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Synthesis of 2(5*H*)-Furanone Derivatives with Bis-1,2,3-triazole Structure

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A series of new chiral 2(5*H*)-furanone derivatives containing bis-1,2,3-triazole moiety were designed and synthesized from (5*S*)-5-alkoxy-3,4-dihalo-2(5*H*)-furanones **1**, dicarboxyl amino acids **2**, propargyl bromide, and organic azides **5** under mild conditions via the sequential three steps, including asymmetric Michael addition-elimination, substitution and no-ligand click reaction. Twelve new intermediates, including *N*-[5-alkoxy-2(5*H*)-furanonyl] dicarboxyl amino acids **3** and their corresponding propargyl esters **4**, and twelve target molecules **6** were characterized by FTIR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. The influences of different synthetic conditions and substrates in each step were investigated. The research provides a new method and idea for the synthesis of 2(5*H*)-furanone compounds with polyheterocyclic structure due to the diversities of four basic unit molecules.

Keywords 2(5*H*)-furanone, bis-1,2,3-triazole, amino acids, synthetic methods, click chemistry

Introduction

Because 1,2,3-triazole compounds have good biological activities, including antifungal,[1] antibacterial,[2] antitubercular,[3] anti-cancer,[4] anti-virus,[5] anti-inflammatory,[6] and so on, more and more importance has been attached to the 1,2,3-triazole drugs, especially bis-1,2,3-triazoles.[7] This makes the syntheses of bis-1,2,3-triazoles more and more interesting.[8]

At the same time, many molecules possessing 2(5*H*)-furanone moiety, a kind of α,β-unsaturated lactone substructure frequently found in natural products, have received considerable interests due to the significant biological activities, such as antibacterial,[9] anti-inflammatory,[10] antitumor,[11] anti-parasitic[12] and so on.[13] In fact, many 2(5*H*)-furanone compounds with relatively simple structure are also important organic intermediates.[14] These made the reports on 2(5*H*)-furanone chemistry intensive recently.[11c,15,16]

Futhermore, many bioactive amino acids have been widely used as building blocks in organic syntheses.[17] However, the studies on the synthesis of 2(5*H*)-furanone derivatives with 1,2,3-triazole and amino acid moieties have seldom been reported.[16] Herein, on the basis of our previous research,[16c] a series of new chiral 2(5*H*)-furanone derivatives **6** with polyheterocyclic structures (Scheme 1) were further designed and prepared by the combination of some bioactive units, such as bis-1,2,3-triazole, 2(5*H*)-furanone and especially using dicarboxyl amino acids as new building blocks.

Experimental

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}. ^{1}H NMR 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. Using furfural, natural menthol, borneol and bromohydrocarbons as starting materials, the intermediates (5*S*)-5-alkoxy-3,4-dihalo-2(5*H*)-furanone **1** and azidoalkanes **5** were prepared according to the literatures [11c, 15f, 16c, 18].

General procedure for the synthesis of compounds 5

A flame-dried 25-mL two-neck flask was charged

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with 1.2 mmol amino acid **2** and 3.5 mmol potassium hydroxide in C_2H_5OH (10 mL). The resulting suspension was stirred at 45 ℃ until dissolution. Then, 1.0 mmol intermediates (5*S*)-5-alkoxy-3,4-dihalo-2(5*H*)-furanones **1** in CH_2Cl_2 (10 mL) was dropped, and the reaction was stirred at room temperature for 48 h. After the reaction was finished, the pH value of the reaction mixture was adjusted to 3—4 with dilute hydrochloric acid, and then extracted with CH_2Cl_2 (10 mL×2). The combined organic layers were dried with anhydrous magnesium sulfate, and concentrated under vacuum to give a crude product, which was purified by column chromatography on silica gel with gradient eluent of mixtures of petroleum ether and ethyl acetate to afford the sample **3a**—**3f** for analysis.

General procedure for the synthesis of compounds 4

A flame-dried 25-mL round-bottomed flask was charged with 1.0 mmol *N*-[5-alkoxy-3-halo-2(5*H*)-furanonyl] amino acid **3** and 4.0 mmol anhydrous potassium carbonate in DMSO (5 mL). The resulting suspension was stirred for 2 h under an atmosphere of nitrogen. Then, 2.5 mmol propargyl bromides were added and the reaction was stirred for 12 h at 40 ℃. The resulting mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL×3) and extracted with ethyl acetate (10 mL×3). The combined organic layers were dried with anhydrous magnesium sulfate, and concentrated under vacuum to give a crude product, which was purified by column chromatography on silica gel with gradient eluent of mixtures of petroleum ether and ethyl acetate to afford the sample **4a**—**4f** for analysis.

General procedure for the synthesis of target compounds 6

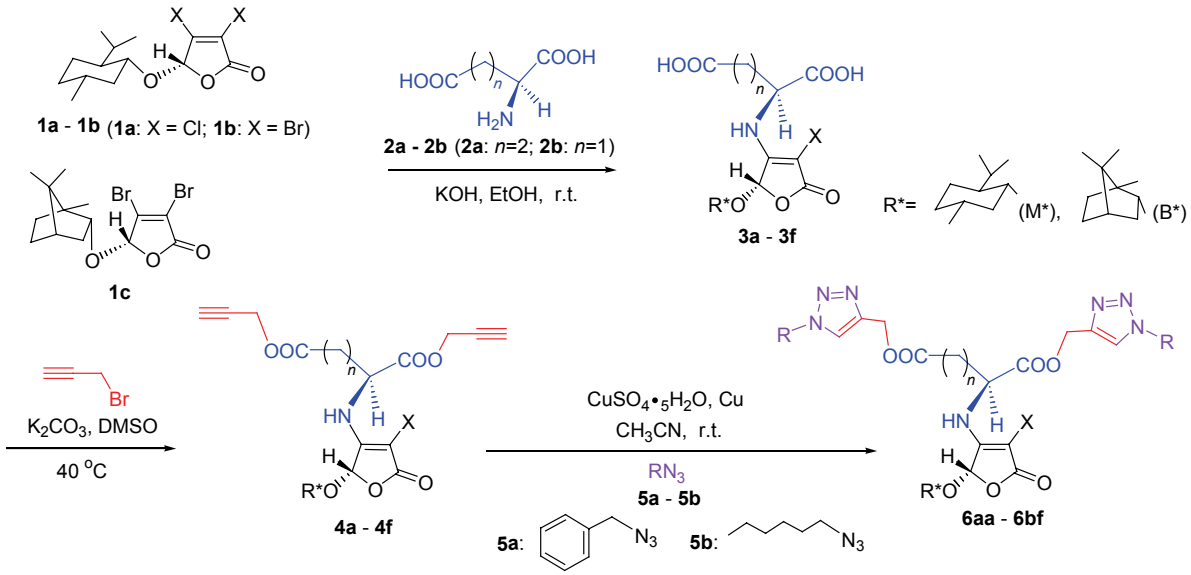
A flame-dried 25-mL round-bottomed flask was charged with 1.0 mmol *N*-[5-alkoxy-3-halo-2(5*H*)-furanonyl] amino acid propargyl esters **4**, 2.0 mmol azidoalkanes **5**, 0.1 mmol copper sulfate pentahydrate and 0.2 mmol copper powder in CH_3CN (5 mL). The mixture was stirred at room temperature, and the reaction was monitored by TLC. After the completion of the reaction (about 48 h), the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL×3) and extracted with ethyl acetate (10 mL×3). Then, the organic layer was dried with anhydrous magnesium sulfate, and concentrated under vacuum to give a crude product, which was purified by column chromatography on silica gel with gradient eluent of mixtures of petroleum ether and ethyl acetate to afford the desired compounds **6aa**—**6bf** for analysis.

Spectral data

(*S*)-2-((*S*)-4-Chloro-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)pentanedioic acid (3a) Yellowish oil, yield 22%; $[\alpha]_{20}^{D}$ +49 (*c* 0.227, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 263 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.76 (d, J=6.8 Hz, 3H, CH_3), 0.83—0.97 (m, 7H, CH, $2CH_3$), 1.00—1.21 (m, 2H, CH_2), 1.35—1.51 (m, 2H, CH), 1.62—1.73 (m, 2H, CH_2), 1.83—2.05 (m, 2H, CH_2), 2.07—2.31 (m, 2H, CH_2), 2.32—2.68 (m, 2H, CH_2), 3.67—3.76 (m, 1H, CH), 4.71—4.87 (m, 1H, CH), 5.75 (b, 1H, NH), 6.32 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 14.06, 21.70, 21.95, 23.09, 25.14, 26.06, 31.33, 34.00, 40.67, 42.11, 46.63, 60.82, 74.97, 97.25, 100.80, 164.36, 168.26, 169.11, 172.23; IR (CH_2Cl_2) ν: 3363, 2951, 2863, 1780, 1750, 1649, 1348, 1251, 1199, 955, 748 cm^{-1}; MS (ESI) *m/z* (%): 416 ($[M-H]^-$, 100). Anal. calcd for $C_{19}H_{28}ClNO_7$: C 54.56, H 6.70, N 3.35; found C 54.47, H 6.76, N 3.40.

