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Synthesis of amino acid derivatives of 5-alkoxy-3,4-dihalo-2(5*H*)-furanones and their preliminary bioactivity investigation as linkers†

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A series of amino acid derivatives are successfully synthesized *via* a metal-free C–N coupling reaction of 5-alkoxy-3,4-dihalo-2(5*H*)-furanones and amino acids. Their structures are well characterized with ^{1}H NMR, ^{13}C NMR, ESI-MS and elemental analysis. As potential linkers of the 2(5*H*)-furanone unit with other drug moieties containing a hydroxyl or amino group, the effect of amino acids is investigated by comparison with other 2(5*H*)-furanone compounds by constructing C–O/C–S bonds. The preliminary results of the biological activity assay by the MTT method on a series of cancer cell lines *in vitro* reveal that the introduction of amino acids basically has no toxic effect. This can lead to these 2(5*H*)-furanone derivatives being further well-linked with other bioactive moieties with amino or hydroxy groups as expected. Thus, the biological activity assay gives a direction for the design of bioactive 2(5*H*)-furanones based on these amino acid linkers.

Introduction

Amino acids are very important living substances in organisms and the basic units of enzymes and proteins.[1] Due to the presence of both amino and carboxyl groups, amino acids are also one of the most versatile building blocks used in many fields, such as organic synthesis,[2] drug design,[3–5] molecular recognition,[6–8] supramolecular chemistry,[9,10] functional materials,[11,12] and so on.[13] Importantly, the fact that amino acids are used as key linkers between the structural molecule and bioactive unit has been widely utilized.[14–19]

Molecules possessing a 2(5*H*)-furanone moiety, a kind of α,β-unsaturated lactone substructure, are frequently found in natural products.[20–22] They have received considerable interest because of their significant biological activities,[23–25] such as antifungal,[26,27] antibacterial,[28] antiviral,[29,30] and anticancer.[31,32] Therefore, the synthesis of different 2(5*H*)-furanones and their applications have drawn much attention in recent years.[33–39] Being interested in the chemistry of 2(5*H*)-furanones, we also reported some studies,[40–47] and investigated the bioactivities of partial 2(5*H*)-furanone derivatives.[48–50]

Nowadays, there are reports on the role of amino acids as linking units.[13,19,51,52] However, it is still necessary to investigate whether the amino acid unit is a safe linker without any impact on the bioactivity of 2(5*H*)-furanones when amino acids are combined with the 2(5*H*)-furanone moiety by C–N coupling to expand the functionalization of 2(5*H*)-furanones. Thus, in order to make full use of two synthons both 2(5*H*)-fur-

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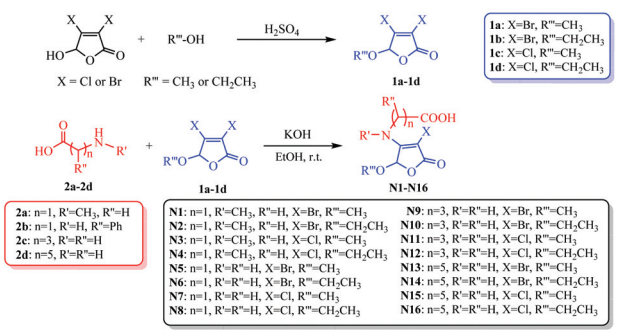


Scheme 1 Synthetic route to target compounds **N1–N16**.

anones and amino acids,[53] and make clear how they work together especially in a small molecular system, a series of amino acid derivatives were synthesized with 5-alkoxy-3,4-dihalo-2(5*H*)-furanones and amino acids, including non-natural amino acids, *via* a metal-free C–N coupling reaction (Scheme 1). And the effect of amino acids as linkers on bioactivity was investigated by comparison with other 5-substituted-3-halo-2(5*H*)-furanone derivatives.

Experimental

Materials and methods

^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 on a Varian DRX-400 MHz spectrometer and tetramethylsilane (TMS) was used as an internal standard. Elemental analysis was performed on a Thermo FlashEA TM 112 elemental analyzer. Mass spectra (MS) were recorded on a Thermo LCQ DECA XP MAX mass spectrometer.

All reagents and solvents were commercially available and used as received. Using furfural, ethanol and methanol as starting materials, 5-substituted-3,4-dihalo-2(5*H*)-furanones **1a–1d** were prepared according to the literature.[44–50]

General procedure for syntheses of compounds N1–N16

Amino acid **2** (4 mmol), KOH (4.48 mmol) and C_2H_5OH (5 mL) were added into a round-bottomed flask equipped with a magnetic stirring bar. After the mixture was dissolved under stirring, 5-substituted 3,4-dihalo-2(5*H*)-furanones **1** (2 mmol) in CH_2Cl_2 (5 mL) were dropped into the above system. The mixed solution was stirred at room temperature under an N_2 atmosphere for 24 h.

After the solvent was removed, the residue was dissolved in CH_2Cl_2, and the pH value was adjusted to 3–4 using 15% HCl. The organic layers were washed with saturated NH_4Cl solution three times and then dried over anhydrous $MgSO_4$. The concentration under vacuum gave a crude product, which was purified by column chromatography on silica gel with gradient eluents of petroleum ether and ethyl acetate to afford pure compounds.

