Supporting Information

Site-Selective Aqueous C–H Acylation of Tyrosine-Containing Oligopeptides with Aldehydes

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1.-General Considerations

**Reagents.** Commercially available materials were used without further purification. Palladium acetate was purchased from Fluorochem. Luperox® (*tert*-butyl hydroperoxide solution, 70 wt % in water) was purchased from Sigma-Aldrich. All the aldehydes except compound 2t were commercially available and were used without further purification.

**Analytical Methods.** $^1$H NMR and $^{13}$C NMR spectra as well as IR, HRMS and melting points (where applicable) are included for all new compounds. $^1$H, $^{13}$C and $^{19}$F NMR spectra were recorded on a Bruker 400 MHz at 20°C. All $^1$H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for CHCl$_3$ (7.26 ppm), unless otherwise indicated. All $^{13}$C NMR spectra were reported in ppm relative to residual CHCl$_3$ (77 ppm), unless otherwise indicated, and were obtained with $^1$H decoupling. Coupling constants, $J$, are reported in Hertz. Melting points were measured using open glass capillaries in a Büchi SMP-20 apparatus. High resolution mass spectra (HRMS) were performed by SGIker and were acquired on a LC/Q-TOF mass spectrometer equipped with an electrospray source ESI Agilent Jet Stream. Infrared spectra were recorded on a Bruker Alpha P. Flash chromatography was performed with EM Science silica gel 60 (230-400 mesh). The yields reported in the manuscript correspond to isolated yields and represent an average of at least two independent runs.
2.-Optimization Details

General Procedure:

A reaction tube containing a stirring bar was charged with 1a (0.15 mmol, 73 mg), oxidant (0.60 mmol) (if solid) and metal source (10 mol %). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, p-anisaldehyde (0.45 mmol, 55 μL), oxidant (if liquid), and the corresponding solvent (0.75 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to the corresponding temperature in a heating block and stirred for 16 hours. The mixture was allowed to cool to room temperature, diluted with EtOAc and washed with a saturated aqueous solution of NaHCO₃. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The resulting crude was either purified by flash chromatography (hexanes/AcOEt, 1/1) or analyzed by ¹H NMR using 1,1-diphenylethylene as internal standard. The purity of the corresponding product 3aa was verified by ¹H NMR.
Table S1. Screening of Solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield(%)&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>60 (8/2)</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>56 (87/13)</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>traces</td>
</tr>
<tr>
<td>4</td>
<td>DMA</td>
<td>traces</td>
</tr>
<tr>
<td>5</td>
<td>1,4-Dioxane</td>
<td>traces</td>
</tr>
<tr>
<td>6</td>
<td>PhCl</td>
<td>66 (75/25)</td>
</tr>
<tr>
<td>7</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>46 (85/15)</td>
</tr>
<tr>
<td>8</td>
<td>HFIP</td>
<td>traces</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 1a (0.15 mmol), 2a (0.45 mmol), Pd(OAc)<sub>2</sub> (10 mol %), TBHP in decane (2.0 equiv.), solvent (0.75 mL), Ar, 16h at 120 °C. <sup>b</sup> Yield of isolated product after column chromatography. <sup>c</sup> Ratio of mono- and diacylated product 3aa:3'aa.

Table S2. Screening of Temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>T (°C)</th>
<th>Yield(%)&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>56 (95:5)</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>65 (93:7)</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>69 (88:12)</td>
</tr>
<tr>
<td>5</td>
<td>110</td>
<td>70 (88:12)</td>
</tr>
<tr>
<td>6</td>
<td>120</td>
<td>74 (87:13)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 1a (0.15 mmol), 2a (0.45 mmol), Pd(OAc)<sub>2</sub> (10 mol %), TBHPaq (2.0 equiv.), H<sub>2</sub>O (0.75 mL), Ar, 16 h. <sup>b</sup> NMR yield using 1,1-diphenylethylene as internal standard. <sup>c</sup> Ratio of mono- and diacylated product 3aa:3'aa.
Table S3. Screening of Metal Catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>[M]</th>
<th>Yield(%)&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>65 (93:7)</td>
</tr>
<tr>
<td>2</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt;(MeCN)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>15 (100:0)</td>
</tr>
<tr>
<td>3</td>
<td>Pd(TFA)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>29 (97:3)</td>
</tr>
<tr>
<td>4</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>23 (95:5)</td>
</tr>
<tr>
<td>5</td>
<td>PdI&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt;(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>RuCl&lt;sub&gt;2&lt;/sub&gt;(p-cymene)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>NiCl&lt;sub&gt;2&lt;/sub&gt;(PCy&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>NiCl&lt;sub&gt;2&lt;/sub&gt;-DME</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: 1a (0.15 mmol), 2a (0.45 mmol), [M] (10 mol %), TBHPaq (2.0 equiv.), H<sub>2</sub>O (0.75 mL), Ar, 16 h at 90 °C. <sup>b</sup>NMR yield using 1,1-diphenylethylene as internal standard. <sup>c</sup>Ratio of mono- and diacylated product 3aa:3'aa.

Table S4. Screening of Aldehyde Equivalents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of 2a</th>
<th>Yield(%)&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>65 (93:7)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>74 (88:12)</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>72 (88:12)</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>71 (89:11)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: 1a (0.15 mmol), 2a (0.45 mmol), [Pd] (10 mol %), TBHPaq (2.0 equiv.), H<sub>2</sub>O (0.75 mL), Ar, 16 h at 90 °C. <sup>b</sup>NMR yield using 1,1-diphenylethylene as internal standard. <sup>c</sup>Ratio of mono- and diacylated product 3aa:3'aa.
Table S5. Screening of Ligands

<table>
<thead>
<tr>
<th>Reaction conditions:</th>
<th>Yield (%)</th>
<th>Ratio of mono- and diacylated product 3aa:3'aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a (0.15 mmol), 2a (0.45 mmol), Pd(OAc)$_2$ (10 mol %), TBHPaq (2.0 equiv.), Ligand (20 mol %), TBHPaq (2.0 equiv.), H$_2$O (0.75 mL), Ar, 16h at 90 °C.</td>
<td>65 (93:7)$^{a,c}$</td>
<td></td>
</tr>
<tr>
<td>2a (0.45 mmol), Pd(OAc)$_2$ (10 mol %), TBHPaq (2.0 equiv.), Ligand (20 mol %), TBHPaq (2.0 equiv.), H$_2$O (0.75 mL), Ar, 16h at 90 °C.</td>
<td>67 (88:12)$^{a,c}$</td>
<td></td>
</tr>
<tr>
<td>Reaction conditions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a (0.15 mmol), 2a (0.45 mmol), Pd(OAc)$_2$ (10 mol %), TBHPaq (n equiv.), H$_2$O (0.75 mL), Ar, 16h at 90 °C.</td>
<td>63 (9:1)$^{a,c}$</td>
<td></td>
</tr>
<tr>
<td>2a (0.45 mmol), Pd(OAc)$_2$ (10 mol %), TBHPaq (n equiv.), H$_2$O (0.75 mL), Ar, 16h at 90 °C.</td>
<td>59 (92:8)$^{a,c}$</td>
<td></td>
</tr>
<tr>
<td>Reaction conditions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a (0.15 mmol), 2a (0.45 mmol), Pd(OAc)$_2$ (10 mol %), TBHPaq (nequiv.), H$_2$O (0.75 mL), Ar, 16h at 90 °C.</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2a (0.45 mmol), Pd(OAc)$_2$ (10 mol %), TBHPaq (nequiv.), H$_2$O (0.75 mL), Ar, 16h at 90 °C.</td>
<td>60 (92:8)$^{a,c}$</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 1a (0.15 mmol), 2a (0.45 mmol), Pd(OAc)$_2$ (10 mol %), TBHPaq (2.0 equiv.), Ligand (20 mol %), TBHPaq (2.0 equiv.), H$_2$O (0.75 mL), Ar, 16h at 90 °C. $^b$NMR yield using 1,1-diphenylethylene as internal standard. $^c$Ratio of mono- and diacylated product 3aa:3'aa.

Table S6. Screening of Oxidant Equivalents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of TBHP$_{aq}$</th>
<th>Yield (%)$^{a,c}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>65 (93:7)</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>75 (82:18)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>78 (82:18)$^d$</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 1a (0.15 mmol), 2a (0.45 mmol), Pd(OAc)$_2$ (10 mol %), TBHPaq (n equiv.), H$_2$O (0.75 mL), Ar, 16h at 90 °C. $^b$NMR yield using 1,1-diphenylethylene as internal standard. $^c$Ratio of mono- and diacylated product 3aa:3'aa. $^d$Yield of isolated product after column chromatography.
Table S7. Screening of Co-Solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Co-solvent</th>
<th>Yield(%)&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>78 (8:2)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>tBuOH</td>
<td>37 (96:4)</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>14 (100:0)</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>18 (100:0)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: 1a (0.15 mmol), 2a (0.45 mmol), Pd(OAc)<sub>2</sub> (10 mol %), TBHPaq (4.0 equiv.), H<sub>2</sub>O (0.4 mL), co-solvent (0.4 mL), Ar, 16h at 90 °C. <sup>b</sup>NMR yield using 1,1-diphenylethylene as internal standard. <sup>c</sup>Ratio of mono- and diacylated product 3aa:3'aa. <sup>d</sup>Yield of isolated product after column chromatography.

Table S8. Unsuitable substrates

<table>
<thead>
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<th>Tyr-containing Peptides</th>
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<tbody>
<tr>
<td>Boc-Tyr(OPy)-Trp-OMe</td>
</tr>
<tr>
<td>Boc-Tyr(OPy)-Trp(Dec)-OMe</td>
</tr>
<tr>
<td>Boc-His-Tyr(OPy)-Leu-OMe</td>
</tr>
<tr>
<td>Boc-Tyr(OPy)-Met-OMe</td>
</tr>
<tr>
<td>Boc-Tyr(OPy)-Cys-OEt</td>
</tr>
<tr>
<td>Boc-Tyr(OPy)-Arg-OMe</td>
</tr>
</tbody>
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**Table S9. Screening with aldehyde 2o**

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from the standard conditions</th>
<th>Yield(%)$^b,c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>traces</td>
</tr>
<tr>
<td>2</td>
<td>toluene as solvent</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>toluene as solvent and PivOH (1.0 equiv.) as additive</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>toluene as solvent and XPhos (20 mol %) as additive</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>toluene as solvent at 120 ºC</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>toluene as solvent at 100 ºC</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>toluene as solvent at 100 ºC with 5.0 equiv. of 2o</td>
<td>55</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 1a (0.15 mmol), 2o (0.45 mmol), Pd(OAc)$_2$ (10 mol %), TBHPaq (4.0 equiv.), H$_2$O (0.75 mL), Ar, 16h at 90 ºC. $^b$ Yield of isolated product after column chromatography.
3.- Preparation of the Starting Materials

Peptide derivatives

Aldehydes
General Procedure for the O-Arylation of Tyr-Containing Peptides

![Chemical structure](image)

A reaction tube containing a stirring bar was charged with the corresponding tyrosine derivative (1.0 equiv.), CuCl (20 mol %), K3PO4 (2.0 equiv.) and 2-picolinic acid (40 mol %). The reaction tube was then evacuated and back-filled with dry Ar (this sequence was repeated up to three times). Then DMSO (2.5 mL/mmol) and 2-iodopyridine (2.0 equiv.) were added under argon atmosphere. The reaction tube was next warmed up to 100 °C and stirred for 16 h. After cooling down to room temperature, brine was added to the above solution, washed with a saturated aqueous solution of NaHCO3, and extracted with EtOAc. Organic layers were combined and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford the corresponding product.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl]-L-leucinate (1a). Following the general procedure, using Boc-Tyr-Leu-OMe (17.96 mmol, 7.33 g) provided 5.86 g (77% yield) of 1a as a white solid. Mp 43-45 °C. Column chromatography (Hex/EtOAc 1:1). 1H NMR (400 MHz, CDCl3) δ 8.19 (dd, J = 4.8, 1.9 Hz, 1H), 7.68 (ddd, J = 8.4, 7.2, 2.0 Hz, 1H), 7.24 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.5 Hz, 2H), 6.99 (dd, J = 6.8, 5.4 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 6.31 (d, J = 8.3 Hz, 1H), 5.01 (s, 1H), 4.66 – 4.51 (m, 1H), 4.34 (d, J = 7.6 Hz, 1H), 3.70 (s, 3H), 3.08 (dd, J = 6.8, 1.8 Hz, 2H), 1.71 – 1.56 (m, 3H), 1.43 (s, 9H), 0.91 (t, J = 6.3 Hz, 6H). 13C NMR (101 MHz, CDCl3) δ 173.0, 171.1, 163.8, 155.5, 153.2, 147.7, 139.6, 133.0, 130.8, 121.4, 118.6, 111.6, 80.4, 55.7, 52.4, 50.9, 41.6, 37.5, 28.4, 24.8, 22.9, 22.0. IR (cm⁻¹):

