 1, entries 2, 3, 5, 10). However, the electronic properties of the substituted azides had a slight influence on the yields of the reaction (Table 1, entries 1-4) .

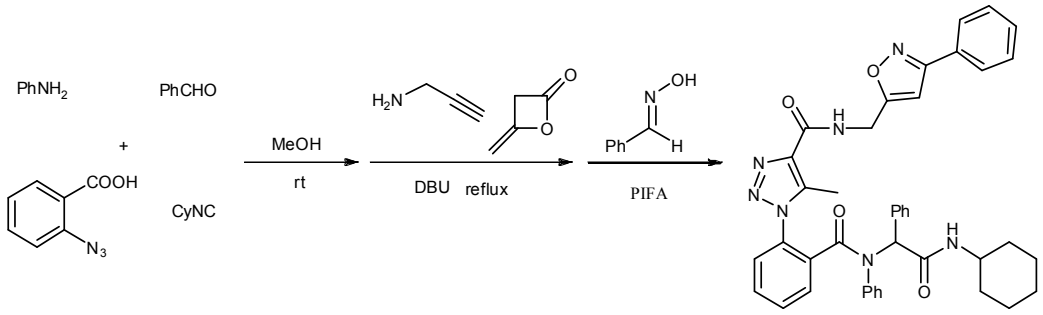
Having demonstrated the viability of chemoselective sequential procedures for the 1,2,3-triazole and isoxazoles motifs containing bisfunctional heterocycles generation, we next investigated bisfunctional-modified peptidomimetics synthesis. Recently, our group discovered a six components reaction to generate 1,2,3-triazole-modified peptidomimetics by conjugating two MCRs in one pot.[19] The chemoselective bisfunctional synthesis opens up an opportunity to introduce this six components reaction to generate complex bisfunctional-modified peptidomimetics by combining three reactions in sequence process. 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.[21] Therefore, Para-azido-benzoic acid **9a** was chosen as the "bridge



Scheme 2 Bisfunctional-modified peptidomimetic synthesis by combination three reactions in sequence proces

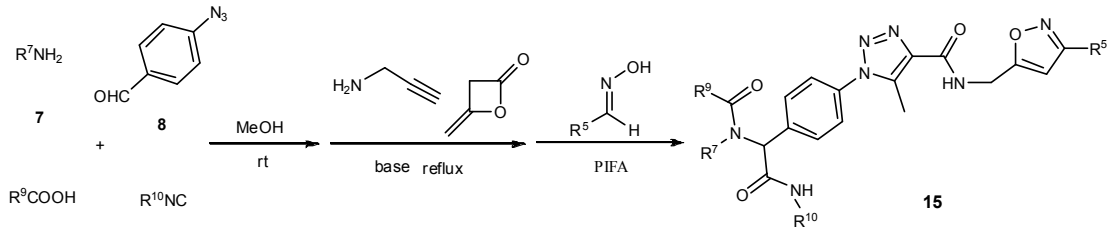
molecule" to combine Ugi 4CR with 3CR monotriazole synthesis to construct monotriazole-modified peptidomimetics blocks. The Ugi reaction was preferred as the first MCR. Based on classical reports on Ugi 4CR, **9a** was reacted with **7**, **8**, and 10 in MeOH at room temperature to form intermediate **11**. Then without isolation of the intermediate, a one-pot combination with 1.1 equiv of **3a**, 1.1 equiv of diketene **2**, and 1.1 equiv of DBU as the second MCR at reflux, led to the intermediate monotriazole-modified peptidomimetics **12**. Next subsequent hypervalent iodine-mediated cycloaddition with oxime gave a 1,2,3-triazole and isoxazoles containing bisfunctional-modified peptidomimetic **13** in good yield (Scheme 3). In addition, the α,β-unsaturated functional group, such as furaldehyde was tolerate in such process (**13c**). The tandem multicomponent reactions open an opportunity to generate such bisfunctional-modified peptidomimetic in a rapid and efficient process.

To further explore the possible conformational preorganization effect of bifunctional-modified peptidomimetics, other kinds of azido containing bifunctional molecules have been used to instead of para-azido-benzoic acid as "bridge molecule" to combine the three reactions (Table 2). 2-azidobenzoic acid **9b** was then incorporated in this combination with no difficulty as a bridge molecule (Scheme 3). However, steric effects were indicated by the slight reduction in yield. Encouraged by these results, we attempted to carry out the analogous reaction with 4-azidobenzaldehyde **8e** (Scheme 4). Thus, a triazole and isoxazoles bisfunctional-modified peptidomimetics containing side-chain were successfully synthesized.



