Supporting Information

Discovery of a Novel Dipeptidyl Boronic Acid Proteasome Inhibitor for the Treatment of Multiple Myeloma and Triple-negative Breast Cancer

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Contents:

1. 1H NMR and mass spectra of intermediates S2-S15
2. 1H NMR, 13C NMR and mass data of final compounds S16-S22
3. 1H NMR spectra of intermediate compounds S23-S38
4. 1H NMR and 13C NMR spectra of final compounds S39-S58
1. **1H NMR and mass spectra of intermediates**

**N-ethoxycarbonylphthalimide (2a)**

![N-ethoxycarbonylphthalimide (2a)](image)

To a solution of phthalimide (7.36 g, 50 mmol) dissolved in anhydrous DMF (25 mL) was added TEA (9 mL, 65 mmol). Then temperature of the reaction system was cooled to 0 °C and ethyl chloroformate (5.7 mL, 60 mmol) was added dropwise. The mixture stirred at room temperature for 2 h and poured into iced water, filtered. The solid was washed with cold water and dried to obtain 8.67 g (79.1% yield) of white solid. mp 81.4-83.6 °C. **1H NMR (400 MHz, CDCl₃)** δ 1.44 (s, 3H), 4.48 (q, J = 7.1 Hz, 2H), 7.80-7.85 (m, 2H), 7.93-7.99 (m, 2H). **MS (ESI) m/z 220.1 [M+H]+.**

**(S)-2-phthalimidopropionic acid (2b)**

![N-ethoxycarbonylphthalimide (2a)](image)

To a stirred solution of 2a in H₂O (100 mL) was added L-alanine (8.9 g, 100 mmol) and Na₂CO₃ (10.6 g, 100 mmol). After 1.5 h, the aqueous solution was slowly acidified with aqueous HCl (1N) until pH = 1-2 and filtered to obtain 17.4 g (79.3% yield) of white solid. mp 145.8-146.6 °C. **1H NMR (400 MHz, CDCl₃)** δ 1.71 (s, 3H), 5.02 (q, J = 7.4 Hz, 1H), 7.69-7.75 (m, 2H), 7.82-7.88 (m, 2H). **MS (ESI) m/z 218.2 [M-H]-.**

**(S)-2-(1,3-dioxoisoindolin-2-yl)-N-(quinolin-8-yl)propanamide (2c)**

![N-ethoxycarbonylphthalimide (2a)](image)

To a solution of 2b (17.4 g, 79.3 mmol) in anhydrous CH₂Cl₂ (80 mL) was added thionyl chloride (29 mL, 396 mmol) and the resulting solution was refluxed for 6 h. The solvent was evaporated to give yellow oil. DIPEA (20.5 g, 159 mmol) and 8-aminoquinoline (11.4 g, 79.3 mmol) was dissolved in anhydrous CH₂Cl₂ (103 mL)
and the obtained yellow oil dissolved in CH$_2$Cl$_2$ (30 mL) was added dropwise at -20 °C for 1 h and then allowed to react at room temperature overnight. After evaporation and purification by column chromatography using petroleum ether/EtOAc/CH$_2$Cl$_2$ (5:1:1) as eluent, an orange solid (18.7 g, 71.9%) was obtained. mp 180.0-181.9°C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.98 (s, 3H), 5.27 (q, $J = 7.5$ Hz, 1H), 7.42 (dd, $J_1 = 4.2$ Hz, $J_2 = 8.3$ Hz, 1H), 7.51 (s, 1H), 7.53 (d, $J = 9.0$, 1H), 7.65-7.85 (m, 2H), 7.90 (dd, $J_1 = 3.6$, $J_2 = 7.1$ Hz, 2H), 8.15 (d, $J = 8.3$ Hz, 1H), 8.69 (d, $J = 4.2$ Hz, 1H), 8.73 (dd, $J_1 = 4.7$, $J_2 = 8.9$ Hz, 1H), 10.33 (s, 1H). MS (ESI) m/z 346.0 [M+H]$^+$. 

(S)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(1,3-dioxoisoindolin-2-yl)-N-(quinolin-8-yl)propanamide (2d)

To a solution of 2c (5.2 g, 15 mmol) in t-BuOH (105 mL) was added 6-iodo-2,3-dihydro-1,4-benzodioxine (5.9 g, 22.5 mmol), Pd(OAc)$_2$ (337 mg, 1.5 mmol) and AgBF$_4$ (3.65 g, 18.8 mmol). The resulting solution was stirred at 85 °C for 24 h. After cooling to room temperature, the reaction was diluted with dichloromethane (100 mL) and triethylamine (6 mL) was added to the mixture. The mixture was maintained for 6 hours and then filtered through a pad of Celite. After evaporation and purification by column chromatography using petroleum ether/EtOAc/CH$_2$Cl$_2$ (7:1:1) as eluent, an orange solid (4.8 g, 66.7%) was obtained. mp 178.3-179.9 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.54-3.81 (m, 2H), 4.06-4.26 (m, 4H), 5.38 (dd, $J_1 = 6.6$ Hz, $J_2 = 9.9$ Hz, 1H), 6.74 (dd, $J_1 = 5.0$ Hz, $J_2 = 16.7$ Hz, 2H), 6.83 (d, $J = 1.7$ Hz, 1H), 7.40 (dd, $J_1 = 4.2$ Hz, $J_2 = 8.3$ Hz, 1H), 7.45-7.56 (m, 2H), 7.65-7.79 (m, 2H), 7.80-7.90 (m, 2H), 8.12 (dd, $J_1 = 1.5$ Hz, $J_2 = 8.3$ Hz, 1H), 8.63 (dd, $J_1 = 1.5$ Hz, $J_2 = 4.2$ Hz, 1H), 8.68-8.78 (m, 1H), 10.29 (s, 1H). MS (ESI) m/z 477.9 [M-H]$^-$. 

(S)-methyl3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(1,3-dioxoisoindolin-2-yl)propanoate (2e)
To a 120 mL sealed bottle was added $2d$ (2 g, 4.2 mmol), BF$_3$·Et$_2$O (5.3 mL, 42 mmol) and anhydrous methanol (96 mL). The mixture was stirred at 100 °C for 25 hours. After cooling to room temperature, Et$_3$N (8.8 mL, 63 mmol) was added dropwise. After evaporation of the solvent and dissolved in CH$_2$Cl$_2$ (50 mL), the solution was washed with 10% hydrochloric acid, 5% NaHCO$_3$ and brine, dried over anhydrous Na$_2$SO$_4$. After evaporation and purification by column chromatography (petroleum ether:EtOAc:CH$_2$Cl$_2$ = 7:1:1), 1 g (65.3% yield) of yellow oil was obtained. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.35-3.55 (m, 2H), 3.77 (s, 3H), 4.17 (d, $J$ = 7.0 Hz, 4H), 5.09 (dd, $J_1$ = 5.4 Hz, $J_2$ = 11.0 Hz, 1H), 6.60 (d, $J$ = 8.2 Hz, 1H), 6.66 (d, $J$ = 8.5 Hz, 1H), 6.68 (s, 1H), 7.71 (d, $J$ = 3.6 Hz, 2H), 7.80 (d, $J$ = 3.4 Hz, 2H). MS (ESI) m/z 368.4 [M+H]$^+$.  