Biochemical approach

The cell viability of the compounds was determined by measuring the ability of cells to transform MTT into a purple formazan dye.[54,55] All compounds were dissolved in DMSO with stock solution at 10 mM. The cells were seeded in 96-well tissue culture plates at 5×10^3 cells per well and incubated in an incubator at 37 °C and 5% CO_2 for 24 h. Then, the cells were incubated with the tested compounds in a concentration range of 4–300 mM, ensuring an equal volume of 200 μL across the wells of the plate. These plates were incubated at 37 °C in a 5% CO_2 incubator for 72 h. After incubation, 20 μL of MTT solution (5 mg mL^{-1}) was added across the plate and further incubated for 4 h. Finally, the medium was aspirated and replaced with a 150 μL per well of DMSO to dissolve the formazan salt formed. The color intensity of the formazan solution, which reflects the cell growth conditions, was measured by using a microplate spectrophotometer at 490 nm.

Characterization data for compounds N1–N16

***N*-(4-Bromo-2-methoxy-5-oxo-2,5-dihydrofuran-3-yl)-*N*-methylglycine (N1).** Brown sticky liquid; yield: 222 mg (79%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 3.26 (s, 3H, NCH_3), 3.46 (s, 3H, OCH_3), 4.34 (s, 2H, CH_2), 5.77 (s, 1H, CH), 6.61 (b, 1H, COOH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 40.5, 53.9, 54.5, 74.4, 98.7, 158.2, 168.9, 172.2; ESI-MS, *m*/*z* (%): calcd for $C_8H_9BrNO_5^-$ ([M − H]$^-$): 277.97 (100.0%), 279.97 (97.3%), found: 277.79 (100.0%), 279.79 (96.1%); anal. calcd for $C_8H_{10}BrNO_5$: C 34.31, H 3.60, N 5.00, found: C 34.43, H 3.52, N 5.02.

***N*-(4-Bromo-2-ethoxy-5-oxo-2,5-dihydrofuran-3-yl)-*N*-methylglycine (N2).** Brown sticky liquid; yield: 208 mg (71%); ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.13 (t, J = 8.0 Hz, 3H, CH_3), 3.00–3.34 (m, 4H, NCH_3, COOH), 3.61–3.70 (m, 2H, OCH_2), 4.08–4.44 (m, 2H, CH_2), 6.14 (s, 1H, CH), 13.02 (b, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 15.1, 40.2, 53.9, 63.8, 71.9, 98.0, 159.3, 168.3, 170.4; ESI-MS, *m*/*z* (%): calcd for $C_9H_{11}BrNO_5^-$ ([M − H]$^-$): 291.98 (100.0%), 293.98 (97.3%), found: 291.74 (100.0%), 293.74 (94.7%); anal. calcd for $C_9H_{12}BrNO_5$: C 36.76, H 4.11, N 4.76, found: C 36.82, H 4.02, N 4.83.

***N*-(4-Chloro-2-methoxy-5-oxo-2,5-dihydrofuran-3-yl)-*N*-methylglycine (N3).** Brown sticky liquid; yield: 157 mg (67%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 3.24 (3H, s, NCH_3), 3.48 (s, 3H, OCH_3), 4.31 (s, 2H, CH_2), 5.74 (s, 1H, CH), 7.46 (b, 1H, COOH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 40.2, 53.4, 54.5, 88.8, 97.7, 155.3, 168.2, 172.6; ESI-MS, *m*/*z* (%): calcd for $C_8H_9ClNO_5^-$ ([M − H]$^-$): 234.02 (100.0%), 236.01 (32.0%), found: 233.71 (100.0%), 235.71 (35.0%); anal. calcd for $C_8H_{10}ClNO_5$: C 40.78, H 4.28, N 5.94, found: C 40.63, H 4.25, N 5.82.

***N*-(4-Chloro-2-ethoxy-5-oxo-2,5-dihydrofuran-3-yl)-*N*-methylglycine (N4).** Brown sticky liquid; yield: 139 mg (56%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 1.27 (t, J = 8.0 Hz, 3H, CH_3), 3.27 (s, 3H, NCH_3), 3.69–3.91 (m, 2H, OCH_2), 4.24–4.39 (m, 2H, CH_2), 5.81 (s, 1H, CH), 8.74 (b, 1H, COOH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 14.7, 40.2, 53.6, 64.5, 88.3, 97.4, 156.2, 169.1, 172.4; ESI-MS, *m*/*z* (%): calcd for $C_9H_{11}ClNO_5^-$ ([M − H]$^-$): 248.03 (100.0%), 250.03 (32.0%), found: 248.46 (100.0%), 250.46 (27.8%); anal. calcd for $C_9H_{12}ClNO_5$: C 43.30, H 4.85, N, 5.61, found: C 43.36, H 4.82, N 5.55.

2-(4-Bromo-2-methoxy-5-oxo-2,5-dihydrofuran-3-yl)amino-2-phenylacetic acid (N5). Brown sticky liquid; yield: 153 mg (45%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 3.41 (s, 3H, OCH_3), 5.35–6.44 (m, 3H, NH, COOH, CH), 5.75 (s, 1H, CH), 7.38–7.42 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 58.6, 65.6, 81.5, 98.1, 127.0, 129.3, 129.4, 135.4, 153.2, 167.7, 172.1; ESI-MS, *m*/*z* (%): calcd for $C_{13}H_{13}BrNO_5^+$ ([M + H]$^+$): 342.00 (100.0%), 344.00 (97.3%), found: 341.64 (100%), 343.64 (93.2%); anal. calcd for $C_{13}H_{12}BrNO_5$: C 45.64, H 3.54, N 4.09, found: C 45.64, H 3.74, N 4.19.