14a 39%

Scheme 3 Chemoselective sequential synthesis of bisfunctional-modified peptidomimetics by using 2-azidobenzoic acid as a bridge molecule



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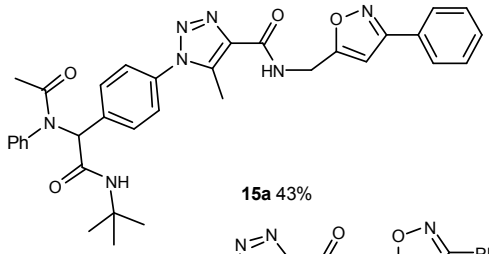
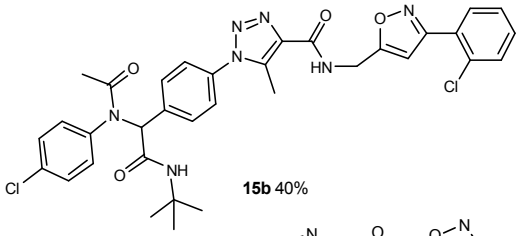
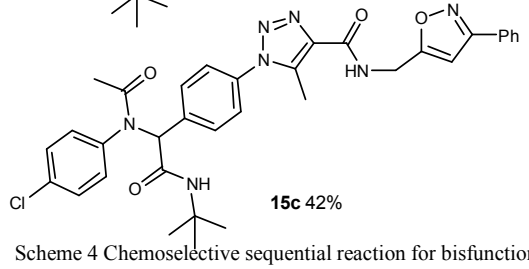


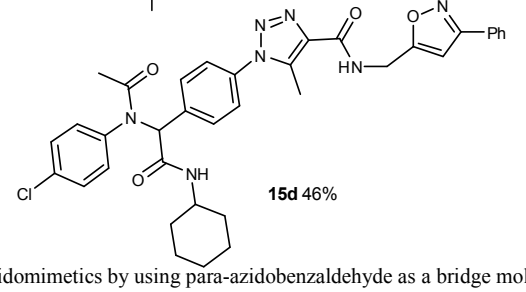
15a 43%



15b 40%



15c 42%



15d 46%

Scheme 4 Chemoselective sequential reaction for bisfunctional-modified peptidomimetics by using para-azidobenzaldehyde as a bridge molecule

Finally, to evaluate this synthetic method, a Lipinski rule-of-five analysis was performed to evaluate the druglikeness of all compounds (Table 2). It was found that the products **6** were within the parameters set by Lipinski. However, for the peptidomimetics, only parameters NHD adhered to Lapinski's rule-of-five. All of the hydrogen bond acceptors for products **12**, **13**, **14** are 11 which is one more than the Lapinski's Rule. The MW of all the peptidomimetics are about 600, which also do not

adhered the Rule of Lapinski. The result suggesting that compounds **6** is very appropriate for highthroughput screening to discover drug leads and biological probes.

Table 4. A "Lapinski type" analysis of the physical properties

Entry	Product	MW[a]	NHD[b]	NHA[c]	tPSA[d]	Log *P*[e]
1	**6a**	393	1	7	78.65	4.03
2	**6b**	359	1	7	78.65	3.38
3	**6c**	373	1	7	78.65	4.15
4	**6d**	404	1	7	130.46	8.52
5	**6e**	393	1	7	78.65	4.11
6	**6f**	387	1	7	78.65	3.92
7	**6g**	421	1	7	78.65	5.45
8	**6h**	435	1	7	78.65	5.58
9	**6i**	404	1	7	130.46	8.33
10	**6k**	407	1	7	78.65	4.22
11	**13a**	693	2	11	128.06	6.35
12	**13b**	727	2	11	128.06	7.71
13	**13c**	727	2	11	128.06	6.95
14	**13d**	659	2	11	128.06	6.11
15	**14a**	693	2	11	106.47	6.35
16	**15a**	605	2	11	106.47	4.08
17	**15b**	673	2	11	106.47	5.88
18	**15c**	639	2	11	106.47	5.26
19	**15d**	665	2	11	106.47	5.23

[a] Molecular Weight. [b] Number of H-donors. [c] Number of H-acceptors. [d] polar surface area were given by ChemBioOffice 2008. [e] Partition coefficient was tested in *n*-octyl alcohol–water system by HPLC analysis.