(S)-methyl 2-amino-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)propanoate (2f)

To a solution of $2e$ (0.89 g, 2.4 mmol) in anhydrous methanol (23 mL) was added ethylenediamine (0.36 g, 6.1 mmol) and the resulting solution was refluxed for 9 h. The insoluble material was filtered off and the filtrate was evaporated and purified by column chromatography using petroleum ether/EtOAc/CH$_2$Cl$_2$ (4:1:1) as eluent to give yellow oil 373 mg (yield 64.9%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.74 (dd, $J_1$ = 7.9 Hz, $J_2$ = 13.6 Hz, 1H), 2.98 (dd, $J_1$ = 5.0 Hz, $J_2$ = 13.6 Hz, 1H), 3.67 (dd, $J_1$ = 5.0 Hz, $J_2$ = 7.9 Hz, 1H), 3.72 (s, 3H), 4.18-4.26 (m, 4H), 6.64 (dd, $J_1$ = 2.0 Hz, $J_2$ = 8.2 Hz, 1H), 6.69 (d, $J$ = 2.0 Hz, 1H), 6.78 (d, $J$ = 8.2 Hz, 1H). MS (ESI) m/z 238.2 [M+H]$^+$.  

Compounds 3d-3f were prepared following a similar procedure described for the synthesis of 3a.
(S)-2-(2,5-dichlorobenzamido)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)propanoic acid (3d)

White solid (0.84 g, 88.4%). mp 194.8-196.6 °C. ¹H NMR (400 MHz, DMSO-⁶) δ 2.80 (dd, J₁ = 10.4 Hz, J₂ = 13.8 Hz, 1H), 3.06 (dd, J₁ = 4.6 Hz, J₂ = 13.9 Hz, 1H), 4.20 (s, 4H), 4.48-4.53 (m, 1H), 6.73 (dd, J₁ = 1.8 Hz, J₂ = 8.3 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.78 (d, J = 1.7 Hz, 1H), 7.15-7.22 (m, 1H), 7.47-7.57 (m, 2H), 8.84 (d, J = 8.2 Hz, 1H), 12.94 (s, 1H). MS (ESI) m/z 393.8 [M-H].

(S)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(5,6,7,8-tetrahydronaphthalene-1-carboxamido)propanoic acid (3e)

White solid (0.32 g, 84.5%). mp 190.9-192.3 °C. ¹H NMR (400 MHz, DMSO-⁶) δ 1.54-1.72 (m, 4H), 2.26-2.58 (m, 2H), 2.71 (t, J = 6.1 Hz, 2H), 2.78 (dd, J₁ = 10.6 Hz, J₂ = 13.7 Hz, 1H), 3.04 (dd, J₁ = 4.2 Hz, J₂ = 13.7 Hz, 1H), 4.19 (s, 4H), 4.42-4.54 (m, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.77 (s, 1H), 6.93 (dd, J₁ = 4.3 Hz, J₂ = 8.4 Hz, 1H), 7.04-7.13 (m, 2H), 8.29 (d, J = 7.9 Hz, 1H), 12.91 (s, 1H). MS (ESI) m/z 380.2 [M-H].

(S)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(pyrazine-2-carboxamido)propanoic acid (3f)
White solid (0.31 g, 90.9%). mp 176.3-178.1 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 3.00-3.16 (m, 2H), 4.09-4.25 (m, 4H), 4.63 (dd, $J_1 = 7.1$ Hz, $J_2 = 13.9$ Hz, 1H), 6.66 (dd, $J_1 = 1.9$ Hz, $J_2 = 8.3$ Hz, 1H), 6.71 (dd, $J_1 = 5.1$ Hz, $J_2 = 6.7$ Hz, 2H), 8.75 (dd, $J_1 = 1.5$ Hz, $J_2 = 2.4$ Hz, 1H), 8.84 (d, $J = 8.1$ Hz, 1H), 8.89 (d, $J = 2.5$ Hz, 1H), 9.15 (d, $J = 1.4$ Hz, 1H), 13.10 (s, 1H). MS (ESI) m/z 328.2 [M-H].

2-amino-N-((R)-3-methyl-1-((3aS,4S,6R,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)-3-phenylpropanamide hydrochloride (6a)

To a cooled solution (-10 °C) of N-Boc-L-phenyl alanine (3.4 g, 12.7 mmol) dissolved in anhydrous CH$_2$Cl$_2$ (40 mL) was added HOBT (2.6 g, 19.1 mmol). After 10 min, EDCI (3.7 g, 19.1 mmol) was added. Finally, 5a (4.8 g, 12.7 mmol) and DIPEA (5.8 g, 44.5 mmol) were added. The mixture stirred at -10 °C for 1 h and at room temperature for 15 h. The mixture was washed with 10% hydrochloric acid, 5% NaHCO$_3$, and brine, dried over anhydrous Na$_2$SO$_4$. After filtration and evaporation, the obtained crude product was directly used in the next reaction.

The prepared boronic acid ester was dissolved in ethyl acetate (22 mL) and was dropwise added 4.5 mol/L HCl in ethyl acetate (40 mL) at 0 °C. Then the mixture was stirred for 2 h at room temperature and the ethyl acetate was evaporated under vacuo. MTBE was added to the residue and filtered to obtain glassy solid 6a (7.05 g, 80.6%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.80 (s, 3H), 0.81-0.86 (m, 6H), 1.20 (d, $J = 7.0$ Hz, 2H), 1.26 (s, 3H), 1.27-1.31 (m, 1H), 1.33 (s, 3H), 1.48 (d, $J = 2.8$ Hz, 1H), 1.80 (d, $J = 15.2$ Hz, 2H), 2.02 (t, $J = 5.3$ Hz, 1H), 2.06-2.15 (m, 1H), 2.22-2.32 (m, 1H), 2.92-2.95 (m, 1H), 3.31 (dd, $J_1 = 13.4$ Hz, $J_2 = 8.0$ Hz, 1H), 3.44 (dd, $J_1 = 13.4$ Hz, $J_2 = 8.1$ Hz, 1H), 4.23 (d, $J = 8.3$ Hz, 1H), 4.67-4.70 (m, 1H), 7.23 (d, $J = 7.1$ Hz, 1H), 7.26-7.30 (m, 2H), 7.35 (d, $J = 7.0$ Hz, 2H), 7.66 (s, 1H), 8.27 (s, 3H). MS (ESI) m/z 413.27 [M+H]$^+$.
Compounds 6b-6e were prepared from the corresponding N-boc-carboxylic acids and 5a following the similar procedure described for the synthesis of 6a.

2-amino-N-((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)acetamide hydrochloride (6b)

Glassy solid (2.17 g, 66.2%). 1H NMR (400 MHz, DMSO-d6) δ 0.84 (dd, J1 = 8.0 Hz, J2 = 13.5 Hz, 9H), 1.19 (d, J = 10.6 Hz, 1H), 1.24 (s, 3H), 1.28 (s, 1H), 1.32 (s, 3H), 1.37-1.48 (m, 1H), 1.67 (dd, J1 = 10.4 Hz, J2 = 21.3 Hz, 2H), 1.84 (s, 1H), 1.94 (t, J = 4.8 Hz, 1H), 2.14 (d, J = 4.9 Hz, 1H), 2.21-2.33 (m, 1H), 3.00 (s, 1H), 3.51 (d, J = 16.4 Hz, 2H), 4.28 (d, J = 8.1 Hz, 1H), 8.14 (s, 3H), 8.52 (s, 1H). MS (ESI) m/z 323.4 [M+H]+.

