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Concise synthesis of chiral 2(5*H*)-furanone derivatives possessing 1,2,3-triazole moiety via one-pot approach

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ABSTRACT

Combining three bioactive units, such as 2(5*H*)-furanone, 1,2,3-triazole, and amino acid together into one potential drug molecule with polyfunctional groups, a series of new chiral 2(5*H*)-furanone derivatives containing 1,2,3-triazole moiety have been designed and synthesized from (5*S*)-5-alkoxy-3,4-dibromo-2(5*H*)-furanones, amino acids, propargyl bromide, and organic azides via the sequential three steps, including asymmetric Michael addition–elimination, substitution, and click reaction. The latter two steps, substitution and click reaction could proceed smoothly in a one-pot process. Furthermore, the target products could be directly synthesized via a four-component one-pot approach.

1. Introduction

Molecules possessing 2(5*H*)-furanone moiety, a kind of α,β-unsaturated lactone substructure frequently found in natural products (Fig. 1), have received considerable interest due to their significant biological activities, such as antifungal, anti-bacterial, anti-inflammatory, and anti-tumor.[1] At the same time, many 2(5*H*)-furanone compounds are important organic intermediates.[2] These made the researches on 2(5*H*)-furanone chemistry become very intensive recently.[3]

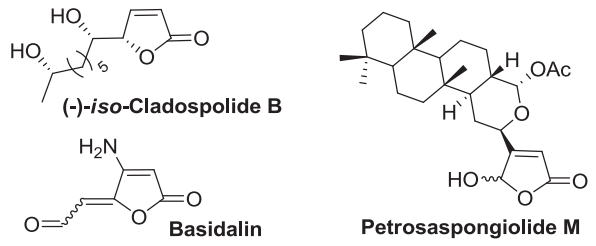

Fig. 1. Some biologically active natural products bearing 2(5*H*)-furanone moiety.

Though more and more methods for 2(5*H*)-furanones with polyfunctional groups have been reported in the researches on 2(5*H*)-furanone, these synthetic methods can be divided into two categories according to different synthetic strategies. One is that introducing substituents first and then producing 2(5*H*)-furanone ring via cyclization.[4–7] The other is that taking simple furanones or other oxygen-containing five-membered cyclic compounds as starting materials and then introducing various substituents as required to synthesize a series of derivatives.[8,9] No matter which approach, the synthesis of 2(5*H*)-furanones with polyfunctional groups has been a challenge for a long time due to the instability of 2(5*H*)-furanone ring under certain conditions and the particularity of various functional groups.[4–9] Besides, the reported methods had some deficiencies, especially the starting materials were not easily available,[4,6] or the process was lengthy,[7] or the catalysts were precious and not easily obtainable.[5,6,9]

As an important pharmacophore, 1,2,3-triazole nitrogen heterocycle plays an significant role in the anti-bacterial,[10] anti-tumor,[11] anti-inflammatory,[12] anti-HIV,[13] and anti-platelet aggregation.[14] This makes many medicinal chemists and biochemists have increasing emphasis on the synthesis of 1,2,3-triazoles with polyfunctional groups.[15] However, the studies on combination 1,2,3-triazole into 2(5*H*)-furanone compounds via different bioactive amino acids as building blocks[16] have not been reported before. Herein, we tried to combine three bioactive units, such as 2(5*H*)-furanone, 1,2,3-triazole, and amino acid to design and synthesize potential bioactive chiral compounds **6** containing

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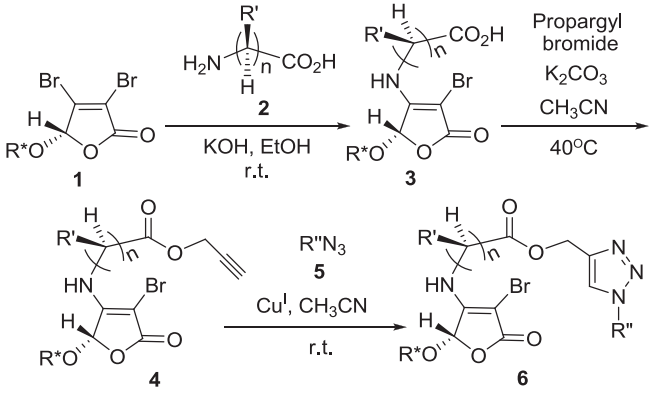
polyfunctional groups, e.g., butenolide ring, amino, ester, 1,2,3-triazole, and halogen (Scheme 1). Meanwhile, based on the mild, simple, economical three-step synthetic method, we further investigated their efficient syntheses via a multi-component one-pot approach.



Scheme 1. Synthetic route of target compounds **6**.

2. Results and discussion

2.1. Synthesis of target compounds by fractional-step method

Based on the synthesis of the intermediates *N*-[(5*S*)-5-alkoxy-2(5*H*)-furanonyl] amino acids **3**[1k,3t] and *N*-[(5*S*)-5-alkoxy-2(5*H*)-furanonyl] amino acid propargyl esters **4**,[3u] we investigated the fractional-step method in preparation the target compounds starting from propargyl esters **4**. According to the most literature on click chemistry,[15,17,18] all reactions in our experiments were carried out at room temperature. Choosing *N*-[(5*S*)-5-menthyl-oxy-2(5*H*)-furanonyl] 6-aminohexanoic acid **4af** and benzyl azide **5a** as the model substrate, we optimized experimental conditions, including the influences of the kinds and dosage of the catalyst, and solvent on the yield of **6afa** (Table 1).

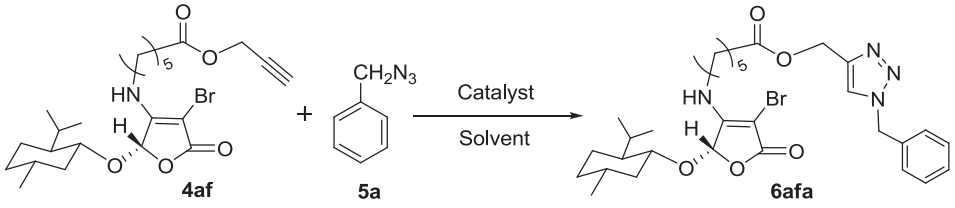
Firstly, the influences of different catalysts were evaluated (entries 1–5). Obviously, when $Cu(OAc)_2\cdot H_2O$/Cu was used as a catalytic system, a satisfactory yield was obtained (entry 2). However, the base PMDETA[19] was not conducive to the reaction here (entry 1). If the catalytic system was replaced by CuBr (or CuBr/Cu), some by-products could be detected according to the monitoring by TLC, and the yield dropped (entries 4 and 5).

The solvent also affected the reaction significantly (entries 2 and 6–10). The monitoring by TLC showed that the reaction could be smoothly carried out in CH_3CN, and the reaction time could be shortened from 10 h to 4 h, even the yield was higher (entries 2 and 6). However, in DMF, if the reaction time was reduced to 4 h, the yield was significantly reduced (entries 2 and 7). Similarly, changing other solvents while maintaining the same reaction time (4 h), the results indicated that CH_3CN was the best solvent of all (entry 6). Especially, though *t*-BuOH/H_2O (1:1)[17] or THF/H_2O (1:1)[20] was suitable solvent system for other click reactions, here they were not suitable due to their bad solubility or polarity for the substrates.

Furthermore, the influences of catalyst system on the yield were investigated (entries 6, 11 and 12). Increasing the ratio of Cu in the component of catalyst system gave higher yield (entry 11). If keeping the higher ratio of Cu unchangeable, even the catalyst dosage was wholly reduced to half, the yield was almost unchangeable (entry 12). Thus, suitable catalyst system should be 0.05 equiv $Cu(OAc)_2\cdot H_2O$ and 0.1 equiv Cu.

Therefore, when choosing 1 equiv *N*-[(5*S*)-5-menthyloxy-2(5*H*)-furanonyl] 6-aminohexanoic acid propargyl ester **4af** and 1.5 equiv benzyl azide **5a** as the model substrates, the optimized reaction conditions could be summarized in the following: CH_3CN as the solvent, 0.05 equiv $Cu(OAc)_2\cdot H_2O$ and 0.1 equiv Cu as the catalytic system, room temperature for 4 h. Under these conditions, changing substrates, more new chiral 2(5*H*)-furanone derivatives containing 1,2,3-triazole moiety have been designed and successfully synthesized with satisfactory yields (mostly equal to or over 67%) except for **6bha** and **6bhb** (Table 2).

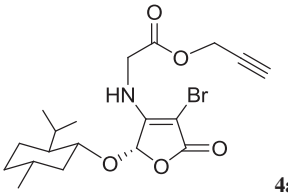
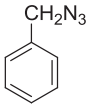
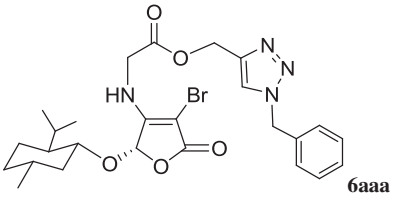
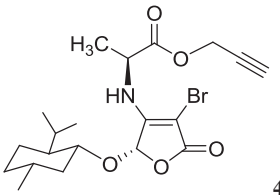
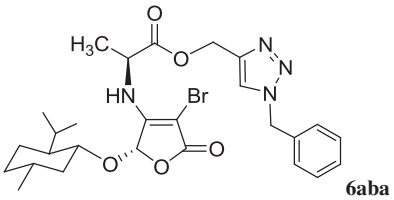
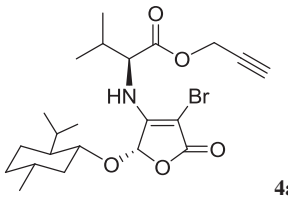
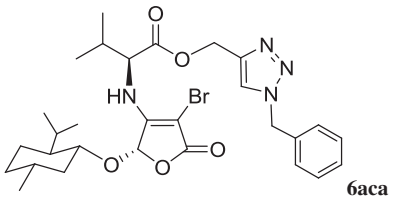
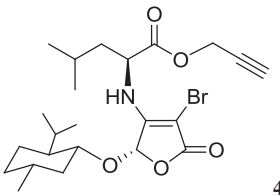
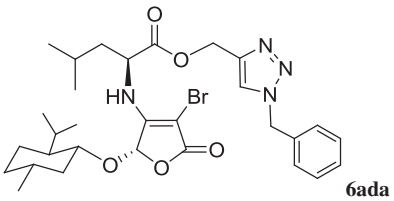
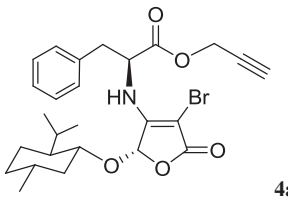
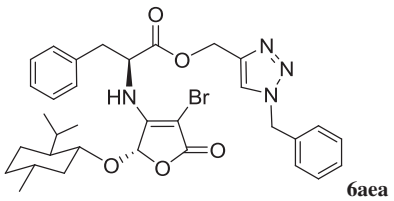
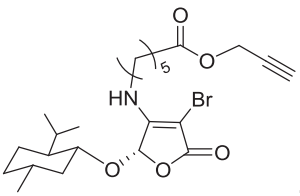
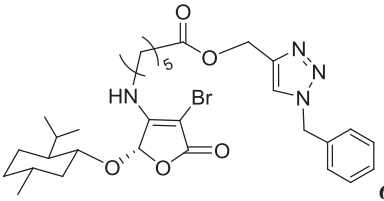
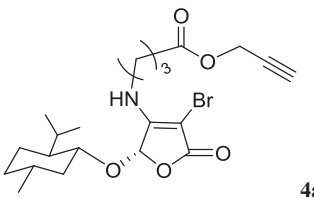
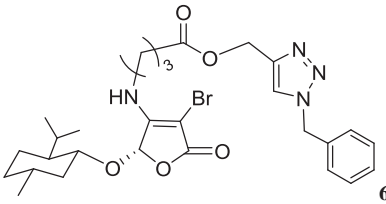
Table 1
Condition optimization for click reaction of *N*-[(5*S*)-5-menthyloxy-2(5*H*)-furanonyl] 6-aminohexanoic acid propargyl ester **4af** with benzyl azide **5a**



Entry[a]	Catalyst	Solvent	Time (h)	Yield[b] (%)
1[c]	$Cu(OAc)_2\cdot H_2O$/Cu	DMF	10	11
2	$Cu(OAc)_2\cdot H_2O$/Cu	DMF	10	66
3	$Cu(OAc)_2\cdot H_2O$/sodium ascorbate	DMF	10	63
4	CuBr/Cu	DMF	10	58
5	CuBr	DMF	10	57
6	$Cu(OAc)_2\cdot H_2O$/Cu	CH_3CN	4	68
7	$Cu(OAc)_2\cdot H_2O$/Cu	DMF	4	21
8	$Cu(OAc)_2\cdot H_2O$/Cu	*t*-BuOH/H_2O (1:1)	4	0
9	$Cu(OAc)_2\cdot H_2O$/Cu	THF/H_2O (1:1)	4	0
10	$Cu(OAc)_2\cdot H_2O$/Cu	CH_2Cl_2	4	31
11[d]	$Cu(OAc)_2\cdot H_2O$/Cu	CH_3CN	4	71
11[e]	$Cu(OAc)_2\cdot H_2O$/Cu	CH_3CN	4	71

[a] Reaction conditions: rt, *N*-protected amino acid propargyl ester **4af** (1 mmol), benzyl azide **5a** (1.5 equiv), catalyst (all components 0.1 equiv except for special explanations).
[b] Isolated yield.
[c] 1,1,4,7,7-Penta-methyldiethylenetriamine (PMDETA) (0.2 equiv) was used as an additive.
[d] $Cu(OAc)_2\cdot H_2O$ 0.1 equiv, Cu 0.2 equiv.
[e] $Cu(OAc)_2\cdot H_2O$ 0.05 equiv, Cu 0.1 equiv.