2-(4-Bromo-2-ethoxy-5-oxo-2,5-dihydrofuran-3-yl)amino-2-phenylacetic acid (N6). Brown sticky liquid; yield: 159 mg (45%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 1.27 (t, J = 8.0 Hz, 3H, CH_3), 3.62–3.79 (m, 2H, OCH_2), 5.20–5.80 (m, 2H, CH), 6.29 (b, 1H, N–H), 6.37 (b, 1H, COOH), 7.35–7.41 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 15.0, 58.7, 65.3, 83.3, 97.5, 127.0, 129.3, 129.5, 135.0, 152.4, 167.4, 172.9; ESI-MS, m/z (%): calcd for $C_{14}H_{15}BrNO_5^+$ ($[M + H]^+$): 356.01 (100.0%), 358.01 (97.3%), found: 355.74 (97.3%), 357.74 (100%); anal. calcd for $C_{14}H_{14}BrNO_5$: C 47.21, H 3.96, N 3.92, found: C 46.91, H 4.06, N 3.93.

2-(4-Chloro-2-methoxy-5-oxo-2,5-dihydrofuran-3-yl)amino-2-phenylacetic acid (N7). Brown sticky liquid; yield: 112 mg (38%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 3.43 (s, 3H, OCH_3), 5.27–5.74 (m, 4H, NH, COOH, 2CH), 7.32–7.46 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 58.6, 64.0, 85.1, 96.4, 127.0, 129.3, 129.4, 132.2, 149.0, 163.5, 172.7; ESI-MS, m/z (%): calcd for $C_{13}H_{13}ClNO_5^+$ ($[M + H]^+$): 298.05 (100.0%), 300.04 (32.0%), found: 297.76 (100.0%), 300.05 (43.0%); anal. calcd for $C_{13}H_{12}ClNO_5$: C 52.45, H 4.06, N 4.71, found: C 52.35, H 4.10, N 4.82.

2-(4-Chloro-2-ethoxy-5-oxo-2,5-dihydrofuran-3-yl)amino-2-phenylacetic acid (N8). Brown sticky liquid; yield: 127 mg (41%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 1.26 (t, J = 8.0 Hz, 3H, CH_3), 3.57–3.82 (m, 2H, CH_2), 5.13–5.79 (m, 3H, NH, 2CH), 6.96 (b, 1H, COOH), 7.31–7.41 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 15.0, 58.9, 65.3, 83.8, 97.2, 127.0, 129.2, 129.4, 135.5, 150.1, 167.5, 172.9; ESI-MS, m/z (%): calcd for $C_{14}H_{15}ClNO_5^+$ ($[M + H]^+$): 312.06 (100.0%), 314.06 (32.0%), found: 311.68 (100.0%), 313.68 (48.6%); anal. calcd for $C_{14}H_{14}ClNO_5$: C 53.94, H 4.53, N 4.49, found: C 54.05, H 4.46, N 4.51.

4-(4-Bromo-2-methoxy-5-oxo-2,5-dihydrofuran-3-yl)amino-butanoic acid (N9). Yellow sticky liquid; yield: 157 mg (54%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 1.63–1.70 (m, 2H, CH_2), 1.96–2.01 (m, 2H, CH_2), 3.51 (s, 3H, OCH_3), 3.55 (b, 1H, COOH), 3.62–3.90 (m, 2H, NCH_2), 5.33 (s, 1H, NH), 5.73 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 25.2, 30.5, 43.2, 65.6, 85.0, 98.3, 149.5, 167.8, 178.0; ESI-MS, m/z (%): calcd for $C_9H_{13}BrNO_5^+$ ($[M + H]^+$): 294.00 (100.0%), 296.00 (97.3%), found: 293.71 (100%), 295.72 (94.8%); anal. calcd for $C_9H_{12}BrNO_5$: C 36.76, H 4.11, N 4.76, found: C 36.75, H 4.38, N 4.84.

4-(4-Bromo-2-ethoxy-5-oxo-2,5-dihydrofuran-3-yl)amino-butanoic acid (N10). Yellow sticky liquid; yield: 187 mg (61%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 1.28 (t, J = 8.0 Hz, 3H, CH_3), 1.90–2.56 (m, 5H, COOH, $2CH_2$), 3.70–3.90 (m, 4H, OCH_2, NCH_2), 5.36 (s, 1H, CH), 5.77 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 15.0, 25.2, 30.5, 43.2, 65.6, 85.0, 98.3, 149.5, 167.8, 178.0; ESI-MS, m/z (%): calcd for $C_{10}H_{15}BrNO_5^+$ ($[M + H]^+$): 308.01 (100.0%), 310.01 (97.3%), found: 307.74 (100.0%), 309.74 (94.8%); anal. calcd for $C_{10}H_{14}BrNO_5$: C 38.98, H 4.58, N 4.55, found: C 39.00, H 4.48, N 4.62.

4-(4-Chloro-2-methoxy-5-oxo-2,5-dihydrofuran-3-yl)amino-butanoic acid (N11). Brown liquid; yield: 136 mg (55%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 1.93–1.99 (m, 2H, CH_2), 2.46–2.50 (m, 2H, CH_2), 3.50–3.60 (m, 5H, NCH_2, OCH_3), 5.19–5.35 (m, 2H, CH, NH), 5.67 (s, 1H, COOH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 25.3, 30.8, 43.0, 55.2, 83.0, 97.5, 155.5, 166.3, 177.9; ESI-MS, m/z (%): calcd for $C_9H_{13}ClNO_5^+$ ($[M + H]^+$): 250.05 (100.0%), 252.04 (32.0%), found: 249.80 (100.0%), 251.80 (30.4%); anal. calcd for $C_9H_{12}ClNO_5$: C 43.30, H 4.85, N 5.61, found: C 43.45, H 5.06, N 5.51.