(S)-2-amino-3,3-dimethyl-N-((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)butanamide hydrochloride (6c)

Glassy solid (1.3 g, 87.3%). 1H NMR (400 MHz, DMSO-d6) δ 0.80 (s, 3H), 0.87 (dd, J1 = 3.8 Hz, J2 = 6.5 Hz, 6H), 0.98 (s, 9H), 1.23 (s, 3H), 1.27 (dd, J1 = 4.9 Hz, J2 = 9.4 Hz, 2H), 1.30 (s, 3H), 1.37-1.47 (m, 1H), 1.64-1.74 (m, 2H), 1.80-1.86 (m, 1H), 1.90 (dd, J1 = 5.1 Hz, J2 = 6.0 Hz, 1H), 2.02-2.11 (m, 1H), 2.21-2.32 (m, 1H), 2.90-3.00 (m, 1H), 3.57 (s, 1H), 4.26 (dd, J1 = 1.9 Hz, J2 = 8.7 Hz, 1H), 8.12-8.26 (m, 3H), 8.58 (d, J = 4.0 Hz, 1H). MS (ESI) m/z 479.4 [M+H]+.

(S)-2-amino-3-(2-fluorophenyl)-N-((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)propanamide hydrochloride (6d)
Glassy solid (1.43 g, 82.5%). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 0.78 (d, \(J = 6.5\) Hz, 6H), 0.82 (s, 3H), 1.24 (s, 3H), 1.25-1.30 (m, 2H), 1.31 (s, 3H), 1.32-1.37 (m, 1H), 1.68 (dd, \(J_1 = 3.3\) Hz, \(J_2 = 8.8\) Hz, 1H), 1.79-1.86 (m, 1H), 1.89-1.95 (m, 2H), 2.11 (dd, \(J_1 = 5.3\) Hz, \(J_2 = 14.8\) Hz, 1H), 2.23-2.31 (m, 1H), 2.75-2.84 (m, 1H), 3.00 (dd, \(J_1 = 8.9\) Hz, \(J_2 = 13.7\) Hz, 1H). 1.32 (dd, \(J_1 = 5.6\) Hz, \(J_2 = 13.8\) Hz, 1H), 4.02 (dd, \(J_1 = 7.2\) Hz, \(J_2 = 14.3\) Hz, 1H), 4.25 (dd, \(J_1 = 1.9\) Hz, \(J_2 = 8.7\) Hz, 1H), 7.08-7.18 (m, 2H), 7.28-7.35 (m, 2H), 8.51 (s, 3H), 8.55 (d, \(J = 4.8\) Hz, 1H). MS (ESI): observed: m/z 431.8[M+H]^+.

\((S)-2\text{-amino-3-(2,6-difluorophenyl)-N-((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[\(d\])1,3,2\text{-dioxaborol-2-yl}butyl)propanamide hydrochloride (6e)\)

Glassy solid (0.58 g, 71.7%). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 0.75 (dd, \(J_1 = 3.4\) Hz, \(J_2 = 6.5\) Hz, 6H), 0.81 (s, 3H), 1.13-1.17 (m, 2H), 1.17-1.21 (m, 1H), 1.24 (s, 3H), 1.30 (s, 3H), 1.65 (d, \(J = 14.2\) Hz, 1H), 1.82 (d, \(J = 2.6\) Hz, 1H), 1.89-1.92 (m, 2H), 2.05-2.13 (m, 1H), 2.20-2.29 (m, 1H), 2.70-2.80 (m, 1H), 3.08 (d, \(J = 7.5\) Hz, 2H), 3.90 (d, \(J = 22.0\) Hz, 1H), 4.21 (dd, \(J_1 = 1.8\) Hz, \(J_2 = 8.6\) Hz, 1H), 7.05 (t, \(J = 7.9\) Hz, 2H), 7.32-7.42 (m, 1H), 8.48 (d, \(J = 5.2\) Hz, 1H), 8.61 (s, 3H). MS (ESI) m/z 449.8 [M+H]^+.

\((S)-N-((R)-3\text{-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[\(d\])1,3,2\text{-dioxaborol-2-yl}butyl)-2-(2-morpholinoacetamido)-3-phenylpropanamide (7a)\)
TEA (1.35 g, 13.4 mmol) and 6a (1.0 g, 2.23 mmol) were dissolved in anhydrous CH₂Cl₂ (15 mL) and 2-morpholinoacetyl chloride (0.36 g, 2.23 mmol) was added dropwise at -0 °C and then allowed to react at room temperature for 1 h. The mixture was washed with H₂O and dried over anhydrous Na₂SO₄. After filtration, evaporation and purification by column chromatography using petroleum ether/EtOAc (2:1) as eluent to give a glassy solid 0.84 g (69.8% yield). ¹H NMR (400 MHz, CDCl₃) δ 0.85 (dd, J₁ = 4.2 Hz, J₂ = 8.2 Hz, 9H), 1.28 (s, 3H), 1.40 (s, 3H), 1.41 (d, J = 7.3 Hz, 2H), 1.48 (dd, J₁ = 6.6 Hz, J₂ = 13.1 Hz, 1H), 1.79-1.82 (m, 1H), 1.83-1.86 (m, 1H), 1.87-1.94 (m, 2H), 2.15-2.19 (m, 1H), 2.22 (dd, J₁ = 4.4 Hz, J₂ = 9.6 Hz, 1H), 2.25-2.39 (m, 4H), 3.05-3.08 (m, 1H), 3.09 (t, J = 3.7 Hz, 2H), 3.11-3.16 (m, 2H), 3.54-3.63 (m, 4H), 4.30 (dd, J₁ = 2.1 Hz, J₂ = 8.8 Hz, 1H), 4.67 (dd, J₁ = 7.8 Hz, J₂ = 15.3 Hz, 1H), 6.29 (d, J = 4.5 Hz, 1H), 7.19-7.29 (m, 5H), 7.53 (d, J = 7.7 Hz, 1H). MS (ESI) m/z 540.7 [M+H]⁺.

Compound 7b was prepared from 6b following the similar procedure described for the synthesis of 7a.

N-((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)-2-(2-morpholinoacetamido)acetamide (7b)

Glassy solid (0.53 g, 41.7%). ¹H NMR (400 MHz, CDCl₃) δ 0.83 (s, 3H), 0.90 (dd, J₁ = 2.8 Hz, J₂ = 6.6 Hz, 6H), 1.27 (s, 3H), 1.38 (s, 3H), 1.45 (t, J = 7.3 Hz, 2H), 1.61 (dd, J₁ = 5.9 Hz, J₂ = 12.7 Hz, 1H), 1.78-1.81 (m, 1H), 1.81-1.86 (m, 1H), 2.00-2.04 (m, 2H), 2.14-2.20 (m, 1H), 2.29-2.33 (m, 1H), 2.51-2.55 (m, 4H), 3.21 (dd, J₁ = 7.0 Hz, J₂ = 12.9 Hz, 1H), 3.70-3.74 (m, 4H), 3.96 (t, J = 5.5 Hz, 2H), 4.28 (dd, J₁ =
2.1 Hz, $J_2 = 8.8$ Hz, 1H), 4.71 (s, 1H), 6.36 (d, $J = 3.9$ Hz, 1H), 7.75 (s, 1H). MS (ESI) m/z 450.7 [M+H]+.