Table 2
The yields of target compounds **6** using *N*-protected amino acid propargyl esters **4** and organic azides **5** as materials

Entry	Propargyl esters **4**	Azides **5**	Compounds **6** [a]	Yield[b] (%)
1	 **4aa**	 **5a**	 **6aaa**	77
2	 **4ab**	**5a**	 **6aba**	63
3	 **4ac**	**5a**	 **6aca**	70
4	 **4ad**	**5a**	 **6ada**	75
5	 **4ae**	**5a**	 **6aea**	67
6	 **4af**	**5a**	 **6afa**	71
7	 **4ag**	**5a**	 **6aga**	80

(*continued on next page*)

Table 2 (*continued*)

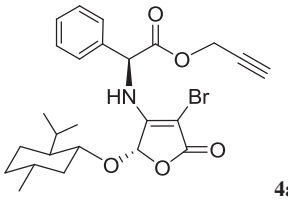
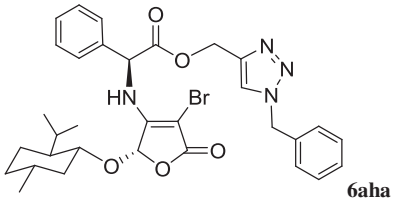
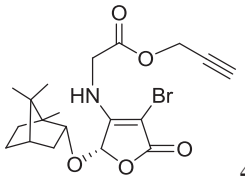
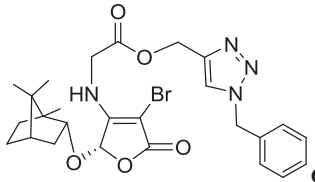
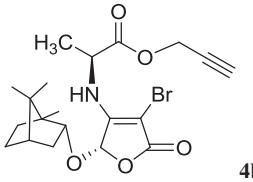
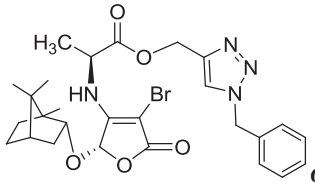
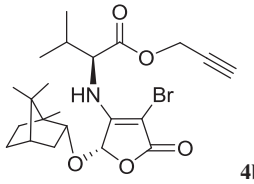
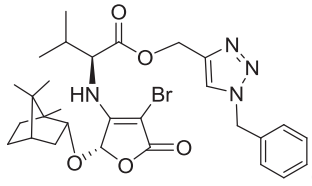
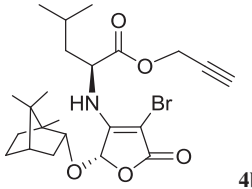
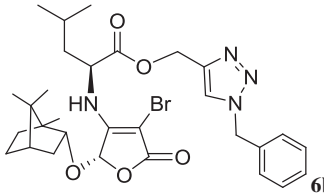
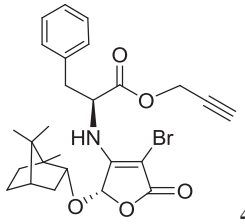
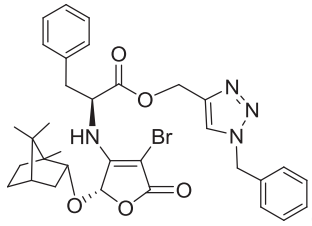
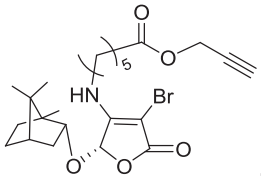
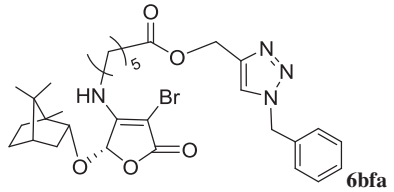
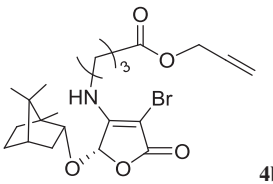
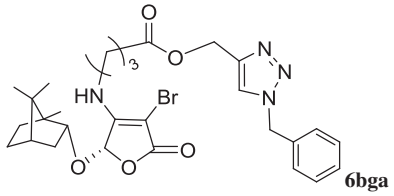
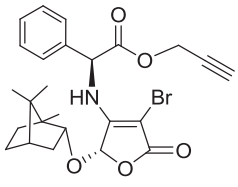
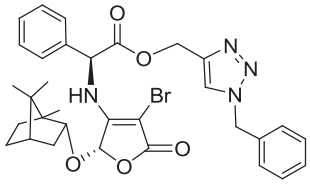
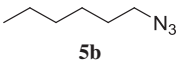
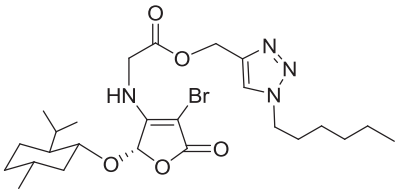
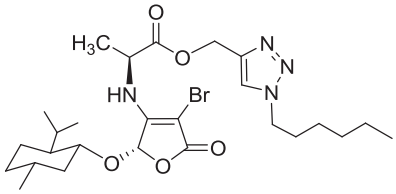
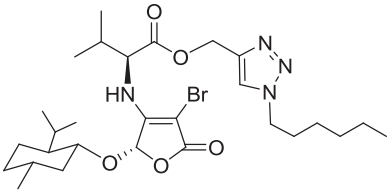
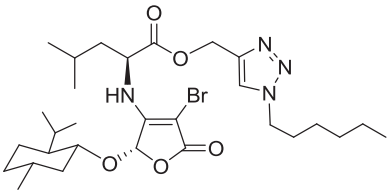
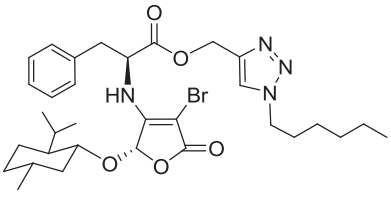
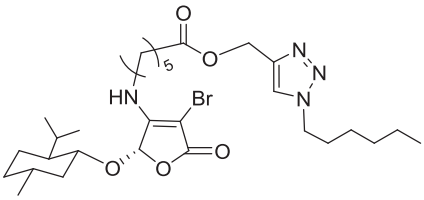
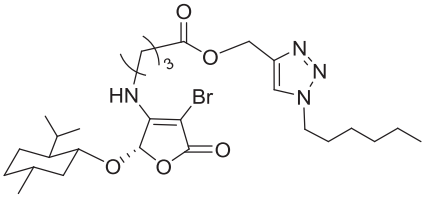
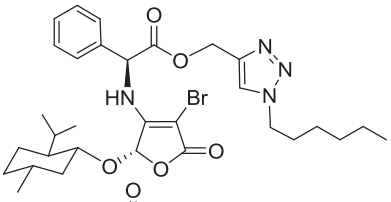
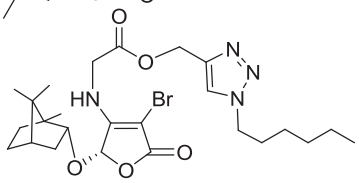
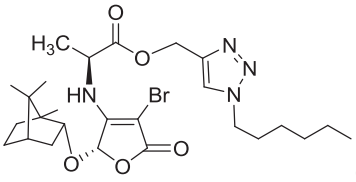
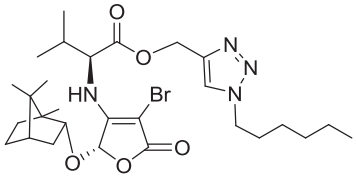
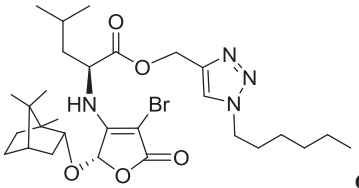
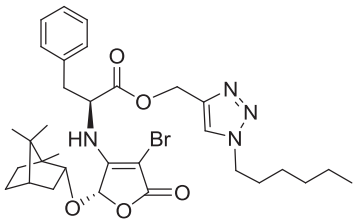
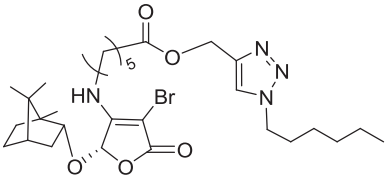
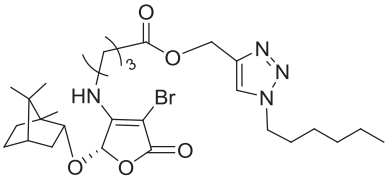
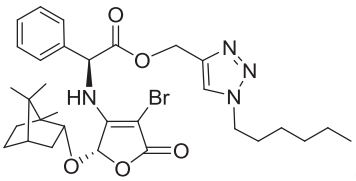
Entry	Propargyl esters **4**	Azides **5**	Compounds **6** [a]	Yield[b] (%)
8	 **4ah**	**5a**	 **6aha**	54
9	 **4ba**	**5a**	 **6baa**	62
10	 **4bb**	**5a**	 **6bba**	74
11	 **4bc**	**5a**	 **6bca**	61
12	 **4bd**	**5a**	 **6bda**	82
13	 **4be**	**5a**	 **6bea**	57
14	 **4bf**	**5a**	 **6bfa**	67
15	 **4bg**	**5a**	 **6bga**	76

Table 2 (*continued*)

Entry	Propargyl esters **4**	Azides **5**	Compounds **6** [a]	Yield[b] (%)
16	 **4bh**	**5a**	 **6bha**	32
17	**4aa**	 **5b**	 **6aab**	75
18	**4ab**	**5b**	 **6abb**	76
19	**4ac**	**5b**	 **6acb**	71
20	**4ad**	**5b**	 **6adb**	73
21	**4ae**	**5b**	 **6aeb**	74
22	**4af**	**5b**	 **6afb**	85
23	**4ag**	**5b**	 **6agb**	83

(*continued on next page*)

Table 2 (*continued*)

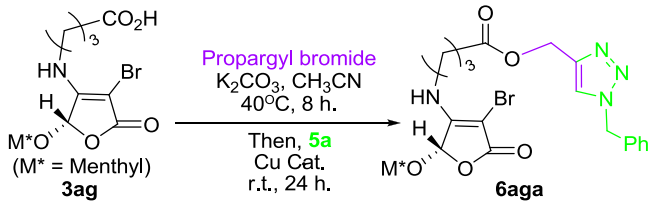
Entry	Propargyl esters **4**	Azides **5**	Compounds **6** [a]	Yield[b] (%)
24	**4ah**	**5b**	 **6ahb**	57
25	**4ba**	**5b**	 **6bab**	76
26	**4bb**	**5b**	 **6bbb**	77
27	**4bc**	**5b**	 **6bcb**	67
28	**4bd**	**5b**	 **6bdb**	75
29	**4be**	**5b**	 **6beb**	82
30	**4bf**	**5b**	 **6bfb**	77
31	**4bg**	**5b**	 **6bgb**	70
32	**4bh**	**5b**	 **6bhb**	34

[a] Reaction conditions: *N*-protected amino acid propargyl esters **4** 1 mmol, organic azides **5** 1.5 equiv, $Cu(OAc)_2 \cdot H_2O$ 0.05 equiv, Cu 0.1 equiv, solvent CH_3CN, rt, 4 h.
[b] Isolated yield.