(*S*)-2-((*S*)-4-Bromo-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)pentanedioic acid (3b) Yellow oil, yield 39%; $[\alpha]_{20}^{D}$ +47 (*c* 0.164, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}:

Scheme 1 The synthetic route of target compounds



267 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.78 (d, J=6.8 Hz, 3H, CH_3), 0.83—0.96 (m, 7H, CH, $2CH_3$), 0.99—1.22 (m, 2H, CH_2), 1.32—1.47 (m, 2H, 2CH), 1.63—1.74 (m, 2H, CH_2), 1.81—2.07 (m, 2H, CH_2), 2.11—2.31 (m, 2H, CH_2), 2.37—2.63 (m, 2H, CH_2), 3.49—3.70 (m, 1H, CH), 4.69—4.90 (m, 1H, CH), 5.56 (s, 1H, NH), 5.78 (s, 1H, CH), 9.35 (s, 2H, 2COOH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 15.68, 20.93, 22.09, 22.78, 25.85, 28.29, 31.59, 34.02, 39.68, 42.19, 47.93, 60.68, 77.46, 82.92, 96.99, 163.44, 167.18, 175.17, 178.16; IR (CH_2Cl_2) v: 3330, 2955, 2869, 1742, 1647, 1373, 1195, 959, 678 cm^{-1}; MS (ESI) *m/z* (%): 460 ([M−H]$^-$, 30). Anal. calcd for $C_{19}H_{28}BrNO_7$: C 49.32, H 6.06, N 3.03; found C 49.36, H 6.11, N 3.01.

(*S*)-2-((*S*)-4-Bromo-5-oxo-2-((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)pentanedioic acid (3c) Brown oil, yield 32%; $[\alpha]_{20}^{D}$ +24 (*c* 0.209, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 270 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.79—0.88 (m, 6H, $2CH_3$), 0.906 (s, 3H, CH_3), 1.25—1.39 (m, 4H, $2CH_2$), 1.66—1.80 (m, 2H, CH_2), 2.06—2.34 (m, 3H, CH, CH_2), 2.44—2.67 (m, 2H, CH_2), 4.00 (d, J=7.6 Hz, 1H, CH), 4.09—4.47 (m, 1H, CH), 5.73 (s, 1H, NH), 5.81 (s, 1H, CH), 7.74 (s, 2H, 2COOH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 14.97, 18.74, 19.55, 26.94, 27.89, 28.07, 38.09, 40.56, 44.84, 47.52, 49.37, 58.12, 77.87, 88.12, 99.00, 163.06, 168.44, 174.23, 177.68; IR (CH_2Cl_2) v: 3457, 2982, 2953, 2880, 1801, 1744, 1720, 1649, 1306, 1185, 952, 599 cm^{-1}; MS (ESI) *m/z* (%): 458 ([M−H]$^-$, 80). Anal. calcd for $C_{19}H_{26}BrNO_7$: C 49.53, H 5.65, N 3.04; found C 49.46, H 5.70, N 3.08.

(*S*)-2-((*S*)-4-Chloro-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)succinic acid (3d) Brown oil, yield 40%; $[\alpha]_{20}^{D}$ −33 (*c* 0.361, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 264 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.78 (d, J=5.2 Hz, 3H, CH_3), 0.79—0.96 (m, 7H, CH, $2CH_3$), 0.98—1.14 (m, 2H, CH_2), 1.26—1.47 (m, 2H, 2CH), 1.61—1.74 (m, 2H, CH_2), 1.98—2.26 (m, 2H, CH_2), 2.87—3.35 (m, 2H, CH_2), 3.50—3.67 (m, 1H, CH), 4.58—4.87 (m, 1H, CH), 5.83 (s, 1H, NH), 5.86 (s, 1H, CH), 8.11 (b, 2H, 2COOH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 15.62, 20.83, 22.10, 22.81, 25.63, 31.33, 33.90, 37.33, 42.22, 47.89, 60.62, 77.25, 83.03, 98.69, 167.84, 168.16, 173.30, 174.41; IR (CH_2Cl_2) v: 3412, 2979, 2954, 2873, 1775, 1644, 1363, 1253, 1148, 960, 746 cm^{-1}; MS (ESI) *m/z* (%): 402 ([M−H]$^-$, 100). Anal. calcd for $C_{18}H_{26}ClNO_5$: C 53.49, H 6.44, N 3.47; found C 53.51, H 6.50, N 3.39.

(*S*)-2-((*S*)-4-Bromo-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)succinic acid (3e) Brown oil, yield 33%; $[\alpha]_{20}^{D}$ +88 (*c* 0.117, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 264 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.79 (d, J=6.8 Hz, 3H, CH_3), 0.84—0.98 (m, 7H, CH, $2CH_3$), 0.99—1.16 (m, 2H, CH_2), 1.32—1.49 (m, 2H, 2CH), 1.61—1.76 (m, 2H, CH_2), 1.97—2.22 (m, 2H, CH_2), 2.80—3.35 (m, 2H, CH_2), 3.42—3.58 (m, 1H, CH), 4.53—4.81 (m, 1H, CH), 5.20 (s, 1H, NH), 5.70 (s, 1H, CH), 8.45 (b, 2H, 2COOH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 15.85, 21.06, 22.14, 22.94, 25.61, 31.59, 34.03, 40.56, 44.27, 49.58, 60.65, 72.18, 83.70, 99.79, 164.10, 171.78, 173.58, 174.48; IR (CH_2Cl_2) v: 3366, 2956, 2873, 1736, 1652, 1376, 1279, 1121, 957, 695 cm^{-1}; MS (ESI) *m/z* (%): 446 ([M−H]$^-$, 85). Anal. calcd for $C_{18}H_{26}BrNO_5$: C 48.18, H 5.80, N 3.12; found C 48.23, H 5.87, N 3.19.

(*S*)-2-((*S*)-4-Bromo-5-oxo-2-((1*S*,2*R*,4*S*)-1,7,7-tri-methylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)succinic acid (3f) Yellow oil, yield 43%; $[\alpha]_{20}^{D}$ +21 (*c* 0.408, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 267 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.78—0.88 (m, 6H, $2CH_3$), 0.91 (s, 3H, CH_3), 1.19—1.49 (m, 4H, $2CH_2$), 1.63—1.74 (m, 2H, CH_2), 2.12—2.38 (m, 1H, CH), 2.86—3.37 (m, 2H, CH_2), 3.80—3.90 (m, 1H, CH), 4.59—5.03 (m, 1H, CH), 5.89 (s, 1H), 6.02 (s, 1H, NH), 8.50 (b, 2H, 2COOH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 13.77, 18.79, 19.59, 26.43, 27.91, 34.31, 36.63, 37.00, 44.32, 47.57, 49.40, 60.72, 81.38, 88.4, 97.7, 159.5, 162.4, 172.2, 173.62; IR (CH_2Cl_2) v: 3294, 2954, 2882, 1743, 1644, 1324, 1226, 1134, 957, 617 cm^{-1}; MS (ESI) *m/z* (%): 444 ([M−H]$^-$, 83). Anal. calcd for $C_{18}H_{24}BrNO_5$: C 48.40, H 5.38, N 3.14; found C 48.34, H 5.23, N 3.17.

(*S*)-Diprop-2-ynyl-2-((*S*)-4-chloro-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydro-furan-3-ylamino)pentanedioate (4a) Brown oil, yield 28%, $[\alpha]_{20}^{D}$ +59 (*c* 0.233, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 267 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.75—0.93 (m, 10H, CH, $3CH_3$), 0.99—1.11 (m, 2H, CH_2), 1.33—1.43 (m, 2H, 2CH), 1.66—1.71 (m, 2H, CH_2), 1.85—2.02 (m, 2H, CH_2), 2.22—2.31 (m, 2H, CH_2), 2.50—2.55 (m, 4H, CH_2, 2CH), 3.66—3.74 (m, 1H, CH), 4.70—4.80 (m, 5H, CH, $2CH_2$), 5.76 (s, 1H, NH), 5.95 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 15.26, 21.00, 22.09, 23.03, 25.04, 25.83, 29.68, 31.39, 34.17, 42.26, 47.71, 52.49, 53.56, 59.51, 75.38, 76.05, 76.22, 77.12, 79.09, 93.14, 96.17, 162.99, 167.2, 170.3, 173.7; IR (CH_2Cl_2) v: 3379, 3288, 2954, 2929, 2864, 2133, 1748, 1658, 1376, 1175, 1122, 966, 757, 645 cm^{-1}; MS (ESI) *m/z* (%): 492 ([M−H]$^-$, 100). Anal. calcd for $C_{25}H_{32}ClNO_7$: C 60.73, H 6.48, N 2.83; found 60.75, H 6.42, N 2.89.