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Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl]-L-phenylalaninate (1b). Following the general procedure, using Boc-Tyr-Phe-OMe (1.20 mmol, 530.0 mg) provided 530 mg (85% yield) of 1b as a white solid. Mp 51-53 °C. Column chromatography (Hex/EtOAc 1:1). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.19 (dd, $J$ = 5.2, 2.0 Hz, 1H), 7.75 – 7.63 (m, 1H), 7.33 – 7.21 (m, 5H), 7.12 – 7.04 (m, 4H), 7.04 – 6.96 (m, 1H), 6.90 (d, $J$ = 8.3 Hz, 1H), 6.45 (d, $J$ = 7.6 Hz, 1H), 5.06 (s, 1H), 4.82 (q, $J$ = 6.3 Hz, 1H), 4.36 (d, $J$ = 6.9 Hz, 1H), 3.70 (s, 3H), 3.17 – 3.00 (m, 4H), 1.44 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.5, 170.9, 163.7, 153.2, 147.7, 139.6, 135.8, 132.9, 130.7, 129.3, 128.7, 128.7, 127.3, 127.2, 121.4, 118.6, 111.6, 80.3, 55.7, 53.4, 52.4, 38.0, 37.7, 28.4. IR (cm$^{-1}$): 3304, 2970, 1741, 1655, 1508, 1467, 1428, 1365, 1266, 1245, 1215, 1168. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{26}$H$_{35}$N$_3$O$_6$): 485.2526, found 485.2532.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl]-L-valinate (1c). Following the general procedure, using Boc-Tyr-Val-OMe (1.20 mmol, 473.1 mg) provided 450 mg (80% yield) of 1c as a white solid. Mp 50-51 °C. Column chromatography (Hex/EtOAc 1:1). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.20 (dd, $J$ = 5.0, 2.0 Hz, 1H), 7.76 – 7.63 (m, 1H), 7.27 (d, $J$ = 8.4 Hz, 2H), 7.09 (d, $J$ = 8.5 Hz, 2H), 7.01 (dd, $J$ = 6.3, 5.0 Hz, 1H), 6.91 (d, $J$ = 8.3 Hz, 1H), 6.52 (d, $J$ = 8.7 Hz, 1H), 5.12 (d, $J$ = 8.0 Hz, 1H), 4.50 (dd, $J$ = 8.6, 5.1 Hz, 1H), 4.38 (d, $J$ = 7.5 Hz, 1H), 3.73 (s, 3H), 3.10 (d, $J$ = 6.8 Hz, 2H), 2.21 – 2.08 (m, 1H), 1.45 (s, 9H), 0.90 (dd, $J$ = 10.7, 6.9 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.9, 171.2, 163.8, 155.5, 153.2, 147.8, 139.6, 133.0, 130.8, 121.4, 118.6, 111.6, 80.4, 57.4, 55.9, 52.3, 37.4, 31.4, 28.4, 19.0, 17.9. IR
(cm⁻¹): 3321, 1969, 1740, 1655, 1508, 1467, 1428, 1366, 1215. HRMS (ESI) m/z: (M⁺) calcd for (C₂₅H₃₃N₃O₆): 471.2369, found 471.2381.

Methyl (S)-[2-((tert-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl]glycinate (1d). Following the general procedure, using Boc-Tyr-Gly-OMe (1.20 mmol, 422.6 mg) provided 360 mg (70% yield) of 1d as a yellowish oil. Column chromatography (Hex/EtOAc 1:1). ¹H NMR (400 MHz, CDCl₃) δ 8.19 (dd, J = 5.1, 1.9 Hz, 1H), 7.70 (ddd, J = 8.3, 7.2, 2.0 Hz, 1H), 7.25 (d, J = 7.8 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 7.01 (ddd, J = 7.2, 5.0, 0.9 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.48 (s, 1H), 4.50 (d, J = 8.6, 5.1 Hz, 1H), 4.09 – 3.91 (m, 2H), 3.74 (s, 3H), 3.10 (d, J = 6.8 Hz, 2H), 1.42 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 171.7, 170.1, 163.8, 153.1, 147.7, 139.6, 133.0, 130.8, 130.5, 121.4, 118.6, 115.7, 80.4, 55.7, 52.5, 41.3, 37.8, 28.4. IR (cm⁻¹): 3305, 2977, 1747, 1663, 1507, 1467, 1428, 1266, 1245, 1207, 1166. HRMS (ESI) m/z: (M⁺) calcd for (C₂₂H₂₇N₃O₆): 429.1900, found 429.1905.

Methyl (S)-2-[(S)-4-amino-2-((tert-butoxycarbonyl)amino)-4-oxobutanamido)-3-(4-(pyridin-2-yloxy)phenyl)propanoate (1e). Following the general procedure, using Boc-Tyr-OMe (7.20 mmol, 2.13 g) provided 2.50 g (93% yield) of Boc-Tyr(OPy)-OMe as a yellowish oil. Column chromatography (Hex/EtOAc 1:1). ¹H NMR (400 MHz, CDCl₃) δ 8.20 (dd, J = 5.0, 2.0 Hz, 1H), 7.69 (ddd, J = 8.3, 7.2, 2.0 Hz, 1H), 7.17 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 7.01 (ddd, J = 7.0, 5.1, 0.9 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 5.07 (d, J = 8.3 Hz, 1H), 4.67 – 4.54 (m, 1H), 3.74 (s, 3H), 3.10 (qd, J = 13.9, 6.0 Hz, 2H), 1.44 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 172.4, 163.7, 155.2, 147.8, 139.5, 132.4, 130.6, 121.3, 118.6, 111.6, 80.0, 54.5, 52.5, 41.3, 37.8, 28.4. HRMS (ESI) m/z: (M⁺) calcd for (C₂₀H₂₄N₂O₅): 372.1685, found 372.1696. Then, a solution of Boc-Tyr(OPy)-OMe (3.25 mmol, 1.21 g) in dichloromethane was treated with trifluoroacetic acid (32.50 mmol, 2.43 mL) and stirred for 5 h. After evaporation of the solvent, the resulting crude
was diluted with EtOAc and washed with a saturated aqueous solution of NaHCO₃. After evaporation of the solvent, the so-obtained crude (without further purification) was dissolved in dichloromethane (10 mL) at 0 ºC. EDC·HCl (3.90 mmol, 748 mg), HOBt (3.90 mmol, 526 mg), Boc-Asn-OH (3.90 mmol, 906 mg) and triethylamine (3.90 mmol, 0.54 mL) were subsequently added and stirred overnight. The resulting solution was washed with water and extracted with dichloromethane. The solvent was removed under reduced pressure and the corresponding product was purified by flash chromatography (EtOAc) to provide 1.10 g (70% yield) of 1e as an orange solid. Mp 112-113 ºC. ¹H NMR (400 MHz, MeOH-d₄) δ 8.15 (dd, J = 5.0, 2.0 Hz, 1H), 7.82 (ddd, J = 8.8, 7.4, 2.0 Hz, 1H), 7.28 (dd, J = 8.1 Hz, 2H), 7.12 (dd, J = 7.2, 5.1 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.92 (d, J = 8.3 Hz, 1H), 4.78 – 4.68 (m, 1H), 4.60 – 4.39 (m, 1H), 3.73 (s, 3H), 3.14 (m, 2H), 2.69 – 2.55 (m, 2H), 1.43 (s, 9H). ¹³C NMR (101 MHz, MeOH-d₄) δ 174.8, 173.6, 172.9, 165.0, 154.5, 148.3, 141.5, 134.4, 131.9, 121.9, 120.1, 112.7, 80.8, 55.0, 52.8, 52.7, 38.2, 37.6, 28.7. IR (cm⁻¹): 3415, 3330, 1733, 1683, 1665, 1637, 1590, 1161. HRMS (ESI) m/z: (M⁺) calcd for (C₂₄H₃₀N₄O₇): 486.2114, found 486.2116.

Methyl (S)-2-[(S)-4-amino-2-[(tert-butoxycarbonyl)amino]-4-oxobutanamido]-3-(4-(pyridin-2-yloxy)phenyl)propanoate (1f). To a solution of Boc-Tyr(OPy)-OMe (1.26 mmol, 469 mg) in THF/H₂O (1:1, 20 mL), LiOH·H₂O (1.89 mmol, 79 mg) was added and stirred at room temperature for 5 h. After evaporation of the solvent, the resulting crude was diluted with EtOAc, washed with a solution of HCl 1M and extracted several times with EtOAc. After evaporation of the solvent, the resulting solid was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, J = 5.1 Hz, 1H), 7.73 (t, J = 7.1 Hz, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 7.9 Hz, 3H), 6.92 (d, J = 8.3 Hz, 1H), 5.18 (d, J = 8.0 Hz, 1H), 4.66 (q, J = 6.3 Hz, 1H), 3.27 – 3.05 (m, 2H), 1.46 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 174.7, 163.6, 155.6, 155.1, 147.3, 140.2, 132.9, 131.0, 121.2, 118.8, 111.9, 80.3, 54.3, 37.4, 28.4. Boc-Tyr(OPy)-OH was dissolved in dichloromethane (10 mL) at 0 ºC. EDC·HCl (1.51 mmol, 288 mg), HOBt·H₂O (1.51 mmol, 203 mg), L-Ser·OMe·HCl (1.51 mmol, 235 mg) and triethylamine (1.51 mmol, 0.19 mL) were subsequently added and stirred overnight. The resulting solution was washed with water and extracted with dichloromethane. The solvent was removed under reduced pressure.
and the corresponding product was purified by flash chromatography (EtOAc/hexanes, 8:2) to provide 350 mg (57% yield) of 1f as a white solid. Mp 63-64 °C. 1H NMR (400 MHz, CDCl3) δ 8.15 – 8.07 (m, 1H), 7.71 (ddd, J = 8.7, 7.4, 2.0 Hz, 1H), 7.27 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 7.9 Hz, 3H), 7.00 (dd, J = 7.2, 5.1 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 5.39 (d, J = 7.8 Hz, 1H), 4.62 (dd, J = 7.5, 3.7 Hz, 1H), 4.46 (d, J = 7.1 Hz, 1H), 3.97 – 3.87 (m, 2H), 3.75 (s, 3H), 3.12 (ddd, J = 7.8 Hz, 1H), 6.83 (d, J = 45.0, 13.9, 6.3 Hz, 2H), 4.15 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 171.2, 170.7, 163.7, 153.0, 147.3, 139.9, 133.0, 130.9, 121.5, 118.6, 111.9, 80.5, 62.6, 55.8, 54.6, 52.7, 37.7, 28.4. IR (cm⁻¹): 3304, 2977, 1741, 1657, 1590, 1265, 1166.


**Dimethyl \((S)-2-((\text{tert}-\text{butoxycarbonyl})\text{amino})-3-(4-(\text{pyridin}-2\text{-yloxy})\text{phenyl})\text{propanoyl}]\text{-L-glutamate (1g).}\)** Following the synthetic sequence for the synthesis of 1f, starting from Boc-Tyr-OH (1.43 mmol, 512 mg) and L-Glu(OMe)·OMe·HCl (1.30 mmol, 275 mg) provided 460 mg (69% yield) of 1g as a yellowish oil. 1H NMR (400 MHz, CDCl3) δ 8.11 (d, J = 3.0 Hz, 1H), 7.68 – 7.58 (m, 1H), 7.19 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 7.8 Hz, 1H), 7.00 (d, J = 8.4 Hz, 2H), 6.94 (dd, J = 7.1, 5.1 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 5.40 (dd, J = 26.2, 8.3 Hz, 1H), 4.54 (dd, J = 8.0, 5.2 Hz, 1H), 4.38 (d, J = 7.4 Hz, 1H), 3.66 (s, 3H), 3.58 (s, 3H), 3.13 – 2.91 (m, 2H), 2.40 – 2.05 (m, 3H), 1.97 – 1.81 (m, 1H), 1.36 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 173.04, 171.70, 171.44, 163.57, 155.36, 152.90, 147.50, 139.45, 132.87, 130.61, 121.13, 118.41, 111.32, 79.99, 55.56, 52.39, 51.66, 51.50, 51.46, 37.45, 29.72, 28.15, 27.05. HRMS (ESI) m/z: (M⁺) calcd for \((\text{C}_{26}\text{H}_{33}\text{N}_{3}\text{O}_{8})\): 515.2268, found 515.2292.

**Methyl \((S)-2-((\text{tert}-\text{butoxycarbonyl})\text{amino})-3-(4-(\text{pyridin}-2\text{-yloxy})\text{phenyl})\text{propanoyl}]\text{-L-tyrosinate (1h).}\)** Following the synthetic sequence for the synthesis of 1f, starting from Boc-Tyr-OH (1.43 mmol, 512 mg) and L-Tyr-OMe·HCl (1.30 mmol, 301 mg)
provided 636 mg (91% yield) of 1h as a white solid. Mp 108-110 °C. 1H NMR (400 MHz, CDCl3) δ 8.19 (dd, J = 5.1, 2.0 Hz, 1H), 7.70 (ddd, J = 8.7, 7.4, 2.1 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.06 – 7.02 (m, 1H), 7.00 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 8.3 Hz, 2H), 6.69 (d, J = 7.9 Hz, 2H), 6.53 (d, J = 7.9 Hz, 1H), 5.19 (d, J = 8.2 Hz, 1H), 4.81 – 4.71 (m, 1H), 4.38 (d, J = 7.7 Hz, 1H), 3.69 (s, 3H), 3.12 – 2.87 (m, 4H), 1.43 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 171.7, 171.1, 163.6, 155.8, 155.5, 153.2, 147.5, 140.0, 132.8, 130.9, 130.2, 126.6, 120.9, 118.9, 115.8, 111.9, 80.4, 55.6, 53.4, 52.4, 37.6, 37.0, 28.3. HRMS (ESI) m/z: (M+) calcd for (C29H33N3O7): 535.2319, found 539.2332.