2.2. Synthesis of target compounds via three-component one-pot approach

How to improve synthetic efficiency and reduce labor intensity is an important goal of synthetic method study. Especially for the synthesis of chiral compounds, it is of great significance to investigate the multi-component one-pot synthesis,[21] and the one-pot three-component reaction involving in the studies of azides has been investigated recently.[22] The above optimized conditions for click reaction showed that CH_3CN was the best solvent, which was the same as the best solvent in the substitution reaction.[3t] This made us believe that to synthesize the target compounds via a three-component one-pot approach using *N*-[(5*S*)-5-alkoxy-2(5*H*)-furanonyl] amino acids **3**, propargyl bromide, and organic azides **5** as starting materials should be possible.

Choosing *N*-[(5*S*)-5-menthyloxy-2(5*H*)-furanonyl]-4-aminobutyric acid **3ag**, propargyl bromide, and benzyl azide **5a** as the model substrates for the three-component one-pot reaction (Scheme 2), once the substitution reaction was completed, the catalytic amount of $Cu(OAc)_2\cdot H_2O$ and Cu was added to the acetonitrile system, hoping that Cu(I) generated in situ could catalyze the subsequent click reaction. However, there was no any target product obtained in the end. The reason might be that catalytic amount $Cu(OAc)_2\cdot H_2O$ was destroyed by the residual K_2CO_3 via hydrolysis in the presence of a little water produced in the step of substitution reaction.



Scheme 2. Synthesis of target compound **6aga** via three-component one-pot approach.

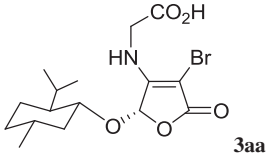
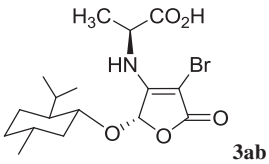
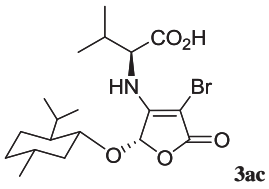
When the amount of Cu(II) and Cu increased to 1.05 equiv and 1.1 equiv of the K_2CO_3 dosage, respectively, the one-pot reaction gave the product **6aga** with the yield of 14% after 12 h. Encouraged by this positive result, we continued to study the experiment. When the reaction time was prolonged to 24 h, and the amount of Cu(II) and Cu increased to 1.2 equiv and 1.5 equiv of the K_2CO_3 dosage, respectively, the monitoring by TLC showed the reaction was completed with a greatly increased yield. And the isolated yield of **6aga** was 57%, which was higher than the corresponding cumulative yield (54%) by fractional-step method. Thus, we examined a variety of other substrates in the next experiments (Table 3).

The results showed that different organic azides **5** could easily take part in the three-component reaction (Table 3). For the substrates *N*-[(5*S*)-5-alkoxy-2(5*H*)-furanonyl] amino acids **3**, whether the main chain of amino acid was long or short, and the side chain of amino acids was alkyl or aryl, the reaction could proceed smoothly, and most of the isolated yields of target compounds reached the middle level (equal to or over 50%). Compared with their corresponding cumulative yields of fractional-step method, three-component one-pot method wholly gave a roughly similar yield. However, the one-pot method didn't need the separation of intermediate products, *N*-[(5*S*)-5-alkoxy-2(5*H*)-furanonyl] amino acid propargyl esters **4**, and had greater advantages due to simplifying the experimental procedure.

2.3. Synthesis of target compounds via four-component one-pot approach

In the whole fractional-step method (Scheme 1), *N*-[(5*S*)-5-alkoxy-2(5*H*)-furanonyl] amino acids **3** were prepared under alkaline conditions, and a neutralization process was needed after the Michael addition–elimination reaction. At the same time, *N*-[(5*S*)-5-alkoxy-2(5*H*)-furanonyl] amino acid propargyl esters **4** were also prepared under alkaline conditions. Therefore, the combination of Michael addition–elimination and substitution

Table 3
A yield comparison between three-component one-pot method and fractional-step method both using *N*-protected amino acids **3** as starting material

Entry	*N*-Protected amino acids **3**	Azides **5**	Compounds **6**	Yield of one-pot[a] (%)	Yield of fractional-step[b] (%)
1	 **3aa**	**5a**	**6aaa**	54	44
2	 **3ab**	**5a**	**6aba**	61	53
3	 **3ac**	**5a**	**6aca**	53	58

(*continued on next page*)

Table 3 (*continued*)

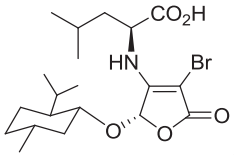
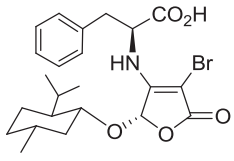
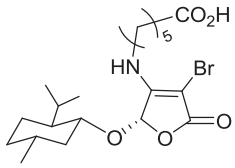
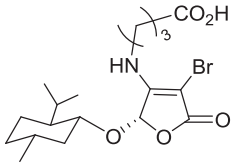
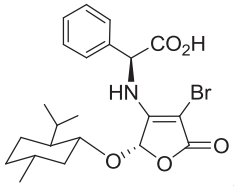
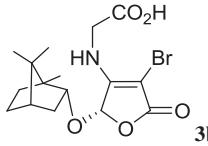
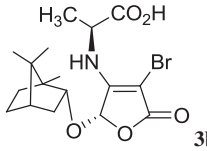
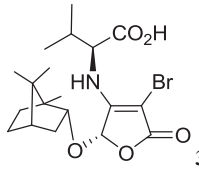
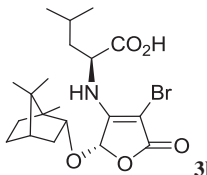
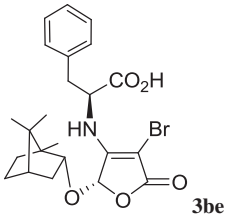
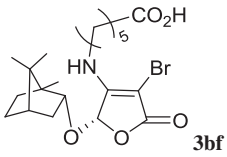
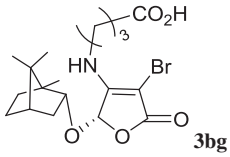
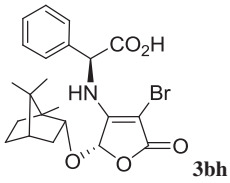
Entry	*N*-Protected amino acids **3**	Azides **5**	Compounds **6**	Yield of one-pot[a] (%)	Yield of fractional-step[b] (%)
4	 **3ad**	**5a**	**6ada**	39	59
5	 **3ae**	**5a**	**6aea**	50	55
6	 **3af**	**5a**	**6afa**	52	52
7	 **3ag**	**5a**	**6aga**	57	54
8	 **3ah**	**5a**	**6aha**	32	28
9	 **3ba**	**5a**	**6baa**	39	39
10	 **3bb**	**5a**	**6bba**	65	55
11	 **3bc**	**5a**	**6bca**	48	51
12	 **3bd**	**5a**	**6bda**	62	67

Table 3 (*continued*)

Entry	*N*-Protected amino acids **3**	Azides **5**	Compounds **6**	Yield of one-pot[a] (%)	Yield of fractional-step[b] (%)
13	 **3be**	**5a**	**6bea**	68	46
14	 **3bf**	**5a**	**6bfa**	58	54
15	 **3bg**	**5a**	**6bga**	54	57
16	 **3bh**	**5a**	**6bha**	31	18
17	**3aa**	**5b**	**6aab**	50	43
18	**3ab**	**5b**	**6abb**	56	64
19	**3ac**	**5b**	**6acb**	43	59
20	**3ad**	**5b**	**6adb**	62	58
21	**3ae**	**5b**	**6aeb**	59	61
22	**3af**	**5b**	**6afb**	50	63
23	**3ag**	**5b**	**6agb**	43	57
24	**3ah**	**5b**	**6ahb**	33	30
25	**3ba**	**5b**	**6bab**	56	48
26	**3bb**	**5b**	**6bbb**	57	57
27	**3bc**	**5b**	**6bcb**	51	56
28	**3bd**	**5b**	**6bdb**	56	61
29	**3be**	**5b**	**6beb**	47	65
30	**3bf**	**5b**	**6bfb**	53	52
31	**3bg**	**5b**	**6bgb**	51	52
32	**3bh**	**5b**	**6bhb**	30	15

[a] Isolated yield under the reaction conditions: *N*-protected amino acids **3** 1 mmol, K_2CO_3 1.5 equiv, propargyl bromide 2 equiv, CH_3CN, 40 °C, 8 h; then, organic azides **5** 2 equiv, $Cu(OAc)_2 \cdot H_2O$ 1.8 equiv, Cu 2.2 equiv, rt, 24 h.

[b] The cumulative yield is based on the isolated yield of two steps according to Scheme 1 using *N*-protected amino acids **3** as starting material.

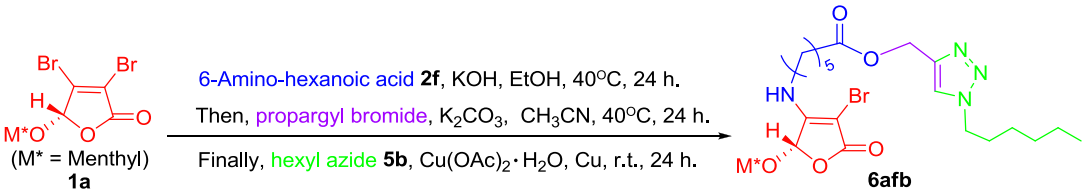
together was also possible. Encouraged by the success of three-component one-pot approach, we hoped to synthesize the target compounds **6** in a one-pot three-step process with four components. Taking the synthesis of products **6afb** from the substrate **1a** as an example, we investigated the reaction conditions (Table 4).

It could be seen that, even the twice catalytic amount of $Cu(OAc)_2 \cdot H_2O$ and Cu were added to the reaction system, the reaction couldn't proceed (entry 1). As mentioned above, may be the small amount of $Cu(OAc)_2 \cdot H_2O$ was ineffective for its reacting with K_2CO_3 in the presence of a little water. When the amount of Cu(II) was increased to 1.2 equiv of the K_2CO_3 dosage, the reaction only gave the desired product with the yield of 10% after 72 h (entry 2). This may be related to the base KOH, and KOH dosage was related to the dosage of amino acid. When controlling the feed ratio of amino acid **2f** and (5*S*)-5-menthoxy-3,4-dibromo-2(5*H*)-furanone **1a** as 1:1, we found that the yield indeed had an increase (entry 3). And further reducing the dosage of base K_2CO_3 made the yield increase to 17% finally (entry 4).

Even so, this result was still very disappointing. Monitored by TLC, we observed that the reaction proceeded very slowly, especially in the later two steps it was difficult to react completely. Compared with the above three-component one-pot reaction, we thought that in this one-pot four-component process the solvent EtOH added in the first step of Michael addition–elimination reaction might seriously affect the consecutive two steps, and the subsequent results proved this guess.