N-((S)-3,3-dimethyl-1-(((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)amino)-1-oxobutan-2-yl)pyrazine-2-carboxamide (7c)

To a cooled solution (-10 °C) of pyrazine-2-carboxylic acid (0.12 g, 0.9 mmol) dissolved in anhydrous CH$_2$Cl$_2$ (6 mL) was added HOBT (0.2 g, 1.4 mmol). After 10 min, EDCI (0.3 g, 1.4 mmol) was added. Finally (R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butan-1-amine 2,2,2-trifluoroacetate 6c (0.4 g, 0.9 mmol) and DIPEA (0.4 g, 3.4 mmol) were added. The mixture stirred at -10 °C for 1 h and at room temperature overnight. The mixture was washed with 1N HCl, 5% NaHCO$_3$, and brine, dried over anhydrous Na$_2$SO$_4$. After filtered, evaporation and purification with chromatography (petroleum ether/EtOAc = 3:1), 0.38 g (81.6%) of glassy solid was obtained. $^1$H NMR (400 MHz, CDCl$_3$) δ 0.83 (s, 3H), 0.89 (dd, $J_1 = 4.7$ Hz, $J_2 = 6.5$ Hz, 6H), 1.07 (s, 9H), 1.25 (d, $J = 1.8$ Hz, 1H), 1.27 (s, 3H), 1.36 (s, 3H), 1.46 (t, $J = 7.4$ Hz, 2H), 1.58-1.68 (m, 2H), 1.87-1.93 (m, 1H), 1.98 (t, $J = 5.5$ Hz, 1H), 2.12-2.19 (m, 1H), 2.32 (m, 1H), 3.26 (dd, $J_1 = 7.6$ Hz, $J_2 = 13.1$ Hz, 1H), 4.30 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.8$ Hz, 1H), 4.39 (d, $J = 9.7$ Hz, 1H), 5.95 (d, $J = 5.1$ Hz, 1H), 8.49 (d, $J = 9.7$ Hz, 1H), 8.55 (dd, $J_1 = 2.4$, $J_2 = 1.5$ Hz, 1H), 8.74 (d, $J = 2.4$ Hz, 1H), 9.37 (d, $J = 1.4$ Hz, 1H). MS (ESI) m/z 485.6 [M+H]+.

Compounds 7d-7h were prepared from the corresponding carboxylic acids and boric acid ester hydrochloride following the similar procedure described for the synthesis of 7c.
N-((S)-3,3-dimethyl-1-((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)amino)-1-oxobut-2-yl)-5,6,7,8-tetrahydronaphthalene-1-carboxamide (7d)

Glassy solid (0.48 g, 81.3%). $^1$H NMR (400 MHz, CDCl$_3$) δ 0.80 (dd, $J_1 = 5.9$ Hz, $J_2 = 19.8$ Hz, 9H), 1.06 (s, 9H), 1.27 (s, 3H), 1.29 (d, $J = 6.4$ Hz, 2H), 1.37 (s, 3H), 1.40 (d, $J = 7.4$ Hz, 1H), 1.57 (dd, $J_1 = 6.7$ Hz, $J_2 = 13.3$ Hz, 1H), 1.77 (d, $J = 4.4$ Hz, 4H), 1.86 (d, $J = 12.8$ Hz, 2H), 2.00 (t, $J = 5.5$ Hz, 1H), 2.1-2.19 (m, 1H), 2.35-2.27 (m, 1H), 2.83 (d, $J = 35.3$ Hz, 4H), 3.12 (dd, $J_1 = 7.5$ Hz, $J_2 = 12.3$ Hz, 1H), 4.23-4.28 (m, 1H), 4.60 (d, $J = 9.6$ Hz, 1H), 6.51 (d, $J = 9.5$ Hz, 1H), 6.75 (d, $J = 3.9$ Hz, 1H), 7.12 (dd, $J_1 = 7.0$ Hz, $J_2 = 11.9$ Hz, 3H). MS (ESI) m/z 537.5[M+H]$^+$.  

2,5-dichloro-N-((S)-3,3-dimethyl-1-((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)amino)-1-oxobut-2-yl)benzamide (7e)

Glassy solid (0.31 g, 57.2%). $^1$H NMR (400 MHz, CDCl$_3$) δ 0.83 (s, 3H), 0.87 (dd, $J_1 = 6.6$ Hz, $J_2 = 8.8$ Hz, 6H), 1.08 (s, 9H), 1.24 (d, $J = 6.6$ Hz, 2H), 1.27 (s, 3H), 1.30 (t, $J = 8.1$ Hz, 1H), 1.37 (s, 3H), 1.62 (dd, $J_1 = 6.6$ Hz, $J_2 = 13.4$ Hz, 1H), 1.81-1.90 (m, 2H), 2.00 (t, $J = 5.5$ Hz, 1H), 2.11-2.19 (m, 1H), 2.28-2.37 (m, 1H), 3.22 (dd, $J_1 = 7.6$ Hz, $J_2 = 13.0$ Hz, 1H), 4.28 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.8$ Hz, 1H), 4.51 (d, $J = 9.3$ Hz, 1H), 6.30 (d, $J = 4.9$ Hz, 1H), 6.88 (d, $J = 9.2$ Hz, 1H), 7.33 (d, $J = 1.9$ Hz, 2H), 7.56 (dd, $J_1 = 1.0$ Hz, $J_2 = 1.8$ Hz, 1H). MS (ESI) m/z 551.3[M+H]$^+$.  

2,5-dichloro-N-((S)-3-(2-fluorophenyl)-1-((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)amino)-1-oxopropan-2-yl)benzamide (7f)
Glassy solid (0.94 g, 53.5%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.84 (s, 3H), 0.87 (dd, $J_1$ = 3.6 Hz, $J_2$ = 6.5 Hz, 6H), 1.28 (s, 3H), 1.32-1.37 (m, 1H), 1.39 (s, 3H), 1.40-1.45 (m, 2H), 1.53 (dd, $J_1$ = 6.5 Hz, $J_2$ = 19.4 Hz, 1H), 1.80-1.86 (m, 1H), 1.88-1.93 (m, 1H), 2.01-2.05 (m, 1H), 2.14-2.23 (m, 1H), 2.28-2.37 (m, 1H), 3.19 (dd, $J_1$ = 7.8 Hz, $J_2$ = 14.1 Hz, 1H), 3.25 (dd, $J_1$ = 6.7 Hz, $J_2$ = 13.9 Hz, 2H), 4.30 (dd, $J_1$ = 2.0 Hz, $J_2$ = 8.8 Hz, 1H), 4.84-4.94 (m, 1H), 6.23 (d, $J$ = 5.6 Hz, 1H), 6.84 (d, $J$ = 8.0 Hz, 1H), 7.00-7.10 (m, 2H), 7.20-7.25 (m, 1H), 7.27-7.33 (m, 3H), 7.43 (dd, $J_1$ = 0.7 Hz, $J_2$ = 1.9 Hz, 1H). MS (ESI) m/z 603.7 [M+H]$^+$.  