Conclusions

In conclusion, we have described an efficient chemoselective approach to synthetize a novel bisfunctional molecules which containing both 1,2,3-triazole and isoxazole motifs. The Lapinski type analysis of the physical properties was given. Our strategy employed alkynyl substituted amines as bifunctional linkers which could generate 1,2,3-trazoles and isoxazoles by copper-free cycloaddition and hypervalent iodine-mediated cycloaddition respectively. In particular, this methodology is suitable for synthetize unsymmetrical bisfunctional-modified peptidomimetics by the combination of mlticomponent reactions in sequence process, which allow direct access to complex structures from simple building blocks and fully lives up to the principle of "Green Chemistry" and atom economy. In addition, the metal free process suggests this chemoselective reaction could be a valuable tool for drug discovery.

Experimental section

General

All chemicals were commercially available and used without further purification. Analytical thin-layer chromatography were performed on glass plates precoated with silica gel impregnated with a fluorescent indicator (254 nm). The plates were visualized by exposure to ultraviolet light. 1H NMR spectra were recorded on Bruker DRX500 (500 MHz) and 13C NMR spectra on Bruker DRX500 (125 MHz) spectrometer. Mass spectra were taken on a Finnigan TSQ Quantum－MS in strument in the electrospray ionization (ESI) mode. Elemental analyses were performed on a Yanagimoto MT3CHN recorder. The distribution of clog P was analyzed by high performance liquid chromatograph (HPLC) on Agilent 1120 (Eclipse XDB-C18, G1214B VWD). Melting points were determined uncorrected.

Typical experimental procedure

Preparation of bisfunctional molecules 6. Azides (2.0 mmol), diketene (2.2 mmol), alkynyl substituted amines (2.2 mmol), DBU (2.2 mmol) in a seal tube with 4 mL MeOH and stirred at reflux for 8 hours. Then, the solvent was removed in vacuo and the residue was purified by column chromatography (hexanes / ethyl acetate 2/ 1). Then to a solution of compound **5** (0.5 mmol), oxime (0.75 mmol) and phenyliodine bis(trifluoroacetate) (0.75 mmol) in 3 mL MeOH. The reaction mixture was stirred at 40℃ 1.5 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatograp hy (hexanes / ethyl acetate 2/ 1).

1-(4-chlorophenyl)-5-methyl-N-((3-phenylisoxazol-5-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (6a). White solid, M.p. 176-178°C. Yield: 0.14 g, 71%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.91 (t, J = 6 Hz, 1H), 7.81-7.79 (m, 2H), 7.58-7.57 (m, 2H), 7.46-7.42 (m, 5H), 6.59 (s, 1H), 4.86 (d, J = 6 Hz, 2H), 2.65 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 161.6, 160.2, 137.2, 136.2, 135.3, 132.9, 129.0, 127.9, 127.3, 125.8, 125.5, 99.4, 33.9, 8.9; ESI-MS: m/z =394 $[M+1]^+$. Found: C, 60.86; H, 4.01; N, 17.64%. Calc. for $C_{20}H_{16}ClN_5O_2$, C, 60.99; H, 4.09; N, 17.78%.

5-methyl-1-phenyl-N-((3-phenylisoxazol-5-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (6b). White solid, M.p. 134-136°C. Yield: 0.10 g, 58%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.95 (t, J = 6 Hz, 1H), 7.81-7.78 (m, 2H), 7.62-7.58 (m, 3H), 7.48-7.44 (m, 5H), 6.60 (s, 1H), 4.86 (d, J = 6 Hz, 2H), 2.66 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 161.6, 160.4, 137.0, 136.2, 134.5，129.1, 129.0, 128.7, 127.9, 125.9, 124.3, 99.4, 8.8; ESI-MS: m/z =360 $[M+1]^+$. Found: C, 66.66; H, 4.65; N, 19.35%. Calc. for $C_{20}H_{17}N_5O_2$, C, 66.84; H, 4.77; N, 19.49%.