Tert-butyl (S)-2-[(S)-1-methoxy-1-oxo-3-(4-(pyridin-2-yl)oxy)phenyl]propan-2-yl]carbamoyl]pyrrolidine-1-carboxylate (1i). Following the general procedure, using Boc-Pro-Tyr-OMe (7.65 mmol, 3.00 g) provided 2.57 g (75% yield) of 1i as a yellowish oil. 1H NMR (400 MHz, CDCl3) δ 8.13 (d, J = 4.9 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.11 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 8.3 Hz, 2H), 6.96 (t, J = 6.1 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 4.82 (s, 1H), 4.23 (d, J = 30.7 Hz, 1H), 3.71 (s, 3H), 3.41 – 3.26 (m, 2H), 3.18 (dd, J = 14.0, 5.7 Hz, 1H), 2.99 (dd, J = 14.0, 7.1 Hz, 1H), 2.47 – 2.32 (m, 1H), 2.06 – 1.69 (m, 3H), 1.42 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 171.8, 171.7, 163.6, 147.6, 139.4, 130.5, 130.3, 121.3, 121.1, 118.5, 111.4, 80.4, 60.9, 59.9, 53.2, 52.6, 52.3, 46.9, 37.4, 30.7, 28.3, 24.4, 23.4. IR (cm⁻¹): 3279, 2975, 1742, 1677, 1466, 1427, 1390, 1365, 1263, 1243, 1205, 1163, 1119, 728. HRMS (ESI) m/z: (M+) calcd for (C25H31N3O6): 469.2213, found 469.2231.

Methyl (S)-2-[(S)-2-[(tert-butoxycarbonyl)amino]propanamido]-3-(4-(pyridin-2-yl)oxy)phenyl]propanoate (1j). Following the general procedure, using Boc-Ala-Tyr-OMe (4.09 mmol, 1.50 g) provided 1.33 g (73% yield) of 1j as a yellowish solid. Column chromatography (Hex/EtOAc 4:6). Mp 46-47 °C. 1H NMR (400 MHz, CDCl3) δ 8.12 (dd, J = 5.1, 2.0 Hz, 1H), 7.63 (ddd, J = 8.5, 7.2, 2.0 Hz, 1H), 7.15 – 7.04 (m, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.97 – 6.90 (m, 1H), 6.83 (dd, J = 8.5, 4.3 Hz, 2H), 5.26 (d, J = 7.4 Hz,
1H), 4.82 (q, J = 6.7 Hz, 1H), 4.29 – 4.01 (m, 1H), 3.67 (s, 3H), 3.19 – 2.95 (m, 2H), 1.38 (s, 9H), 1.26 (d, J = 7.1 Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 172.8, 172.1, 163.9, 155.7, 153.4, 148.0, 147.9, 139.8, 132.5, 130.9, 121.5, 118.8, 111.8, 111.8, 80.2, 53.4, 52.7, 50.3, 37.6, 28.6, 18.5. IR (cm\(^{-1}\)): 3303, 1741, 1663, 1427, 1162. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{23}\)H\(_{29}\)N\(_3\)O\(_6\)): 443.2056, found 443.2064.

Methyl (S)-2-[(S)-6-(((benzyloxy)carbonyl)amino)-2-((tert-butoxycarbonyl)amino)hexanamido]-3-[4-(pyridin-2-yloxy)phenyl]propanoate (1k). Following the general procedure, using Boc-Lyz(Cbz)-Tyr-OMe (3.23 mmol, 1.80 g) provided 1.35 g (68% yield) of 1k as a yellowish solid. Mp 46-47 °C. \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.19 (dd, J = 5.1, 1.9 Hz, 1H), 7.70 (dd, J = 8.8, 7.3, 2.0 Hz, 1H), 7.36 (s, 4H), 7.16 (d, J = 8.6 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 7.00 (dd, J = 7.1, 5.1 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 5.10 (s, 3H), 4.93 – 4.83 (m, 1H), 4.15 – 4.03 (m, 1H), 3.71 (s, 3H), 3.27 – 3.00 (m, 4H), 1.85 – 1.71 (m, 1H), 1.63 – 1.47 (m, 3H), 1.44 (s, 9H), 1.38 – 1.31 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 171.9, 163.6, 156.7, 155.7, 153.3, 147.7, 139.7, 136.7, 132.2, 130.7, 128.6, 128.2, 121.3, 118.7, 111.7, 80.1, 66.7, 54.3, 53.1, 52.5, 40.4, 37.4, 31.9, 29.5, 28.4, 22.4. IR (cm\(^{-1}\)): 3312, 1702, 1507, 1428, 1428, 1245, 1167. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{34}\)H\(_{42}\)N\(_4\)O\(_8\)): 634.3003, found 634.3012.

Methyl ((S)-2-((tert-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl)-L-isoleucyl-L-leucinate (1l). Following the general procedure, using Boc-Tyr-Ile-OMe OMe (10.00 mmol, 4.10 g) provided 2.41 g (50% yield) of Boc-Tyr(OPy)-Ile-OMe as a white solid. \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.22 (dd, J = 5.2, 2.0 Hz, 1H), 7.72 (ddd, J = 8.4, 7.2, 2.1 Hz, 1H), 7.26 (d, J = 6.7 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 7.03 (ddd, J = 7.2, 5.0, 0.9 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.44 (d, J = 8.5 Hz, 1H), 5.05 (d, J = 4.52 (dd, J = 8.5, 5.1 Hz, 1H), 4.35 (dd, J = 13.7, 6.1 Hz, 1H), 3.71 (s, 3H), 3.09 (d, J =
7.5 Hz, 2H), 1.91 – 1.78 (m, 1H), 1.44 (s, 9H), 1.11 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 171.9, 171.0, 163.7, 153.2, 147.7, 139.7, 133.0, 130.8, 121.4, 118.7, 111.7, 80.4, 56.7, 55.9, 52.2, 38.0, 37.4, 28.4, 25.2, 15.5, 11.7. HRMS (ESI) m/z: (M⁺) calcd for (C26H35N3O6): 485.2526, found 485.2534.

Then, starting from Boc-Tyr(OPy)-Ile-OMe (4.18 mmol, 1.97 g) the hydrolysis/peptide coupling sequence was applied to deliver 1.80 g (72% yield) of 1l as a white solid. Mp 103-104 °C. 1H NMR (400 MHz, CDCl3) δ 8.19 (dd, J = 5.0, 2.0 Hz, 1H), 7.69 (ddd, J = 8.6, 7.2, 2.0 Hz, 1H), 7.22 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 7.00 (dd, J = 7.1, 4.9 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 5.24 (d, J = 7.8 Hz, 1H), 4.64 – 4.52 (m, 1H), 4.48 – 4.31 (m, 2H), 3.73 (s, 3H), 3.17 – 2.99 (m, 2H), 1.9 (s, 1H), 1.72 – 1.55 (m, 5H), 1.42 (s, 9H), 0.97 – 0.87 (m, 12H). 13C NMR (101 MHz, CDCl3) δ 173.1, 171.4, 170.8, 163.7, 155.7, 153.2, 147.7, 139.6, 132.9, 130.7, 121.3, 118.6, 111.6, 80.4, 57.9, 55.8, 52.3, 50.9, 41.2, 37.2, 28.3, 24.9, 22.8, 22.0, 15.4, 11.4. IR (cm⁻¹): 3269, 2960, 1746, 1687, 1640, 1507, 1466, 1428, 1245, 1159, 729. HRMS (ESI) m/z: (M⁺) calcd for (C32H46N4O7): 598.3366, found 598.3410.

Methyl [(S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl]-L-leucinate (1m). Following the general procedure, using Boc-Phe-Tyr-Leu-OMe (1.20 mmol, 660 mg) provided 480 mg (63% yield) of 1m as a white solid. Mp 169-170 °C. 1H NMR (400 MHz, CDCl3) δ 8.14 (dd, J = 5.0, 2.0 Hz, 1H), 7.68 (ddd, J = 8.9, 7.2, 2.0 Hz, 1H), 7.29 (d, J = 7.5 Hz, 2H), 7.26 (d, J = 7.1 Hz, 1H), 7.19 (d, J = 6.6 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.99 (dd, J = 7.2, 5.1 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.53 (d, J = 8.0 Hz, 1H), 5.04 (d, J = 7.3 Hz, 1H), 4.70 (q, J = 7.0 Hz, 1H), 4.59 – 4.50 (m, 1H), 4.38 (d, J = 7.1 Hz, 1H), 3.72 (s, 3H), 3.19 – 2.95 (m, 4H), 1.65 – 1.47 (m, 3H), 1.37 (s, 9H), 0.91 (d, J = 4.2 Hz, 6H). 13C NMR (101 MHz, CDCl3) δ 172.8, 171.2, 170.2, 163.7, 155.6, 153.2, 147.7, 139.5, 136.5, 132.6, 130.8, 129.3, 128.8, 127.1, 121.4, 118.5, 111.5, 80.5, 55.9, 54.1, 52.4, 51.0, 41.3, 38.0, 37.3, 28.3, 24.7, 22.8, 21.9. HRMS (ESI) m/z: (M⁺) calcd for (C35H44N4O7): 632.3210, found 632.3235.
Methyl 1{(S)-2-((S)-5-amino-2-(tert-butoxycarbonyl)amino)-5-oxopentanamido)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl}-L-leucinate (1n). Following the synthetic sequence for the synthesis of 1e, starting from Boc-Tyr(OPy)-Leu-OMe (2.06 mmol, 1.00 g) and L-Boc-Gln-OH (2.27 mmol, 558 mg) provided 530 mg (69% yield) of 1n as a white solid. Mp 186-187 °C. 1H NMR (400 MHz, MeOH-d4) δ 8.12 (dd, J = 5.1, 2.0 Hz, 1H), 7.79 (ddd, J = 8.8, 7.3, 2.0 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.09 (dd, J = 7.2, 5.1 Hz, 1H), 7.05 – 6.96 (m, 2H), 6.89 (d, J = 8.3 Hz, 1H), 4.74 – 4.58 (m, 1H), 4.45 (dd, J = 9.3, 5.6 Hz, 1H), 4.06 – 3.92 (m, 1H), 3.68 (s, 3H), 3.29 (p, J = 1.6 Hz, 1H), 3.15 (dd, J = 13.9, 6.0 Hz, 1H), 2.96 (dd, J = 13.9, 8.0 Hz, 1H), 2.21 (t, J = 8.2 Hz, 2H), 2.06 – 1.72 (m, 2H), 1.72 – 1.54 (m, 3H), 1.40 (s, 9H), 0.90 (dd, J = 16.4, 6.2 Hz, 6H). 13C NMR (101 MHz, MeOH-d4) δ 177.8, 174.3, 174.2, 173.2, 165.2, 157.7, 154.5, 148.4, 141.6, 134.7, 132.1, 121.9, 120.1, 112.6, 80.7, 55.5, 52.7, 52.1, 41.5, 38.3, 32.6, 29.2, 28.7, 25.8, 23.3, 21.8. IR (cm⁻¹): 3319, 1714, 1685, 1660, 1635, 1206. HRMS (ESI) m/z: (M⁺) calcd for (C₃₁H₄₃N₅O₈): 613.3112, found 613.3112.

Dimethyl 1{(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl}-L-leucyl-L-phenylalanyl-L-glutamate (1o). Following the synthetic sequence for the synthesis of 1f, starting from Boc-Tyr(OPy)-Leu-OMe (1.10 mmol, 533 mg) and using Phe-Glu(OMe)-OMe·HCl (1.30 mmol, 301 mg) provided 700 mg (82 % yield) of 1o as a white solid. Mp 166-168 °C. 1H NMR (400 MHz, CDCl₃) δ 8.17 (dd, J = 5.0, 2.0 Hz, 1H), 7.71 (t, J = 8.0 Hz 1H), 7.25 – 7.14 (m, 7H), 7.08 (d, J = 8.4 Hz, 2H), 7.01 (dd, J = 7.1, 5.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 2H), 6.80 (d, J = 8.3 Hz, 1H), 6.38 (d, J = 6.4 Hz, 1H), 4.96 (d, J = 5.6 Hz, 1H), 4.76 (d, J = 7.0 Hz, 1H), 4.56 (td, J = 8.2, 5.0 Hz, 1H), 4.31 – 4.19 (m, 2H), 3.72 (s, 3H), 3.63 (s, 3H), 3.32 (d, J = 14.0 Hz, 1H), 3.13 – 3.03 (m, 1H), 3.02 – 2.88 (m, 2H), 2.43 – 2.31 (m, 2H), 2.28 – 2.14 (m, 2H), 2.10 –
1.96 (m, 2H), 1.55 – 1.43 (m, 1H), 1.41 (s, 9H), 0.83 (dd, J = 10.4, 6.0 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 173.4, 172.2, 171.7, 171.5, 171.0, 163.5, 156.3, 153.4, 147.5, 139.9, 137.1, 132.3, 130.6, 129.2, 128.6, 126.9, 121.6, 118.8, 112.0, 81.2, 56.4, 54.0, 52.9, 52.6, 51.9, 40.5, 37.5, 36.8, 30.2, 28.4, 27.2, 24.8, 23.0, 21.8. IR (cm$^{-1}$): 3277, 2954, 1740, 1687, 1639, 1543, 1429, 1366, 1248, 1170. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{41}$H$_{53}$N$_5$O$_{10}$): 775.3792, found 775.3797.