4-(4-Chloro-2-ethoxy-5-oxo-2,5-dihydrofuran-3-yl)amino-butanoic acid (N12). Brown liquid; yield: 183 mg (70%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 1.29 (3H, t, J = 8.0 Hz, CH_3), 1.95–2.25 (m, 2H, CH_2), 2.50 (t, J = 8.0 Hz, 2H, CH_2), 3.51–3.61 (m, 2H, NCH_2), 3.70–3.91 (m, 2H, OCH_2), 4.63 (b, 1H, COOH), 5.31 (s, 1H, NH), 5.74 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 14.9, 25.3, 30.9, 43.0, 64.9, 82.5, 96.8, 156.5, 163.1, 178.3; ESI-MS, m/z (%): calcd for $C_{10}H_{13}ClNO_5^-$ ($[M - H]^-$): 262.05 (100.0%), 264.05 (32.0%), found: 261.80 (100.0%), 263.75 (42.1%); anal. calcd for $C_{10}H_{14}ClNO_5$: C 45.55, H 5.35, N 5.31, found: C 45.45, H 5.36, N 5.30.

6-(4-Bromo-2-methoxy-5-oxo-2,5-dihydrofuran-3-yl)amino-hexanoic acid (N13). Yellow sticky liquid; yield: 244 mg (76%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 1.43–1.48 (m, 2H, CH_2), 1.63–1.71 (m, 4H, $2CH_2$), 2.40 (t, J = 8.0 Hz, 2H, CH_2), 3.32–3.47 (m, 2H, NCH_2), 3.50 (s, 3H, OCH_3), 4.94 (s, 1H, COOH), 5.35 (b, 1H, NH), 5.72 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 24.0, 25.7, 30.1, 33.6, 43.5, 54.8, 84.6, 98.4, 157.1, 163.4, 178.9; ESI-MS, m/z (%): calcd for $C_{11}H_{17}BrNO_5^+$ ($[M + H]^+$): 322.03 (100.0%), 324.03 (97.3%), found: 321.65 (100%), 323.65 (88.7%); anal. calcd for $C_{11}H_{16}BrNO_5$: C 41.01, H 5.01, N 4.35, found: C 40.92, H 5.16, N 4.45.

6-(4-Bromo-2-ethoxy-5-oxo-2,5-dihydrofuran-3-yl)amino-hexanoic acid (N14). Yellow sticky liquid; yield: 267 mg (80%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 1.28 (t, J = 8.0 Hz, 3H, CH_3), 1.34–1.47 (m, 2H, CH_2), 1.61–1.70 (m, 4H, $2CH_2$), 2.33–2.41 (m, 2H, CH_2), 3.36–3.60 (m, 2H, NCH_2), 3.70–3.89 (m, 2H, OCH_2), 5.36 (s, 1H, CH), 5.78 (b, 1H, NH), 6.88 (b, 1H, COOH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 15.0, 24.0, 25.7, 30.2, 33.6, 40.7, 64.5, 84.7, 97.6, 138.8, 163.5, 178.8; ESI-MS, m/z (%): calcd for $C_{12}H_{19}BrNO_5^+$ ($[M + H]^+$): 336.04 (100.0%), 338.04 (97.3%), found: 335.73 (100%), 337.75 (94.5%); anal. calcd for $C_{12}H_{18}BrNO_5$: C 42.87, H 5.40, N 4.17, found: C 43.02, H 5.45, N 4.20.

6-(4-Chloro-2-methoxy-5-oxo-2,5-dihydrofuran-3-yl)amino-hexanoic acid (N15). Brown liquid; yield: 214 mg (78%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 1.26–1.36 (m, 2H, CH_2), 1.40–1.55 (m, 2H, CH_2), 1.62–1.70 (m, 2H, CH_2), 2.34–2.41 (m, 2H, CH_2), 3.37–3.47 (m, 2H, NCH_2), 3.50 (s, 3H, OCH_3), 5.26 (b, 1H, NH), 5.32 (s, 1H, CH), 5.69 (b, 1H, COOH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 24.0, 25.7, 30.2, 33.7, 43.4, 55.0, 84.3, 97.6, 156.0, 167.8, 179.2; ESI-MS, m/z (%): calcd for $C_{11}H_{17}ClNO_5^+$ ($[M + H]^+$): 278.08 (100.0%), 280.08 (32.0%), found: 277.78 (100%), 279.78 (30.2%); anal. calcd for $C_{11}H_{16}ClNO_5$: C 47.58, H 5.81, N 5.04, found: C 47.62, H 5.86, N 5.05.

6-(4-Chloro-2-ethoxy-5-oxo-2,5-dihydrofuran-3-yl)amino-hexanoic acid (N16). Brown liquid; yield: 228 mg (79%); ^{1}H NMR (400 MHz, $CDCl_3$-TMS), δ, ppm: 1.25 (t, J = 8.0 MHz, 3H, CH_3), 1.31–1.44 (m, 2H, CH_2), 1.58–1.65 (m, 4H, $2CH_2$), 2.31–2.37 (m, 2H, CH_2), 3.31–3.55 (m, 2H, NCH_2), 3.67–3.86 (m, 2H, OCH_2), 5.31 (s, 1H, CH), 5.39 (b, 1H, NH), 5.72 (b, 1H, COOH); ^{13}C NMR (100 MHz, $CDCl_3$-TMS), δ, ppm: 14.9, 24.0, 25.7, 30.2, 33.7, 43.4, 64.6, 85.5, 96.9, 156.0, 167.8, 179.2; ESI-MS, m/z (%): calcd for $C_{12}H_{19}ClNO_5^+$ ($[M + H]^+$): 292.09 (100.0%), 294.09 (32.0%), found: 291.84 (100%); 293.84 (25.8%); anal. calcd for $C_{12}H_{18}ClNO_5$: C 49.41, H 6.22, N 4.80, found: C 49.42, H 6.42, N 4.75.