5-methyl-N-((3-phenylisoxazol-5-yl)methyl)-1-p-tolyl-1H-1,2,3-triazole-4-carboxamide (6c). White solid, M.p. 146-148°C. Yield: 0.13 g, 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.80-7.79 (m, 2H), 7.45-7.43 (t, J = 4 Hz, 3H), 7.38-7.28 (m, 4H), 6.59 (s, 1H), 4.86 (d, J = 6.5 Hz, 2H), 2.62 (s, 3H), 2.47 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 161.6, 160.5, 139.4, 136.9, 136.2, 132.0, 129.3, 129.0, 127.9, 125.9, 124.1, 99.4, 33.9, 20.3, 8.7; ESI-MS: m/z =374 $[M+1]^+$. Found: C, 67.38; H, 5.26; N, 17.57%. Calc. for $C_{21}H_{19}N_5O_2$, C, 67.55; H, 5.13; N, 18.76%.

5-methyl-1-(4-nitrophenyl)-N-((3-phenylisoxazol-5-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (6d). White solid, M.p. 166-168°C. Yield: 0.14 g, 71%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, J = 9 Hz, 2H), 7.96-7.94 (t, J = 6 Hz, 1H), 7.80-7.73 (m, 4H), 7.46-7.44 (t, J = 3 Hz, 3H), 6.59 (s, 1H), 4.86 (d, J = 6.5 Hz, 2H), 2.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 161.6, 159.9, 147.3, 139.3, 137.7, 136.3, 129.1, 127.9, 125.8, 124.7, 124.2, 99.5, 33.9, 9.0; ESI-MS: m/z =405 $[M+1]^+$. Found: C, 59.26; H, 4.11; N, 20.63%. Calc. for $C_{20}H_{16}N_6O_4$, C, 59.40; H, 3.99; N, 20.78%.

1-(2-chlorophenyl)-5-methyl-N-((3-phenylisoxazol-5-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (6e). White solid, M.p. 124-126°C. Yield: 0.12 g, 61%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12-8.10 (t, J = 6 Hz, 1H), 7.80-7.78 (m, 2H), 7.63-7.62 (m, 1H), 7.57-7.54 (m, 1H), 7.50-7.47 (m, 1H), 7.44-7.42 (m, 4H), 6.60 (s, 1H), 4.86 (d, J = 6 Hz, 2H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 161.6, 160.3, 138.0, 136.5,

132.1, 131.2, 130.8, 129.7, 129.0, 128.2, 127.9, 127.1, 125.9, 99.4, 33.9, 8.1; ESI-MS: m/z =394 $[M+1]^+$. Found: C, 60.91; H, 4.14; N, 17.70%. Calc. for $C_{20}H_{16}ClN_5O_2$, C, 60.99; H, 4.09; N, 17.78%.

5-methyl-1-phenyl-N-(2-(3-phenylisoxazol-5-yl)propan-2-yl)-1H-1,2,3-triazole-4-carboxamide (6f). White solid, M.p. 180-182°C. Yield: 0.13 g, 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83-7.81 (m, 2H), 7.63 (s, 1H), 7.58-7.56 (m, 2H), 7.45-7.40 (m, 5H), 2.58 (s, 3H), 1.93 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 161.3, 159.5, 137.6, 136.0, 135.2, 133.0, 129.0, 128.2, 127.8, 125.9, 125.5, 97.5, 50.9, 26.4, 8.7; ESI-MS: m/z =389 $[M+1]^+$. Found: C, 68.07; H, 5.54; N, 17.97%. Calc. for $C_{22}H_{21}N_5O_2$, C, 68.20; H, 5.46; N, 18.08%.

5-methyl-1-phenyl-N-(3-(3-phenylisoxazol-5-yl)phenyl)-1H-1,2,3-triazole-4-carboxamide (6g). White solid, M.p. 180-182°C. Yield: 0.14 g, 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.34 (s, 1H), 7.89 (d, J = 6 Hz, 2H), 7.75-7.60 (m, 5H), 7.50-7.48 (m, 6H), 6.92 (s, 1H), 2.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 162.0, 158.4, 137.5, 137.4, 136.6 134.5, 129.2, 129.0, 128.8, 127.9, 127.3, 125.9, 124.3, 120.6, 120.3, 116.0, 97.0, 8.9; ESI-MS: m/z =422 $[M+1]^+$. Found: C,71.11; H, 4.39; N, 16.75%. Calc. for $C_{25}H_{19}N_5O_2$, C, 71.25; H, 4.54; N, 16.62%.