Methyl [($S$)-2-([tert-butoxycarbonyl]amino)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl]-L-prolyl-L-phenylalanyl-L-phenylalaninate (1p). Following the general procedure, using Boc-Tyr-Pro-Phe-Phe-OMe (1.46 mmol, 1.00 g) provided 900 mg (81% yield) of 1p as a white solid. Column chromatography (Hex/EtOAc 2:8). Mp 80-81 ºC. $^1$H NMR (500 MHz, DMSO-d$_6$ at 80 ºC) δ 8.15 (d, J = 5.9 Hz, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.80 (td, J = 7.8, 2.2 Hz, 1H), 7.57 (s, 1H), 7.38 – 7.14 (m, 11H), 7.10 (dd, J = 7.3, 4.9 Hz, 1H), 7.06 – 6.90 (m, 2H), 6.52 (s, 1H), 4.67 – 4.19 (m, 4H), 3.59 (s, 3H), 3.52 – 3.45 (m, 1H), 3.02 – 2.73 (m, 4H), 2.06 – 1.65 (m, 4H), 1.34 (s, 9H). $^{13}$C NMR (126 MHz, DMSO-d$_6$ at 80 ºC) δ 170.9, 170.5, 170.2, 162.7, 152.3, 147.0, 139.4, 137.2, 136.6, 133.4, 130.0, 128.6, 128.6, 128.5, 128.5, 127.7, 127.5, 127.4, 127.4, 126.0, 125.7, 120.0, 118.4, 111.0, 77.9, 59.3, 53.3, 53.1, 53.0, 51.1, 46.3, 36.9, 36.6, 36.5, 36.0, 28.0, 27.7. IR (cm$^{-1}$): 3285, 1741, 1633, 1590, 1571, 1427, 1163. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{43}$H$_{49}$N$_5$O$_8$): 763.3581, found 763.3596.
Methyl [(S)-2-((S)-1-(N\text{\textsuperscript{2},N\text{\textsuperscript{6}}-bis(tert-butoxycarbonyl)-L-lysyl-L-isoleucyl)pyrrolidine-2-carboxamido)-3-(4-(pyridin-2-yloxy)phenyl)propanoyl)-L-isoleucyl-L-leucinate (1q). Following the general procedure, using Boc-Lys(Boc)-Ile-Pro-Tyr-OMe (5.46 mmol, 4.00 g) provided 2.58 g (58% yield) of Boc-Lys(Boc)-Ile-Pro-Tyr(OPy)-OMe as a white solid. Then, subsequent hydrolysis/peptide couplings with L-Ile-OMe·HCl and L-Leu-OMe·HCl afforded the target hexapeptide 1q. Starting from Boc-Lys(Boc)-Ile-Pro-Tyr(OPy)-Ile-OMe (1.36 mmol, 1.26 g) provided 1.00 g (71%) of 1q as a white solid. Column chromatography (EtOAc). Mp 115-116 ºC. \(^1\)H NMR (500 MHz, DMSO-\(d_6\) at 80 ºC) \(\delta\) 8.16 (dd, \(J = 4.8, 1.9\) Hz, 1H), 7.95 (d, \(J = 7.7\) Hz, 1H), 7.90 – 7.76 (m, 1H), 7.65 (d, \(J = 7.6\) Hz, 1H), 7.47 (dd, \(J = 41.1, 8.8\) Hz, 3H), 7.25 (d, \(J = 8.0\) Hz, 2H), 7.10 (dd, \(J = 7.2, 4.9\) Hz, 1H), 6.96 (p, \(J = 9.3, 8.2\) Hz, 3H), 6.52 (s, 1H), 6.30 (s, 1H), 4.62 – 4.51 (m, 1H), 4.51 – 4.30 (m, 4H), 4.26 (t, \(J = 7.9\) Hz, 1H), 4.02 – 3.82 (m, 1H), 3.78 – 3.66 (m, 1H), 3.62 (d, \(J = 7.8\) Hz, 4H), 3.58 – 3.44 (m, 1H), 2.98 – 2.75 (m, 4H), 2.09 – 1.36 (m, 12H), 1.12 (dd, \(J = 21.7, 10.6, 5.9\) Hz, 2H), 0.97 – 0.71 (m, 26H). \(^{13}\)C NMR (126 MHz, DMSO-\(d_6\)) \(\delta\) 172.6, 171.9, 171.2, 171.0, 170.3, 169.9, 163.1, 155.5, 155.2, 152.3, 147.4, 140.0, 133.7, 130.4, 120.5, 120.4, 118.9, 111.4, 78.0, 77.3, 59.3, 56.4, 54.4, 54.2, 53.6, 52.4, 51.7, 50.2, 47.1, 43.8, 37.0, 36.5, 36.4, 31.5, 29.1, 29.1, 28.3, 28.1, 28.0, 24.2, 24.1, 23.9, 22.9, 22.8, 22.7, 22.3, 21.8, 21.2, 15.0, 10.9, 10.7. IR (cm\(^{-1}\)): 3288, 1740, 1645, 1626, 1591, 1163. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{54}\)H\(_{84}\)N\(_8\)O\(_{12}\)): 1036.6209, found 1036.6215.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(3-formylphenoxy)phenyl)propanoyl]-L-phenylalaninate (2t). Following the general procedure starting from Boc-Tyr-Phe-OMe (5.10 mmol, 2.26 g) and 3-iodobenzaldehyde (10.20 mmol, 2.35 g) provided 1.24 g (45 % yield) of 2t as a yellow solid. Mp 54-55 ºC. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.96 (s, 1H), 7.65 – 7.58 (m, 1H), 7.5 6 – 7.38 (m, 2H), 7.34 – 7.10 (m, 6H), 7.10 – 6.88 (m, 4H), 6.40 (d, \(J = 7.7\) Hz, 1H), 5.05 (d, \(J = 8.7\) Hz, 1H), 4.85 (dd, \(J = 15.1, 7.3\) Hz, 1H), 4.51 – 4.22 (m, 1H), 3.70 (d, \(J = 1.3\) Hz, 3H), 3.05 (ddd, \(J = 27.4, 17.5, 11.3, 6.5\) Hz, 4H), 1.43 (d, \(J = 9.1\) Hz, 9H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 191.7, 171.7, 171.5, 170.9, 170.8, 158.3, 155.3, 138.1, 135.7, 132.5, 131.2, 131.1, 130.5, 129.3, 129.3,
128.8, 128.7, 127.3, 124.7, 119.6, 118.5, 80.4, 55.7, 53.3, 53.2, 52.5, 38.0, 28.4. HRMS (ESI) m/z: (M⁺) calcd for (C₃₁H₃₄N₂O₇): 546.2366, found 546.2369.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(3-formylphenoxy)phenyl)propanoyl]-L-valinate (2s). Following the general procedure starting from Boc-Tyr-Val-OMe (2.79 mmol, 1.10 g) and 3-iodobenzaldehyde (5.58 mmol, 1.29 g) provided 500 mg (36 % yield) of 2s as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.96 (s, 1H), 7.60 (dt, J = 7.6, 1.3 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.25 – 7.17 (m, 2H), 7.01 – 6.90 (m, 2H), 6.38 (d, J = 8.7 Hz, 1H), 5.07 (d, J = 8.1 Hz, 1H), 4.48 (dd, J = 8.7, 5.0 Hz, 1H), 4.42 – 4.18 (m, 1H), 3.70 (s, 3H), 3.07 (d, J = 6.9 Hz, 2H), 2.25 – 2.06 (m, 1H), 1.43 (s, 9H), 0.87 (dd, J = 11.2, 6.9 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 191.5, 171.8, 171.1, 158.2, 155.3, 155.0, 137.9, 132.5, 130.8, 130.3, 124.4, 124.3, 119.4, 118.2, 80.0, 57.1, 55.7, 52.0, 37.3, 31.1, 28.1, 18.7, 17.6. IR (cm⁻¹): 3308, 1741, 1696, 1655, 1504, 1246, 1162. HRMS (ESI) m/z: (M⁺) calcd for (C₂₇H₃₄N₂O₇): 498.2366, found 498.2366.
4.-Pd-Catalyzed C(sp²)-H Acylation of Tyr-Containing Oligopeptides

**General Procedure:** A reaction tube containing a stirring bar was charged with the corresponding peptide (0.15 mmol), the aldehyde (0.45 mmol, if solid) and Pd(OAc)₂ (10 mol %, 3.4 mg). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, the aldehyde (0.45 mmol, if liquid), a commercially available solution of Luperox® (0.60 mmol, 84 µL) and water (0.75 mL) were added by syringe under argon atmosphere. The reaction tube was next warmed up to the corresponding temperature in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, diluted with EtOAc and washed with aq. NaHCO₃ (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), dried over MgSO₄ and evaporated under vacuum. The resulting crude was then purified by column chromatography to afford the corresponding product.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-ylxyloxy)phenyl)propanoyl]-L-leucinate (3aa). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and 1a (0.15 mmol, 73 mg) provided 72 mg (78% yield) (8:2 ratio) of 3aa/3’aa. The characterization of the major mono-functionalized peptide 3aa is provided. Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.97 (dd, J = 5.0, 1.9 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.55 – 7.49 (m, 1H), 7.38 (dd, J = 8.3, 2.3 Hz, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.15 (d, J = 8.3 Hz, 1H), 6.86 (dd, J = 6.3, 5.0 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 8.3 Hz, 1H), 6.53 (d, J = 7.7 Hz, 1H), 5.16 (d, 1H), 4.61 – 4.52 (m, 1H), 4.38 (d, J = 8.0 Hz, 1H), 3.82 (s, 3H),
3.65 (s, 3H), 3.20 – 3.02 (m, 2H), 1.66 – 1.47 (m, 3H), 1.40 (s, 9H), 0.89 (dd, \( J = 6.0, 3.5 \) Hz, 6H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 193.7, 173.0, 170.9, 163.6, 163.1, 155.5, 150.4, 147.0, 139.4, 133.2, 132.8, 132.5, 130.9, 130.2, 122.9, 118.6, 113.4, 111.6, 80.4, 80.0, 55.5, 52.4, 50.9, 41.6, 37.3, 28.3, 24.8, 22.9, 21.9. IR (cm\(^{-1}\)): 3289, 2956, 1656, 1596, 1427, 1227, 1253, 1167. HRMS (ESI) m/z: (M\(^{+}\)) \textit{calcd} for (C\(_{34}\)H\(_{41}\)N\(_3\)O\(_8\)): 619.2894, \textit{found} 619.2906.