(*S*)-Diprop-2-ynyl-2-((*S*)-4-bromo-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)pentanedioate (4b) Yellowish oil, yield 70%, $[\alpha]_{20}^{D}$ +29 (*c* 0.355, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 271 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.75 (d, J=6.8 Hz, 3H, CH_3), 0.84—0.96 (m, 7H, CH, $2CH_3$), 0.99—1.14 (m, 2H, CH_2), 1.27—1.40 (m, 2H, 2CH), 1.65—1.70 (m, 2H, CH_2), 1.88—2.01 (m, 2H, CH_2), 2.22—2.32 (m, 2H, CH_2), 2.48—2.57 (m, 4H, CH_2, 2CH), 3.57—3.71 (m, 1H, CH), 4.69—4.80 (m, 5H, CH, $2CH_2$), 5.45 (s, 1H, NH), 5.77 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 15.78, 21.01, 22.09,

22.81, 25.83, 26.89, 29.82, 31.62, 33.90, 42.28, 47.98, 52.48, 53.55, 60.68, 75.38, 76.22, 76.37, 77.13, 79.09, 82.59, 97.27, 162.46, 164.44, 170.18, 171.57; IR (CH_2Cl_2) *v*: 3393, 3281, 2962, 2915, 2870, 2130, 1755, 1644, 1382, 1187, 1116, 960, 633, 522 cm^{-1}; MS (ESI) *m/z* (%): 538 ($[M+H]^+$, 88). Anal. calcd for $C_{25}H_{32}BrNO_7$: C 55.72, H 5.94, N 2.60; found C 55.76, H 5.91, N 2.73.

(*S*)-Diprop-2-ynyl-2-((*S*)-4-bromo-5-oxo-2-((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)pentanedioate (4c) Yellow oil, yield 62%, $[\alpha]_{20}^{D}$ +72 (*c* 0.085, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 267 nm; ^1H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.86 (s, 3H, CH_3), 0.87 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.25—1.30 (m, 4H, $2CH_2$), 1.66—1.80 (m, 2H, CH_2), 2.14—2.33 (m, 3H, CH, CH_2), 2.51—2.55 (m, 4H, CH_2, 2CH), 4.01 (d, *J*=8.8 Hz, 1H, CH), 4.62—4.85 (m, 5H, CH, $2CH_2$), 5.49 (s, 1H, NH), 5.77 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 13.87, 18.78, 19.59, 26.54, 27.93, 28.18, 29.14, 37.13, 44.82, 47.61, 49.46, 52.50, 53.49, 54.58, 75.40, 76.11, 76.37, 77.09, 77.65, 88.28, 99.42, 157.84, 167.04, 170.20, 171.67; IR (CH_2Cl_2) *v*: 3386, 3294, 2981, 2955, 2884, 2114, 1762, 1638, 1396, 1194, 1142, 967, 626, 547 cm^{-1}; MS (ESI) *m/z* (%): 536 ($[M+H]^+$, 85), 558 ($[M+Na]^+$, 81). Anal. calcd for $C_{25}H_{32}BrNO_7$: C 55.93, H 5.59, N 2.61; found C 55.98, H 5.63, N 2.57.

(*S*)-Diprop-2-ynyl-2-((*S*)-4-chloro-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydro-furan-3-ylamino)succinate (4d) Brown oil, yield 43%, $[\alpha]_{20}^{D}$ +60 (*c* 0.136, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 265 nm; ^1H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.82—0.84 (m, 3H, CH_3), 0.88—0.95 (m, 7H, CH, $2CH_3$), 0.97—1.10 (m, 2H), 1.25—1.37 (m, 2H, 2CH), 1.63—1.70 (m, 2H, CH_2), 1.96—2.13 (m, 2H, CH_2), 2.24—2.54 (m, 2H, 2CH), 2.98—3.19 (m, 2H, CH_2), 3.53—3.58 (m, 1H, CH), 4.70—4.80 (m, 5H, CH, $2CH_2$), 5.57 (s, 1H, NH), 5.72 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 15.97, 20.99, 22.07, 22.94, 25.94, 31.62, 33.93, 38.80, 42.44, 48.01, 51.59, 52.81, 53.82, 75.78, 76.14, 76.29, 76.60, 83.14, 91.36, 98.61, 156.71, 166.88, 168.98, 170.78; IR (CH_2Cl_2) *v*: 3476, 3307, 2954, 2909, 2864, 2127, 1761, 1664, 1331, 1187, 1136, 946, 737, 626 cm^{-1}; MS (ESI) *m/z* (%): 478 ($[M-H]^-$, 46). Anal. calcd for $C_{24}H_{30}ClNO_7$: C 60.00, H 6.25, N 2.92; found C 60.13, H 6.21, N 2.94.

(*S*)-Diprop-2-ynyl-2-((*S*)-4-bromo-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)succinate (4e) Yellow oil, yield 69%, $[\alpha]_{20}^{D}$ +107 (*c* 0.177, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 261 nm; ^1H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.83 (d, *J* = 7.2 Hz, 3H, CH_3), 0.86—0.95 (m, 7H, CH, $2CH_3$), 0.98—1.11 (m, 2H, CH_2), 1.28—1.40 (m, 2H, 2CH), 1.66—1.69 (m, 2H, CH_2), 2.05—2.15 (m, 2H, CH_2), 2.24—2.52 (m, 2H, 2CH), 2.96—3.18 (m, 2H, CH_2), 3.53—3.60 (m, 1H, CH), 4.58—4.84 (m, 4H, $2CH_2$), 5.06—5.13 (m, 2H, NH, CH), 5.74 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 15.95, 21.02, 22.09, 22.91, 25.83, 31.60, 33.93, 40.23, 42.40, 48.01, 50.18, 52.87, 53.39, 77.28, 77.55, 77.97, 78.97, 79.24, 82.98, 99.45, 160.12, 167.44, 171.83, 172.01; IR (CH_2Cl_2) *v*: 3464, 3300, 2950, 2925, 2870, 2139, 1742, 1650, 1316, 1182, 1125, 937, 632, 528 cm^{-1}; MS (ESI) *m/z* (%): 524 ($[M+H]^+$, 46.0). Anal. calcd for $C_{24}H_{30}BrNO_7$: C 54.92, H 5.72, N 2.67; found C 54.88, H 5.69, N 2.78.

(*S*)-Diprop-2-ynyl-2-((*S*)-4-bromo-5-oxo-2-((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)succinate (4f) Brown oil, yield 55%, $[\alpha]_{20}^{D}$ +65 (*c* 0.109, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 264 nm; ^1H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.87 (s, 6H, $2CH_3$), 0.90 (s, 3H, CH_3), 1.22—1.29 (m, 4H, $2CH_2$), 1.65—1.77 (m, 2H, CH_2), 2.05—2.18 (m, 1H, CH), 2.24—2.56 (m, 2H, $2CH_2$), 3.00—3.03 (m, 2H, CH_2), 4.00 (d, *J*=7.2 Hz, 1H, CH), 4.68—4.87 (m, 5H, CH, $2CH_2$), 5.82 (s, 1H, NH), 6.12 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 13.91, 18.77, 19.59, 26.47, 27.91, 37.19, 39.56, 44.79, 47.57, 50.08, 52.08, 52.83, 53.48, 75.78, 76.01, 76.47, 76.74, 79.29, 87.71, 98.58, 158.68, 168.51, 169.50, 171.46; IR (CH_2Cl_2) *v*: 3471, 3290, 2981, 2953, 2880, 2130, 1742, 1658, 1337, 1176, 1129, 972, 644, 588 cm^{-1}; MS (ESI) *m/z* (%): 522 ($[M+H]^+$, 100). Anal. calcd for $C_{24}H_{28}BrNO_7$: C 55.13, H 5.36, N 2.68; found C 55.11, H 5.41, N 2.63.