1-(2-chlorophenyl)-5-methyl-N-((3-phenylisoxazol-5-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (6h). White solid, M.p. 184-186°C. Yield: 0.15 g, 71%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.35 (s, 1H), 7.89 (d, J = 6 Hz, 2H), 7.75-7.66 (m, 2H), 7.50-7.38 (m, 7H), 6.93 (s, 1H), 2.69 (s, 3H), 2.49 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 162.0, 158.5, 139.5, 137.5, 137.3 136.6, 132.0, 129.3, 129.0, 128.8, 128.2, 127.9, 127.3, 125.9, 124.1, 120.6, 120.3, 116.0, 97.0, 20.3, 8.8; ESI-MS: m/z =436 $[M+1]^+$. Found: C,71.85; H, 4.98; N, 15.93%. Calc. for $C_{26}H_{21}N_5O_2$, C, 71.71; H, 4.86; N, 16.08%.

5-methyl-N-((3-(4-nitrophenyl)isoxazol-5-yl)methyl)-1-phenyl-1H-1,2,3-triazole-4-carboxamide (6i). White solid, M.p. 168-170°C. Yield: 0.13 g, 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, J = 6 Hz, 2H), 8.00 (d, J = 9 Hz, 2H), 7.88 (s, 1H), 7.61 (d, J = 7 Hz, 3H), 7.49-7.47 (m, 2H), 6.69 (s, 1H), 4.88 (d, J = 6 Hz, 2H), 2.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 160.5, 159.8, 147.8, 136.9, 136.3, 134.4, 134.0, 130.7, 128.8, 126.7, 124.2, 123.2, 99.6, 33.9, 8.7; ESI-MS: m/z =405 $[M+1]^+$. Found: C, 59.21; H, 4.07; N, 20.67%. Calc. for $C_{20}H_{16}N_6O_4$, C, 59.40; H, 3.99; N, 20.78%.

N-((3-(2-chlorophenyl)isoxazol-5-yl)methyl)-5-methyl-1-p-tolyl-1H-1,2,3-triazole-4-carboxamide (6j). White solid, M.p. 128-130°C. Yield: 0.13 g, 66%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 4.5 Hz, 1H), 7.73-7.71 (m, 1H), 7.48 (d, J = 8 Hz 1H), 7.39-7.33 (m, 6H), , 6.73 (s, 1H), 4.89 (d, J = 6 Hz, 2H), 2.63 (s, 3H), 2.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 160.4, 160.2, 139.4, 136.9, 136.2, 132.0, 131.9, 130.0, 129.8, 129.4, 129.2, 127.3, 126.1, 124.1, 102.6, 33.9, 20.3, 8.7; ESI-MS: m/z =408 $[M+1]^+$. Found: C, 61.65; H, 4.37; N, 17.03%. Calc. for $C_{21}H_{18}ClN_5O_2$, C, 61.84; H, 4.45; N, 17.17%.

Bisfunctional modified peptidomimetics 13, 14, 15. Amine (1 mmol), aldehyde (1 mmol) were dissolved in a seal tube with 2 mL MeOH and stirred at room temperature for 30 minutes. Then Acid (1 mmol) and isocyanide (1 mmol) were added. The mixture was stirred for 24 hours. Then corresponding aniline (0.55 mmol), diketene (1.1 mmol) and DBU (1.1 mmol) were added in the seal tube and raised the reaction temperature to 80 °C for 24 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography (hexanes / ethyl acetate 3/ 1) to give intermediates **12**. Then, to a solution of compound **12** (0.5 mmol) Last, to a solution of compound **12** (0.5 mmol), oxime (0.75 mmol) and phenyliodine bis(trifluoroacetate) (0.75 mmol) in 3 mL MeOH. The reaction mixture was stirred at 60℃ for 4 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatograp hy (hexanes / ethyl acetate 2/ 1).