Methyl \([(S)-2-((\textit{tert}-butoxycarbonyl)amino)-3-(3-(2,6-dimethoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-leucinate (3ab)]. Following the general procedure, using commercially available 2,6-dimethoxybenzaldehyde (0.45 mmol, 74.8 mg) and \( 1a \) (0.15 mmol, 73 mg) provided 76 mg (74% yield) (8:2 ratio) of 3\textit{ab}/3\textquoteleft\textit{ab}. The characterization of the major mono-functionalized peptide 3\textit{ab} is provided. Colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.99 (dd, \( J = 5.1, 1.9 \) Hz, 1H), 7.55 (d, \( J = 2.3 \) Hz, 1H), 7.50 – 7.43 (m, 1H), 7.40 (dd, \( J = 8.3, 2.3 \) Hz, 1H), 7.10 (d, \( J = 8.3 \) Hz, 1H), 6.89 – 6.82 (m, 2H), 6.75 (d, \( J = 3.2 \) Hz, 1H), 6.72 (d, \( J = 9.0 \) Hz, 1H), 6.57 (d, \( J = 8.4 \) Hz, 1H), 6.39 (d, \( J = 8.3 \) Hz, 1H), 5.15 (d, \( J = 7.1 \) Hz, 1H), 4.63 – 4.55 (m, 1H), 4.38 (d, \( J = 7.4 \) Hz, 1H), 3.69 (s, 3H), 3.63 (s, 3H), 3.54 (s, 3H), 3.21 – 3.03 (m, 2H), 1.65 – 1.48 (m, 3H), 1.42 (s, 9H), 0.90 (dd, \( J = 6.0, 4.3 \) Hz, 6H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 194.0, 173.0, 171.0, 163.3, 155.5, 153.2, 152.6, 150.8, 146.9, 139.1, 133.8, 133.6, 131.3, 129.9, 123.2, 119.0, 118.1, 114.1, 113.0, 111.0, 80.4, 56.4, 55.8, 55.6, 52.4, 50.9, 41.6, 37.2, 28.3, 24.8, 22.9, 21.9. IR (cm\(^{-1}\)): 3316, 2956, 1659, 1593, 1493, 1465, 1426, 1242, 1223, 1170, 1043, 728. HRMS (ESI) m/z: (M\(^{+}\)) \textit{calcd} for (C\(_{35}\)H\(_{43}\)N\(_3\)O\(_9\)): 649.3000, \textit{found} 649.3014.
Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)-3-(2,4,6-trimethoxybenzoyl)phenyl)propanoyl]-L-leucinate (3ac). Following the general procedure, using commercially available 2,4,6-trimethoxybenzaldehyde (0.45 mmol, 88.3 mg) and 1a (0.15 mmol, 73 mg) provided 55 mg (54% yield) of 3ac as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.99 (dd, $J$ = 5.1, 1.9 Hz, 1H), 7.73 (d, $J$ = 2.3 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.39 (dd, $J$ = 8.4, 2.3 Hz, 1H), 7.03 (d, $J$ = 8.2 Hz, 1H), 6.86 (dd, $J$ = 6.3, 5.0 Hz, 1H), 6.62 – 6.52 (m, 1H), 6.47 (d, $J$ = 8.3 Hz, 1H), 5.89 (s, 2H), 5.12 (s, 1H), 4.67 – 4.54 (m, 1H), 4.37 (d, $J$ = 8.2 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.53 (s, 6H), 3.22 – 3.04 (m, 2H), 1.66 – 1.50 (m, 1H), 1.43 (s, 9H), 0.91 (dd, $J$ = 6.0, 4.1 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 192.1, 173.0, 171.0, 163.5, 162.5, 159.0, 155.6, 151.3, 146.7, 139.0, 134.2, 133.8, 133.4, 132.0, 124.0, 117.8, 113.8, 111.1, 90.5, 80.5, 55.8, 55.5, 52.4, 50.9, 41.6, 37.2, 28.4, 24.8, 22.9, 22.0. IR (cm$^{-1}$): 3315, 2957, 1664, 1604, 1467, 1427, 1265, 1206, 1158, 1130. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{36}$H$_{45}$N$_3$O$_{10}$): 679.3105, found 679.3122.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-(2,4-dimethoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-leucinate (3ad). Following the general procedure, using commercially available 2,4-dimethoxybenzaldehyde (0.45 mmol, 74.8 mg) and 1a (0.15 mmol, 73 mg) provided 48 mg (48% yield) (83:17 ratio) of 3ad/3’ad. The characterization of the major mono-functionalized peptide 3ad is provided. Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.02 (d, $J$ = 4.6 Hz, 1H), 7.50 (t, $J$ = 7.7 Hz, 1H), 7.46
(s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.3 Hz, 1H), 6.91 – 6.83 (m, 1H), 6.55 (d, J = 8.4 Hz, 1H), 6.51 (d, J = 8.3 Hz, 1H), 6.37 (d, J = 6.8 Hz, 1H), 6.33 (s, 1H), 5.15 (s, 1H), 4.61 (q, J = 8.3 Hz, 1H), 4.39 (d, J = 6.7 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.62 (s, 3H), 3.14 (qd, J = 14.1, 6.7 Hz, 2H), 1.69 – 1.53 (m, 3H), 1.44 (s, 9H), 0.93 (dd, J = 5.9, 4.0 Hz, 6H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 192.8, 173.0, 171.0, 164.2, 163.4, 160.8, 155.5, 150.4, 147.0, 139.1, 134.7, 133.3, 132.8, 131.0, 122.9, 122.0, 118.2, 111.1, 104.6, 98.4, 80.4, 55.7, 55.5, 52.4, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 22.0. IR (cm\(^{-1}\)): 3315, 2957, 1656, 1598, 1465, 1427, 1265, 1244, 1161. HRMS (ESI) m/z: (M\(^{+}\)) calcd for (C\(_{35}\)H\(_{43}\)N\(_3\)O\(_9\)): 649.2999, found 649.3015.

**Methyl [(S)-2-((tert-butoxycarbonylamino)-3-(3-(4-fluorobenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-leucinate (3ae).** Following the general procedure, using commercially available 4-fluorobenzaldehyde (0.45 mmol, 48.3 µL) and 1a (0.15 mmol, 73 mg) provided 73 mg (76% yield) (75:25 ratio) of 3ae/3'ae. The characterization of the major mono-functionalized peptide 3ae is provided. Colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.97 (dd, J = 5.1, 1.9 Hz, 1H), 7.77 (dd, J = 8.7, 5.5 Hz, 2H), 7.52 (ddd, J = 8.8, 7.2, 2.0 Hz, 1H), 7.41 (dd, J = 8.3, 2.3 Hz, 1H), 7.36 (d, J = 2.2 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.99 (t, J = 8.6 Hz, 2H), 6.88 (dd, J = 7.1, 5.0 Hz, 1H), 6.61 (d, J = 8.3 Hz, 1H), 6.48 (d, J = 8.2 Hz, 1H), 5.13 (d, J = 8.3 Hz, 1H), 4.64 – 4.51 (m, 1H), 4.38 (d, J = 8.7 Hz, 1H), 3.67 (s, 3H), 3.26 – 3.00 (m, 2H), 1.67 – 1.48 (m, 3H), 1.41 (s, 9H), 0.90 (dd, J = 6.1, 3.2 Hz, 6H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 193.6, 173.0, 170.8, 165.75 (d, J\(_{C-F}\) = 252.5 Hz), 162.9, 150.5, 155.5, 147.0, 139.6, 133.8 (d, J\(_{C-F}\) = 3.0 Hz), 133.4, 133.3, 132.6 (d, J\(_{C-F}\) = 10.1 Hz), 132.1, 131.0, 123.0, 118.7, 115.3 (d, J\(_{C-F}\) = 20.2 Hz), 111.6, 80.5, 55.6, 52.4, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 21.9. \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -105.3. IR (cm\(^{-1}\)): 3314, 2957, 1657, 1596, 1465, 1428, 1241, 1154. HRMS (ESI) m/z: (M\(^{+}\)) calcd for (C\(_{33}\)H\(_{38}\)FN\(_3\)O\(_7\)): 607.2694, found 607.2711.
Methyl [(S)-3-(3-(3-bromobenzoyl)-4-(pyridin-2-yloxy)phenyl)-2-((tert-butoxy carbonyl)amino)propanoyl]-L-leucinate (3af). Following the general procedure, using commercially available 3-bromobenzaldehyde (0.45 mmol, 52.7 µL) and 1a (0.15 mmol, 73 mg) provided 90 mg (58% yield) (8:2 ratio) of 3af/3'af. The characterization of the major mono-functionalized peptide 3af is provided. Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.99 (dd, $J = 5.1$, 1.9 Hz, 1H), 7.84 (s, 1H), 7.65 (d, $J = 7.8$ Hz, 1H), 7.60 – 7.55 (m, 1H), 7.54 – 7.49 (m, 1H), 7.44 (dd, $J = 8.3$, 2.3 Hz, 1H), 7.40 (d, $J = 2.3$ Hz, 1H), 7.23 – 7.14 (m, 2H), 6.89 (dd, $J = 7.1$, 4.9 Hz, 1H), 6.58 (d, $J = 8.3$ Hz, 1H), 6.47 (d, $J = 8.3$ Hz, 1H), 5.14 (d, $J = 8.3$ Hz, 1H), 4.66 – 4.52 (m, 1H), 4.38 (d, $J = 7.5$ Hz, 1H), 3.67 (s, 3H), 3.23 – 3.04 (m, 2H), 1.65 – 1.48 (m, 3H), 1.41 (s, 9H), 0.90 (dd, $J = 6.1$, 3.2 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 193.8, 173.0, 170.8, 162.8, 155.5, 150.7, 147.1, 139.6, 139.5, 135.6, 133.8, 133.5, 132.5, 131.6, 131.2, 129.7, 128.4, 123.1, 122.4, 118.8, 111.5, 80.5, 55.6, 52.5, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 21.9. IR (cm$^{-1}$): 3315, 2957, 1744, 1661, 1428, 1245. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{33}$H$_{38}$BrN$_3$O$_7$): 667.1893, found 667.1906.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-(3-chlorobenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-leucinate (3ag). Following the general procedure, using commercially available 3-chlorobenzaldehyde (0.45 mmol, 51.0 µL) and 1a (0.15 mmol, 73 mg) provided 58 mg (58% yield) (75:25 ratio) of 3ag/3'ag. The characterization of the major mono-functionalized peptide 3ag is provided. Colorless oil. $^1$H NMR (400 MHz,
CDCl$_3$) $\delta$ 8.02 (dd, $J = 5.1$, 1.9 Hz, 1H), 7.73 (t, $J = 1.9$ Hz, 1H), 7.63 (dt, $J = 7.7$, 1.3 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.49 – 7.40 (m, 3H), 7.32 – 7.26 (m, 1H), 7.21 (d, $J = 8.3$ Hz, 1H), 6.92 (dd, $J = 7.1$, 5.0 Hz, 1H), 6.62 (d, $J = 8.3$ Hz, 1H), 6.48 (d, $J = 8.3$ Hz, 1H), 5.15 (d, $J = 8.0$ Hz, 1H), 4.66 – 4.53 (m, 1H), 4.41 (d, $J = 7.5$ Hz, 1H), 3.70 (s, 3H), 3.28 – 3.04 (m, 2H), 1.69 – 1.52 (m, 3H), 1.44 (s, 9H), 0.93 (dd, $J = 6.1$, 3.2 Hz, 6H). 13C NMR (101 MHz, CDCl$_3$) $\delta$ 193.9, 173.0, 170.8, 162.8, 147.1, 139.6, 139.3, 134.4, 133.7, 133.5, 132.7, 131.7, 131.2, 129.6, 129.5, 128.0, 123.1, 118.8, 111.5, 80.5, 55.6, 52.5, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 22.0. IR (cm$^{-1}$): 3315, 2957, 1744, 1660, 1466, 1428, 1244. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{33}$H$_{38}$ClN$_3$O$_7$): 623.2398, found 623.2411.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)-3-(4-(trifluoromethyl)benzoyl)phenyl)propanoyl]-L-leucinate (3ah). Following the general procedure, using commercially available 4-trifluoromethylbenzaldehyde (6.15 mmol, 842 µL) and 1a (2.05 mmol, 1.00 g) provided 759 mg and 294 mg of 3ah/3’ah, respectively, (73% yield) (75:25 ratio). The characterization of the major monofunctionalized peptide 3ah is provided. White solid. Mp 67-68°C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.96 (dd, $J = 5.0$, 1.9 Hz, 1H), 7.81 (d, $J = 8.1$ Hz, 2H), 7.56 (d, $J = 8.2$ Hz, 2H), 7.53 – 7.47 (m, 1H), 7.46 (dd, $J = 8.3$, 2.3 Hz, 1H), 7.42 (d, $J = 2.2$ Hz, 1H), 7.19 (d, $J = 8.3$ Hz, 1H), 6.88 (dd, $J = 7.2$, 5.0 Hz, 1H), 6.54 (d, $J = 8.3$ Hz, 1H), 6.43 (d, $J = 8.3$ Hz, 1H), 5.12 (d, $J = 8.2$ Hz, 1H), 4.64 – 4.51 (m, 1H), 4.38 (d, $J = 7.9$ Hz, 1H), 3.67 (s, 3H), 3.25 – 2.99 (m, 2H), 1.67 – 1.49 (m, 4H), 1.41 (s, 9H), 0.90 (dd, $J = 6.1$, 3.2 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 194.2, 173.0, 170.7, 162.7, 150.8, 146.9, 140.6, 139.7, 134.0, 133.9 (q, $J_{C-F} = 32.5$ Hz), 133.6, 131.5, 131.3, 130.0, 125.1 (q, $J_{C-F} = 4.0$ Hz), 123.3, 123.0 (q, $J_{C-F} = 272.6$ Hz), 118.8, 111.5, 80.6, 55.6, 52.5, 50.9, 41.6, 37.4, 28.4, 24.8, 22.9, 21.9. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -63.08. IR (cm$^{-1}$): 3313, 2957, 1745, 1659, 1466, 1428, 1325, 1244, 1168, 1131, 1065. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{34}$H$_{38}$F$_3$ClN$_3$O$_7$): 657.2662, found 657.2676.
Methyl [(S)-3-(3-(4-acetamidobenzoyl)-4-(pyridin-2-yloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoyl]-L-leucinate (3ai). Following the general procedure in toluene as solvent, using commercially available N-(4-formylphenyl)acetamide (0.45 mmol, 73.4 mg) and 1a (0.15 mmol, 73 mg) provided 50 mg (52% yield) of 3ai as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.99 (s, 1H), 7.95 (dd, $J$ = 4.9, 2.0 Hz, 1H), 7.69 (d, $J$ = 8.7 Hz, 2H), 7.49 (dd, $J$ = 8.7, 6.8 Hz, 3H), 7.37 (dd, $J$ = 8.3, 2.2 Hz, 1H), 7.32 (d, $J$ = 2.2 Hz, 1H), 7.14 (d, $J$ = 8.3 Hz, 1H), 6.85 (dd, $J$ = 7.1, 5.0 Hz, 1H), 6.63 (d, $J$ = 8.2 Hz, 2H), 5.18 (d, $J$ = 8.2 Hz, 1H), 4.61−4.51 (m, 1H), 4.38 (d, $J$ = 7.5 Hz, 1H), 3.65 (s, 3H), 3.09 (ddd, $J$ = 46.6, 14.0, 6.8 Hz, 2H), 2.14 (s, 3H), 1.65−1.47 (m, 3H), 1.39 (s, 9H), 0.88 (dd, $J$ = 6.0, 2.8 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 193.9, 173.0, 171.0, 168.9, 163.1, 155.5, 150.5, 147.1, 142.6, 139.6, 133.3, 133.0, 132.7, 132.5, 131.5, 131.0, 122.9, 118.7, 118.5, 111.6, 80.5, 55.5, 52.4, 50.9, 41.5, 37.3, 28.4, 24.8, 22.9, 21.9. IR (cm$^{-1}$): 3307, 2958, 1658, 1591, 1527, 1428, 1287, 1261, 1173, 731. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{35}$H$_{42}$N$_4$O$_8$): 646.3003, found 646.3022.