(*S*)-Bis((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-((*S*)-4-chloro-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)-pentanedioate (6aa) Yellow oil, yield 66%; $[\alpha]_{20}^{D}$ +76 (*c* 0.082, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 270 nm; ^1H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.73—0.91 (m, 10H, CH, $3CH_3$), 0.98—1.09 (m, 2H, CH_2), 1.33—1.42 (m, 2H, 2CH), 1.61—1.68 (m, 2H, CH_2), 1.96—2.11 (m, 2H, CH_2), 2.18—2.30 (m, 2H, CH_2), 2.31—2.48 (m, 2H, CH_2), 3.54—3.65 (m, 1H, CH), 4.70—4.86 (m, 1H, NH), 5.20—5.37 (m, 5H, CH, $2CH_2$), 5.52 (s, 4H, $2CH_2$), 5.66 (s, 1H, CH), 7.25—7.41 (m, 10H, 2PhH), 7.53 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 14.16, 20.96, 22.08, 22.71, 25.81, 28.16, 29.72, 31.42, 33.60, 42.29, 47.95, 54.23, 54.25, 58.30, 58.60, 61.09, 77.24, 84.61, 98.66, 123.61, 123.70, 128.18, 128.22, 128.81, 128.89, 129.14, 129.17, 134.37, 134.92, 142.26, 142.99, 165.60, 166.44, 171.65, 172.21; IR (CH_2Cl_2) *v*: 3359, 3144, 3078, 3037, 2961, 2915, 2857, 1748, 1664, 1555, 1497, 1459, 1370, 1181, 1116, 966, 796, 723, 698 cm^{-1}; MS (ESI) *m/z* (%): 759 ($[M-H]^-$, 100). Anal. calcd for $C_{39}H_{46}ClN_7O_7$: C 61.66, H 6.06, N 12.91; found C 61.72, H 6.11, N 12.87.

(*S*)-Bis((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-((*S*)-4-bromo-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)-pentanedioate (6ab) Yellow oil, yield 63%; $[\alpha]_{20}^{D}$ +121 (*c* 0.053, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 270 nm; ^1H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.69 (d, *J*=6.4 Hz, 3H, CH_3), 0.76—0.85 (m, 7H, CH, $2CH_3$), 0.88—1.03 (m, 2H, CH_2), 1.24—1.43 (m, 2H, 2CH), 1.53—

1.64 (m, 2H, CH_2), 1.95—2.07 (m, 2H, CH_2), 2.09—2.22 (m, 2H, CH_2), 2.26—2.42 (m, 2H, CH_2), 3.43—3.62 (m, 1H, CH), 4.75 (b, 1H, NH), 4.98—5.29 (m, 5H, CH, $2CH_2$), 5.44 (s, 4H, $2CH_2$), 5.46 (s, 1H, CH), 7.18—7.32 (m, 10H, 2PhH), 7.50 (s, 2H, 2CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 15.74, 20.96, 22.11, 22.79, 25.74, 28.16, 29.10, 31.58, 33.87, 42.25, 47.93, 54.23, 54.25, 58.05, 58.98, 61.06, 77.33, 82.59, 99.19, 123.70, 124.03, 128.15, 128.19, 128.85, 128.91, 129.14, 129.18, 134.22, 134.34, 142.58, 142.58, 161.83, 167.53, 170.63, 172.24; IR (CH_2Cl_2) ν: 3320, 3144, 3066, 3027, 2954, 2923, 2857, 1755, 1650, 1533, 1500, 1455, 1324, 1181, 1122, 946, 737, 698, 587 cm^{-1}; MS (ESI) *m/z* (%): 803 ([M−H]$^-$, 35). Anal. calcd for $C_{39}H_{46}BrN_7O_7$: C 58.28, H 5.73, N 12.20; found C 58.46, H 5.77, N 12.25.

(*S*)-Bis((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-((*S*)-4-bromo-5-oxo-2-((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)pentanedioate (6ac) Yellowish oil, yield 54%; $[\alpha]_{20}^{D}$ +66 (*c* 0.044, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 269 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.76—0.91 (m, 9H, $3CH_3$), 1.20—1.34 (m, 4H, $2CH_2$), 1.61—1.70 (m, 2H, CH_2), 2.04—2.09 (m, 1H, CH), 2.15—2.24 (m, 2H, CH_2), 2.34—2.43 (m, 2H, CH_2), 3.96 (d, *J*=8.4 Hz, 1H, CH), 4.77 (b, 1H, NH), 5.09—5.35 (m, 5H, CH, $2CH_2$), 5.52 (s, 4H, $2CH_2$), 5.71 (s, 1H, CH), 7.23—7.42 (m, 10H, 2PhH), 7.57 (s, 2H, 2CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 13.77, 18.79, 19.61, 26.43, 27.90, 29.39, 31.58, 37.91, 44.75, 47.57, 49.40, 54.23, 54.83, 58.04, 58.93, 60.41, 77.33, 80.12, 99.41, 123.67, 123.97, 128.14, 128.19, 128.84, 128.91, 129.14, 129.18, 134.23, 134.34, 141.96, 142.56, 158.49, 167.36, 170.64, 172.15; IR (CH_2Cl_2) ν: 3314, 3151, 3060, 3033, 2962, 2935, 2864, 1736, 1644, 1566, 1494, 1462, 1318, 1187, 1116, 952, 731, 692, 581 cm^{-1}; MS (ESI) *m/z* (%): 802 ([M+H]$^+$, 25), 824 ([M+Na]$^+$, 100). Anal. calcd for $C_{39}H_{44}BrN_7O_7$: C 58.30, H 5.48, N 12.21; found C 58.51, H 5.53, N 12.18.

(*S*)-Bis((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-((*S*)-4-chloro-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)-succinate (6ad) Brown oil, yield 52%; $[\alpha]_{20}^{D}$ +70 (*c* 0.055, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 260 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.81 (d, *J*=6.8 Hz, 3H, CH_3), 0.85—0.93 (m, 7H, CH, $2CH_3$), 0.96—1.09 (m, 2H, CH_2), 1.31—1.38 (m, 2H, 2CH), 1.64—1.70 (m, 2H, CH_2), 1.94—2.11 (m, 2H, CH_2), 2.91—3.02 (m, 2H, CH_2), 3.52—3.58 (m, 1H, CH), 4.79—5.18 (m, 5H, CH, $2CH_2$), 5.22—5.33 (m, 1H, CH), 5.51 (s, 4H, $2CH_2$), 5.72 (s, 1H, CH), 6.98—7.46 (m, 10H, 2PhH), 7.55 (s, 2H, 2CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 15.95, 21.01, 22.08, 22.93, 25.86, 31.61, 33.93, 40.27, 42.41, 48.02, 50.08, 54.24, 54.32, 62.02, 62.12, 83.02, 90.89, 98.61, 124.40, 125.34, 128.15, 128.18, 128.84, 128.91, 129.10, 129.16, 134.15, 134.39, 142.06, 144.43, 156.97, 167.05, 169.40, 171.75; IR (CH_2Cl_2) ν: 3347, 3183, 3144, 3072, 2954, 2929, 2870, 1755, 1677, 1507, 1455, 1324, 1175, 1136, 946, 790, 743, 704 cm^{-1}; MS (ESI) *m/z* (%): 744 ([M−H]$^-$, 100). Anal. calcd for $C_{38}H_{44}ClN_7O_7$: C 61.11, H 5.76, N 13.13; found C 61.29, H 5.68, N 13.18.

(*S*)-Bis((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-((*S*)-4-bromo-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)-succinate (6ae) Yellowish oil, yield 69%; $[\alpha]_{20}^{D}$ −52 (*c* 0.038, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 266 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.76 (d, *J*=6.8 Hz, 3H, CH_3), 0.82—0.94 (m, 7H, CH, $2CH_3$), 0.96—1.10 (m, 2H, CH_2), 1.27—1.39 (m, 2H, 2CH), 1.61—1.70 (m, 2H, CH_2), 1.99—2.14 (m, 2H, CH_2), 2.85—3.10 (m, 2H, CH_2), 3.50—3.61 (m, 1H, CH), 4.94—5.31 (m, 5H, CH, $2CH_2$), 5.52 (s, 2H, CH_2), 5.54 (s, 2H, CH_2), 5.70—5.78 (m, 1H, NH), 5.84 (s, 1H, CH), 7.10—7.42 (m, 10H, 2PhH), 7.49 (s, 1H, CH), 7.57 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 15.56, 20.96, 22.12, 22.73, 25.56, 31.57, 33.90, 37.53, 42.24, 47.87, 51.54, 54.08, 54.24, 58.31, 59.21, 82.97, 94.50, 99.43, 123.55, 124.07, 128.16, 128.18, 128.88, 128.91, 129.13, 129.16, 134.24, 134.32, 141.91, 142.22, 159.99, 167.25, 169.52, 169.81; IR (CH_2Cl_2) ν: 3359, 3152, 3072, 3033, 2954, 2926, 2870, 1761, 1664, 1527, 1494, 1455, 1331, 1187, 1128, 940, 723, 692, 575 cm^{-1}; MS (ESI) *m/z* (%): 812 ([M+Na]$^+$, 85). Anal. calcd for $C_{38}H_{44}BrN_7O_7$: C 57.67, H 5.56, N 12.39; found C 56.85, H 5.61, N 12.44.