**2,5-dichloro-N-((S)-3-(2,6-difluorophenyl)-1-(((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)amino)-1-oxopropan-2-yl)benzamide (7g)**

Glassy solid (0.37 g, 50.4%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.84 (-CH$_3$, s, 3H), 0.90 (-CH$_3$, dd, $J_1$ = 3.9 Hz, $J_2$ = 6.5 Hz, 6H), 1.33 (-CH$_3$, s, 3H), 1.37 (-CH$_2$, dd, $J_1$ = 5.8 Hz, $J_2$ = 11.2 Hz, 2H), 1.40 (-CH$_3$, s, 3H), 1.46-1.49 (-CH, m, 1H), 1.80-1.88 (-CH, m, 1H), 1.89-1.94 (-CH, m, 1H), 1.99-2.07 (-CH$_2$, m, 2H), 2.17-2.23 (-CH$_2$, m, 1H), 2.29-2.38 (-CH$_2$, m, 1H), 3.19 (-CH, dd, $J_1$ = 9.7 Hz, $J_2$ = 14.2 Hz, 1H), 3.24-3.34 (-CH$_2$, m, 2H), 4.31 (-CH, dd, $J_1$ = 1.9 Hz, $J_2$ = 8.8 Hz, 1H), 4.92 (-CH, dd, $J_1$ = 5.2 Hz, $J_2$ = 9.3 Hz, 1H), 6.31 (-CONH, d, $J$ = 5.7 Hz, 1H), 6.85 (-CONH, d, $J$ = 8.3 Hz, 1H), 6.89 (-Ph, d, $J$ = 7.7 Hz, 1H), 7.17-7.25 (-Ph, m, 1H), 7.26-7.55 (-Ph, m, 4H). MS (ESI) m/z 619.8 [M-H]$^-$. 
2,5-dichloro-N-((S)-1-(((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)amino)-1-oxo-3-phenylpropan-2-yl)benzamide (7h)

Glassy solid (0.71 g, 76.8%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.84 (dd, $J_1 = 2.2$ Hz, $J_2 = 4.0$ Hz, 9H), 1.29 (s, 3H), 1.39 (s, 3H), 1.47 (dd, $J_1 = 6.6$ Hz, $J_2 = 13.9$ Hz, 1H), 1.61-1.67 (m, 2H), 1.78-1.94 (m, 3H), 2.01-2.05 (m, 1H), 2.16-2.21 (m, 1H), 2.30-2.37 (m, 1H), 3.13 (dd, $J_1 = 7.8$ Hz, $J_2 = 13.7$ Hz, 1H), 3.17-3.27 (m, 2H), 4.30 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.8$ Hz, 1H), 4.82 (dd, $J_1 = 6.2$ Hz, $J_2 = 7.8$ Hz, 1H), 5.93 (d, $J = 4.7$ Hz, 1H), 6.89 (d, $J = 7.6$ Hz, 1H), 7.22-7.34 (m, 8H), 7.48 (dd, $J_1 = 1.0$ Hz, $J_2 = 1.9$ Hz, 1H). MS (ESI) m/z 585.7[M+H]$^+$. Compounds 7k-7m and 7o-7p were prepared following a similar procedure described for the synthesis of 7i.

2,5-dichloro-N-((S)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)amino)-1-oxopropan-2-yl)benzamide (7k)

Glassy solid (0.14 g, 74.5%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.84 (d, $J = 5.4$ Hz, 3H), 0.87 (d, $J = 6.7$ Hz, 6H), 1.19 (d, $J = 12.5$ Hz, 1H), 1.28 (s, 3H), 1.29-1.36 (m, 1H), 1.41 (s, 3H), 1.44-1.52 (m, 1H), 1.85 (dd, $J_1 = 12.0$ Hz, $J_2 = 19.5$ Hz, 2H), 1.99 (dd, $J_1 = 8.9$ Hz, $J_2 = 14.9$ Hz, 1H), 2.04 (d, $J = 3.2$ Hz, 1H), 2.12-2.25 (m, 1H), 2.33 (dd, $J_1 = 8.5$ Hz, $J_2 = 14.2$ Hz, 1H), 2.92-3.06 (m, 1H), 3.07-3.36 (m, 2H), 4.23 (s,
4H), 4.27-4.37 (m, 1H), 4.67-4.80 (m, 1H), 5.90 (dd, \( J_1 = 5.1 \) Hz, \( J_2 = 56.0 \) Hz, 1H), 6.70-6.83 (m, 3H), 6.86 (t, \( J = 7.9 \) Hz, 1H), 7.30 (d, \( J = 8.5 \) Hz, 2H), 7.45-7.58 (m, 1H). MS (ESI) m/z 643.2 [M+H]+.

N-((S)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)amino)-1-oxopropan-2-yl)-5,6,7,8-tetrahydronaphthalene-1-carboxamide (7l)

Glassy solid (0.15 g, 85.5%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.84 (t, \( J = 3.5 \) Hz, 3H), 0.85-0.94 (m, 6H), 1.25 (d, \( J = 2.6 \) Hz, 1H), 1.27 (s, 3H), 1.34 (dd, \( J_1 = 4.6 \) Hz, \( J_2 = 11.2 \) Hz, 1H), 1.43 (s, 3H), 1.52 (dd, \( J_1 = 7.3 \) Hz, \( J_2 = 13.6 \) Hz, 1H), 1.59-1.67 (m, 1H), 1.74 (s, 4H), 1.80-1.96 (m, 2H), 1.98-2.06 (m, 1H), 2.12-2.25 (m, 1H), 2.26-2.38 (m, 1H), 2.67-2.78 (m, 4H), 2.93-3.11 (m, 2H), 3.14-3.23 (m, 1H), 4.22 (s, 4H), 4.31 (dd, \( J_1 = 4.4 \) Hz, \( J_2 = 9.1 \) Hz, 1H), 4.66-4.83 (m, 1H), 6.12 (dd, \( J_1 = 5.3 \) Hz, \( J_2 = 49.1 \) Hz, 1H), 6.27-6.42 (m, 1H), 6.70-6.76 (m, 1H), 6.76-6.83 (m, 2H), 6.99-7.14 (m, 3H). MS (ESI) m/z 627.3 [M-H]-.