Results and discussion

Chemical synthesis by metal-free C–N coupling reaction

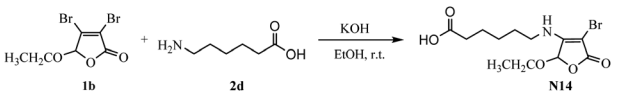
Based on our previous work,[40–47] the reaction conditions were optimized firstly. Using 2 mmol 3,4-dibromo-5-ethoxy-2(5*H*)-furanone (**1b**) and 6-aminohexanoic acid (**2d**)[56] as representative reactants, the reaction parameters, such as catalysts, bases, additives and temperature, were examined. The obtained results are listed in Table 1.

It is well known that the formation of a C_{sp2}–N bond between a C_{sp2}–X bond and N–H is usually catalyzed by transition metal catalysts,[57–60] especially the inexpensive Cu(I) salts.[61–64] Thus, under the same conditions, we initially investigated the effect of the available Cu(I) salt. Using three sets of test comparisons, it can be found that CuI (0.015 mmol) does not work well as a catalyst in this reaction system irrespective of the base (Table 1, entries 1–6). And obviously, among the selected bases, KOH (1.12 equiv. of amino acid **2d**) is the best and the isolated yield of the target compound, 6-(4-bromo-2-ethoxy-5-oxo-2,5-dihydrofuran-3-yl)aminohexanoic acid (**N14**), is 71% (entry 6). However, mixing the additive of KI into the base system is not effective irrespective of the proportion it is used in (entries 7–9). In addition, we did not notice any significant advantages when altering the reaction temperature (entries 10 and 11 *vs.* entry 6). Fortunately, when the dosage ratio of **2d** with **1b** is increased to 2 equiv., the desired product **N14** can be obtained in 80% yield (Table 1, entry 12). Thus, using C_2H_5OH/CH_2Cl_2 as a solvent and KOH (4.48 mmol) as a base, we successfully achieved the reaction of **1b** (2 mmol) and **2d** (4 mmol) at room temperature for 24 h to obtain a satisfactory yield.

Under the optimized reaction conditions, four typical amino acids were used in the transformation to establish the scope and generality of this protocol (Table 2). Generally, irrespective of whether bromine or chlorine is used in 5-alkoxyl-3,4-dihalo-2(5*H*)-furanones **1**, the reaction can work well. What's more, the type of amino acid also has some effects on the yield. In most cases, on using secondary amine sarcosine as the substrate, the yield of products is higher than that when using primary amines (*e.g.* phenylglycine and 4-aminobutyric acid, **N1–N4** *vs.* **N5–N11**). This means that the secondary amine is beneficial for this reaction. Furthermore, the yield of products is increased with the increase in the alkyl chain length of primary amines, especially for 6-aminohexanoic acid (**N13–N16**). This is because, the longer the chain, the greater the flexibility and the smaller the steric resistance. In addition, due to the large steric hindrance of the benzene ring, though the yield of products obtained by phenylglycine can be over 38% (**N5–N8**), it is obviously lower than that of others.

The structures of all amino acid derivatives have been systematically characterized by ^{1}H NMR, ^{13}C NMR, ESI-MS and elemental analysis. In the ^{1}H NMR spectra, there is a single peak between 5.27–6.14 ppm, and the chemical shift belongs to the C–H of the furanone ring. The significant chemical shift of NH and COOH in the amino acid unit usually appears near

Table 1 Optimization of the reaction conditions[a]

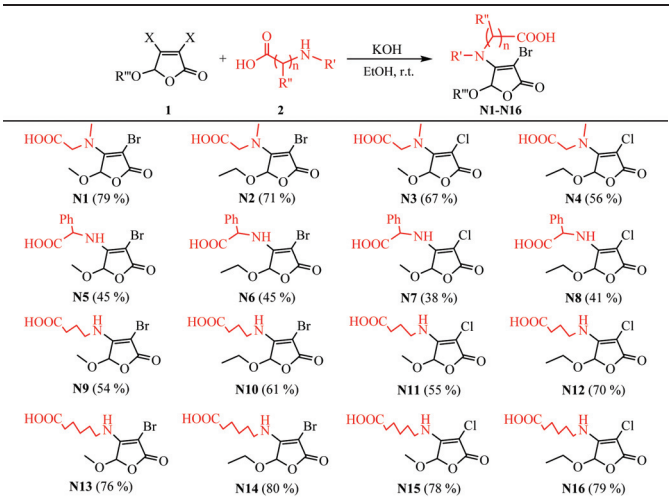


1b **2d** **N14**

Entry	**2d** : **1b**	Base (equiv.)	Cat.	Temp. (°C)	Yield[b] (%)
1	1.5	K_3PO_4 (1.12)	CuI	r.t.	45
2	1.5	K_3PO_4 (1.12)	—	r.t.	57
3	1.5	^{t}BuOK (1.12)	CuI	r.t.	47
4	1.5	^{t}BuOK (1.12)	—	r.t.	39
5	1.5	KOH (1.12)	CuI	r.t.	66
6	1.5	KOH (1.12)	—	r.t.	71
7	1.5	KOH + KI (1.12, 1 : 1)	—	r.t.	58
8	1.5	KOH + KI (1.12, 1 : 2)	—	r.t.	30
9	1.5	KOH + KI (1.12, 2 : 1)	—	r.t.	49
10	1.5	KOH (1.12)	—	40	45
11	1.5	KOH (1.12)	—	60	45
12	**2.0**	**KOH (1.12)**	—	**r.t.**	**80**

[a] Using C_2H_5OH/CH_2Cl_2 as a solvent, the reaction was carried out for 24 h. [b] Isolated yield.