(*S*)-Bis((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-((*S*)-4-bromo-5-oxo-2-((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)succinate (6af) White powder, yield 59%, m.p. 103.7—105.2 ℃; $[\alpha]_{20}^{D}$ +118 (*c* 0.063, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 263 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.80 (s, 3H, CH_3), 0.82 (s, 3H, CH_3), 0.84 (s, 3H, CH_3), 1.19—1.34 (m, 4H, $2CH_2$), 1.62—1.71 (m, 2H, CH_2), 2.05—2.22 (m, 1H, CH), 2.96—3.11 (m, 2H, CH_2), 3.96 (d, *J*=6.8 Hz, 1H, CH), 5.03—5.34 (m, 5H, CH, $2CH_2$), 5.53 (s, 4H, $2CH_2$), 5.69 (s, 1H, NH), 5.71 (s, 1H, CH), 7.25—7.41 (m, 10H, 2PhH), 7.52 (s, 1H, CH), 7.58 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 13.74, 18.77, 19.58, 26.35, 27.87, 37.02, 37.44, 44.78, 47.54, 49.37, 54.24, 58.28, 59.14, 60.45, 77.31, 84.59, 99.48, 123.75, 124.08, 127.61, 128.15, 128.18, 128.88, 129.16, 130.25, 134.20, 134.27, 141.92, 142.17, 163.58, 167.90, 169.70, 169.80; IR (CH_2Cl_2) ν: 3353, 3191, 3053, 3033, 2948, 2876, 1748, 1638, 1507, 1462, 1331, 1181, 1128, 960, 717, 614, 575 cm^{-1}; MS (ESI) *m/z* (%): 810 ([M+Na]$^+$, 56); Anal. calcd for $C_{38}H_{42}BrN_7O_7$: C 57.82, H 5.33, N 12.43; found C 57.87, H 5.20, N 12.54.

(*S*)-Bis((1-hexyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-((*S*)-4-chloro-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)-pentanedioate (6ba) Yellow oil, yield 66%; $[\alpha]_{20}^{D}$ +58 (*c* 0.031, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 268 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.73—0.92 (m, 16H, CH, $5CH_3$), 0.95—1.03 (m, 2H, CH_2), 1.25—1.34 (m, 12H, $6CH_2$), 1.38—1.47 (m, 2H, 2CH), 1.66—1.71 (m, 2H, CH_2), 1.76—2.06 (m, 6H, $3CH_2$), 2.14—2.27

(m, 2H, 2CH), 2.46—2.57 (m, 2H, 2CH), 3.63—3.74 (m, 1H, CH), 4.28—4.38 (m, 4H, $2CH_2$), 5.05—5.44 (m, 5H, CH, $2CH_2$), 5.54—6.04 (m, 2H, NH, CH), 7.66 (s, 2H, 2CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 13.95, 15.73, 20.91, 22.08, 22.39, 22.82, 25.21, 26.10, 29.68, 30.16, 31.10, 31.40, 31.58, 34.06, 42.27, 47.70, 50.06, 50.58, 58.44, 58.83, 59.42, 79.28, 82.60, 96.27, 122.66, 124.10, 140.83, 141.57, 162.28, 167.05, 169.26, 170.79; IR (CH_2Cl_2) v: 3269, 3152, 2968, 2923, 2857, 1748, 1650, 1455, 1376, 1175, 1136, 960, 751 cm^{-1}; MS (ESI) *m/z* (%): 770 ([M + Na]$^+$, 100). Anal. calcd for $C_{37}H_{58}ClN_7O_7$: C 64.27, H 7.75, N 13.10; found C 64.39, H 7.70, N 13.26.

(*S*)-Bis((1-hexyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-((*S*)-4-bromo-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)pentanedioate (6bb) Yellow oil, yield 59%; $[\alpha]_{20}^{D}$ +93 (*c* 0.087, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 270 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.68—0.93 (m, 16H, CH, $5CH_3$), 0.96—1.12 (m, 2H, CH_2), 1.22—1.31 (m, 12H, $6CH_2$), 1.34—1.47 (m, 2H, 2CH), 1.58—1.69 (m, 2H, CH_2), 1.76—2.07 (m, 6H, $3CH_2$), 2.14—2.27 (m, 2H, CH_2), 2.37—2.50 (m, 2H, CH_2), 3.54—3.67 (m, 1H, CH), 4.25—4.37 (m, 4H, $2CH_2$), 5.06—5.39 (m, 5H, CH, $2CH_2$), 5.48—5.61 (m, 1H, NH), 5.72 (s, 1H, CH), 7.58 (s, 1H, CH), 7.62 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 13.94, 15.75, 20.97, 22.07, 22.39, 22.78, 25.78, 26.11, 29.16, 30.19, 31.07, 31.09, 31.59, 33.87, 42.28, 47.94, 50.46, 50.50, 58.13, 58.42, 59.09, 79.29, 82.01, 99.21, 123.60, 123.91, 141.41, 142.18, 163.62, 166.32, 170.70, 172.17; IR (CH_2Cl_2) v: 3347, 3144, 3099, 2954, 2929, 2864, 1736, 1638, 1519, 1461, 1363, 1187, 1116, 952, 626 cm^{-1}; MS (ESI) *m/z* (%): 814 ([M +Na]$^+$, 100). Anal. calcd for $C_{37}H_{58}BrN_7O_7$: C 56.00, H 7.32, N 12.36; found: C 56.14, H 7.29, N 12.40.

(*S*)-Bis((1-hexyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-((*S*)-4-bromo-5-oxo-2-((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)pentanedioate (6bc) Yellow oil, yield 56%; $[\alpha]_{20}^{D}$ +73 (*c* 0.064, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 273 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.65—0.95 (m, 15H, $5CH_3$), 1.03—1.38 (m, 16H, $8CH_2$), 1.58—1.69 (m, 2H, CH_2), 1.76—1.91 (m, 4H, $2CH_2$), 2.07—2.25 (m, 3H, CH, CH_2), 2.36—2.48 (m, 2H, CH_2), 3.91 (d, *J*=7.2 Hz, 1H, CH), 4.18—4.36 (m, 4H, $2CH_2$), 4.83—5.29 (m, 5H, CH, $2CH_2$), 5.46—5.59 (m, 1H, NH), 5.67 (s, 1H, CH), 7.58 (s, 2H, 2CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 13.80, 13.95, 18.77, 19.58, 22.40, 26.11, 26.44, 27.95, 29.44, 30.21, 31.07, 31.10, 37.11, 44.77, 47.58, 49.42, 50.45, 50.50, 54.88, 58.15, 59.06, 77.29, 88.16, 99.93, 123.65, 123.94, 141.67, 142.01, 163.85, 169.21, 170.71, 172.24; IR (CH_2Cl_2) v: 3308, 3132, 2968, 2923, 2876, 1761, 1650, 1449, 1331, 1194, 1136, 960, 672 cm^{-1}; MS (ESI) *m/z* (%): 812 ([M+Na]$^+$, 95). Anal. calcd for $C_{37}H_{58}BrN_7O_7$: C 56.15, H 7.33, N 12.39; found C 56.34, H 7.38, N 12.53.

(*S*)-Bis((1-hexyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-((*S*)-4-chloro-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)succinate (6bd) Red oil, yield 66%; $[\alpha]_{20}^{D}$ +76 (*c* 0.063, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 271 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.80—0.93 (m, 16H, CH, $5CH_3$), 0.95—1.03 (m, 2H, CH_2), 1.28—1.37 (m, 12H, $6CH_2$), 1.38—1.46 (m, 2H, 2CH), 1.66—1.71 (m, 2H, CH_2), 1.86—1.95 (m, 4H, $2CH_2$), 1.99—2.13 (m, 2H, CH_2), 2.95—3.11 (m, 2H, CH_2), 3.54—3.60 (m, 1H, CH), 4.31—4.40 (m, 4H, $2CH_2$), 4.96—5.31 (m, 5H, CH, $2CH_2$), 5.62—5.71 (m, 1H, NH), 5.74 (s, 1H, CH), 7.59 (s, 1H, CH), 7.65 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 13.96, 15.93, 20.99, 22.06, 22.41, 22.93, 25.89, 26.13, 30.22, 31.11, 31.61, 33.93, 37.49, 42.41, 48.02, 50.53, 51.72, 52.37, 58.44, 59.32, 83.06, 91.10, 98.60, 123.45, 124.01, 141.49, 141.85, 156.83, 166.92, 169.66, 171.45; IR (CH_2Cl_2) v: 3328, 3216, 3144, 2962, 2935, 2870, 1755, 1664, 1519, 1460, 1324, 1187, 1128, 952, 743 cm^{-1}; MS (ESI) *m/z* (%): 756 ([M+Na]$^+$, 100). Anal. calcd for $C_{36}H_{56}ClN_7O_7$: C 58.83, H 7.63, N 13.35; found C 58.79, H 7.77, N 13.41.