N-((S)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(((R)-3-methyl-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)butyl)amino)-1-oxopropan-2-yl)pyrazine-2-carboxamide (7m)
Glassy solid (0.56 g, 85.4%). $^1$H NMR (400 MHz, CDCl$_3$) δ 0.82 (d, $J = 2.2$ Hz, 3H), 0.85 (d, $J = 6.3$ Hz, 6H), 0.93 (s, 1H), 1.22 (d, $J = 10.8$ Hz, 1H), 1.28 (s, 3H), 1.40 (s, 3H), 1.46 (dd, $J_1 = 6.8$ Hz, $J_2 = 13.2$ Hz, 1H), 1.66 (s, 1H), 1.79-1.93 (m, 2H), 2.02 (dd, $J_1 = 7.3$ Hz, $J_2 = 12.6$ Hz, 1H), 2.14-2.23 (m, 1H), 2.27-2.38 (m, 1H), 2.96-3.07 (m, 1H), 3.07-3.26 (m, 2H), 4.21 (s, 4H), 4.24-4.37 (m, 1H), 4.74 (dd, $J_1 = 7.8$ Hz, $J_2 = 14.3$ Hz, 1H), 5.90 (dd, $J_1 = 5.1$ Hz, $J_2 = 39.8$ Hz, 1H), 6.71-6.85 (m, 3H), 8.38 (dd, $J_1 = 8.3$ Hz, $J_2 = 14.3$ Hz, 1H), 8.54 (d, $J = 5.1$ Hz, 1H), 8.74 (d, $J = 2.2$ Hz, 1H), 9.35 (s, 1H). MS (ESI) m/z 575.3 [M-H]$^-$.

2,5-dichloro-N-((S)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-oxo-1-(((R)-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)pentyl)amino)propan-2-yl)benzamide (7o)

The obtained crude product was directly used in the next reaction without purification.

2,5-dichloro-N-((S)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-oxo-1-(((R)-2-(p-tolyl)-1-((3aS,4S,6S,7aR)-3a,5,5-trimethylhexahydro-4,6-methanobenzo[d][1,3,2]dioxaborol-2-yl)ethyl)amino)propan-2-yl)benzamide (7p)

The obtained crude product was directly used in the next reaction without purification.
2. $^1$H NMR, $^{13}$C NMR and mass spectra of target compounds 8a-8m, 8o-8p

Compounds 8a-8m and 8o-8p were prepared from the corresponding starting materials described for the synthesis of 8n.

((R)-3-methyl-1-((S)-2-(2-morpholinoacetamido)-3-phenylpropanamido)butyl)boronic acid (8a)

Yellow foam solid (0.49 g, 84.6%). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 0.85 (dd, $J_1$ = 4.8 Hz, $J_2$ = 6.5 Hz, 6H), 1.17 (t, $J$ = 7.3 Hz, 2H), 1.40 (dd, $J_1$ = 6.7 Hz, $J_2$ = 13.4 Hz, 1H), 2.69 (t, $J$ = 7.4 Hz, 1H), 3.03-3.21 (m, 4H), 3.23 (d, $J$ = 7.3 Hz, 1H), 3.49 (d, $J$ = 12.0 Hz, 1H), 3.73-3.87 (m, 2H), 3.94-4.09 (m, 4H), 4.87 (d, $J$ = 8.0 Hz, 1H), 7.22-7.36 (m, 5H). $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 22.14, 23.67, 26.64, 38.51, 40.63, 47.87, 52.84, 58.02, 64.62, 128.29, 129.75, 130.54, 136.86, 165.12, 176.92. MS (ESI) m/z 404.6 [M-H]. HRMS (ESI): calcd for C$_{20}$H$_{32}$BN$_3$NaO$_5$ [M+Na]$^+$, 428.2330; found, 428.2337.

(R)-(3-methyl-1-(2-(2-morpholinoacetamido)acetamido)butyl)boronic acid (8b)

Yellow foam solid (0.25 g, 69.1%). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 0.93 (d, $J$ = 6.6 Hz, 6H), 1.32-1.39 (m, 2H), 1.63-1.70 (m, 1H), 2.78 (t, $J$ = 7.5 Hz, 1H), 3.19-3.29 (m, 2H), 3.56 (d, $J$ = 12.4 Hz, 2H), 3.81-3.89 (m, 2H), 4.06 (d, $J$ = 17.1 Hz, 4H), 4.15 (s, 2H). $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 22.49, 23.54, 26.73, 40.75, 53.93, 54.30, 58.20, 64.69, 166.05, 166.13. MS (ESI) m/z 314.1 [M-H]. HRMS (ESI): calcd for C$_{13}$H$_{26}$BN$_3$NaO$_5$ [M+Na]$^+$, 338.1860; found, 338.1864.

((R)-1-((S)-3,3-dimethyl-2-(pyrazine-2-carboxamido)butanamido)-3-methylbutyl)boronic acid (8c)
Yellow foam solid (0.15 g, 56.3%). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 0.93 (dd, $J_1$ = 1.5 Hz, $J_2$ = 6.5 Hz, 6H), 1.12 (s, 9H), 1.33-1.39 (m, 2H), 1.65 (dd, $J_1$ = 6.6 Hz, $J_2$ = 13.4 Hz, 1H), 2.74 (dd, $J_1$ = 6.5 Hz, $J_2$ = 8.8 Hz, 1H), 4.72 (d, $J$ = 6.2 Hz, 1H), 8.73 (s, 1H), 8.85 (d, $J$ = 2.3 Hz, 1H), 9.25 (s, 1H). $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 22.27, 23.80, 26.88, 27.02, 35.93, 41.15, 58.64, 144.84, 144.87, 145.24, 149.19, 164.70, 176.00. MS (ESI) m/z 349.4 [M-H$^-$. HRMS (ESI) calcd for C$_{16}$H$_{27}$BN$_4$NaO$_4$ [M+Na]$^+$, 373.2021; found, 373.2014.

((R)-1-((S)-3,3-dimethyl-2-(5,6,7,8-tetrahydronaphthalene-1-carboxamido)butanamido)-3-methylbutyl)boronic acid (8d)

Yellow foam solid (0.19 g, 56.7%). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 0.94 (dd, $J_1$ = 1.0 Hz, $J_2$ = 6.5 Hz, 6H), 1.10 (s, 9H), 1.34-1.39 (m, 2H), 1.62-1.71 (m, 1H), 1.78 (d, $J$ = 13.0 Hz, 4H), 2.75 (dd, $J_1$ = 6.0 Hz, $J_2$ = 9.3 Hz, 1H), 2.80 (d, $J$ = 5.3 Hz, 4H), 4.70 (s, 1H), 7.09-7.17 (m, 3H). $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 22.15, 23.91, 23.94, 24.09, 27.05, 27.12, 27.84, 30.69, 35.49, 41.30, 59.04, 125.34, 126.40, 131.86, 135.27, 137.72, 139.06, 173.59, 176.97. MS (ESI) m/z 401.5 [M-H$^-$. HRMS (ESI) calcd for C$_{22}$H$_{35}$BN$_2$NaO$_4$ [M+Na]$^+$, 425.2586; found, 425.2577.

((R)-1-((S)-2-(2,5-dichlorobenzamido)-3,3-dimethylbutanamido)-3-methylbutyl)boronic acid (8e)

White foam solid (0.15 g, 68.9%). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 0.96 (dd, $J_1$ = 2.1 Hz, $J_2$ = 6.6 Hz, 6H), 1.13 (s, 9H), 1.32 (dd, $J_1$ = 7.9 Hz, $J_2$ = 15.5 Hz, 2H), 1.65-
1.73 (m, 1H), 2.78 (dd, $J_1 = 6.1$ Hz, $J_2 = 9.3$ Hz, 1H), 4.73 (s, 1H), 7.45–7.50 (m, 3H).