Table 2 Substrate scope of various 5-substituted 3,4-dihalo-2(5*H*)-furanones **1** and amino acids **2**[a,b]



[a] Using KOH as a base and C_2H_5OH/CH_2Cl_2 as a solvent at room temperature. [b] Isolated yield.

5.35 ppm and 6.88 ppm, respectively. The characteristic chemical shift of the furanone ring and amino acid moiety also can be found in ^{13}C NMR spectra. Furthermore, the ESI-MS results are consistent with the data of their corresponding theoretical value. Thus, all structural testing results confirm that the metal-free C–N coupling reaction between 5-substituted 3,4-dihalo-2(5*H*)-furanones and amino acids is carried out indeed.

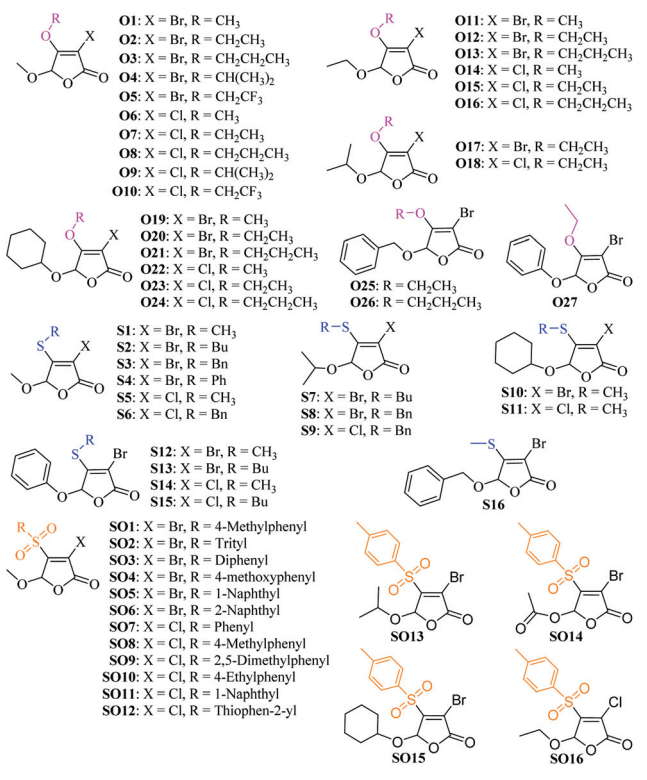
There have been many research studies to make the C–N bond construction reaction more eco-friendly.[64–66] Particularly, due to high cost and environmental pollution in transition metal catalysis, the development of metal-free methodologies in the C–N coupling reaction is becoming popular.[67–69] Therefore, our design for the formation of the C_{sp2}–N bond is practical and allows for the successful combination of amino acids with the 2(5*H*)-furanone unit.

Inhibition activities on various anticancer cells *in vitro*

In order to investigate the potential bioactive compounds with no/less cytotoxicity, other 2(5*H*)-furanone compounds **O1–O27**,[70] **S1–S16**,[46] and **SO1–SO16**[47] were selected as contrasting substances (their structures can be seen in Scheme 2) by constructing C–O/C–S bonds at the same site of 5-substituted 3,4-dihalo-2(5*H*)-furanones (their corresponding synthesis procedures are described in the ESI†); the effect of amino acids as potential linkers in the 2(5*H*)-furanone unit with other drug moieties containing amino or hydroxy groups was investigated through the biological activity assay by the MTT method on a series of cancer cell lines *in vitro*, such as C6 (rat glioma cells), EC-1 (human esophageal carcinoma cells), MDA-MB-231 (estrogen receptor-negative human breast cells), MCF-7 (estrogen receptor-positive human breast cells), HepG2 (human hepatoma cells), CNE-1 (nasopharyngeal carcinoma cells) and A549 (human lung adenocarcinoma cells).[54,55] Using cisplatin as the positive control, the antitumor activities of the above-mentioned 2(5*H*)-furanone derivatives are summarized in Table 3.

It can be seen that, **N1–N16**, the serial amino acid derivatives of 5-alkoxy-3,4-dihalo-2(5*H*)-furanones basically have no obvious antiproliferative activity, so the tumor cells can grow without exerting cytotoxicity from the target compounds. However, most of the **O1–O27** furanone derivatives have certain cytotoxic activity on HepG2 hepatocellular carcinoma cells, especially for **O5** and **O10** both containing a trifluoroethyl group. For **S1–S16** and **SO1–SO16** series, most derivatives of furanones have certain antiproliferative activity on MDA-MB-231 breast cancer cells, C6 brain glioma cells and MCF-7 breast cancer cells. Therefore, the preliminary results reveal that the introduction of amino acids as safe linkers basically has no toxic effect as anticipated.