Firstly, if only EtOH was as the solvent, there was no target product generated (entry 5). The failure was due to that no click

Table 4
Condition optimization for four-component one-pot method



Entry[a]	**1a**/**2f**/K_2CO_3/Cu(II)/Cu	Solvent (EtOH/CH_3CN, volume ratio)	Yield[b] (%)
1	1.0:1.5:1.0:0.1:0.2	1:1	0
2	1.0:1.5:1.0:1.2:1.5	1:1	10
3	1.0:1.0:1.0:1.2:1.5	1:1	13
4	1.0:1.0:0.5:0.6:0.75	1:1	17
5	1.0:1.0:0.5:0.6:0.75	1:0	0
6	1.0:1.0:0.5:0.6:0.75	0:1	0
7	1.0:1.0:0.5:0.6:0.75	1:4	25
8	1.0:1.0:0.5:0.6:0.75	1:8	40
9	1.0:1.0:0.5:0.6:0.75	1:10	40
10[c]	1.0:1.0:0.5:0.6:0.75	1:8	37
11[d]	1.0:1.0:0.5:0.6:0.75	1:8	44

[a] Reaction conditions: (5*S*)-5-menthoxy-3,4-dibromo-2(5*H*)-furanone **1a** 1.0 mmol, KOH 1.3 equiv of **2f**, propargyl bromide 1.0 equiv, hexyl azide **5b** 1.5 equiv.
[b] Isolated yield.
[c] Molecular sieves (4 Å) were used as an additive.
[d] Tetrabutyl ammonium bromide (TBAB) (0.2 equiv) was used as an additive.

reaction proceeded in the last step according to the monitoring by TLC. So, it was not appropriate to choose EtOH as solvent for this one-pot four-component process. However, the test of using pure CH_3CN as solvent also failed (entry 6), because amino acid **2f** and KOH added in the first step could not dissolve in this solvent, and Michael addition–elimination reaction couldn't take place.

Therefore, the process of adding CH_3CN into the reaction system after the first step reaction was completed and the selection of the mixed solvent should be necessary in the one-pot reaction. It could be seen from the entries 4 and 7–9, the higher the ratio of CH_3CN in mixed solvent (EtOH/CH_3CN), the higher the yield of the product. While the ratio of CH_3CN further increased, the yield would not continue to improve. Thus, we chose the mixed solvent (EtOH/CH_3CN=1:8) as the best solvent system (entry 8).

Because water was disadvantageous for the substitution,[3u] but small amount of water was generated in the first step of the one-pot reaction, a little 4 Å molecular sieve was added to avoid the interference of water. However, the effect was not obvious, even the yield dropped slightly (entry 10). At the same time, in consideration of involving a variety of substances in the reaction system, especially some inorganic compounds, which may be disadvantageous for the final cycloaddition reaction, TBAB as phase-transfer agent was added, and it played a certain role (entry 11).

In these cases, the appropriate conditions for this four-component one-pot reaction can be summarized below: (5*S*)-5-menthoxy-3,4-dibromo-2(5*H*)-furanone **1a** 1 equiv, amino acid **2f** 1 equiv, K_2CO_3 0.5 equiv, $Cu(OAc)_2 \cdot H_2O$ 0.6 equiv, Cu 0.75 equiv, additive TBAB 0.2 equiv, and using mixed solvent EtOH/CH_2Cl_2/CH_3CN (1:2:8, volume ratio).

Under the optimized conditions, the reactions of some representative substrates were examined (Table 5). It could be seen that, most of isolated yields were equal to or over 38%. Compared with the fractional-step method, some yields of one-pot method were basically equal to the corresponding cumulative yields. However, it was obvious that the four-component one-pot method was advantageous to effectively improve the yields for the cases that fractional-step method gave the lower cumulative yields.

Table 5
A yield comparison between four-component one-pot method and fractional-step method both using (5*S*)-5-alkoxy-3,4-dibromo-2(5*H*)-furanones **1** and amino acids **2** as starting materials

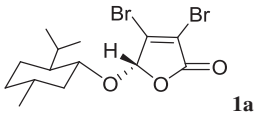
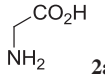
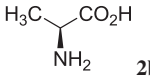
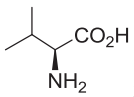
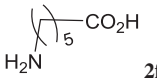
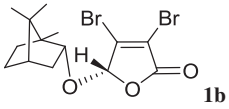
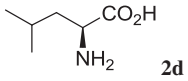
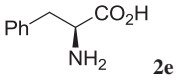
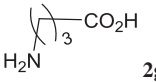
Entry	(5*S*)-5-Alkoxy-2(5*H*)-furanones **1**	Amino acids **2**	Compounds **6**	Yield of one-pot[a] (%)	Yield of fractional-step[b] (%)
1	 **1a**	 **2a**	**6aab**	28	14
2	**1a**	 **2b**	**6abb**	44	35
3	**1a**	 **2c**	**6acb**	45	42

Table 5 (*continued*)

Entry	(5*S*)-5-Alkoxy-2(5*H*)-furanones **1**	Amino acids **2**	Compounds **6**	Yield of one-pot[a] (%)	Yield of fractional-step[b] (%)
4	**1a**	 **2f**	**6afb**	44	41
5	 **1b**	**2a**	**6bab**	28	15
6	**1b**	 **2d**	**6bdb**	33	36
7	**1b**	 **2e**	**6beb**	42	44
8	**1b**	**2f**	**6bfb**	38	39
9	**1b**	 **2g**	**6bgb**	41	26

[a] Isolated yield under the reaction conditions: 5-alkoxy-3,4-dibromo-2(5*H*)-furanones **1** 1 mmol, amino acids **2** 1 equiv, KOH 1.3 equiv, 1 mL, 40 °C, 24 h; then, K_2CO_3 0.5 equiv, propargyl bromide 1 equiv, TBAB 0.2 equiv, CH_3CN 8 mL, 40 °C, 24 h; finally, hexyl azide **5b** 1.5 equiv, $Cu(OAc)_2\cdot H_2O$ 0.6 equiv, Cu 0.75 equiv, rt, 24 h.

[b] The cumulative yield is based on the isolated yield of three steps according to Scheme 1 using 5-alkoxy-3,4-dibromo-2(5*H*)-furanones **1** and amino acids **2** as starting materials.

3. Conclusion

In summary, a series of novel chiral 2(5*H*)-furanone derivatives containing 1,2,3-triazole moiety with potential biological activity were designed and synthesized from available (5*S*)-5-alkoxy-3,4-dibromo-2(5*H*)-furanones, amino acids, propargyl bromide, and organic azides through an asymmetric Michael addition–elimination, substitution, and cycloaddition under mild conditions with economical catalysts. They also could be generated via a simple and efficient multi-component one-pot approach. Due to the diversity of 5-alkoxy-3,4-dihalo-2(5*H*)-furanones,[1k,3s] amino acids, and organic azides, these serial investigations provide a theoretical and practical basis for the combination of three bioactive units, which is very advantageous for the synthesis of more 2(5*H*)-furanone derivatives, especially chiral 2(5*H*)-furanone compounds with polyfunctional groups. Future efforts will continue to focus on their biological evaluation and the new development of other diverse and functionalized libraries.

4. Experimental section

4.1. General

All the melting points were determined on an X-5 digital melting points apparatus and were uncorrected. Infrared spectra were recorded on a Bruker Vector 33 FT-IR instrument by liquid film method in the absorption range of 4000–400 cm^{-1}. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Varian DRX-400 MHz spectrometer and tetramethylsilane (TMS) was used as an internal standard. UV absorption peaks were measured by Shimazu UV-2550 ultraviolet absorption detector with dichloromethane as a solvent. Optical rotations were determined with an Autopol IV polarimeter in C_2H_5OH in a 10 cm cell. Elemental analysis was performed on a Thermo Flashea TM 112 elemental analyzer. The mass spectra (MS) were recorded on Thermo LCQ DECA XP MAX mass spectrometer.

All reagents and solvents were commercially available and used as received. The intermediates *N*-[(5*S*)-5-alkoxy-2(5*H*)-furanonyl] amino acids **3** and *N*-[(5*S*)-5-alkoxy-2(5*H*)-furanonyl] amino acid propargyl esters **4** were prepared according to the literature.[1k,3s–3u]

4.2. General procedure for the synthesis of target compounds 6 from propargyl esters 4 (fractional-step method)

A flame-dried 25-mL round-bottomed flask was charged with *N*-[(5*S*)-5-alkoxy-2(5*H*)-furanonyl] amino acid propargyl esters **4** (1 mmol) organic azides **5**[17] (1.5 mmol), copper acetate monohydrate [$Cu(OAc)_2\cdot H_2O$] (5% mmol), and copper powder (10% mmol) in CH_3CN (5 mL). The mixture was stirred at room temperature, and the reaction was monitored by TLC. After the completion of the reaction (about 4 h), the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with ethyl acetate (3×30 mL). Then, the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The purification of the residue by silica gel column chromatography yielded the desired compounds **6** in 32–85% isolated yields (mostly equal to or over 67%, Table 2, entries 1–32).

4.3. General procedure for the synthesis of target compounds 6 via three-component one-pot approach

A flame-dried flask was charged with *N*-[(5*S*)-5-alkoxy-2(5*H*)-furanonyl] amino acids **3** (1 mmol) and anhydrous K_2CO_3 (1.5 mmol) in CH_3CN (5 mL). The mixture was stirred for 30 min under N_2 atmosphere. Then, propargyl bromide (2 mmol) was added, and the resulting mixture was stirred at 40 °C. After 8 h, the chiral synthon **3** had been consumed according to the monitoring by TLC. At last, organic azides **5** (2 mmol), $Cu(OAc)_2\cdot H_2O$ (1.8 mmol), and Cu (2.2 mmol) were added in order, and the mixture was stirred at room temperature and monitored by TLC. Once the reaction was completed (about 24 h), the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and

extracted with ethyl acetate (3×30 mL). The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography using the mixture of petroleum ether and ethyl acetate as eluent to obtain the target compounds **6** in 30–68% isolated yields (mostly equal to or over 50%, Table 3, entries 1–32).

4.4. General procedure for the synthesis of target compounds 6 via four-component one-pot approach

A solution of (5*S*)-5-alkoxy-3,4-dibromo-2(5*H*)-furanones **1** (1 mmol) in dichloromethane (2 mL) was added in dropwise with vigorous stirring into a solution of amino acids **2** (1 mmol) and KOH (1.3 mmol) in ethanol (1 mL), and the mixture was stirred at 40 °C for 24 h under N_2 atmosphere. Then, propargyl bromide (1 mmol), K_2CO_3 (0.5 mmol), tetrabutyl ammonium bromide (0.2 mmol), and solvent CH_3CN (8 mL) were added, and the reaction continued for 24 h. Finally, organic azides **5** (1.5 mmol), $Cu(OAc)_2\cdot H_2O$ (0.6 mmol), and Cu (0.75 mmol) were added to the flask, and the resulting mixture was stirred at room temperature until the monitoring by TLC showed almost complete conversion of the substrate (about 24 h). Then, according to the procedure mentioned above, the reaction mixture was treated to obtain some representative target compounds **6** in 28–48% isolated yields (mostly equal to or over 38%, Table 5, entries 1–9).

4.5. Characterization data for compounds 6

*4.5.1. (1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)acetate (**6aaa**).* Yellow oil, yield 77%. $[\alpha]_D^{20}$ 150.1 (*c* 0.059, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 269 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.79 (d, *J*=4.0 Hz, 3H), 0.82–0.95 (m, 7H), 0.96–1.12 (m, 2H), 1.30–1.42 (m, 2H), 1.61–1.71 (m, 2H), 2.04–2.26 (m, 2H), 3.50–3.64 (m, 1H), 4.33 (s, 2H), 5.31 (s, 2H), 5.48 (b, 1H), 5.53 (s, 2H), 5.74 (s, 1H), 7.26–7.46 (m, 5H), 7.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 15.71, 21.03, 22.10, 22.73, 25.60, 31.56, 33.88, 42.25, 44.51, 48.00, 54.25, 58.81, 77.33, 82.36, 98.97, 123.98, 128.16, 128.91, 129.17, 134.16, 141.98, 158.30, 167.53, 168.85; IR (film) ν, cm^{-1}: 3357, 3046, 2954, 2923, 2852, 1753, 1652, 1528, 1454, 1331, 1191, 1128, 936, 744, 697, 549; ESI-MS *m*/*z* (%): 561 ($[M+H]^+$, 34), 583 ($[M+Na]^+$, 94); Anal. Calcd for $C_{26}H_{33}BrN_4O_5$: C 55.62, H 5.92, N 9.98, found: C 55.55, H 5.98, N 10.08.