(*S*)-Bis((1-hexyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-((*S*)-4-bromo-2-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)-5-oxo-2,5-dihydrofuran-3-ylamino)succinate (6be) Brown oil, yield 48%; $[\alpha]_{20}^{D}$ +72 (*c* 0.016, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 269 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.75 (d, *J*=6.4 Hz, 3H, CH_3), 0.77—0.92 (m, 13H, CH, $4CH_3$), 0.95—1.07 (m, 2H, CH_2), 1.14—1.42 (m, 14H, 2CH, $6CH_2$), 1.56—1.66 (m, 2H, CH_2), 1.74—1.94 (m, 4H, $2CH_2$), 2.04—2.21 (m, 2H, CH_2), 2.69—3.04 (m, 2H, CH_2), 3.52—3.63 (m, 1H, CH), 4.17—4.42 (m, 4H, $2CH_2$), 4.99—5.49 (m, 5H, CH, $2CH_2$), 5.73 (s, 1H, CH), 5.80 (s, 1H, NH), 7.63 (s, 2H, 2CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 13.94, 15.90, 21.00, 22.08, 22.38, 22.87, 25.67, 26.09, 30.19, 31.09, 31.56, 33.93, 40.13, 42.40, 48.01, 50.49, 52.08, 52.81, 58.34, 59.26, 78.87, 82.70, 99.40, 123.74, 124.01, 141.38, 141.69, 160.48, 167.60, 168.55, 169.88; IR (CH_2Cl_2) v: 3334, 3203, 3138, 2962, 2929, 2864, 1755, 1664, 1461, 1318, 1175, 1128, 940, 606 cm^{-1}; MS (ESI) *m/z* (%): 800 ([M+Na]$^+$, 75). Anal. calcd for $C_{36}H_{56}BrN_7O_7$: C 55.47, H 7.19, N 12.58; found C 55.64, H 7.22, N 12.61.

(*S*)-Bis((1-hexyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-((*S*)-4-bromo-5-oxo-2-((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)-2,5-dihydrofuran-3-ylamino)succinate (6bf) Yellow oil, yield 67%; $[\alpha]_{20}^{D}$ +160 (*c* 0.036, C_2H_5OH); UV-vis (CH_2Cl_2) λ_{max}: 262 nm; ^{1}H NMR (400 MHz, $CDCl_3$-TMS) δ: 0.77—0.86 (m, 15H, $5CH_3$), 1.10—1.33 (m, 16H, $8CH_2$), 1.59—1.66 (m, 2H, CH_2), 1.80—1.93 (m, 4H, $2CH_2$), 2.17—2.24 (m, 1H, CH), 2.94—3.11 (m, 2H, CH_2), 3.95 (d, *J*=9.2 Hz, 1H, CH), 4.24—4.40 (m, 4H, $2CH_2$), 5.09—5.45 (m, 5H, CH, $2CH_2$), 5.73 (s, 1H, CH), 5.94 (s, 1H, NH), 7.57 (s, 1H, CH), 7.62 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS) δ: 13.95, 14.02, 18.78, 19.67, 22.39, 26.11, 26.32, 28.14, 30.21, 31.09, 36.61, 37.02, 44.78, 47.99, 49.16, 50.06, 50.50, 52.11,

58.43, 59.25, 77.31, 84.52, 97.68, 123.60, 123.88, 141.52, 141.95, 160.36, 167.54, 169.64, 169.80; IR (CH_2Cl_2) *v*: 3470, 3191, 2974, 2935, 2864, 1748, 1644, 1455, 1331, 1233, 1136, 952, 600 cm^{-1}; MS (ESI) *m/z* (%): 798 ([M + Na]$^+$, 85). Anal. calcd for $C_{36}H_{54}BrN_7O_7$: C 55.62, H 6.95, N 12.62; found C 55.46, H 7.06, N 12.58.

Results and Discussion

Syntheses of new intermediates *N*-[5-alkoxy-2(5*H*)-furanonyl] amino acids 3

In our previous research, we have prepared *N*-[5-alkoxy-2(5*H*)-furanonyl] amino acids[18] and their propargyl esters[15f] starting from monocarboxyl amino acids. Herein, in order to further combine bis-1,2,3-triazole with 2(5*H*)-furanone moiety, we use bioactive dicarboxyl amino acids (*e.g.* glutamic acid, Glu, **2a** and aspartic acid, Asp, **2b**)[19] in place of monocarboxyl amino acids[18] to synthesize new intermediates **3**. The investigations on the similar asymmetric Michael addtion-elimination reaction show that the reaction conditions, including the dosage of the base, the reaction temperature and time, affect the reaction. Taking (5*S*)-5-bornyloxy-3,4-dibromo-2(5*H*)-furanone **1c** and Glu **2a** as the model substrates (Scheme 2), the results are summarized in Table 1.

Scheme 2 The reaction of **1c** and Glu **2a**

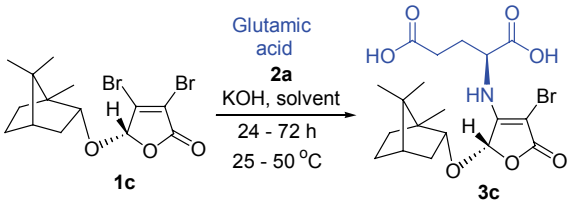


Table 1 Condition optimization for the reaction of **1c** with **2a**

Entry[a]	KOH/mmol	Solvent	Temp./℃	Time/h	Yield[b]/%
1	3.0	EtOH	25	72	19
2	3.5	EtOH	25	72	32
3	4.0	EtOH	25	72	29
4	3.5	EtOH	50	72	28
5	3.5	EtOH	25	48	32
6	3.5	EtOH	25	24	25
7	3.5	MeOH	25	48	28

[a] Reaction conditions: **1c** (1.0 mmol), **2a** (1.2 equiv.). [b] Isolated yield.

Firstly, the investigation results of the dosages of the base KOH (Table 1, Entries 1—3) indicate that 3.5 mmol KOH is the most effective (Entry 2). Once reducing the base dosage, the yield is lowered obviously (Entry 1). While excessive base may cause the side reaction, which makes the yield lowered slightly (Entry 3). When the dosage of the base KOH is kept unchanged, increasing the reaction temperature does not give good result (Entry 4). Therefore, the temperature is controlled at room temperature (25 ℃) in the following tests. The reaction time also affects the reaction (Entries 2, 5 and 6), but it is possible to shorten the reaction time from 72 h to 48 h (Entry 5). When the reaction is carried out for the same time (48 h), the influences of some common alcohol solvents indicate that ethanol is still more effective than methanol (Entry 7).

Thus, when 1.0 mmol (5*S*)-5-bornyloxy-3,4-dibromo-2(5*H*)-furanone **1c** is reacted with 1.2 equiv. Glu **2a**, the optimized reaction conditions can be summarized in the following: 25 ℃, 48 h, 3.5 equiv. KOH as the base, and anhydrous EtOH as the solvent. Under the above conditions, a series of *N*-[2(5*H*)-furanonyl] amino acids derived from Glu **2a** and Asp **2b** are synthesized (Table 2).

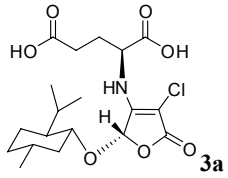
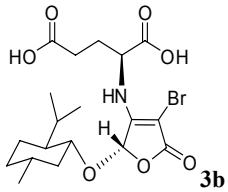
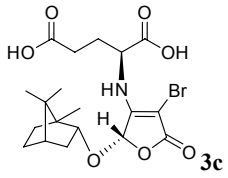
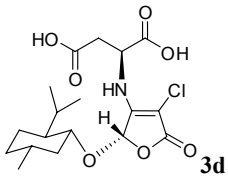
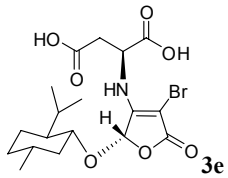
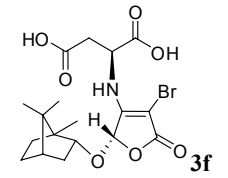
Compared with the results from monocarboxyl amino acids,[18] it can be seen from Table 2 that dicarboxyl amino acids have an important influence on the asymmetric Michael addtion-elimination reaction. The existence of another carboxyl group not only reduces the nucleophilicity of the amino, but also increases the steric hindrance of the substrate. Both are disadvantageous for the tandem reaction. Therefore, the yields (22%—43%) are usually lower than those before.[18] On the other hand, Asp **2b** is more likely to get the products with the higher yields than Glu **2a** (*e.g.* Entries 4 vs. 1, and 6 vs. 3). This might be related to the shorter chain of Asp **2b**, which is advantageous to lower the lipid solubility of Asp **2b**, and increase the solubility of its mixture with potassium hydroxide in ethanol.