At the same time, due to the presence of an amino acid structural unit in **N1–N16** series, they can be expected to be further studied in the field of cell compatibility. And in combination with other bioactive results, it is possible to introduce a fluorine-containing group into **N1–N16** series *via* esterification with trifluoroethanol to develop the potential 2(5*H*)-furanone drugs. Studies on these aspects are in progress.



Scheme 2 2(5*H*)-Furanone derivatives synthesized previously.

Conclusions and outlook

A series of amino acid derivatives are synthesized with 5-alkoxy-3,4-dihalo-2(5*H*)-furanones and amino acids *via* a metal-free C–N coupling reaction as expected after the optimal reaction conditions are established. As linkers, the effect of amino acids has been investigated by comparison with other 2(5*H*)-furanone compounds by constructing C–O/C–S bonds. The results of the biological activity assay reveal that the amino acids in these 2(5*H*)-furanone derivatives exhibiting good biocompatibility can be good linkers as expected. What's more, a fluorine-containing group is beneficial for improving the bioactivity of 2(5*H*)-furanone drugs. The introduction of fluorine-containing groups into 2(5*H*)-furanones will be our future work.

Importantly, as linkers of potential 2(5*H*)-furanone drugs, amino acids can provide a well-reactive site into 2(5*H*)-furanone derivatives by reacting with the carboxyl group in our amino acid linking unit under mild conditions. Particularly, some amino acids with long chains may improve the tolerance of 2(5*H*)-furanone substrates for the introduction of some complex, sensitive and sterically hindered bioactive moieties with amino or hydroxy groups.[71–73] Thus, the introduction of amino acids as linkers will provide a new effective approach for the development of 2(5*H*)-furanone derivative drugs with good biocompatibility.

Table 3 Inhibitory effects of target molecules **N1–N16**, contrasting substances and cisplatin against the growth of the selected cell lines

	IC_{50}/μM (Max concentration: 300 μM)						
No.	HepG2	MDA-MB-231	C6	MCF-7	A549	EC-1	CNE-1
N1	>300	>300	>300	>300	>300	>300	**66.69 ± 2.25**
N2	>300	>300	>300	>300	>300	>300	>300
N3	>300	>300	>300	>300	>300	>300	>300
N4	>300	>300	>300	>300	>300	>300	>300
N5	>300	>300	>300	>300	>300	284.98 ± 20.15	>300
N6	>300	>300	>300	>300	>300	>300	>300
N7	>300	>300	>300	104.67 ± 8.50	>300	>300	>300
N8	>300	>300	>300	>300	>300	>300	>300
N9	>300	>300	>300	>300	>300	>300	>300
N10	>300	>300	>300	>300	>300	>300	>300
N11	>300	>300	>300	>300	>300	>300	>300
N12	>300	>300	>300	>300	>300	>300	>300
N13	>300	>300	>300	>300	>300	>300	>300
N14	>300	>300	>300	>300	>300	>300	>300
N15	>300	>300	>300	>300	>300	>300	>300
N16	>300	>300	>300	>300	>300	>300	>300
O1	196.08 ± 8.46	>300	>300	239.43 ± 12.43	299.79 ± 8.33	223.73 ± 12.06	>300
O2	190.05 ± 3.85	>300	>300	>300	>300	>300	299.13 ± 3.03
O3	152.40 ± 2.28	161.59 ± 33.99	>300	>300	>300	>300	230.58 ± 3.54
O4	151.04 ± 3.26	>300	>300	>300	>300	>300	>300
O5	**40.22 ± 0.57**	127.06 ± 1.25	73.11 ± 0.61	73.53 ± 1.57	127.38 ± 0.76	286.20 ± 12.94	>300
O6	>300	>300	266.23 ± 6.85	>300	271.60 ± 7.83	>300	220.98 ± 12.11
O7	127.48 ± 2.55	>300	>300	>300	>300	>300	>300
O8	268.65 ± 4.28	>300	>300	>300	>300	229.70 ± 7.49	274.53 ± 2.00
O9	149.64 ± 6.47	>300	>300	>300	>300	>300	>300
O10	**41.12 ± 0.94**	123.49 ± 1.96	58.47 ± 0.52	**19.67 ± 0.37**	108.36 ± 1.09	44.68 ± 0.68	>300
O11	120.68 ± 4.39	>300	279.32 ± 6.40	>300	>300	>300	>300
O12	107.51 ± 2.41	>300	>300	>300	>300	284.35 ± 10.33	256.45 ± 6.08
O13	195.15 ± 7.25	>300	>300	223.30 ± 10.27	150.25± 8.62	281.50 ± 16.25	295.63 ± 7.74
O14	292.53 ± 3.82	257.21 ± 9.05	>300	>300	>300	>300	>300
O15	110.13 ± 2.91	>300	>300	>300	>300	>300	>300
O16	>300	>300	>300	>300	>300	>300	>300
O17	>300	>300	>300	>300	>300	>300	>300
O18	>300	>300	>300	>300	>300	>300	203.88 ± 3.24
O19	186.63 ± 3.68	288.69 ± 3.81	>300	193.52 ± 3.58	186.87± 3.96	246.71 ± 5.86	>300
O20	>300	>300	>300	>300	>300	159.90 ± 3.95	>300
O21	>300	181.45 ± 1.93	109.13 ± 2.39	145.12 ± 1.23	182.53 ± 3.50	>300	185.65 ± 2.58
O22	>300	>300	>300	>300	>300	>300	>300
O23	>300	>300	269.43 ± 5.91	>300	>300	>300	>300
O24	>300	297.26 ± 7.76	>300	299.34 ± 9.65	>300	293.68 ± 7.9	154.90 ± 2.82
O25	>300	233.76 ± 10.25	>300	>300	>300	>300	>300
O26	416.03 ± 4.1	221.64 ± 2.6	231.35 ± 2.24	192.44 ± 3.80	212.16 ± 4.57	197.19 ± 7.37	108.72 ± 1.57
O27	85.79 ± 3.04	215.44 ± 6.57	158.83 ± 1.21	130.73 ± 2.20	152.05 ± 1.23	>300	>300
S1	>300	>300	175.32 ± 1.41	252.41 ± 8.31	>300	224.25 ± 8.04	>300
S2	>300	>300	176.68 ± 4.81	165.10 ± 4.34	218.16 ± 5.70	185.17 ± 10.56	>300
S3	184.70 ± 1.27	180.77 ± 2.77	138.88 ± 2.18	181.02 ± 3.18	296.80 ± 2.70	229.75 ± 9.35	>300
S4	>300	116.69 ± 2.38	**84.52 ± 1.44**	86.19 ± 2.84	143.73 ± 5.42	248.79 ± 3.73	>300
S5	>300	>300	>300	>300	>300	>300	>300
S6	259.97 ± 4.51	249.08 ± 5.48	147.08 ± 3.32	196.05 ± 9.83	262.89 ± 7.59	160.80 ± 9.25	>300
S7	155.90 ± 1.65	218.76 ± 2.17	207.33 ± 3.58	175.37 ± 5.75	262.98 ± 3.59	112.53 ± 3.56	>300
S8	>300	176.29 ± 3.62	178.15 ± 1.58	212.89 ± 4.82	>300	250.79 ± 8.83	>300
S9	>300	167.66 ± 1.48	165.51 ± 2.64	187.98 ± 4.19	230.93 ± 3.95	169.95 ± 3.08	190.79 ± 3.73
S10	231.03 ± 1.44	214.58 ± 3.42	166.01 ± 2.14	184.67 ± 3.13	239.34 ± 1.98	>300	>300
S11	>300	197.28 ± 4.77	162.49 ± 3.17	211.02 ± 7.35	>300	224.22 ± 12.31	>300
S12	224.00 ± 3.05	215.34 ± 3.43	157.99 ± 2.07	130.12 ± 5.53	>300	144.78 ± 11.34	>300
S13	>300	168.41 ± 4.70	152.69 ± 2.97	178.06 ± 6.30	268.61 ± 7.82	205.52 ± 4.64	>300
S14	>300	>300	158.05 ± 2.64	>300	>300	>300	>300
S15	>300	185.54 ± 6.72	146.55 ± 1.72	191.93 ± 11.57	256.50 ± 8.67	207.351 ± 10.57	>300
S16	251.28 ± 2.72	295.29 ± 8.66	167.40 ± 3.88	175.21 ± 5.34	258.95 ± 2.16	187.75 ± 11.82	>300
SO1	>300	184.71 ± 4.58	198.43 ± 4.76	181.12 ± 7.73	>300	>300	>300
SO2	>300	>300	128.90 ± 3.52	168.99 ± 2.74	>300	>300	>300
SO3	246.52 ± 3.72	142.23 ± 1.94	115.98 ± 2.15	119.12 ± 1.69	173.78 ± 2.67	>300	>300
SO4	>300	175.28 ± 3.36	129.44 ± 6.93	134.66 ± 5.44	282.91 ± 9.71	>300	>300
SO5	>300	216.38 ± 3.32	101.25 ± 3.43	216.78 ± 7.16	>300	>300	>300