*4.5.2. (S)-(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)propanoate (**6aba**).* Yellow oil, yield 63%. $[\alpha]_D^{20}$ 89.3 (*c* 0.073, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 269 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.82 (d, *J*=4.0 Hz, 3H), 0.83–0.97 (m, 7H), 0.98–1.13 (m, 2H), 1.29–1.42 (m, 2H), 1.50 (d, *J*=4.0 Hz, 3H), 1.59–1.73 (m, 2H), 2.05–2.26 (m, 2H), 3.51–3.62 (ddd, J_1=4.0 Hz, J_2=4.0 Hz, J_3=4.0 Hz, 1H), 4.80 (b, 1H), 5.26–5.35 (m, 2H), 5.36–5.44 (m, 1H), 5.53 (s, 2H), 5.72 (s, 1H), 7.27–7.45 (m, 5H), 7.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 15.87, 20.26, 20.89, 22.07, 22.91, 25.88, 31.52, 33.88, 42.22, 47.89, 50.79, 54.18, 58.86, 82.63, 99.10, 104.99, 123.95, 128.10, 128.83, 129.11, 134.26, 141.99, 157.08, 167.62, 171.76; IR (film) ν, cm^{-1}: 3374, 3065, 3028, 2951, 2923, 2868, 1750, 1649, 1523, 1493, 1454, 1325, 1196, 1130, 955, 744, 697, 576; ESI-MS *m*/*z* (%): 577 ([M+H], 23), 599 ($[M+Na]^+$, 100); Anal. Calcd for $C_{27}H_{35}BrN_4O_5$: C 56.35, H 6.13, N 9.74, found: C 56.30, H 6.05, N 9.68.

*4.5.3. (S)-(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)-3-methylbutanoate (**6aca**).* Yellow solid, yield 70%. Mp 118.2–119.0 °C; $[\alpha]_D^{20}$ 75.9 (*c* 0.057, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 269 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.82 (d, *J*=8.0 Hz, 3H), 0.84–0.96 (m, 13H), 0.97–1.12 (m, 2H), 1.30–1.44 (m, 2H), 1.60–1.71 (m, 2H), 2.08–2.28 (m, 3H), 3.51–3.60 (ddd, J_1=4.0 Hz, J_2=4.0 Hz, J_3=4.0 Hz, 1H), 4.77 (b, 1H), 5.23 (d, *J*=8.0 Hz, 1H), 5.27–5.35 (m, 2H), 5.49–5.58 (m, 2H), 5.70 (s, 1H), 7.26–7.31 (m, 5H), 7.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 15.67, 17.23, 17.87, 20.87, 22.07, 22.71, 25.78, 31.50, 32.13, 33.86, 42.22, 47.88, 54.18, 58.54, 59.64, 77.38, 83.20, 99.83, 124.00, 128.04, 128.82, 129.10, 134.31, 142.10, 157.27, 167.66, 170.43; IR (film) ν, cm^{-1}: 3379, 3060, 2956, 2929, 2868, 1745, 1652, 1520, 1454, 1328, 1191, 1133.09, 955, 746, 697, 557; ESI-MS *m*/*z* (%): 603 ($[M+H]^+$, 63), 625 ($[M+Na]^+$, 96); Anal. Calcd for $C_{29}H_{39}BrN_4O_5$: C 57.71, H 6.51, N 9.28, found: C 57.46, H 6.76, N 8.99.

*4.5.4. (S)-(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)-4-methylpentanoate (**6ada**).* Yellowish oil, yield 75%. $[\alpha]_D^{20}$ 40.4 (*c* 0.069, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 268 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.80 (d, *J*=8.0 Hz, 3H), 0.82–0.96 (m, 13H), 0.97–1.10 (m, 2H), 1.28–1.45 (m, 2H), 1.59–1.75 (m, 5H), 2.06–2.25 (m, 2H), 3.51–3.62 (ddd, J_1=4.0 Hz, J_2=4.0 Hz, J_3=4.0 Hz, 1H), 4.69–4.90 (m, 1H), 5.21–5.35 (m, 3H), 5.53 (s, 2H), 5.73 (s, 1H), 7.26–7.41 (m, 5H), 7.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 15.83, 20.93, 21.81, 22.09, 22.62, 22.75, 24.56, 25.79, 31.47, 33.85, 42.06, 42.22, 47.88, 54.12, 58.41, 58.64, 77.48, 82.39, 99.10, 124.06, 128.05, 128.77, 129.08, 134.34, 142.11, 157.80, 167.77, 171.67; IR (film) ν, cm^{-1}: 3302, 3066, 2956, 2923, 2874, 1748, 1649, 1556, 1454, 1328, 1188, 1128, 958, 7468, 700, 576; ESI-MS *m*/*z* (%): 619 ($[M+H]^+$, 58), 641 ($[M+Na]^+$, 100); Anal. Calcd for $C_{30}H_{41}BrN_4O_5$: C 58.34, H 6.69, N 9.07, found: 58.08, H 6.92, N 9.29.

*4.5.5. (S)-(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)-3-phenylpropanoate (**6aea**).* Yellowish solid, yield 67%. Mp 58.3–58.9 °C; $[\alpha]_D^{20}$ 105.8 (*c* 0.093, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 272 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.70 (d, *J*=4.0 Hz, 3H), 0.74–0.91 (m, 7H), 0.92–1.07 (m, 2H), 1.19–1.39 (m, 2H), 1.53–1.70 (m, 2H), 1.85–2.15 (m, 2H), 3.04–3.24 (m, 2H), 3.34–3.54 (m, 1H), 5.09 (b, 1H), 5.28 (s, 2H), 5.32–5.44 (m, 1H), 5.51 (s, 3H), 6.97–7.25 (m, 5H), 7.26–7.46 (m, 5H), 7.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 15.51, 21.02, 22.13, 22.61, 25.40, 31.50, 33.88, 39.82, 42.23, 47.83, 54.16, 56.08, 58.89, 77.56, 82.86, 99.38, 124.24, 127.53, 128.18, 128.65, 128.84, 129.13, 129.49, 134.34, 141.84, 156.91, 167.52, 170.08; IR (film) ν, cm^{-1}: 3374, 3027, 2951, 2923, 2868, 1750, 1652, 1517, 1495, 1454, 1325, 1182, 1122, 955, 744, 700, 562; ESI-MS *m*/*z* (%): 653 ($[M+H]^+$, 54), 675 ($[M+Na]^+$, 100); Anal. Calcd for $C_{33}H_{39}BrN_4O_5$: C 60.83, H 6.03, N 8.60, found: C 61.01, H 6.10, N 8.32.

*4.5.6. (1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 6-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)hexanoate (**6afa**).* Yellow oil, yield 71%. $[\alpha]_D^{20}$ 46.5 (*c* 0.073, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 273 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.80 (d, *J*=8.0 Hz, 3H), 0.86–0.98 (m, 7H), 1.00–1.15 (m, 2H), 1.31–1.43 (m, 4H), 1.57–1.72 (m, 6H), 2.08–2.28 (m, 2H), 2.34 (t, *J*=8.0 Hz, 2H), 3.37–3.52 (m, 2H), 3.53–3.62 (ddd, J_1=4.0 Hz, J_2=4.0 Hz, J_3=4.0 Hz, 1H), 4.84 (s, 1H), 5.19 (s, 2H), 5.53 (s, 2H), 5.74 (s, 1H), 7.26–7.45 (m, 5H), 7.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 15.86, 21.08, 22.13, 22.73, 24.23, 25.39, 25.71, 30.16, 31.53, 33.69, 33.88, 42.35, 43.59, 48.04, 54.11, 57.42, 77.42, 81.57, 98.46, 123.70, 128.07, 128.74, 129.06, 134.39, 142.95, 159.82, 168.00, 173.06; IR (film) ν, cm^{-1}: 3346, 3072, 3026, 2918, 2852, 1734, 1638, 1495, 1454, 1314, 1155, 1119, 933, 744, 694, 574; ESI-MS *m*/*z* (%): 619 ($[M+H]^+$, 18), 641 ($[M+Na]^+$, 100); Anal. Calcd for $C_{30}H_{41}BrN_4O_5$: C 58.34, H 6.69, N 9.07, found: 58.20, H 6.75, N 9.13.

*4.5.7. (1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 4-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)butanoate (**6aga**).* Yellow oil, yield 80%. $[\alpha]_D^{20}$ 88.9 (*c* 0.049, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 273 nm; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.77 (d, *J*=4.0 Hz, 3H), 0.81–0.95 (m, 7H), 0.96–1.13 (m, 2H), 1.26–1.41 (m, 2H), 1.59–1.70 (m, 2H), 1.89–1.99 (m, 2H), 2.10–2.27 (m, 2H), 2.43 (t, *J*=8.0 Hz, 2H), 3.46–3.64 (m, 3H), 5.19 (s, 2H), 5.52 (s, 2H), 5.64 (s, 1H), 5.78 (s, 1H), 7.26–7.44 (m, 5H), 7.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 15.80, 21.11, 22.15, 22.72, 25.10, 25.34, 30.89, 31.53, 33.89, 42.33, 43.03, 48.06, 54.15, 57.75, 77.44, 81.56, 98.43, 123.70, 128.11, 128.78, 129.09, 134.36, 142.71, 159.73, 168.08, 172.74; IR (film) ν, cm^{-1}: 3324, 3069, 3039, 2951, 2923, 2868, 1742, 1646, 1525, 1498, 1454, 1325, 1166, 1122, 947, 746, 697, 582; ESI-MS *m*/*z* (%): 589 ($[M+H]^+$, 44), 611 ($[M+Na]^+$, 100); Anal. Calcd for $C_{28}H_{37}BrN_4O_5$: C 57.05, H 6.33, N 9.50, found: C 57.17, H 6.44, N 9.48.

*4.5.8. (S)-(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)-2-phenylacetate (**6aha**).* Yellow oil, yield 54%. $[\alpha]_D^{20}$ 90.8 (c 0.054, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 269 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.78 (d, *J*=8.0 Hz, 3H), 0.82–0.97 (m, 7H), 0.98–1.17 (m, 2H), 1.23–1.39 (m, 2H), 1.57–1.78 (m, 2H), 2.05–2.33 (m, 2H), 3.48–3.62 (m, 1H), 5.17–5.37 (m, 2H), 5.40–5.55 (m, 2H), 5.56–6.06 (m, 3H), 7.06–7.74 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 15.83, 21.01, 22.09, 22.82, 25.78, 31.54, 33.88, 42.10, 47.98, 54.17, 58.49, 59.36, 83.29, 85.38, 100.21, 123.66, 126.45, 126.80, 128.06, 128.86, 129.14, 129.27, 134.24, 135.57, 141.91, 163.44, 167.58, 169.85; IR (film) ν, cm^{-1}: 3374, 3028, 2951, 2923, 2868, 1750, 1652, 1512, 1495, 1454, 1317, 1169, 1125, 958, 746, 697, 576; ESI-MS *m*/*z* (%): 637 ($[M+H]^+$, 41), 659 ($[M+Na]^+$, 100); Anal. Calcd for $C_{32}H_{37}BrN_4O_5$: C 60.28, H 5.85, N 8.79, found: C 60.31, H 5.78, N 8.82.

*4.5.9. (1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)acetate (**6baa**).* Yellowish oil, yield 62%. $[\alpha]_D^{20}$ 49.1 (*c* 0.024, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 267 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.85 (s, 9H), 1.22–1.28 (m, 4H), 1.65–1.79 (m, 2H), 2.20–2.29 (m, 1H), 3.91–3.99 (m, 1H), 4.28 (s, 2H), 5.32 (s, 2H), 5.34–5.40 (m, 1H), 5.53 (s, 2H), 5.71 (s, 1H), 7.27–7.45 (m, 5H), 7.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.96, 18.77, 19.60, 26.55, 27.94, 36.98, 44.67, 44.80, 47.61, 49.42, 54.30, 58.78, 77.26, 87.84, 99.28, 123.96, 128.19, 128.97, 129.21, 134.12, 141.98, 158.58, 167.25, 168.90; IR (film) ν, cm^{-1}: 3346, 3072, 3034, 2945, 2923, 2852, 1753, 1649, 1528, 1492, 1454, 1320, 1188, 1130, 952, 746, 697, 576; ESI-MS *m*/*z* (%): 561 ($[M+H]^+$, 100), 583 ($[M+Na]^+$, 94); Anal. Calcd for $C_{26}H_{31}BrN_4O_5$: C 55.82, H 5.59, N 10.01, found: C 55.75, H 5.52, N 9.97.