Methyl [(S)-3-(3-(1,1'-biphenyl)-4-carbonyl)-4-(pyridin-2-yloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoyl]-L-leucinate (3aj). Following the general procedure, using commercially available 4-phenylbenzaldehyde (0.45 mmol, 82.0 mg) and 1a (0.15 mmol, 73 mg) provided 77 mg (73% yield) (8:2 ratio) of 3aj/3’aj. The characterization of the major mono-functionalized peptide 3aj is provided. Colorless oil.
$^1$H NMR (400 MHz, CDCl$_3$) δ 8.00 (dd, $J = 5.0, 1.9$ Hz, 1H), 7.81 (d, $J = 8.4$ Hz, 2H), 7.61 – 7.53 (m, 4H), 7.53 – 7.48 (m, 1H), 7.48 – 7.36 (m, 5H), 7.20 (d, $J = 8.2$ Hz, 1H), 6.87 (dd, $J = 7.1, 5.0$ Hz, 1H), 6.63 (d, $J = 8.3$ Hz, 1H), 6.51 (d, $J = 8.2$ Hz, 1H), 5.15 (d, $J = 7.6$ Hz, 1H), 4.65 – 4.53 (m, 1H), 4.39 (d, $J = 7.5$ Hz, 1H), 3.67 (s, 3H), 3.22 – 3.06 (m, 2H), 1.64 – 1.50 (m, 3H), 1.41 (s, 9H), 0.90 (dd, $J = 6.0, 3.5$ Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 194.7, 173.0, 170.8, 163.1, 155.5, 150.6, 147.0, 145.6, 140.1, 139.5, 136.2, 133.4, 133.2, 132.4, 131.1, 130.6, 129.0, 128.3, 127.4, 126.8, 123.1, 118.6, 111.2, 80.5, 55.6, 52.4, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 22.0. IR (cm$^{-1}$): 3306, 2957, 1743, 1658, 1599, 1465, 1427, 1243, 1166. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{39}$H$_{43}$N$_3$O$_7$): 665.3101, found 665.3118.

**Methyl [(S)-3-(3-(1-naphthoyl)-4-(pyridin-2-yloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoyl]-L-leucinate (3ak).** Following the general procedure, using commercially available 1-naphthaldehyde (0.45 mmol, 61.1 µL) and 1a (0.15 mmol, 73 mg) provided 68 mg (68% yield) (84:16 ratio) of 3ak/3’ak. The characterization of the major mono-functionalized peptide 3ak is provided. Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.39 – 8.30 (m, 1H), 7.95 (dd, $J = 5.1, 1.9$ Hz, 1H), 7.88 (d, $J = 8.2$ Hz, 1H), 7.85 – 7.80 (m, 1H), 7.67 – 7.57 (m, 2H), 7.52 – 7.45 (m, 3H), 7.35 – 7.30 (m, 1H), 7.30 – 7.25 (m, 1H), 7.18 (d, $J = 8.2$ Hz, 1H), 6.79 – 6.71 (m, 1H), 6.55 (d, $J = 7.3$ Hz, 1H), 6.23 (d, $J = 8.2$ Hz, 1H), 5.18 (d, $J = 8.2$ Hz, 1H), 4.67 – 4.57 (m, 1H), 4.42 (d, $J = 7.5$ Hz, 1H), 3.69 (s, 3H), 3.28 – 3.05 (m, 2H), 1.70 – 1.52 (m, 3H), 1.44 (s, 9H), 0.93 (dd, $J = 6.1, 4.1$ Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 196.4, 173.0, 170.8, 162.9, 155.5, 151.1, 146.7, 139.1, 135.9, 134.1, 133.7, 133.6, 132.3, 132.0, 130.8, 130.6, 129.9, 128.2, 127.6, 126.3, 125.7, 124.2, 123.7, 118.4, 111.1, 80.5, 55.6, 52.4, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 22.0. IR (cm$^{-1}$): 3307, 2957, 1743, 1658, 1599, 1465, 1427, 1243, 1166. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{37}$H$_{41}$N$_3$O$_7$): 639.2945, found 639.2963.
Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-heptanoyl-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-leucinate (3am). Following the general procedure, using commercially available heptanal (0.45 mmol, 63.0 µL) and 1a (0.15 mmol, 73 mg) provided 42 mg (47% yield) of 3am as a colorless oil. The performance of the process in PhCl with 5.0 equiv. of heptanal provided 51 mg (56% yield) of 3am. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.13 (d, \(J = 3.1\) Hz, 1H), 7.75 – 7.67 (m, 1H), 7.58 (d, \(J = 2.3\) Hz, 1H), 7.36 (dd, \(J = 8.3, 2.3\) Hz, 1H), 7.03 (d, \(J = 8.2\) Hz, 1H), 7.00 (dd, \(J = 7.2, 5.0\) Hz, 1H), 6.94 (d, \(J = 8.3\) Hz, 1H), 6.49 (d, \(J = 8.2\) Hz, 1H), 5.12 (d, \(J = 8.4\) Hz, 1H), 4.64 – 4.52 (m, 1H), 4.36 (d, \(J = 8.7\) Hz, 1H), 3.69 (s, 3H), 3.19 – 3.00 (m, 2H), 2.83 (t, \(J = 7.4\) Hz, 2H), 1.65 – 1.48 (m, 5H), 1.41 (s, 9H), 1.25 – 1.12 (m, 6H), 0.90 (dd, \(J = 6.1, 3.4\) Hz, 6H), 0.82 (t, \(J = 6.8\) Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 201.7, 173.0, 170.9, 163.3, 155.5, 151.3, 147.7, 139.9, 133.9, 133.6, 132.4, 130.8, 123.2, 118.9, 111.8, 80.5, 55.6, 52.4, 50.9, 42.9, 41.6, 37.4, 31.7, 29.0, 28.4, 24.8, 24.1, 22.9, 22.6, 22.0, 14.1. IR (cm\(^{-1}\)): 3304, 2955, 2929, 2870, 1744, 1681, 1656, 1428, 1243, 1167. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{33}\)H\(_{47}\)N\(_3\)O\(_7\)): 597.3414, found 597.3426.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-(cyclohexanecarbonyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-leucinate (3an). Following the general procedure, using commercially available cyclohexylcarboxaldehyde (0.45 mmol, 54.5 µL) and 1a (0.15 mmol, 73 mg) provided 42 mg (46% yield) of 3an as a colorless oil. The performance of the process in PhCl with 5.0 equiv. of aldehyde provided 51 mg (57% yield) of 3an. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.13 (d, \(J = 3.3\) Hz, 1H), 7.74 – 7.65 (m, 1H), 7.45 (d, \(J = 2.3\) Hz, 1H), 7.03 (d, \(J = 8.2\) Hz, 1H), 6.94 (d, \(J = 8.3\) Hz, 1H), 6.49 (d, \(J = 8.2\) Hz, 1H), 5.12 (d, \(J = 8.4\) Hz, 1H), 4.64 – 4.52 (m, 1H), 4.36 (d, \(J = 8.7\) Hz, 1H), 3.69 (s, 3H), 3.19 – 3.00 (m, 2H), 2.83 (t, \(J = 7.4\) Hz, 2H), 1.65 – 1.48 (m, 5H), 1.41 (s, 9H), 1.25 – 1.12 (m, 6H), 0.90 (dd, \(J = 6.1, 3.4\) Hz, 6H), 0.82 (t, \(J = 6.8\) Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 201.7, 173.0, 170.9, 163.3, 155.5, 151.3, 147.7, 139.9, 133.9, 133.6, 132.4, 130.8, 123.2, 118.9, 111.8, 80.5, 55.6, 52.4, 50.9, 42.9, 41.6, 37.4, 31.7, 29.0, 28.4, 24.8, 24.1, 22.9, 22.6, 22.0, 14.1. IR (cm\(^{-1}\)): 3304, 2955, 2929, 2870, 1744, 1681, 1656, 1428, 1243, 1167. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{33}\)H\(_{47}\)N\(_3\)O\(_7\)): 597.3414, found 597.3426.
2.2 Hz, 1H), 7.34 (dd, J = 8.3, 2.2 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 7.00 (dd, J = 7.2, 5.1 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.54 (s, 1H), 5.14 (d, J = 8.4 Hz, 1H), 4.64 – 4.49 (m, 1H), 4.36 (q, J = 7.3 Hz, 1H), 3.69 (s, 3H), 3.19 – 2.94 (m, 3H), 1.83 – 1.46 (m, 8H), 1.41 (s, 9H), 1.35 – 1.04 (m, 5H), 0.89 (dd, J = 6.0, 3.6 Hz, 6H). 13C NMR (101 MHz, CDCl3) δ 205.8, 173.0, 170.9, 163.3, 155.5, 150.8, 147.6, 139.8, 133.4, 132.6, 130.7, 123.1, 121.4, 118.9, 118.6, 111.7, 80.5, 55.5, 52.4, 50.9, 49.6, 41.5, 37.3, 28.9, 28.9, 28.3, 26.0, 25.8, 24.8, 22.9, 22.0. IR (cm⁻¹): 3306, 2930, 1744, 1656, 1466, 1428, 1265, 1243, 1164. HRMS (ESI) m/z: (M⁺) calcd for (C33H45N3O7): 595.3258, found 595.3257.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)-3-(thiophene-2-carbonyl)phenyl)propanoyl]-L-leucinate (3ao). Following the general procedure in toluene as solvent, using commercially available 2-thiophenecarboxaldehyde (0.45 mmol, 42.0 µL) and 1a (0.15 mmol, 73 mg) provided 49 mg (55% yield) of 3ao as a colorless oil. The performance of the process in toluene at 100 ºC with 5.0 equiv. of aldehyde provided 55 mg (62% yield) of 3ao. 1H NMR (400 MHz, CDCl3) δ 8.00 (dd, J = 5.1, 1.9 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.60 – 7.54 (m, 2H), 7.45 – 7.37 (m, 2H), 7.18 (d, J = 8.3 Hz, 1H), 7.04 (dd, J = 4.9, 3.8 Hz, 1H), 6.94 – 6.87 (m, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 5.15 (d, J = 8.2 Hz, 1H), 4.64 – 4.52 (m, 1H), 4.39 (d, J = 7.4 Hz, 1H), 3.66 (s, 3H), 3.21 – 3.03 (m, 2H), 1.62 – 1.49 (m, 2H), 1.40 (s, 9H), 0.89 (dd, J = 6.0, 3.1 Hz, 6H). 13C NMR (101 MHz, CDCl3) δ 186.7, 173.0, 170.8, 163.2, 155.5, 150.3, 147.0, 144.1, 139.7, 135.8, 134.8, 133.2, 133.2, 132.2, 130.7, 128.1, 123.1, 118.7, 111.8, 80.5, 55.5, 52.4, 50.9, 41.6, 37.3, 28.9, 28.4, 24.8, 22.9, 21.9. IR (cm⁻¹): 3315, 2958, 1742, 1653, 1428, 1243, 1209, 1168, 730. HRMS (ESI) m/z: (M⁺) calcd for (C31H37N3O7S): 595.2352, found 595.2378.
Methyl \([(S)-2-((\text{tert-butoxycarbonyl})\text{amino})-3-(3-(\text{furan-2-carbonyl})-4-(\text{pyridin-2-yloxy})\text{phenyl})\text{propanoyl})-\text{L-leucinate}\] (3ap). Following the general procedure \textit{in toluene as solvent}, using commercially available 2-furanal (0.45 mmol, 37.3 µL) and 1a (0.15 mmol, 73 mg) provided 42 mg (48% yield) of 3ap as a colorless oil. The performance of the process in toluene at 100 ºC with 5.0 equiv. of aldehyde provided 48 mg (55% yield) of 3ap. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.02 (dd, \(J = 5.2, 2.0\) Hz, 1H), 7.64 – 7.57 (m, 1H), 7.55 (d, \(J = 1.6\) Hz, 1H), 7.45 (d, \(J = 2.2\) Hz, 1H), 7.40 (dd, \(J = 8.4, 2.3\) Hz, 1H), 7.17 (d, \(J = 8.3\) Hz, 1H), 7.13 (d, \(J = 3.6\) Hz, 1H), 6.92 (dd, \(J = 7.2, 5.0\) Hz, 1H), 6.81 (d, \(J = 8.3\) Hz, 1H), 6.47 (dd, \(J = 3.6, 1.7\) Hz, 2H), 5.13 (d, \(J = 8.4\) Hz, 1H), 4.67 – 4.51 (m, 1H), 4.39 (d, \(J = 8.0\) Hz, 1H), 3.67 (s, 3H), 3.13 (qd, \(J = 14.0, 6.7\) Hz, 2H), 1.64 – 1.47 (m, 3H), 1.41 (s, 9H), 0.89 (dd, \(J = 6.1, 3.5\) Hz, 6H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 181.5, 173.0, 170.8, 163.2, 155.5, 152.4, 150.7, 147.4, 147.1, 139.6, 133.4, 133.2, 131.5, 130.9, 123.1, 121.1, 118.8, 112.4, 111.8, 80.5, 55.5, 52.5, 50.9, 41.6, 37.3, 28.4, 24.8, 22.9, 21.9. IR (cm\(^{-1}\)): 3324, 2958, 2937, 1742, 1657, 1465, 1428, 1244, 1166. HRMS (ESI) m/z: (M\(^+\)) \textit{calc} for (C\(_{31}\)H\(_{37}\)N\(_3\)O\(_8\)): 579.2581, \textit{found} 579.2601.