Table 3 *(Contd.)*

No.	IC_{50}/μM (Max concentration: 300 μM)						
	HepG2	MDA-MB-231	C6	MCF-7	A549	EC-1	CNE-1
SO6	295.97 ± 4.38	**86.19 ± 1.95**	67.87 ± 1.32	>300	>300	199.58 ± 10.07	154.22 ± 6.66
SO7	>300	174.93 ± 3.96	96.39 ± 1.21	122.02 ± 4.57	>300	>300	>300
SO8	>300	183.81 ± 6.59	106.69 ± 2.66	112.87 ± 3.65	>300	>300	>300
SO9	266.74 ± 2.41	145.58 ± 2.23	**49.80 ± 0.97**	83.24 ± 2.68	253.47 ± 3.74	>300	>300
SO10	>300	216.27 ± 3.60	117.68 ± 3.70	150.63 ± 6.98	>300	>300	>300
SO11	>300	283.00 ± 5.54	>300	262.22 ± 10.25	>300	>300	>300
SO12	>300	198.36 ± 5.51	105.17 ± 2.12	124.86 ± 1.81	255.38 ± 1.52	>300	>300
SO13	>300	159.93 ± 2.74	153.07 ± 3.29	123.13 ± 3.62	240.55 ± 4.87	>300	>300
SO14	>300	131.58 ± 4.22	92.70 ± 3.62	>300	>300	293.03 ± 11.18	186.76 ± 7.86
SO15	>300	161.48 ± 1.97	108.28 ± 2.73	117.14 ± 4.25	235.38 ± 7.38	>300	>300
SO16	>300	147.13 ± 4.65	65.93 ± 2.73	86.30 ± 2.18	216.27 ± 8.55	170.43 ± 2.80	123.23 ± 2.67
Cisplatin	**93.1 ± 0.9**	**17.8 ± 0.9**	**18.7 ± 0.5**	**76.9 ± 0.9**	**ND**	**ND**	**19.1 ± 0.5**

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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