*4.5.10. (S)-(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bro-mo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)propanoate (**6bba**).* Yellow oil, yield 74%. $[\alpha]_D^{20}$ 117.5 (*c* 0.046, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 269 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.84 (s, 6H), 0.86 (s, 3H), 1.18–1.27 (m, 4H), 1.50 (d, *J*=8.0 Hz, 3H), 1.63–1.77 (m, 2H), 2.18–2.28 (m, 1H), 3.95 (d, *J*=12.0 Hz, 1H), 4.72 (b, 1H), 5.30 (s, 2H), 5.38–5.47 (m, 1H), 5.54 (s, 2H), 5.71 (s, 1H), 7.26–7.43 (m, 5H), 7.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.85, 18.76, 19.59, 20.12, 26.49, 27.91, 37.06, 44.78, 47.58, 49.41, 51.10, 54.26, 58.85, 77.32, 87.61, 99.28, 123.87, 128.12, 128.90, 129.16, 134.19, 142.07, 157.44, 167.32, 171.79; IR (film) ν, cm^{-1}: 3313, 3071, 3035, 2951, 2923, 2854, 1750, 1649, 1557, 1496, 1454, 1325, 1199, 1141, 958, 744, 700, 554; ESI-MS *m*/*z* (%): 573 ($[M+H]^+$, 30), 595 ($[M+Na]^+$, 100); Anal. Calcd for $C_{27}H_{33}BrN_4O_5$: C 56.55, H 5.80, N 9.77, found: C 56.61, H 5.74, N 9.82.

*4.5.11. (S)-(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bro-mo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)-3-methylbutanoate (**6bca**).* Yellow oil, yield 61%. $[\alpha]_D^{20}$ −141.8 (*c* 0.049, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 269 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.71–0.94 (m, 15H), 1.10–1.34 (m, 4H), 1.63–1.75 (m, 2H), 2.13–2.29 (m, 2H), 3.96 (d, *J*=8.0 Hz, 1H), 4.53 (b, 1H), 5.24–5.36 (m, 3H), 5.54 (s, 2H), 5.68 (s, 1H), 7.26–7.44 (m, 5H), 7.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.89, 17.26, 18.16, 18.75, 19.57, 26.40, 27.86, 32.14, 36.97, 44.77, 47.52, 49.41, 54.14, 58.52, 60.16, 77.42, 87.97, 99.58, 124.01, 128.00, 128.79, 129.08, 134.35, 142.12, 158.83, 167.52, 170.47; IR (film) ν, cm^{-1}: 3321, 3074, 2953, 2877, 1748, 1649, 1523, 1455, 1329, 1195, 1134, 956, 745, 696, 545; ESI-MS *m*/*z* (%): 601 ($[M+H]^+$, 33), 623 ($[M+Na]^+$, 100); Anal. Calcd for $C_{29}H_{37}BrN_4O_5$: C 57.90, H 6.20, N 9.31, found: C 57.82, H 6.27, N 9.29.

*4.5.12. (S)-(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bro-mo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)-4-methylpentanoate (**6bda**).* Yellow oil, yield 82%. $[\alpha]_D^{20}$ 102.1 (*c* 0.019, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 270 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.84 (s, 6H), 0.86 (s, 3H), 0.92 (d, *J*=4.0 Hz, 6H), 1.08–1.32 (m, 4H), 1.60–1.75 (m, 5H), 2.14–2.27 (m, 1H), 3.95 (d, *J*=8.0 Hz, 1H), 4.65 (b, 1H), 5.18–5.34 (m, 3H), 5.53 (s, 2H), 5.68 (s, 1H), 7.26–7.44 (m, 5H), 7.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.85, 18.76, 19.59, 21.86, 22.71, 24.65, 26.37, 27.88, 37.10, 42.24, 44.78, 47.55, 49.40, 54.22, 54.54, 58.68, 77.33, 88.03, 99.43, 123.90, 128.09, 128.88, 129.16, 134.25, 142.18, 158.12, 167.17, 171.66; IR (film) ν, cm^{-1}: 3313, 3071, 2951, 2874, 1748, 1649, 1556, 1454, 1331, 1144, 1130, 958, 746, 697, 573; ESI-MS *m*/*z* (%): 617 ($[M+H]^+$, 67), 639 ($[M+Na]^+$, 100); Anal. Calcd for $C_{30}H_{39}BrN_4O_5$: C 58.54, H 6.39, N 9.10, found: 58.47, H 6.32, N 9.07.

*4.5.13. (S)-(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bro-mo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)-3-phenylpropanoate (**6bea**).* White solid, yield 57%. Mp 62.8–64.4 °C; $[\alpha]_D^{20}$ 93.7 (*c* 0.078, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 270 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.81 (s, 3H), 0.82 (s, 3H), 0.83 (s, 3H), 1.10–1.30 (m, 4H), 1.59–1.72 (m, 2H), 2.03–2.23 (m, 1H), 2.92–3.22 (m, 2H), 3.72–3.87 (m, 1H), 4.74 (b, 1H), 5.22–5.35 (m, 3H), 5.53 (s, 3H), 7.02–7.10 (m, 2H), 7.17–7.25 (m, 3H), 7.26–7.45 (m, 5H), 7.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.98, 18.74, 19.60, 26.46, 27.91, 36.84, 39.88, 44.77, 47.53, 49.37, 54.25, 56.55, 58.89, 77.35, 88.10, 99.38, 124.04, 127.70, 128.16, 128.89, 128.93, 129.19, 129.41, 134.22, 141.97, 157.55, 167.12, 170.23; IR (film) ν, cm^{-1}: 3357, 3055, 3033, 2951, 2923, 2852, 1751, 1649, 1521, 1495, 1454, 1322, 1177, 1128, 955, 744, 700, 560; ESI-MS *m*/*z* (%): 649 ($[M+H]^+$, 36), 671 ($[M+Na]^+$, 100); Anal. Calcd for $C_{33}H_{37}BrN_4O_5$: C 61.02, H 5.74, N 8.63, found: C 61.30, H 5.46, N 8.38.

*4.5.14. (1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 6-((S)-4-bromo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)hexanoate (**6bfa**).* Yellow oil, yield 67%. $[\alpha]_D^{20}$ 55.0 (*c* 0.068, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 273 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.85 (s, 6H), 0.88 (s, 3H), 1.14–1.33 (m, 4H), 1.34–1.44 (m, 2H), 1.62–1.91 (m, 6H), 2.18–2.28 (m, 1H), 2.32 (t, *J*=8.0 Hz, 2H), 3.35–3.57 (m, 2H), 3.99 (d, *J*=8.0 Hz, 1H), 5.17 (s, 2H), 5.53 (s, 2H), 5.78 (s, 2H), 7.26–7.41 (m, 5H), 7.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.92, 18.78, 19.60, 24.23, 25.77, 26.54, 27.97, 30.15, 33.70, 37.00, 43.90, 44.78, 47.48, 49.37, 54.07, 57.40, 77.54, 87.21, 99.14, 123.81, 128.05, 128.70, 129.03, 134.45, 142.92, 160.19, 168.08, 173.10; IR (film) ν, cm^{-1}: 3313, 3066, 3029, 2951, 2874, 1742, 1646, 1540.72, 1495, 1454, 1320, 1155, 1128, 955, 741, 697, 579; ESI-MS *m*/*z* (%): 617 ($[M+H]^+$, 35), 639 ($[M+Na]^+$, 100); Anal. Calcd for $C_{30}H_{39}BrN_4O_5$: C 58.54, H 6.39, N 9.10, found: C 58.47, H 6.41, N 9.06.

*4.5.15. (1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 4-((S)-4-bromo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)butanoate (**6bga**).* Yellowish oil, yield 76%. $[\alpha]_D^{20}$ 87.5 (*c* 0.034, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 272 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.85 (s, 6H), 0.87 (s, 3H), 1.17–1.32 (m, 4H), 1.64–1.86 (m, 2H), 1.92–2.02 (m, 2H), 2.20–2.29 (m, 1H), 2.45 (t, *J*=8.0 Hz, 2H), 3.44–3.60 (m, 2H), 3.98 (d, *J*=8.0 Hz, 1H), 5.20 (s, 2H), 5.53 (s, 2H), 5.58 (b, 1H), 5.73 (s, 1H), 7.26–7.43 (m, 5H), 7.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.99, 18.79, 19.61, 25.27, 26.58, 27.97, 31.07, 37.02, 43.39, 44.81, 47.56, 49.42, 54.21, 57.80, 77.33, 87.52, 99.15, 123.61, 128.14, 128.85, 129.13, 134.32, 142.74, 159.78, 167.78, 172.86; IR (film) ν, cm^{-1}: 3313, 3060, 2951, 2879, 1742, 1646, 1528, 1495, 1454, 1322, 1166, 1130, 949, 746, 697, 576; ESI-MS *m*/*z* (%): 589 ($[M+H]^+$, 66), 611 ($[M+Na]^+$, 100); Anal. Calcd for $C_{28}H_{35}BrN_4O_5$: C 57.24, H 6.00, N 9.54, found: C 57.15, H 5.96, N 9.58.

*4.5.16. (S)-(1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bro-mo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)-2-phenylacetate (**6bha**).* Yellow oil, yield 32%. $[\alpha]_D^{20}$ 130.5 (*c* 0.053, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 269 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.79–0.95 (m, 9H), 1.21–1.30 (m, 4H), 1.63–1.86 (m, 2H), 2.11–2.31 (m, 1H), 3.83–3.99 (m, 1H), 5.22–5.36 (m, 2H), 5.40–5.53 (m, 2H), 5.54–5.73 (m, 2H), 6.05 (b, 1H), 7.05–7.59 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 14.27, 18.76, 19.62, 26.63, 27.96, 36.80, 44.81, 47.52, 49.49, 54.22, 58.47, 59.45, 77.24, 87.83, 99.57, 123.51, 126.47, 126.82, 128.05, 128.92, 129.17, 129.29, 134.16, 135.44, 141.97, 157.74, 167.26, 169.96; IR (film) ν, cm^{-1}: 3368, 3060, 3027, 2951, 2923, 1753, 1649, 1495, 1454, 1317, 1169, 1128, 958, 746, 694, 557; ESI-MS *m*/*z* (%): 637 ($[M+H]^+$, 20), 659 ($[M+Na]^+$, 100); Anal. Calcd for $C_{32}H_{35}BrN_4O_5$: C 60.47, H 5.55, N 8.82, found: C 60.54, H 5.49, N 8.78.

*4.5.17. (1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)acetate (**6aab**).* Yellow oil, yield 75%. $[\alpha]_D^{20}$ 170.5 (*c* 0.046, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 268 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.70 (d, *J*=8.0 Hz, 3H), 0.72–1.10 (m, 12H), 1.11–1.38 (m, 8H), 1.50–1.64 (m, 2H), 1.73–1.89 (m, 2H), 1.98–2.17 (m, 2H), 3.43–3.55 (ddd, J_1=4.0 Hz, J_2=4.0 Hz, J_3=4.0 Hz, 1H), 4.26 (t, *J*=8.0 Hz, 4H), 5.24 (s, 2H), 5.62 (s, 1H), 5.70 (s, 1H), 7.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.88, 15.67, 21.00, 22.06, 22.32, 22.69, 25.51, 26.02, 30.13, 31.01, 31.51, 33.85, 42.23, 44.51, 47.99, 50.44, 58.81, 77.37, 82.13, 98.86, 123.95, 141.49, 158.55, 167.57, 168.90; IR (film) ν, cm^{-1}: 3357, 3099, 2956, 2923, 2868, 1753, 1654, 1527, 1454, 1325, 1191, 1125, 936, 691; ESI-MS *m*/*z* (%): 557 ($[M+H]^+$, 48), 579 ($[M+Na]^+$, 100); Anal. Calcd for $C_{25}H_{39}BrN_4O_5$: C 54.05, H 7.08, N 10.09, found: C 53.94, H 7.16, N 9.97.