Syntheses of new intermediates *N*-[5-alkoxy-2(5*H*)-furanonyl] amino acid propargyl esters 4

Usually, amino acid propargyl esters are synthesized via condensation using *N*-protected amino acid and propargyl alcohol as materials, and the reported synthetic methods have many drawbacks.[15f,20,21] Only recently, there are a few reports on the synthesis of amino acid propargyl esters using *N*-protected amino acid and propargyl bromide as materials.[15f,21] Due to the introduction of dicarboxyl amino acids, we have to optimize experimental conditions again according to the reported before.[15f] Using the substitution reaction of *N*-[5-bornyloxy-2(5*H*)-furanonyl] glutamic acid **3c** with propargyl bromide as an example (Scheme 3), the reuslts are shown in Table 3.

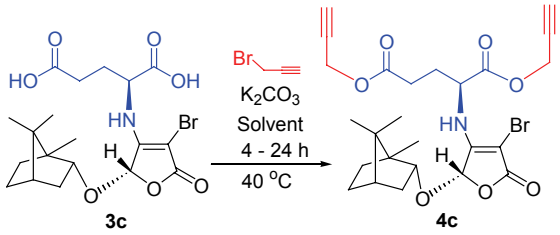
The dosages of the base K_2CO_3 are first examined (Table 3, Entries 1—4), and the results indicate that 4.0 mmol K_2CO_3 is the most effective, and the corresponding yield of amino acid ester **4c** is 41% (Entry 3). Once reducing the base dosage, the reaction is slightly incomplete. The more base dosage may bring about the side-reaction, and make the yield lowered (Entry 4). In fact, the solvent has a bigger effect on the substitution reaction (Entries 3 and 5—8), and DMSO is the best solvent (Entry 8). Even in DMSO, the reaction time can be

Table 2 Syntheses of different 2(5*H*)-furanone intermediates **3**

Entry[a]	1	2	Products 3	Yield[b]/%
1	**1a**	**2a**	 **3a**	22
2	**1b**	**2a**	 **3b**	38
3	**1c**	**2a**	 **3c**	32
4	**1a**	**2b**	 **3d**	40
5	**1b**	**2b**	 **3e**	33
6	**1c**	**2b**	 **3f**	43

[a] Reaction conditions: 2(5*H*)-furanone material **1** (1.0 mmol), amino acid **2** (1.2 equiv.), 25 ℃, 48 h, 3.5 equiv. KOH as the base, and anhydrous EtOH as the solvent. [b] Isolated yield.

Scheme 3 The reaction of **3c** with propargyl bromide



3c **4c**

shortened from 24 to 12 h (Entry 9). However, the relatively less time is obviously disadvantageous for the reaction (Entries 10 and 11).

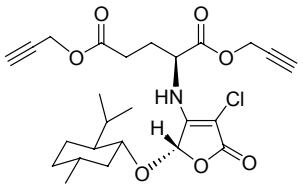
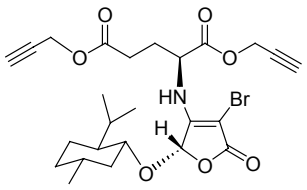
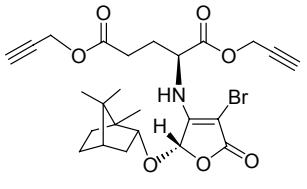
Table 3 Condition optimization for the substitution reaction of **3c** with propargyl bromide

Entry[a]	K_2CO_3/mmol	Solvent	Time/h	Yield[b]/%
1	2.0	CH_3CN	24	25
2	3.0	CH_3CN	24	31
3	4.0	CH_3CN	24	41
4	4.5	CH_3CN	24	40
5	4.0	EtOH	24	0
6	4.0	CH_2Cl_2	24	40
7	4.0	DMF	24	49
8	4.0	DMSO	24	62
9	4.0	DMSO	12	62
10	4.0	DMSO	8	54
11	4.0	DMSO	4	39

[a] Reaction conditions: 2(5*H*)-furanone intermediate **3c** (1.0 mmol), propargyl bromide (2.5 equiv.). [b] Isolated yield.

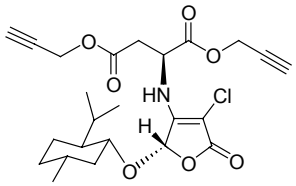
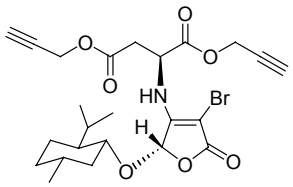
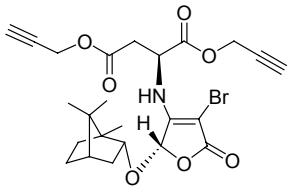
Thus, when choosing 1.0 mmol *N*-[5-bornyloxy-2(5*H*)-furanonyl] glutamic acid **3c** and 2.5 mmol propargyl bromide as the model substrates, the optimized reaction conditions can be summarized in the following: 40 ℃, 12 h, 4.0 mmol K_2CO_3 as the base, and anhydrous DMSO as the solvent. Under the optimized conditions, the substitution of a series of *N*-[2(5*H*)-furanonyl] amino acids derived from Glu **2a** and Asp **2b** are examined, and six new *N*-[5-alkoxy-2(5*H*)-furanonyl] amino acid propargyl esters **4** are obtained with the yields of 28%—70% (Table 4).

Table 4 Syntheses of different 2(5*H*)-furanone intermediates **4**

Entry[a]	3	Products 4	Yield[b]/%
1	**3a**	 **4a**	28
2	**3b**	 **4b**	70
3	**3c**	 **4c**	62

CHINESE JOURNAL OF CHEMISTRY

Continued

Entry[a]	3	Products 4	Yield[b]/%
4	**3d**	 **4d**	43
5	**3e**	 **4e**	69
6	**3f**	 **4f**	55

[a] Reaction conditions: 2(5*H*)-furanone intermediate **3** (1.0 mmol), propargyl bromide (2.5 equiv.), 40 ℃, 12 h, 4.0 mmol K_2CO_3 as the base, and anhydrous DMSO as the solvent. [b] Isolated yield.

On one hand, it can be seen from Table 4 that different halogen atoms in 2(5*H*)-furanone intermediates **3** may have an effect on the reaction, and the yields of the products **4** containing chlorine atom are relatively lower (Entries 1 and 4). This may be related to the stronger electronegativity value of chlorine atom, which will lead to the formation of the hydrogen bond between the carboxyl in amino acid and chlorine atom, and further hindering the expected substitution reaction. On the other hand, different 5-substituents in 2(5*H*)-furanone intermediates **3** also have an influence on the reaction, and usually the intermediates **3** with 5-menthoxy group give the products **4** with the higher yield than that with 5-bornyloxy group (Entries 2 vs. 3, and 5 vs. 6). Perhaps the less steric hindrance of 5-menthoxy group than that of 5-borneoxy group makes the reaction proceed more smoothly.

Syntheses of target compounds bis-1,2,3-triazoles 6

Based on the above syntheses of the intermediates **3** and **4**, the preparations of the target compounds **6** are investigated. Choosing *N*-[5-bornyloxy-2(5*H*)-furanonyl] glutamic acid propargyl ester **4c** and benzyl azide **5a** as the model substrates of the click reaction (Scheme 4), the experimental conditions are optimized (Table 5).

The influences of different catalysts are evaluated first (Table 5, Entries 1—3). Obviously, when using $CuSO_4$•$5H_2O$/Cu as catalytic system, a satisfactory yield

Scheme 4 Reaction of **4c** with benzyl azide **5a**

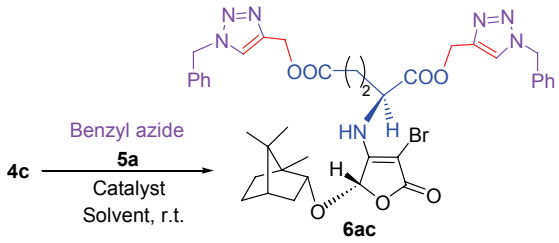


Table 5 Condition optimization for the click reaction of **4c** with benzyl azide **5a**

Entry[a]	Catalyst system	Solvent	Time/h	Yield[d]/%
1	CuBr	CH_3CN	48	12
2[b]	$CuSO_4$•$5H_2O$/SA	CH_3CN	48	39
3	$CuSO_4$•$5H_2O$/Cu	CH_3CN	48	54
4[c]	$CuSO_4$•$5H_2O$/Cu	CH_3CN	48	50
5	$CuSO_4$•$5H_2O$/Cu	EtOH	48	0
6	$CuSO_4$•$5H_2O$/Cu	CH_2Cl_2	48	37
7	$CuSO_4$•$5H_2O$/Cu	DMF	48	44
8	$CuSO_4$•$5H_2O$/Cu	DMSO	48	50
9	$CuSO_4$•$5H_2O$/Cu	CH_3CN	24	39
10	$CuSO_4$•$5H_2O$/Cu	CH_3CN	72	53

[a] Reaction conditions: 2(5*H*)-furanone intermediate **4c** (1.0 mmol), benzyl azide **5a** (2.0 equiv.), catalyst (Cu^I 0.2 equiv., except for special explanations). [b] Sodium ascorbate (SA, 0.2 equiv.) was used instead of Cu. [c] $CuSO_4$•$5H_2O$ (0.05 equiv.), Cu (0.1 equiv.). [d] Isolated yield.

is obtained (Entry 3). If the catalytic system is replaced by CuBr (Entry 1) or $CuSO_4$•$5H_2O$/sodium ascorbate (Entry 2), some by-products can be detected according to the TLC monitoring, and the yield also drops. Furthermore, if decreasing the dosage of catalysts into the half, the yield becomes lower (Entry 4). Thus, the suitable catalyst system should be 0.1 mmol $CuSO_4$•$5H_2O$ and 0.2 mmol Cu.