1-(4-((2-(cyclohexylamino)-2-oxo-1-phenylethyl)(phenyl)carbamoyl)phenyl)-5-methyl-N-((3-phenylisoxazol-5-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (13a). White solid, M.p. 132-134°C. Yield: 0.16 g, 47%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.76 (m, 2H), 7.73-7.71 (t, J = 6 Hz, 1H), 7.52 (d, J = 8.5 Hz 2H), 7.43-7.40 (t, J = 4 Hz, 3H), 7.25-7.24 (m, 8H), 7.03 (s, 4H), 6.54 (s, 1H), 6,19(s, 1H), 6.53 (s, 1H), 5.60 (d, J = 8 Hz 1H), 4.79 (d, J = 6 Hz, 2H), 3.91-3.87 (m, 1H), 2.52 (s, 3H), 1.98-1.90 (m, 2H), 1.67-1.60 (m, 3H), 1.38-1.33 (m, 2H), 1.16-1.05 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 168.4, 167.2, 161.6, 160.2, 139.6, 137.1, 136.1, 134.8, 133.5, 129.4, 129.0, 128.9, 127.9, 127.7, 126.7, 125.8, 123.3, 99.4, 65.7, 48.0, 33.8, 31.9, 24.5, 23.8, 23.7, 8.7; ESI-MS: m/z =716 $[M+23]^+$. Found: C, 70.87; H, 5.59; N, 14.05%. Calc. for $C_{41}H_{39}N_7O_4$, C, 70.98; H, 5.67; N, 14.13%.

N-((3-(2-chlorophenyl)isoxazol-5-yl)methyl)-1-(4-((2-(cyclohexylamino)-2-oxo-1-phenylethyl)(phenyl)carbamoyl)phenyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide (13b). White solid, M.p. 114-116°C. Yield: 0.16 g, 43%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.75 (t, J = 6 Hz, 1H), 7.69-7.67 (m, 1H), 7.51 (d, J = 8.5 Hz 2H), 7.46-7.44 (m, 1H), 7.36-7.31 (m, 2H), 7.24-7.21 (m, 7H), 7.02 (s, 5H), 6.68 (s, 1H), 6,19(s, 1H), 5.65 (d, J = 8 Hz 1H), 4.81 (d, J = 6 Hz, 2H), 3.89-3.86 (m, 1H), 2.51 (s, 3H), 1.97-1.89 (m, 2H), 1.66-1.62 (m, 3H), 1.37-1.32 (m, 2H), 1.15-1.07 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.6, 167.3, 160.2, 139.6, 137.1, 136.1, 134.8, 133.5, 131.9, 130.0, 129.9, 129.4, 129.3, 128.9, 127.6, 127.2, 126.6, 126.1, 123.3, 102.6, 65.7, 48.0, 33.8, 31.8, 24.5, 23.8, 23.7, 8.7; ESI-MS: m/z =750 $[M+23]^+$. Found: C, 67.89; H, 5.45; N, 13.23%. Calc. for $C_{41}H_{38}ClN_7O_4$, C, 67.62; H, 5.26; N, 13.46%.

1-(4-((2-(cyclohexylamino)-1-(furan-2-yl)-2-oxoethyl)(phenyl)carbamoyl)phenyl)-5-methyl-N-((3-phenylisoxazol-5-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (13c). White solid, M.p. 116-118°C. Yield: 0.18 g, 49%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.78 (t, J = 6.5 Hz, 1H), 7.76-7.75 (m, 2H), 7.52-7.50 (t, J = 6.5 Hz 2H), 7.42-7.41 (m, 3H), 7.34-7.33 (m, 1H), 7.25-7.23 (m, 2H), 7.11-7.09 (m, 3H), 7.06 (s, 2H), 6.53 (s, 1H), 6.38 (d, J = 8 Hz 1H), 6.30 (s, 1H), 6.27-6.26 (m, 1H), 6.02 (d, J = 8 Hz, 1H), 4.78 (d, J = 6.5 Hz, 2H), 3.88-3.84 (m, 1H), 2.52 (s, 3H), 1.97-1.91 (m, 2H), 1.71-1.66 (m, 2H), 1.61-1.58 (m, 1H), 1.38-1.33 (m, 2H), 1.19-1.44 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 165.1, 160.2, 146.8, 139.6, 137.1, 136.5, 136.1, 135.0, 129.0, 128.5, 127.9, 127.8, 126.9, 125.8, 123.4, 111.4, 109.9, 99.4, 59.16, 47.9, 33.9, 31.8, 24.5, 23.7, 8.7; ESI-MS: m/z =706 $[M+23]^+$. Found: C, 68.35; H, 5.58; N, 14.53%. Calc. for $C_{39}H_{37}N_7O_5$, C, 68.51; H, 5.45; N, 14.34%.