*4.5.18. (S)-(1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)propanoate (**6abb**).* Yellow oil, yield 76%. $[\alpha]_D^{20}$ 72.7 (*c* 0.066, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 268 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.84 (d, *J*=8.0 Hz, 3H), 0.86–0.95 (m, 10H), 0.98–1.13 (m, 2H), 1.27–1.39 (m, 8H), 1.52 (d, *J*=8.0 Hz, 3H), 1.61–1.73 (m, 2H), 1.82–1.97 (m, 2H), 2.01–2.26 (m, 2H), 3.48–3.66 (ddd, J_1=4.0 Hz, J_2=4.0 Hz, J_3=8.0 Hz, 1H), 4.37 (t, *J*=8.0 Hz, 2H), 4.82 (s, 1H), 5.17–5.47 (m, 3H), 5.74 (s, 1H), 7.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.88, 15.86, 20.30, 20.87, 22.02, 22.34, 22.91, 25.91, 26.03, 30.13, 31.02, 31.53, 33.88, 42.23, 47.90, 50.45, 50.80, 58.90, 77.32, 82.70, 99.11, 123.82, 141.51, 157.08, 167.56, 171.82; IR (film) ν, cm^{-1}: 3324, 3091, 2951, 2923, 2863, 1750, 1652, 1557.35, 1518, 1454, 1328, 1199, 1133, 958, 672; ESI-MS *m*/*z* (%): 569 ($[M+H]^+$, 37), 591 ($[M+Na]^+$, 100); Anal. Calcd for $C_{26}H_{41}BrN_4O_5$: C 54.83, H 7.26, N 9.84, found: C 54.87, H 7.19, N 9.80.

*4.5.19. (S)-(1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bro-mo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)-3-methylbutanoate (**6acb**).* Yellow oil, yield 71%. $[\alpha]_D^{20}$ −103.4 (*c* 0.046, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 269 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.85 (d, *J*=4.0 Hz, 3H), 0.86–1.01 (m, 16H), 1.02–1.14 (m, 2H), 1.23–1.45 (m, 8H), 1.61–1.73 (m, 2H), 1.84–1.97 (m, 2H), 2.08–2.30 (m, 3H), 3.52–3.62 (ddd, J_1=4.0 Hz, J_2=4.0 Hz, J_3=4.0 Hz, 1H), 4.37 (t, *J*=8.0 Hz, 2H), 4.79 (b, 1H), 5.21–5.42 (m, 3H), 5.72 (s, 1H), 7.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.91, 15.69, 17.27, 17.88, 20.87, 22.05, 22.36, 22.74, 25.82, 26.03, 30.18, 31.05, 31.53, 32.19, 33.87, 42.24, 47.91, 50.44, 58.64, 59.74, 77.31, 83.15, 99.76, 123.87, 141.61, 157.32, 167.71, 170.53; IR (film) ν, cm^{-1}: 3319, 3083, 2956.04, 2929, 2868, 1745, 1652, 1525, 1465, 1328, 1193, 1136, 955, 664; ESI-MS *m*/*z* (%): 599 ($[M+H]^+$, 100), 621 ($[M+Na]^+$, 99); Anal. Calcd for $C_{28}H_{45}BrN_4O_5$: C 56.28, H 7.59, N 9.38, found: C 56.32, H 7.65, N 9.41.

*4.5.20. (S)-(1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)-4-methylpentanoate (**6adb**).* Yellow oil, yield 73%. $[\alpha]_D^{20}$ −132.1 (*c* 0.050, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 268 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.82 (d, *J*=8.0 Hz, 3H), 0.83–0.99 (m, 16H), 1.00–1.13 (m, 2H), 1.24–1.44 (m, 8H), 1.59–1.79 (m, 5H), 1.84–1.96 (m, 2H), 2.06–2.26 (m, 2H), 3.53–3.64 (ddd, J_1=4.0 Hz, J_2=4.0 Hz, J_3=4.0 Hz, 1H), 4.37 (t, *J*=8.0 Hz, 2H), 4.82 (b, 1H), 5.15–5.38 (m, 3H), 5.75 (s, 1H), 7.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.89, 15.79, 20.88, 21.81, 22.03, 22.33, 22.59, 22.74, 24.57, 25.81, 26.01, 30.13, 31.00, 31.48, 33.83, 42.15, 42.22, 47.86, 50.39, 54.14, 58.72, 77.38, 82.58, 99.10, 123.90, 141.61, 157.68, 167.67, 171.74; IR (film) ν, cm^{-1}: 3302, 3084, 2956, 2929, 2868, 1748, 1649,1558, 1462, 1325, 1188, 1128, 958, 667; ESI-MS *m*/*z* (%): 611 ($[M+H]^+$, 100), 633 ($[M+Na]^+$, 80); Anal. Calcd for $C_{29}H_{47}BrN_4O_5$: C 56.95, H 7.75, N 9.16, found: C 57.03, H 7.72, N 9.22.

*4.5.21. (S)-(1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)-3-phenylpropanoate (**6aeb**).* Yellow oil, yield 74%. $[\alpha]_D^{20}$ 92.6 (*c* 0.040, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 272 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.72 (d, *J*=8.0 Hz, 3H), 0.81 (d, *J*=8.0 Hz, 3H), 0.84–0.95 (m, 7H), 0.96–1.11 (m, 2H), 1.21–1.39 (m, 8H), 1.56–1.71 (m, 2H), 1.86–1.94 (m, 2H), 2.07–2.41 (m, 2H), 3.07–3.26 (m, 2H), 3.37–3.50 (m, 1H), 4.36 (t, *J*=8.0 Hz, 2H), 4.81–5.17 (m, 2H), 5.33 (s, 3H), 7.01–7.12 (m, 2H), 7.24–7.33 (m, 3H), 7.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.93, 15.48, 20.97, 22.07, 22.36, 22.59, 25.41, 26.07, 30.16, 31.05, 31.51, 33.85, 39.96, 42.22, 47.83, 50.42, 55.99, 58.96, 77.40, 82.96, 98.67, 124.09, 127.54, 128.66, 129.49, 134.31, 141.38, 156.84, 167.44, 170.14; IR (film) ν, cm^{-1}: 3374, 3092, 3072, 3031, 2951, 2929, 2863, 1750, 1652, 1516, 1495, 1454, 1322, 1182, 1117, 955, 744, 700, 571; ESI-MS *m*/*z* (%): 647 ($[M+H]^+$, 98), 669 ($[M+Na]^+$, 100); Anal. Calcd for $C_{32}H_{45}BrN_4O_5$: C 59.53, H 7.03, N 8.68, found: C 59.48, H 6.97, N 8.62.

*4.5.22. (1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 6-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)hexanoate (**6afb**).* Yellow oil, yield 85%. $[\alpha]_D^{20}$ 165.2 (*c* 0.059, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 273 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.64–1.01 (m, 13H), 1.02–1.17 (m, 2H), 1.18–1.49 (m, 10H), 1.53–1.79 (m, 6H), 1.83–1.99 (m, 2H), 2.10–2.28 (m, 2H), 2.30–2.46 (m, 2H), 3.38–3.57 (m, 2H), 3.58–3.70 (m, 1H), 4.28–4.49 (m, 2H), 5.21 (s, 2H), 5.71 (s, 1H), 5.84 (s, 1H), 7.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.86, 15.78, 21.02, 22.08, 22.27, 22.66, 24.20, 25.23, 25.68, 25.95, 29.52, 30.08, 30.97, 31.43, 33.66, 33.83, 42.28, 43.43, 47.99, 50.28, 57.38, 77.51, 81.31, 98.36, 123.66, 142.36, 159.66, 168.15, 173.02; IR (film) ν, cm^{-1}: 3242, 3093, 2951, 2923, 2863, 1734, 1649, 1457, 1317, 1166, 1125,

938, 664; ESI-MS *m/z* (%): 613 ([M+H]$^+$, 19), 635 ([M+Na]$^+$, 100); Anal. Calcd for $C_{29}H_{47}BrN_4O_5$: C 56.95, H 7.75, N 9.16, found: C 57.04, H 7.81, N 9.20.

*4.5.23. (1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 4-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)butanoate (**6agb**).* Yellowish solid, yield 83%. Mp 115.0–115.6 °C; $[\alpha]_D^{20}$ 69.1 (*c* 0.080, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 273 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.79 (d, *J*=4.0 Hz, 3H), 0.81–1.00 (m, 10H), 1.01–1.17 (m, 2H), 1.24–1.44 (m, 8H), 1.61–1.74 (m, 2H), 1.84–1.93 (m, 2H), 1.94–2.04 (m, 2H), 2.11–2.28 (m, 2H), 2.46 (t, *J*=8.0 Hz, 2H), 3.43–3.65 (m, 3H), 4.36 (t, *J*=8.0 Hz, 2H), 5.23 (s, 2H), 5.46 (s, 1H), 5.78 (s, 1H), 7.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.92, 15.79, 21.09, 22.11, 22.36, 22.73, 25.36, 25.39, 26.07, 30.18, 30.96, 31.06, 31.57, 33.89, 42.35, 43.12, 48.07, 50.42, 57.86, 77.33, 81.65, 98.50, 123.53, 142.22, 159.79, 167.89, 172.81; IR (film) ν, cm^{-1}: 3324, 3090, 2951, 2923, 2868, 1742, 1649, 1525, 1457, 1322, 1166, 1122, 947, 667; ESI-MS *m/z* (%): 585 ([M+H]$^+$, 66), 607 ([M+Na]$^+$, 100); Anal. Calcd for $C_{27}H_{43}BrN_4O_5$: C 55.57, H 7.43, N 9.60, found: C 55.62, H 7.37, N 9.55.

*4.5.24. (S)-(1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-2-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)-2-phenylacetate (**6ahb**).* Yellow oil, yield 57%. $[\alpha]_D^{20}$ 72.9 (*c* 0.071, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 268 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.81 (d, *J*=8.0 Hz, 3H), 0.83–1.01 (m, 10H), 1.02–1.17 (m, 2H), 1.19–1.48 (m, 8H), 1.58–1.75 (m, 2H), 1.78–1.94 (m, 2H), 2.05–2.37 (m, 2H), 3.51–3.85 (ddd, J_1=4.0 Hz, J_2=4.0 Hz, J_3=4.0 Hz, 1H), 4.30 (t, *J*=8.0 Hz, 2H), 5.13–5.43 (m, 2H), 5.53–6.14 (m, 3H), 7.22–7.76 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ, ppm: 13.93, 15.80, 20.96, 22.05, 22.35, 22.78, 25.74, 26.00, 30.11, 31.03, 31.51, 33.86, 42.08, 47.96, 50.36, 58.49, 59.43, 83.22, 85.26, 100.18, 123.60, 126.46, 129.11, 129.24, 135.62, 141.37, 162.65, 169.60, 171.64; IR (film) ν, cm^{-1}: 3357, 3072, 3036, 2951, 2923, 2863, 1748, 1652, 1512, 1454, 1317, 1166, 1122, 958, 746, 697, 653; ESI-MS *m/z* (%): 633 ([M+H]$^+$, 95), 655 ([M+Na]$^+$, 100); Anal. Calcd for $C_{31}H_{43}BrN_4O_5$: C 58.95, H 6.86, N 8.87, found: C 59.03, H 6.91, N 8.85.