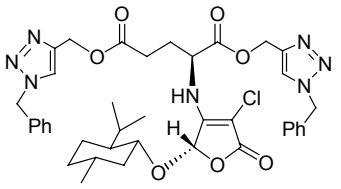
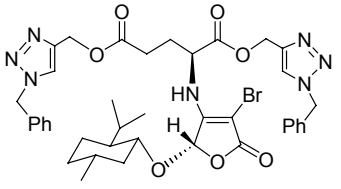
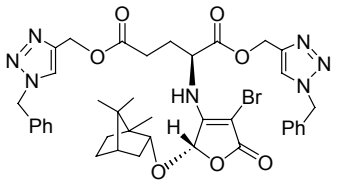
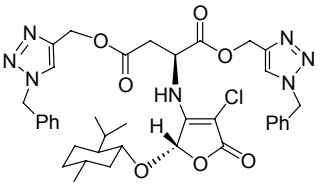
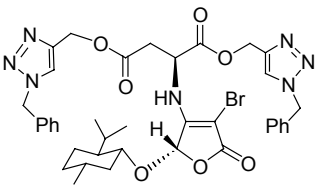
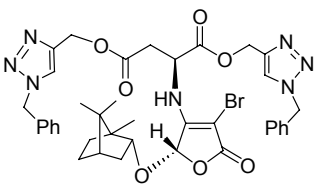
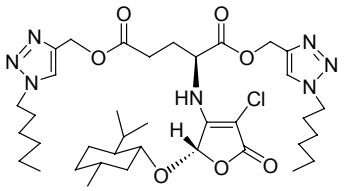
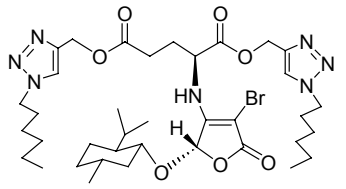
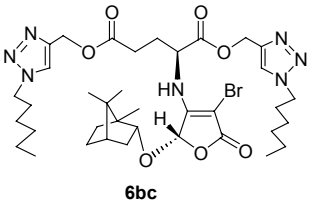
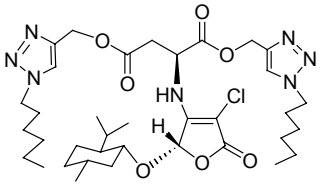
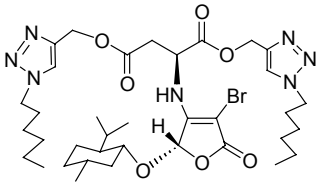
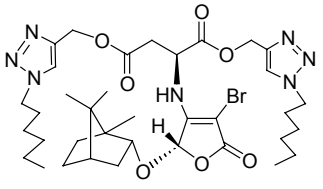
The solvent also affects the reaction significantly (Table 5, Entries 5—8). For example, in EtOH, the reaction does not take place. Similarly, changing other solvents while maintaining the same reaction time (48 h), the results indicate that CH_3CN is the best of all (Entry 3). However, once the reaction time is shortened (Entry 9) or lengthened (Entry 10), the yield is not satisfied. Therefore, when choosing 1.0 mmol **4c** and 2.0 equiv. benzyl azide **5a** as the model substrates, the optimized reaction conditions can be summarized in the following: CH_3CN as the solvent, 0.1 equiv. $CuSO_4$•$5H_2O$ and 0.2 equiv. Cu as the catalytic system, room temperature for 48 h.

Under these conditions, changing substrates, more new 2(5*H*)-furanone derivatives **6** containing bis-1,2,3-triazole moiety are designed and successfully synthesized with the yields of 48%—69% (Table 6). It can be seen that, though the side-reactions, especially Glasser coupling reaction of diyne,[22] maybe occur, the click

reaction proceeds smoothly whether the main chain of amino acid is long or short, and whether the side chain in azidoalkanes is hexyl or benzyl.

However, different intermediate *N*-[5-alkoxy-2(5*H*)-furanonyl] amino acid propargyl ester **4** has some influences. For example, when 5-substituent in 2(5*H*)-furanones **4** is different, 5-menthoxy with less steric hinderance generally results in a higher yield than 5-bornyloxy (Table 6, Entries 2 vs. 3, 5 vs. 6, and 8 vs. 9).

Table 6 Syntheses of different bis-1,2,3-triazoles **6**

Entry[a]	4	5	Target compounds **6**	Yield[b]/%
1	**4a**	**5a**	 **6aa**	66
2	**4b**	**5a**	 **6ab**	63
3	**4c**	**5a**	 **6ac**	54
4	**4d**	**5a**	 **6ad**	52
5	**4e**	**5a**	 **6ae**	69
6	**4f**	**5a**	 **6af**	59
7	**4a**	**5b**	 **6ba**	66
8	**4b**	**5b**	 **6bb**	59
9	**4c**	**5b**	 **6bc**	56
10	**4d**	**5b**	 **6bd**	66
11	**4e**	**5b**	 **6be**	48
12	**4f**	**5b**	 **6bf**	67

[a] Reaction conditions: 2(5*H*)-furanone intermediate **4** (1.0 mmol), azidoalkane **5** (2.0 equiv.), CH_3CN as the solvent, 0.1 equiv. $CuSO_4$•$5H_2O$ and 0.2 equiv. Cu as the catalytic system, room temperature for 48 h. [b] Isolated yield.

What's more, it can be seen that 3-chloro-2(5*H*)-furanone intermediates **4** usually give the higher yields than 3-bromo-2(5*H*)-furanones (Table 6, Entries 1 vs. 2, 7 vs. 8, and 10 vs. 11). This may be related to the reaction mechanism of click reaction.[23] Because chlorine

atom has bigger electronegativity value than bromine atom, it is more likely to attract the hydrogen atom of terminal alkyne, which makes the leave of hydrogen atom more easier and promotes the click reaction.

Structure characterization of all new compounds

All new chiral 2(5*H*)-furanone compounds are systematically characterized. In the following discussions, we choose the characterizations of target compounds **6** as examples.

In the IR spectra, the N—H groups show stretching absorption in the region of 3350—3490 cm^{-1}, while unsaturated C—H groups of aromatic rings or triazole rings show stretching absorption in the region of 3030—3200 cm^{-1}. At the same time, the strong C=O stretching band appears at 1740—1755 cm^{-1}, and the C=C stretching band occurs in 1634—1664 cm^{-1} region. Besides, skeletal stretching vibrations of aromatic rings or triazole rings absorb in the region of 1450—1570 cm^{-1}.

In the UV spectra, for most compounds, there are strong absorption peaks in the region of 261—274 nm caused by $\pi\rightarrow\pi^*$ transition of C=C—C=O conjugated system in 2(5*H*)-furanone ring.

In ^{1}H NMR, there is a singlet peak in the region of δ 5.61—5.74, which is the characteristic peak of 5-H in 2(5*H*)-furanone. Furthermore, there is a singlet peak in the region of δ 7.50—7.63 for the proton of bis-1,2,3-triazoles **6**. In a word, the structures of all newly synthesized compounds are right as expected.

In our previous research,[16c] it has been proved that different 2(5*H*)-furanone derivatives containing mono-1,2,3-triazole moiety could be synthesized from available 5-alkoxy-3,4-dihalo-2(5*H*)-furanones, amino acids, propargyl bromide and azidoalkanes through Michael addition-elimination, substitution and cycloaddition via a simple and efficient multi-component one-pot approach. Therefore, it is also possible to get bis-1,2,3-triazoles **6** by the similar way.

Conclusions

In summary, using dicarboxyl amino acids as new building blocks, a series of new chiral 2(5*H*)-furanone derivatives containing bis-1,2,3-triazole moiety are designed and synthesized under mild conditions via three sequential steps, such as asymmetric Michael addition-elimination, substitution and no-ligand click reaction in this research. Meanwhile, those new compounds, including intermediates, are characterized by FTIR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. The research provides a new method and idea for the synthesis of 2(5*H*)-furanone compounds with polyheterocyclic structure. Due to the diversities of four basic unit molecules, it also provides a theoretical and practical basis for further bioactive investigations.

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