1-(4-((1-(cyclohexylamino)-3-methyl-1-oxobutan-2-yl)(phenyl)carbamoyl)phenyl)-5-methyl-N-((3-phenylisoxazol-5-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (13d). White solid, M.p. 106-108°C. Yield: 0.15 g, 45%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.85 (t, J = 6 Hz, 1H), 7.76-7.74 (m, 2H), 7.41-7.40 (t, J = 3.5 Hz, 5H), 7.24 (d, J = 8.5 Hz, 2H), 7.21-7.15 (m, 5H), 6.94 (s, 1H), 6.53 (s, 1H), 4.79 (d, J = 6.5 Hz, 2H), 4.48 (d, J = 11 Hz, 2H), 3.84-3.78 (m, 1H), 2.52 (s, 3H), 1.92-1.88 (m, 2H), 1.71-1.68 (m, 2H), 1.59-1.56 (m, 1H), 1.38-1.35 (m, 2H), 1.26-1.18 (m, 3H), 1.04-1.02 (t, J = 7 Hz 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 168.4, 168.2, 161.6, 160.2, 140.3, 137.2, 136.1, 135.0, 129.0, 128.7, 128.1, 127.9, 126.8, 125.8, 123.5, 99.4, 70.3, 47.0, 33.9, 31.9, 25.9, 24.5, 23.7, 19.1, 18.9, 8.7; ESI-MS: m/z =682 $[M+23]^+$. Found: C, 69.03; H, 6.51; N, 14.75%. Calc. for $C_{38}H_{41}N_7O_4$, C, 69.18; H, 6.26; N, 14.86%.

1-(2-((2-(cyclohexylamino)-2-oxo-1-phenylethyl)(phenyl)carbamoyl)phenyl)-5-methyl-N-((3-phenylisoxazol-5-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (14a). White solid, M.p. 108-110°C. Yield: 0.13 g, 39%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.80-7.78 (t, J = 3 Hz, 2H), 7.43-7.42 (m, 3H), 7.34-7.30 (m, 4H), 7.25-7.23 (m, 1H), 7.15-7.13 (m, 3H), 7.12-7.09 (m, 3H), 7.02-6.96 (m, 3H), 6.63 (s, 1H), 5.95 (s, 1H), 5.71 (d, J = 7.5 Hz, 1H), 4.87-4.85 (m, 2H), 3.84-3.80 (m, 1H), 2.52 (s, 3H), 1.91-1.86 (m, 2H), 1.62-1.53 (m, 3H), 1.32-1.29 (m, 2H), 1.11-1.04 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.1, 166.0, 161.7, 160.4, 139.3, 138.4, 136.5, 133.9, 131.7, 129.1, 129.0, 128.5, 127.9, 127.4, 126.5, 125.9, 125.5, 99.6, 65.6, 48.0, 33.9, 31.7, 24.5, 23.8, 8.6; ESI-MS: m/z =716 $[M+23]^+$. Found: C, 70.76; H, 5.58; N, 14.05%. Calc. for $C_{41}H_{39}N_7O_4$, C, 70.98; H, 5.67; N, 14.13%.

1-(4-(2-(tert-butylamino)-2-oxo-1-(N-phenylacetamido)ethyl)phenyl)-5-methyl-N-((3-phenylisoxazol-5-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (15a). White solid, M.p. 166-168°C. Yield: 0.15 g, 43%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95-7.92 (t, J = 3 Hz, 2H), 7.80-7.78 (m, 2H), 7.45-7.43 (m, 3H), 7.38 (d, J = 8.5 Hz, 2H), 7.28-7.24 (m, 6H), 7.11 (s, 1H), 6.58 (s, 1H), 6.10 (s, 1H), 6.03 (s, 1H), 4.84 (d, J = 6.5 Hz, 2H), 2.55 (s, 3H), 1.90 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 168.5, 167.3, 161.6, 160.3, 139.2, 137.1, 136.1, 134.1, 130.7, 129.2, 129.0, 128.2, 127.9, 127.4, 125.8, 123.8, 99.4, 63.3, 50.8, 33.9, 27.7, 22.3, 8.7; ESI-MS: m/z =728 $[M+23]^+$. Found: C, 67.57; H, 5.92; N, 16.03%. Calc. for $C_{34}H_{35}N_7O_4$, C, 67.42; H, 5.82; N, 16.19%.