*4.5.25. (1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicy-clo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)acetate (**6bab**).* Yellow oil, yield 76%. $[\alpha]_D^{20}$ 159.5 (*c* 0.021, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 270 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.65–1.03 (m, 12H), 1.15–1.41 (m, 10H), 1.60–1.76 (m, 2H), 1.80–1.94 (m, 2H), 2.20–2.36 (m, 1H), 3.97 (d, *J*=12.0 Hz, 1H), 4.32 (s, 2H), 4.36 (t, *J*=8.0 Hz, 2H), 5.34 (s, 2H), 5.77 (s, 2H), 7.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.88, 13.92, 18.74, 19.56, 22.36, 26.06, 26.51, 27.92, 30.17, 31.05, 36.96, 44.67, 44.78, 47.57, 49.38, 50.49, 58.76, 77.31, 87.73, 99.30, 123.99, 141.49, 158.80, 167.43, 169.00; IR (film) ν, cm^{-1}: 3346, 3091, 2951, 2929, 2868, 1756, 1652, 1529, 1454, 1438, 1322, 1188, 1130, 952, 568; ESI-MS *m/z* (%): 555 ([M+H]$^+$, 14), 577 ([M+Na]$^+$, 100); Anal. Calcd for $C_{25}H_{37}BrN_4O_5$: C 54.25, H 6.74, N 10.12, found: C 54.30, H 6.69, N 10.08.

*4.5.26. (S)-(1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl-oxy)-2,5-dihydrofuran-3-ylamino)propanoate (**6bbb**).* Yellow oil, yield 77%. $[\alpha]_D^{20}$ 129.3 (*c* 0.048, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 270 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.67–1.03 (m, 12H), 1.09–1.45 (m, 10H), 1.53 (d, *J*=8.0 Hz, 3H), 1.62–1.73 (m, 2H), 1.78–1.93 (m, 2H), 2.18–2.29 (m, 1H), 3.97 (d, *J*=12.0 Hz, 1H), 4.37 (t, *J*=8.0 Hz, 2H), 4.75 (b, 1H), 5.34 (s, 2H), 5.43–5.58 (m, 1H), 5.75 (s, 1H), 7.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.83, 13.91, 18.74, 19.57, 20.14, 22.36, 26.05, 26.48, 27.91, 30.16, 31.04, 37.06, 44.79, 47.57, 49.41, 50.46, 51.11, 58.93, 77.32, 87.62, 99.28, 123.82, 141.57, 157.62, 167.36, 171.84; IR (film) ν, cm^{-1}: 3297, 3093, 2951, 2929, 2873, 1750, 1649, 1561, 1523, 1454, 1328, 1199, 1144, 955, 658; ESI-MS *m/z* (%): 569 ([M+H]$^+$, 97), 591 ([M+Na]$^+$, 100); Anal. Calcd for $C_{26}H_{39}BrN_4O_5$: C 55.03, H 6.93, N 9.87, found: C 54.98, H 7.04, N 9.82.

*4.5.27. (S)-(1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl-oxy)-2,5-dihydrofuran-3-ylamino)-3-methylbutanoate (**6bcb**).* Yellowish oil, yield 67%. $[\alpha]_D^{20}$ 132.5 (*c* 0.024, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 270 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.63–1.06 (m, 18H), 1.12–1.40 (m, 10H), 1.63–1.75 (m, 2H), 1.86–1.97 (m, 2H), 2.16–2.32 (m, 2H), 3.97 (d, *J*=8.0 Hz, 1H), 4.36 (t, *J*=8.0 Hz, 2H), 4.60 (b, 1H), 5.22–5.40 (m, 3H), 5.69 (s, 1H), 7.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.88, 17.26, 18.32, 18.71, 19.53, 22.33, 26.00, 26.40, 27.85, 30.15, 31.02, 32.19, 36.98, 44.79, 47.52, 49.41, 50.40, 58.58, 60.31, 77.33, 87.99, 99.53, 123.88, 141.59, 157.93, 167.17, 170.51; IR (film) ν, cm^{-1}: 3324, 3085, 2956, 2929, 2868, 1748, 1649, 1551, 1462, 1331, 1193, 1136, 955, 675; ESI-MS *m/z* (%): 597 ([M+H]$^+$, 12), 619 ([M+Na]$^+$, 100); Anal. Calcd for $C_{28}H_{43}BrN_4O_5$: C 56.47, H 7.28, N 9.41, found: C 56.51, H 7.36, N 9.38.

*4.5.28. (S)-(1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl-oxy)-2,5-dihydrofuran-3-ylamino)-4-methylpentanoate (**6bdb**).* Yellow oil, yield 75%. $[\alpha]_D^{20}$ 130.5 (*c* 0.062, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 270 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.58–1.06 (m, 18H), 1.07–1.47 (m, 10H), 1.62–1.79 (m, 5H), 1.85–1.97 (m, 2H), 2.15–2.32 (m, 1H), 3.98 (d, *J*=8.0 Hz, 1H), 4.37 (t, *J*=8.0 Hz, 2H), 4.74 (b, 1H), 5.32 (s, 2H), 5.57–5.68 (m, 1H), 5.75 (s, 1H), 7.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.71, 13.88, 18.69, 19.51, 21.72, 22.31, 22.69, 24.58, 25.97, 26.29, 27.84, 30.12, 30.99, 37.03, 42.00, 44.73, 47.44, 49.31, 50.34, 54.61, 58.67, 77.46, 87.78, 99.54, 123.90, 141.59, 158.52, 167.42, 171.65; IR (film) ν, cm^{-1}: 3286, 3085, 2956, 2929, 2868, 1750, 1649, 1559, 1465, 1333, 1144, 958, 678; ESI-MS *m/z* (%): 611 ([M+H]$^+$, 92), 633 ([M+Na]$^+$, 96); Anal. Calcd for $C_{29}H_{45}BrN_4O_5$: C 57.14, H 7.44, N 9.19, found: C 57.08, H 7.51, N 9.23.

*4.5.29. (S)-(1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl-oxy)-2,5-dihydrofuran-3-ylamino)-3-phenylpropanoate (**6beb**).* Yellow oil, yield 82%. $[\alpha]_D^{20}$ 73.2 (*c* 0.053, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 270 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.66–0.98 (m, 12H), 1.03–1.45 (m, 10H), 1.59–1.74 (m, 2H), 1.85–1.96 (m, 2H), 2.10–2.26 (m, 1H), 2.95–3.28 (m, 2H), 3.70–3.88 (m, 1H), 4.36 (t, *J*=8.0 Hz, 2H), 4.70 (b, 1H), 5.04–5.53 (m, 4H), 7.02–7.15 (m, 2H), 7.20–7.33 (m, 3H), 7.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.94, 13.95, 18.71, 19.56, 22.37, 26.08, 26.43, 27.89, 30.19, 31.06, 36.84, 39.88, 44.75, 47.50, 49.35, 50.44, 57.64, 58.94, 77.37, 88.06, 100.06, 124.03, 127.66, 128.87, 129.43, 134.79, 141.46, 158.73, 167.13, 170.25; IR (film) ν, cm^{-1}: 3313, 3092, 3060, 3030, 2951, 2929, 2868, 1753, 1652, 1526, 1496, 1454, 1322, 1177, 1130, 955, 744, 700, 560; ESI-MS *m/z* (%): 645 ([M+H]$^+$, 38), 667 ([M+Na]$^+$, 100); Anal. Calcd for $C_{32}H_{43}BrN_4O_5$: C 59.72, H 6.73, N 8.71, found: C 59.76, H 6.67, N 8.65.

*4.5.30. (1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 6-((S)-4-bromo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)hexanoate (**6bfb**).* Yellow oil, yield 77%. $[\alpha]_D^{20}$ 25.3 (*c* 0.051, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 273 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.68–0.99 (m, 12H), 1.03–1.51 (m, 12H), 1.52–1.81 (m, 6H), 1.84–1.94 (m, 2H), 2.17–2.29 (m, 1H), 2.35 (t, *J*=8.0 Hz, 2H), 3.35–3.61 (m, 2H), 4.00 (d, *J*=8.0 Hz, 1H), 4.37 (t, *J*=8.0 Hz, 2H), 5.20 (s, 2H), 5.81 (s, 1H), 5.97 (b, 1H), 7.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.80, 13.86, 18.69, 19.51, 22.27, 24.20, 25.75, 25.95, 26.46, 27.90, 30.09, 30.97, 33.67, 36.93, 43.94, 44.72, 47.40, 49.29, 50.28, 57.39, 77.55, 87.09, 99.07, 123.68, 142.38,

160.53, 167.98, 173.06; IR (film) ν, cm^{-1}: 3319, 3087, 2951, 2929, 2868, 1742, 1646, 1536, 1457, 1320, 1155, 1130, 952, 672; ESI-MS *m/z* (%): 611 ($[M+H]^+$, 100), 633 ($[M+Na]^+$, 77); Anal. Calcd for $C_{29}H_{45}BrN_4O_5$: C 57.14, H 7.44, N 9.19, found: C 57.26, H 7.50, N 9.13.

*4.5.31. (1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 4-((S)-4-bromo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)butanoate (**6bgb**).* Yellow oil, yield 70%. $[\alpha]_D^{20}$ 65.7 (*c* 0.113, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 272 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.76–0.96 (m, 12H), 1.12–1.43 (m, 10H), 1.61–1.76 (m, 2H), 1.86–1.94 (m, 2H), 1.95–2.05 (m, 2H), 2.20–2.30 (m, 1H), 2.43–2.53 (m, 2H), 3.45–3.64 (m, 2H), 4.00 (d, *J*=8.0 Hz, 1H), 4.36 (t, *J*=8.0 Hz, 2H), 5.22 (s, 2H), 5.79 (s, 1H), 5.96 (b, 1H), 7.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.87, 13.90, 18.73, 19.55, 22.31, 25.31, 26.02, 26.50, 27.93, 30.13, 31.01, 36.94, 43.24, 44.76, 47.46, 49.34, 50.37, 57.78, 77.45, 87.30, 99.13, 123.62, 142.20, 160.20, 168.02, 172.81; IR (film) ν, cm^{-1}: 3319, 3095, 2951, 2929, 2868, 1742, 1649, 1526, 1460, 1322, 1166, 1130, 952, 675; ESI-MS *m/z* (%): 583 ($[M+H]^+$, 72), 605 ($[M+Na]^+$, 100); Anal. Calcd for $C_{27}H_{41}BrN_4O_5$: C 55.76, H 7.11, N 9.63, found: C 55.81, H 7.17, N 9.56.

*4.5.32. (S)-(1-Hexyl-1H-1,2,3-triazol-4-yl)methyl 2-((S)-4-bromo-5-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl-oxy)-2,5-dihydrofuran-3-ylamino)-2-phenylacetate (**6bhb**).* Yellow oil, yield 34%. $[\alpha]_D^{20}$ 174.6 (*c* 0.015, CH_3CH_2OH); UV–vis (CH_2Cl_2) λ_{max}: 271 nm; ^1H NMR (400 MHz, $CDCl_3$) δ, ppm: 0.77–0.98 (m, 12H), 1.20–1.34 (m, 10H), 1.63–1.71 (m, 2H), 1.82–1.91 (m, 2H), 2.14–2.32 (m, 1H), 3.85–4.01 (m, 1H), 4.21–4.37 (m, 2H), 5.26–5.42 (m, 2H), 5.55–5.87 (m, 2H), 6.07 (b, 1H), 7.27–7.49 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, ppm: 13.95, 14.29, 18.76, 19.60, 22.39, 26.05, 26.63, 27.96, 30.15, 31.07, 36.81, 44.82, 47.52, 49.49, 50.43, 58.50, 59.56, 77.21, 87.88, 99.58, 123.45, 126.51, 129.22, 129.32, 135.54, 141.47, 160.84, 167.10, 170.04; IR (film) ν, cm^{-1}: 3357, 3058, 3034, 2951, 2923, 2852, 1753, 1652, 1515, 1454, 1320, 1166, 1130, 955, 744, 694, 557; ESI-MS *m/z* (%): 629 ($[M+H]^+$, 36), 651 ($[M+Na]^+$, 100); Anal. Calcd for $C_{31}H_{41}BrN_4O_5$: C 59.14, H 6.56, N 8.90, found: C 59.24, H 6.55, N 9.02.

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Supplementary data

Experimental procedures, spectroscopic data for all new compounds **6aaa**–**6bhb**, and copies of ^1H NMR and ^{13}C NMR spectra for **6aaa**–**6bhb** are provided and can be found in the online version. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.01.092.

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