Methyl \([(S)-2-((\text{tert-butoxycarbonyl})\text{amino})-3-(3-(1\text{-methyl-1H-pyrrole-2-carbonyl})-4-(\text{pyridin-2-yloxy})\text{phenyl})\text{propanoyl})-\text{L-leucinate}\] (3aq). Following the general procedure \textit{in toluene as solvent}, using commercially available 1-methyl-1H-pyrrole-2-carboxaldehyde (0.45 mmol, 49.5 mg) and 1a (0.15 mmol, 73 mg) provided 33 mg (37% yield) of 3aq as a colorless oil. The performance of the process in toluene at 100 ºC with
5.0 equiv. of aldehyde provided 39 mg (44% yield) of 3aq. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.09 (dd, \(J = 5.1, 1.9 \text{ Hz}, 1\text{H}\)), 7.62 (dd, \(J = 8.3, 7.2, 2.0 \text{ Hz}, 1\text{H}\)), 7.40 (d, \(J = 2.2 \text{ Hz}, 1\text{H}\)), 7.36 (dd, \(J = 8.3, 2.3 \text{ Hz}, 1\text{H}\)), 7.14 (d, \(J = 8.3 \text{ Hz}, 1\text{H}\)), 6.94 (dd, \(J = 7.1, 4.9, 0.9 \text{ Hz}, 1\text{H}\)), 6.86 – 6.79 (m, 2H), 6.68 (dd, \(J = 4.2, 1.7 \text{ Hz}, 1\text{H}\)), 6.53 (d, \(J = 8.2 \text{ Hz}, 1\text{H}\)), 6.08 (dd, \(J = 4.2, 2.4 \text{ Hz}, 1\text{H}\)), 5.13 (d, \(J = 7.9 \text{ Hz}, 1\text{H}\)), 4.61 (td, \(J = 8.5, 4.8 \text{ Hz}, 1\text{H}\)), 4.40 (d, \(J = 7.4 \text{ Hz}, 1\text{H}\)), 3.90 (s, 3H), 3.71 (s, 3H), 3.13 (dq, \(J = 46.4, 14.0, 6.5 \text{ Hz}, 2\text{H}\)), 1.68 – 1.50 (m, 3H), 1.44 (s, 9H), 0.93 (dd, \(J = 6.1, 3.2 \text{ Hz}, 6\text{H}\)). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 183.8, 173.0, 170.9, 163.6, 155.6, 150.4, 147.3, 139.4, 133.7, 132.2, 132.7, 132.2, 131.8, 131.0, 130.9, 123.8, 122.8, 118.5, 111.7, 108.5, 80.5, 55.6, 52.4, 50.9, 41.6, 37.4, 37.2, 28.4, 24.8, 22.9, 22.0. IR (cm\(^{-1}\)): 3308, 2957, 1659, 1630, 1465, 1427, 1243, 1163, 730. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{32}\)H\(_{40}\)N\(_4\)O\(_7\)): 592.2897, found 592.2942.

Methyl \(((S)-2-((tert-butoxycarbonyl)amino)-3-(3-(1-methyl-1H-indole-3-carbonyl)-4-(pyridin-2-yloxy)phenyl)propanoyl)-L-leucinate\) (3ar). Following the general procedure \textit{in toluene as solvent}, using commercially available 1-methyl-1H-indole-3-carboxaldehyde (0.45 mmol, 42.0 µL) and 1a (0.15 mmol, 73 mg) provided 60 mg (61% yield) (95:5 ratio) of 3ar/3’ar. The characterization of the major mono-functionalized peptide 3ar is provided. Colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.37 (d, \(J = 5.8 \text{ Hz}, 1\text{H}\)), 8.08 (dd, \(J = 5.0, 1.9 \text{ Hz}, 1\text{H}\)), 7.64 – 7.54 (m, 2H), 7.42 (d, \(J = 2.2 \text{ Hz}, 1\text{H}\)), 7.38 – 7.28 (m, 4H), 7.15 (d, \(J = 8.3 \text{ Hz}, 1\text{H}\)), 6.91 (dd, \(J = 7.1, 5.0 \text{ Hz}, 1\text{H}\)), 6.83 (d, \(J = 8.3 \text{ Hz}, 1\text{H}\)), 6.61 (d, \(J = 8.3 \text{ Hz}, 1\text{H}\)), 5.22 (d, \(J = 8.3 \text{ Hz}, 1\text{H}\)), 4.61 (td, \(J = 8.6, 4.6 \text{ Hz}, 1\text{H}\)), 4.48 (d, \(J = 7.9 \text{ Hz}, 1\text{H}\)), 3.76 (s, 3H), 3.56 (s, 3H), 3.15 (ddd, \(J = 46.4, 14.0, 6.5 \text{ Hz}, 2\text{H}\)), 1.66 – 1.51 (m, 3H), 1.44 (s, 9H), 0.92 (dd, \(J = 6.1, 4.2 \text{ Hz}, 6\text{H}\)). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 188.5, 173.1, 171.0, 163.6, 155.5, 150.2, 147.1, 140.0, 139.6, 137.7, 134.7, 132.8, 131.9, 130.6, 126.7, 123.5, 122.8, 122.8, 118.6, 116.5, 112.1, 109.6, 80.4, 55.4, 52.4, 50.8, 41.6, 37.5, 33.4, 28.4, 24.8, 22.9, 21.9. IR (cm\(^{-1}\)): 3314, 2957, 1666, 1525, 1465, 1427, 1243, 1163, 730. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{32}\)H\(_{40}\)N\(_4\)O\(_7\)): 592.2897, found 592.2942.
1244, 1207. 733. HRMS (ESI) m/z: (M⁺) calcd for (C₃₆H₄₂N₄O₇): 642.3053, found 642.3071.

**Methyl (S)-3-(3-(3-bromobenzoyl)-4-(pyridin-2-yloxy)-5-(4-(trifluoromethyl)benzoyl)phenyl)-2-[(tert-butoxycarbonyl)amino]propanoyl]-L-leucinate (3as).**

Following the general procedure in toluene as solvent, using commercially available 3-bromobenzaldehyde (0.60 mmol, 70 µL) and 3ah (0.15 mmol, 98.6 mg) provided 69.5 mg (55% yield) of 3as as a colorless oil. Column chromatography (EtOAc/hexanes, 1:1). ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, J = 7.8 Hz, 3H), 7.75 (dd, J = 5.1, 1.9 Hz, 1H), 7.66 – 7.59 (m, 3H), 7.57 – 7.49 (m, 3H), 7.31 – 7.23 (m, 1H), 7.17 (t, J = 7.9 Hz, 1H), 6.75 (dd, J = 7.1, 5.0 Hz, 1H), 6.44 (d, J = 8.3 Hz, 1H), 6.08 (d, J = 8.3 Hz, 1H), 5.20 (d, J = 8.3 Hz, 1H), 4.58 (td, J = 8.6, 4.5 Hz, 1H), 4.44 (q, J = 7.3 Hz, 1H), 3.62 (s, 3H), 3.29 (dd, J = 14.0, 6.6 Hz, 1H), 3.12 (dd, J = 14.0, 6.8 Hz, 1H), 1.68 – 1.53 (m, 3H), 1.40 (s, 9H), 0.97 – 0.83 (m, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 193.5, 193.1, 173.0, 170.4, 161.7, 155.4, 147.9, 146.0, 140.2, 139.7, 139.0, 135.8, 134.2, 134.1, 134.0, 133.2, 132.9, 132.4, 129.9, 129.7, 128.3, 125.1, 125.1, 122.4, 118.9, 110.7, 80.6, 55.3, 52.5, 50.9, 41.5, 37.4, 31.1, 28.3, 24.9, 22.9, 21.9. ¹⁹F NMR (376 MHz, CDCl₃) δ -63.14. IR (cm⁻¹): 3325, 2959, 1666, 1440, 1322, 1240, 1166, 1131, 1109, 1065, 732. HRMS (ESI) m/z: (M⁺) calcd for (C₄₁H₄₁BrF₃N₃O₈): 839.2029, found 839.2071.

**Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-phenylalaninate (3ba).**

Following the general procedure,
using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Tyr(OPy)-Phe-OMe (1b) (0.15 mmol, 77.9 mg) provided 50 mg (49% yield) (8:2 ratio) of 3ba/3’ba. The characterization of the major mono-functionalized peptide 3ba is provided. Colorless oil. 1H NMR (400 MHz, CDCl3) δ 8.00 (dd, J = 5.1, 2.0 Hz, 1H), 7.76 (d, J = 8.9 Hz, 2H), 7.55 (ddd, J = 8.7, 7.2, 2.0 Hz, 1H), 7.38 (dd, J = 8.5, 2.2 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.32 – 7.24 (m, 3H), 7.19 (d, J = 8.3 Hz, 1H), 7.08 (d, J = 6.4 Hz, 2H), 6.89 (dd, J = 6.6, 4.7 Hz, 1H), 6.84 (d, J = 8.9 Hz, 2H), 6.67 (d, J = 8.3 Hz, 1H), 6.51 (d, J = 7.7 Hz, 1H), 5.10 (s, 1H), 4.82 (q, J = 6.0 Hz, 1H), 4.51 – 4.30 (m, 1H), 3.85 (s, 3H), 3.68 (s, 3H), 3.23 – 2.97 (m, 4H), 1.43 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 193.7, 171.5, 170.7, 163.6, 155.4, 150.4, 147.1, 139.5, 135.8, 133.1, 132.8, 132.7, 132.5, 130.9, 130.2, 129.4, 128.7, 127.3, 123.0, 118.6, 113.5, 111.6, 80.5, 55.6, 53.4, 53.3, 52.5, 38.0, 37.6, 28.4. IR (cm⁻¹): 3312, 2970, 1740, 1711, 1658, 1596, 1429, 1385, 1254, 1218, 1168, 908, 728. HRMS (ESI) m/z: (M⁺) calcd for (C₃₇H₃₉N₃O₈): 653.2737, found 653.2771.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-ylxy)phenyl)propanoyl]-L-valinate (3ca). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Tyr(OPy)-Val-OMe (1c) (0.15 mmol, 70.7 mg) provided 60 mg (65% yield) (8:2 ratio) of 3ca/3’ca. The characterization of the major mono-functionalized peptide 3ca is provided. Colorless oil. 1H NMR (400 MHz, CDCl3) δ 7.98 (dd, J = 5.0, 1.9 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.57 – 7.48 (m, 1H), 7.38 (dd, J = 8.3, 2.3 Hz, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.89 – 6.84 (m, 1H), 6.81 (d, J = 8.9 Hz, 2H), 6.65 (d, J = 8.3 Hz, 1H), 6.61 (d, J = 9.2 Hz, 1H), 5.14 (d, J = 8.2 Hz, 1H), 4.48 (dd, J = 8.7, 5.0 Hz, 1H), 4.38 (d, J = 7.5 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.21 – 3.04 (m, 2H), 2.20 – 2.07 (m, 1H), 1.41 (s, 10H), 0.87 (dd, J = 10.1, 6.9 Hz, 7H). 13C NMR (101 MHz, CDCl3) δ 193.6, 172.0, 171.0, 163.6, 163.1, 155.6, 147.0, 139.5, 133.2, 132.8, 132.7, 132.5, 132.2, 130.9, 130.2, 123.0, 118.6, 113.5, 111.7, 80.5, 57.4, 55.7, 55.6, 52.3, 37.2,
Methyl (S)-(2-((tert-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-ylxyloxy)phenyl)propanoyl)glycinate (3da). Following the general procedure in toluene as solvent, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Tyr(OPy)-Gly-OMe (1d) (0.15 mmol, 64.0 mg) provided 53 mg (49% yield) (75:25 ratio) of 3da/3’da. The characterization of the major mono-functionalized peptide 3da is provided. Colorless oil. 1H NMR (400 MHz, CDCl3) δ 7.98 (dd, J = 5.2, 1.9 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.58 – 7.50 (m, 1H), 7.40 (dd, J = 8.3, 2.2 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 6.87 (dd, J = 6.3, 5.0 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.65 (d, J = 8.2 Hz, 2H), 5.18 (d, J = 8.1 Hz, 1H), 4.43 (d, J = 8.2 Hz, 1H), 4.08 – 3.93 (m, 2H), 3.83 (s, 3H), 3.71 (s, 3H), 3.19 – 3.07 (m, 2H), 1.41 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 193.7, 171.4, 170.0, 163.7, 163.1, 155.5, 150.4, 146.9, 139.6, 133.3, 132.9, 132.8, 132.5, 130.9, 130.2, 123.0, 118.6, 113.6, 113.5, 111.7, 80.6, 55.6, 52.5, 41.3, 37.7, 28.40. IR (cm⁻¹): 3315, 2952, 1743, 1660, 1596, 1428, 1255, 1168. HRMS (ESI) m/z: (M⁺) calcd for (C₃₃H₃₉N₃O₈): 605.2737, found 605.2759.