$^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 22.14, 23.91, 27.04, 27.08, 35.66, 41.27, 59.15, 129.8, 130.46, 132.14, 132.43, 133.89, 138.63, 168.61, 176.45. MS (ESI) m/z 415.3[M-H]. HRMS (ESI) calcd for C$_{18}$H$_{27}$BCl$_2$N$_2$NaO$_4$ [M+Na]$^+$, 439.1336; found, 439.1346.

$\text{(R)-1-((S)-2-(2,5-dichlorobenzamido)-3-(2-fluorophenyl)propanamido)-3-methylbutyl} \text{boronic acid (8f)}$

![Chemical structure](image)

White foam solid (0.46 g, 62.8%). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 0.85 (t, $J = 6.2$ Hz, 6H), 1.17 (t, $J = 7.3$ Hz, 2H), 1.34-1.43 (m, 1H), 2.72 (t, $J = 7.6$ Hz, 1H), 3.22 (d, $J = 8.0$ Hz, 2H), 5.05 (t, $J = 8.0$ Hz, 1H), 7.13 (dd, $J_1 = 8.2$ Hz, $J_2 = 14.8$ Hz, 2H), 7.32 (dd, $J_1 = 7.6$ Hz, $J_2 = 14.7$ Hz, 3H), 7.42-7.48 (m, 2H). $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 21.99, 23.89, 26.70, 32.07, 40.93, 51.59, 116.32, 116.54, 123.88, 125.52, 129.86, 130.64, 132.32, 132.56, 133.12, 133.88, 138.10, 161.57, 164.01, 168.11, 176.51. MS (ESI) m/z 467.7 [M-H]. HRMS (ESI): calcd for C$_{21}$H$_{24}$BCl$_2$FN$_2$NaO$_4$ [M+Na]$^+$, 491.1086; found, 491.1095.

$\text{(R)-1-((S)-2-(2,5-dichlorobenzamido)-3-(2,6-difluorophenyl)propanamido)-3-methylbutyl} \text{boronic acid (8g)}$

![Chemical structure](image)

White foam solid (0.11 g, 55.5%). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 0.88 (dd, $J_1 = 1.9$ Hz, $J_2 = 6.5$ Hz, 6H), 1.22 (t, $J = 7.4$ Hz, 2H), 1.40-1.48 (m, 1H), 2.75 (t, $J = 7.6$ Hz, 1H), 3.23 (dd, $J_1 = 8.1$ Hz, $J_2 = 13.8$ Hz, 1H), 3.28-3.36 (m, 1H), 5.09 (t, $J = 7.9$ Hz, 1H), 6.95-7.04 (m, 2H), 7.31-7.41 (m, 2H), 7.43-7.48 (m, 2H). $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 23.85, 25.69, 26.73, 30.71, 40.93, 50.93, 112.33, 112.39, 112.52,
112.58, 129.84, 130.63, 130.79, 132.35, 132.58, 133.88, 137.99, 161.94, 162.02, 
164.40, 164.48, 168.07, 176.21. MS (ESI) m/z 485.6 [M-H]$^-$. HRMS (ESI): calcd for 
C$_{21}$H$_{23}$BCl$_2$F$_2$N$_2$NaO$_4$ [M+Na]$^+$, 509.1001; found, 509.0992.

((R)-1-((S)-2-(2,5-dichlorobenzamido)-3-phenylpropanamido)-3-
methylbutyl)boronic acid (8h)

White foam solid (0.31 g, 61.9%). $^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 0.85 (t, $J$ = 
6.8 Hz, 6H), 1.26-1.33 (m, 2H), 1.37 (dd, $J_1 = 7.0$ Hz, $J_2 = 13.6$ Hz, 1H), 2.65-2.73 (m, 
1H), 3.12-3.19 (m, 2H), 4.94-5.01 (m, 1H), 7.24-7.37 (m, 6H), 7.45 (d, $J = 1.1$ Hz, 
2H). $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 21.92, 23.91, 26.67, 38.55, 40.88, 53.03, 128.30, 
129.73, 129.87, 130.55, 130.62, 132.28, 132.53, 133.84, 136.98, 138.13, 168.14, 
176.83. MS (ESI) m/z 449.6[M-H]$^-$. HRMS (ESI): calcd for C$_{21}$H$_{25}$BCl$_2$N$_2$NaO$_4$ 
[M+Na]$^+$, 473.1180; found, 473.1188.

((R)-1-((S)-2-cyclohexyl-2-(2,5-dichlorobenzamido)acetamido)-3-
methylbutyl)boronic acid (8i)

Yellow foam solid (0.16 g, 71.4%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.65-0.83 (m, 
3H), 0.83-0.96 (m, 3H), 1.01-1.27 (m, 5H), 1.31-1.51 (m, 2H), 1.52-1.62 (m, 1H), 
1.67 (d, $J = 11.3$ Hz, 1H), 1.75 (s, 5H), 2.80-3.09 (m, 1H), 4.39-4.75 (m, 1H), 7.29-
7.43 (m, 2H), 7.50-7.62 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 23.05, 25.83, 28.85, 
29.35, 29.64, 39.98, 40.62, 56.60, 58.10, 129.02, 129.62, 131.34, 133.10, 135.82, 
135.98, 165.34, 172.59. MS (ESI) m/z 441.2 [M-H]$^-$. HRMS (ESI) calcd for 
C$_{20}$H$_{29}$BCl$_2$N$_2$NaO$_4$ [M+Na]$^+$, 465.1493; found, 465.1497.
((R)-1-((R)-2-cyclohexyl-2-(2,5-dichlorobenzamido)acetamido)-3-methylbutyl)boronic acid (8j)

Yellow foam solid (0.17 g, 68.5%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.80 (d, $J =$ 8.1 Hz, 3H), 0.82-0.90 (m, 3H), 1.13-1.29 (m, 5H), 1.29-1.45 (m, 2H), 1.47-1.58 (m, 1H), 1.68 (s, 1H), 1.83 (dd, $J_1 =$ 23.0 Hz, $J_2 =$ 26.6 Hz, 5H), 3.09 (d, $J =$ 109.8 Hz, 1H), 4.50-4.81 (m, 1H), 7.28-7.88 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 23.08, 25.65, 25.77, 26.09, 29.65, 39.86, 39.92, 57.29, 57.37, 129.17, 129.77, 131.17, 132.91, 136.00, 165.32, 172.40. MS (ESI) m/z 441.3 [M-H]: HRMS (ESI) calcd for C$_{20}$H$_{29}$Cl$_2$N$_2$O$_4$ [M+Na]$^+$, 465.1493; found, 465.1495.