1-(4-(2-(tert-butylamino)-1-(N-(4-chlorophenyl)acetamido)-2-oxoethyl)phenyl)-N-((3-(2-chlorophenyl)isoxazol-5-yl)methyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide (15b). White solid, M.p. 154-156°C. Yield: 0.13 g, 40%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.70 (d, J = 3.5 Hz, 1H), 7.49-7.47 (m, 1H), 7.40-7.35 (m, 4H), 7.33-7.30 (m, 2H), 7.20 (d, J = 7 Hz, 2H), 7.07 (s, 2H), 6.72 (d, J = 0.5 Hz, 1H), 6.09 (s, 1H), 5.85 (s, 1H), 4.87 (d, J = 6 Hz, 2H), 2.56 (s, 3H), 1.89 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 167.7, 167.2, 160.2, 137.6, 137.1, 136.1, 135.8, 134.4, 133.4, 131.9, 130.8, 130.7, 129.9, 129.4, 128.3, 127.2, 126.1, 124.0, 102.6, 63.0, 50.9, 33.8, 27.6, 22.3, 8.7; ESI-MS: m/z =696 $[M+23]^+$. Found: C, 60.71; H, 5.02; N, 14.39%. Calc. for $C_{34}H_{33}Cl_2N_7O_4$, C, 60.54; H, 4.93; N, 14.53%.

1-(4-(2-(tert-butylamino)-1-(N-(4-chlorophenyl)acetamido)-2-oxoethyl)phenyl)-5-methyl-N-((3-phenylisoxazol-5-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (15c). White solid, M.p. 196-198°C. Yield: 0.14 g, 42%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.79 (m, 3H), 7.46-7.45 (m, 3H), 7.39-7.38 (m, 2H), 7.32-7.31 (m, 2H), 7.22-7.20 (m, 2H), 6.59 (s, 1H), 6.09 (s, 1H), 5.81 (s, 1H), 4.84 (d, J = 6 Hz, 2H), 2.58 (s, 3H), 1.91 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 168.4, 167.1, 161.6, 160.2, 137.6, 137.1, 136.1, 135.8, 134.4, 133.5, 130.7, 129.0, 128.3, 127.9, 125.8, 124.0, 99.5, 63.0, 50.9, 33.9, 27.7, 22.2, 8.7; ESI-MS: m/z =662 $[M+23]^+$. Found: C, 63.57; H, 5.51; N, 15.17%. Calc. for $C_{34}H_{34}ClN_7O_4$, C, 63.79; H, 5.35; N, 15.32%.

1-(4-(1-(N-(4-chlorophenyl)acetamido)-2-(cyclohexylamino)-2-oxoethyl)phenyl)-5-methyl-N-((3-phenylisoxazol-5-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (15d). White solid, M.p. 180-182°C. Yield: 0.15 g, 46%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.84 (t, J = 6 Hz,, 1H), 7.81-7.79 (m, 2H), 7.46-7.45 (m, 3H), 1.39 (d, J = 7.5 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 7.21 (d, J = 7 Hz, 2H), 7.8-7.13 (m, 2H), 6.59 (s, 1H), 6.16 (s, 1H), 5.87 (7.32 (d, J = 7 Hz, 2H), 4.84 (d, J = 6 Hz, 2H), 3.85-3.84 (m, 1H), 2.58 (s, 3H), 2.01-1.99 (m, 1H), 1.99 (s, 3H), 1.87-1.86 (m, 1H), 1.69-1.61 (m, 3H), 1.39-1.35 (m, 2H), 1.22-1.14 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 170.2, 168.4, 167.0, 161.6, 160.2, 137.7, 137.1, 136.1, 135.7, 134.4, 133.5, 130.8, 129.1, 128.3, 127.9, 125.8, 124.1, 99.5, 62.7, 48.0, 33.9, 31.8, 24.4, 23.8, 22.2, 8.7; ESI-MS: m/z =688 $[M+23]^+$. Found: C, 65.16; H, 5.57; N, 14.53%. Calc. for $C_{36}H_{36}ClN_7O_4$, C, 64.91; H, 5.45; N, 14.72%.

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Notes and references

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