((R)-1-((S)-2-(2,5-dichlorobenzamido)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)propanamido)-3-methylbutyl)boronic acid (8k)

Yellow foam solid (0.85 g, 52.4%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.76-0.83 (m, 3H), 0.83-0.91 (m, 3H), 1.29 (dd, $J_1 =$ 8.8 Hz, $J_2 =$ 15.0 Hz, 1H), 1.39-1.56 (m, 2H), 2.92 (d, $J =$ 35.0 Hz, 1H), 3.09 (t, $J =$ 6.2 Hz, 2H), 4.21 (d, $J =$ 5.5 Hz, 4H), 4.91 (t, $J =$ 19.8 Hz, 1H), 6.66 (dd, $J_1 =$ 12.5 Hz, $J_2 =$ 27.4 Hz, 1H), 6.71-6.80 (m, 2H), 7.21-7.59 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 22.98, 25.82, 37.32, 39.90, 50.52, 52.82, 64.25, 117.35, 118.30, 122.46, 128.74, 129.09, 129.48, 131.25, 132.94, 135.75, 142.68, 143.36, 165.24, 172.64. MS (ESI) m/z 507.2 [M-H]: HRMS (ESI) calcd for C$_{23}$H$_{27}$Cl$_2$N$_4$O$_6$ [M+Na]$^+$, 531.1325; found, 531.1246.
((R)-1-((S)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(5,6,7,8-tetrahydronaphthalene-1-carboxamido)propanamido)-3-methylbutyl)boronic acid (8l)

Yellow foam solid (0.47 g, 59.2%). $^1\text{H} \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta 0.83 (d, J = 4.7 \text{ Hz}, 3\text{H}), 0.86 (d, J = 10.6 \text{ Hz}, 3\text{H}), 1.41-1.51 (m, 2\text{H}), 1.52-1.64 (m, 1\text{H}), 1.73 (s, 4\text{H}), 2.50-2.67 (m, 2\text{H}), 2.73 (s, 2\text{H}), 2.88-2.98 (m, 1\text{H}), 2.99-3.15 (m, 2\text{H}), 4.11-4.31 (m, 4\text{H}), 4.82-4.99 (m, 1\text{H}), 6.44-6.62 (m, 1\text{H}), 6.63-6.82 (m, 3\text{H}), 6.99-7.10 (m, 3\text{H}), 7.37-7.97 (m, 1\text{H}). $^{13}\text{C} \text{ NMR} (100 \text{ MHz, CDCl}_3) \delta 22.41, 22.54, 22.87, 25.82, 26.54, 29.71, 31.88, 39.97, 52.20, 52.69, 64.25, 117.23, 118.17, 122.18, 124.03, 125.12, 129.14, 131.09, 134.83, 135.61, 138.02, 142.49, 143.37, 170.43, 173.44. MS (ESI) m/z 493.2 [M-H]. HRMS (ESI) calcd for C_{23}H_{27}BCl_2N_2NaO_6 [M+Na]^+, 517.2485; found, 517.2480.

((R)-1-((S)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(pyrazine-2-carboxamido)propanamido)-3-methylbutyl)boronic acid (8m)

Yellow foam solid (0.14 g, 63.2%). $^1\text{H} \text{ NMR} (400 \text{ MHz, DMSO-d}_6) \delta 0.74 (d, J = 5.4 \text{ Hz}, 3\text{H}), 0.84 (m, 3\text{H}), 1.02-1.21 (m, 1\text{H}), 1.30-1.41 (m, 1\text{H}), 1.51 (dd, J_1 = 6.6 Hz, J_2 = 13.1 \text{ Hz}, 1\text{H}), 2.82-3.01 (m, 2\text{H}), 3.02-3.15 (m, 1\text{H}), 4.14 (d, J = 5.5 \text{ Hz}, 4\text{H}), 4.62-4.88 (m, 1\text{H}), 6.64 (d, J = 10.7 \text{ Hz}, 2\text{H}), 6.71 (d, J = 4.2 \text{ Hz}, 1\text{H}), 8.62 (t, J = 8.3 Hz, 1\text{H}), 8.68-8.78 (m, 1\text{H}), 8.79-8.93 (m, 2\text{H}), 9.05-9.17 (m, 1\text{H}). $^{13}\text{C} \text{ NMR} (100\text{MHz, DMSO-d}_6) \delta 22.96, 25.89, 31.88, 37.60, 52.41, 58.34, 64.21, 117.30,
((R)-1-((S)-2-(2,5-dichlorobenzamido)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)propanamido)penty1)boronic acid (8o)

Yellow foam solid (0.03 g, 46.4%). $^1$H NMR (400 MHz, CDCl$_3$) δ 0.82 (s, 3H), 1.25 (s, 2H), 1.27-1.38 (m, 2H), 1.52-2.07 (m, 2H), 2.60-3.00 (m, 1H), 3.06 (s, 2H), 4.20 (d, $J = 5.4$ Hz, 4H), 4.86 (d, $J = 68.6$ Hz, 1H), 6.71 (dd, $J_1 = 13.6$ Hz, $J_2 = 29.0$ Hz, 3H), 7.04 (d, $J = 38.7$ Hz, 1H), 7.17-7.25 (m, 1H), 7.27-7.44 (m, 2H), 7.47-7.86 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 14.25, 22.49, 22.82, 29.83, 36.05, 55.36, 64.44, 117.64, 118.41, 122.53, 129.21, 129.27, 130.05, 131.45, 133.18, 133.32, 142.88, 143.69, 165.12, 171.26. MS (ESI) m/z 507.1 [M-H$^-$. HRMS (ESI): calcd for C$_{23}$H$_{21}$BN$_4$NaO$_6$ [M+Na]$^+$, 531.1236; found, 531.1239.

((R)-1-((S)-2-(2,5-dichlorobenzamido)-3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)propanamido)-2-(p-tolyl)ethyl)boronic acid (8p)

Yellow foam solid (0.03 g, 27.9%). $^1$H NMR (400 MHz, CDCl$_3$) δ 2.23 (s, 3H), 2.73 (d, $J = 23.3$ Hz, 2H), 2.91-3.05 (m, 2H), 3.05-3.23 (m, 1H), 3.97-4.33 (m, 4H), 4.71-5.02 (m, 1H), 6.26-6.46 (m, 1H), 6.58-6.86 (-Ph, m, 4H), 6.85-7.00 (-Ph, m, 3H), 7.01-7.11 (-Ph, m, 3H), 7.32-7.93 (-CONH, m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 22.52, 29.74, 36.13, 46.62, 52.26, 64.27, 117.34, 118.17, 122.19, 128.82, 134.91,
135.20, 137.50, 138.07, 143.56, 170.20, 174.00. MS (ESI) m/z 555.4 [M-H]. HRMS (ESI): calcd for C_{27}H_{27}BN_{2}NaO_{6} [M+Na]^+, 579.1236; found, 579.1237.
3. $^1$H NMR spectra of intermediate compounds

Compound 1c

Compound 2a
Compound 2b

![Compound 2b](image)

Compound 2c

![Compound 2c](image)
Compound 2d

Compound 2e
Compound 2f

Compound 3a
Compound 3b

Compound 3c
Compound 3d

Compound 3e
Compound 3f

Compound 6a
Compound 6b

Compound 6c
Compound 6d

Compound 6e
Compound 7a

Compound 7b
Compound 7c

Compound 7d
Compound 7e

Compound 7f
Compound 7g

Compound 7h
Compound 7i

Compound 7j
Compound 7k

Compound 7l
Compound 7m

Compound 7n
4. $^1$H NMR and $^{13}$C NMR spectra of final compounds

Compound 8a
Compound 8b
Compound 8c
Compound 8d
Compound 8e
Compound 8f
Compound 8g
Compound 8h
Compound 8i
Compound 8j
Compound 8k
Compound 8l
Compound 8m
Compound 8n
Compound 80
Compound 8p
Compound 8q
Compound 8r
Compound 8s
Compound 8t