Methyl (S)-2-(((S)-4-amino-2-((tert-butoxycarbonyl)amino)-4-oxobutanamido)-3-(4-(pyridin-2-ylxyloxy)-3-[4-(trifluoromethyl)benzoyl]phenyl)propanoate (3eh). Following the general procedure in toluene as solvent, using commercially available 4-trifluoromethylbenzaldehyde (0.45 mmol, 61 µL) and Boc-Asn-Tyr(OPy)-OMe (1e) (0.15 mmol, 73 mg) provided 39.6 mg and 5 mg of 3eh and 3’eh, respectively (44% yield) (9:1 ratio). The characterization of the major mono-functionalized peptide 3eh is
provided. Column chromatography (EtOAc). White solid. Mp 113-115 ºC. 1H NMR (400 MHz, CDCl3) δ 7.97 (dd, J = 5.1, 1.9 Hz, 1H), 7.80 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.51 (ddd, J = 8.7, 7.2, 1.9 Hz, 1H), 7.48 – 7.28 (m, 3H), 7.19 (d, J = 8.3 Hz, 1H), 6.90 (dd, J = 7.1, 5.1 Hz, 1H), 6.52 (d, J = 8.3 Hz, 1H), 6.18 (d, J = 7.5 Hz, 1H), 5.95 (d, J = 13.8 Hz, 2H), 4.93 – 4.88 (m, 1H), 4.49 – 4.47 (m, 1H), 3.73 (s, 3H), 3.29 (dd, J = 14.1, 5.0 Hz, 1H), 3.04 (dd, J = 14.2, 8.1 Hz, 1H), 2.95 – 2.72 (m, 1H), 2.48 (dd, J = 15.2, 6.1 Hz, 1H), 1.43 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 194.5, 173.4, 171.5, 171.4, 162.53, 155.8, 150.7, 146.7, 140.5, 139.8, 134.0 (q, J C-F = 33.3 Hz), 133.9, 133.1, 131.2 (q, J C-F = 4.0 Hz), 129.9, 125.2, 125.1, 123.6 (q, J C-F = 273.7 Hz), 123.2, 118.9, 111.6, 80.4, 53.2, 52.7, 51.5, 37.3, 36.9, 28.3. 19F NMR (376 MHz, CDCl3) δ -63.07. IR (cm⁻¹): 3320, 3302, 1752, 1685, 1167, 1643, 1466. HRMS (ESI) m/z: (M⁺) calcd for (C₃₂H₃₃F₃N₄O₈): 658.2250, found 658.2255.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(pyridin-2-yloxy)-3-(4-(trifluoromethyl)benzoyl)phenyl)propanoyl]-L-serinate (3fh). Following the general procedure in toluene as solvent, using commercially available 4-trifluoromethylbenzaldehyde (0.75 mmol, 102 µL) and Boc-Tyr(OPy)-Ser-OMe (1f) (0.25 mmol, 138 mg) provided 84 mg and 14 mg of 3fh and 3fh', respectively (60% yield) (9/1 ratio). The characterization of the major mono-functionalized peptide 3fh is provided. Column chromatography (Hexanes/EtOAc 2:8). Yellow oil. 1H NMR (400 MHz, CDCl3) δ 7.96 (dd, J = 5.2, 1.9 Hz, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.60 – 7.40 (m, 5H), 7.20 (d, J = 8.2 Hz, 1H), 7.02 (d, J = 7.4 Hz, 1H), 6.91 (dd, J = 7.2, 5.1 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 5.32 (d, J = 8.0 Hz, 1H), 4.61 – 4.57 (m, 1H), 4.46 (q, J = 6.6 Hz, 1H), 3.92 – 3.91 (m, 2H), 3.73 (s, 3H), 3.29 (dd, J = 13.9, 6.0 Hz, 1H), 3.10 (dd, J = 13.8, 6.2 Hz, 1H), 1.42 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 194.5, 170.9, 170.6, 162.6, 155.6, 150.6, 146.6, 140.4, 140.1, 134.4, 133.8 (q, J C-F = 23.2 Hz), 131.5, 131.4, 129.9, 128.0, 125.2 (q, J C-F = 4.04 Hz), 123.6 (q, J C-F = 273.7 Hz), 123.3, 118.9, 111.7, 80.8, 62.5, 55.7, 54.9, 52.8, 37.5, 28.5, 28.4. 19F NMR (376 MHz, CDCl3) δ -63.11. IR (cm⁻¹): 3302, 1743, 1661, 1594, 1428, 1064. HRMS (ESI) m/z: (M⁺) calcd for (C₃₁H₃₂F₃N₃O₈): 631.2141, found 631.2138.
Dimethyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-ylxy)phenyl)propanoyl]-L-glutamate (3ga). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Tyr(OPy)-Glu(OMe)-OMe (1g) (0.15 mmol, 77.3 mg) provided 50 mg (50% yield) (9:1 ratio) of 3ga/3’ga. The characterization of the major mono-functionalized peptide 3ga is provided. Colorless oil. 1H NMR (400 MHz, CDCl3) δ 8.04 – 7.98 (m, 1H), 7.76 (d, J = 8.9 Hz, 2H), 7.58 – 7.52 (m, 1H), 7.41 (dd, J = 8.4, 2.2 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.19 (d, J = 8.3 Hz, 1H), 6.92 – 6.87 (m, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.82 – 6.76 (m, 1H), 6.67 (d, J = 8.3 Hz, 1H), 5.23 – 5.11 (m, 1H), 4.64 – 4.55 (m, 1H), 4.40 (d, J = 7.7 Hz, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 3.66 (s, 3H), 3.26 – 3.02 (m, 2H), 2.46 – 2.28 (m, 2H), 2.28 – 2.14 (m, 1H), 2.03 – 1.91 (m, 1H), 1.43 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 193.6, 173.3, 171.8, 171.1, 163.6, 163.1, 155.5, 150.4, 147.0, 139.5, 133.1, 132.7, 132.6, 132.5, 130.9, 130.2, 123.0, 118.6, 113.4, 111.6, 80.5, 55.7, 55.6, 52.7, 51.9, 51.8, 37.4, 29.9, 28.3, 27.3. IR (cm⁻¹): 3305, 2953, 1737, 1656, 1595, 1427, 1244, 1165, 730. HRMS (ESI) m/z: (M⁺) calcd for (C₃₄H₃₉N₃O₁₀): 649.2635, found 649.2674.

Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-ylxy)phenyl)propanoyl]-L-tyrosinate (3ha). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Tyr(OPy)-Tyr-OMe (1h) (0.15 mmol, 80.25 mg) provided 51 mg (49% yield) (75:25 ratio) of 3ha/3’ha. The characterization of the major mono-functionalized peptide 3ha is
provided. Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.01 (dd, $J = 5.0, 1.9$ Hz, 1H), 7.74 (d, $J = 8.9$ Hz, 2H), 7.62 – 7.53 (m, 1H), 7.33 (ddd, $J = 8.3, 2.3$ Hz, 1H), 7.30 – 7.26 (m, 1H), 7.11 (d, $J = 8.3$ Hz, 1H), 6.92 (ddd, $J = 7.2, 4.9$ Hz, 1H), 6.88 – 6.80 (m, 4H), 6.68 (ddd, $J = 8.3, 6.0$ Hz, 3H), 6.48 (d, $J = 8.0$ Hz, 1H), 5.00 (d, $J = 8.5$ Hz, 1H), 4.82 – 4.71 (m, 1H), 4.46 – 4.32 (m, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.17 – 2.84 (m, 4H), 1.41 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 193.9, 171.8, 170.7, 163.8, 163.0, 155.6, 155.5, 150.5, 146.9, 139.9, 133.1, 132.6, 132.5, 131.2, 130.3, 130.1, 126.9, 122.5, 118.9, 115.8, 113.6, 113.5, 112.1, 80.5, 55.6, 55.3, 53.3, 52.5, 37.0, 28.4. IR (cm$^{-1}$): 3325, 1749, 1689, 1167, 1643. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{37}$H$_{39}$N$_3$O$_9$): 669.2686, found 669.2711.

**Tert-butyl (S)-2-(((S)-1-methoxy-1-oxo-3-(4-(pyridin-2-yloxy)-3,5-bis(4-(trifluoromethyl)benzoyl)phenyl)propan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (3’ih).**

Following the general procedure in toluene as solvent, using commercially available 4-trifluoromethylbenzaldehyde (0.75 mmol, 102 µL) and Boc-Pro-Tyr(OPy)-OMe (1i) (0.25 mmol, 117 mg) provided 160 mg (79% yield) of 3’ih. Column chromatography (EtOAc/hexanes, 1:1). Yellowish solid. Mp 99-100 ºC. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.82 – 7.70 (m, 4H), 7.69 – 7.61 (m, 3H), 7.49 (d, $J = 8.0$ Hz, 4H), 7.20 (ddd, $J = 8.7, 7.2, 2.0$ Hz, 1H), 6.68 (ddd, $J = 7.1, 5.0$ Hz, 1H), 6.02 (d, $J = 8.3$ Hz, 1H), 5.43 (d, $J = 8.5$ Hz, 1H), 4.76 (dt, $J = 8.6, 6.2$ Hz, 1H), 4.48 (ddd, $J = 8.6, 4.3$ Hz, 1H), 3.70 (dt, $J = 10.2, 3.1$ Hz, 2H), 3.52 (ddd, $J = 10.0, 6.8$ Hz, 1H), 3.41 (s, 3H), 3.25 (ddd, $J = 13.8, 6.2$ Hz, 1H), 3.02 (dd, $J = 13.8, 6.0$ Hz, 1H), 2.21 – 2.05 (m, 1H), 2.05 – 1.85 (m, 3H), 1.34 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 193.5, 172.1, 169.8, 161.6, 155.2, 147.8, 145.9, 140.2, 139.5, 134.4, 134.1, 133.5 (q, $J_{C,F} = 28.3$ Hz), 132.8, 129.9, 125.0 (q, $J_{C,F} = 4.04$ Hz), 123.5 (q, $J_{C,F} = 272.7$ Hz), 118.8, 110.5, 80.0, 58.8, 52.6, 52.1, 47.1, 37.5, 29.0, 28.3, 24.9. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -63.16. IR (cm$^{-1}$): 1744, 1707, 1673, 1643, 1449, 1322, 1064. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{41}$H$_{37}$F$_6$N$_3$O$_8$): 813.2485, found 813.2486.

![Structure of 3’ih](image-url)
Tert-butyl \((S)-2-[(\text{(S)-1-methoxy-3-}(3-(4-methoxybenzoyl)4-(pyridin-2-yloxy)phenyl)-1-oxopropan-2-yl)carbamoyl|pyrrolidine-1-carboxylate\) (3ia). Following the general procedure in toluene as solvent, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Pro-Tyr(OPy)-OMe (1i) (0.15 mmol, 66.5 mg) provided 77 mg (81% yield) (8:2 ratio) of 3ia/3’ia. The characterization of the major mono-functionalized peptide 3ia is provided. Colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.00 (dd, \(J = 5.0, 1.9\) Hz, 1H), 7.75 (d, \(J = 8.8\) Hz, 2H), 7.54 (ddd, \(J = 8.7, 7.2, 2.0\) Hz, 1H), 7.32 (d, \(J = 7.0\) Hz, 1H), 7.25 (d, \(J = 2.0\) Hz, 1H), 7.18 (d, \(J = 8.3\) Hz, 1H), 6.92 – 6.87 (m, 1H), 6.84 (d, \(J = 8.9\) Hz, 2H), 6.66 (d, \(J = 8.3\) Hz, 1H), 4.89 (s, 1H), 4.26 (d, \(J = 29.3\) Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.41 (m, 2H), 3.26 (dd, \(J = 13.9, 5.6\) Hz, 1H), 3.08 (dd, \(J = 14.0, 6.8\) Hz, 1H), 2.06 (s, 2H), 1.80 (s, 2H), 1.45 (s, 9H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 193.4, 171.6, 171.5, 163.5, 162.9, 150.3, 150.3, 146.9, 139.3, 132.5, 132.4, 132.3, 130.5, 130.0, 122.7, 118.5, 113.5, 111.5, 80.4, 61.1, 60.1, 55.4, 53.2, 52.4, 47.0, 37.4, 30.9, 28.2, 24.4, 23.6. IR (cm\(^{-1}\)): 2970, 1742, 1687, 1662, 1596, 1427, 1256, 1167. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{33}\)H\(_{37}\)N\(_3\)O\(_8\)): 603.2581, found 603.2616.

Methyl \((S)-2-[(\text{tert-butoxycarbonyl}amino)propanamido]-3-(4-(pyridin-2-yloxy)-3-(4-(trifluoromethyl)benzoyl)phenyl)propanoate\) (3jh). Following the general procedure in toluene as solvent, using commercially available 4-trifluoromethylbenzaldehyde (0.45 mmol, 61 µL) and Boc-Ala-Tyr(OPy)-OMe (1j) (0.15 mmol, 66 mg) provided 54 mg and 19.5 mg of 3jh and 3jh’, respectively, 74% yield (8:2 ratio). The characterization of the major mono-functionalized peptide 3jh is provided. Column chromatography (EtOAc/hexanes, 1:1). Colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.97 (dd, \(J = 5.0, 1.9\) Hz, 1H), 7.78 (d, \(J = 8.1\) Hz, 2H), 7.58 – 7.40 (m, 3H), 7.38 – 7.28 (m, 2H), 7.18 (d, \(J = 8.3\) Hz, 1H), 6.93 – 6.76 (m, 2H), 6.48 (d, \(J = 8.2\) Hz,
1H), 5.23 (d, J = 7.5 Hz, 1H), 4.87 (t, J = 6.7 Hz, 1H), 4.17 (t, J = 7.6 Hz, 1H), 3.71 (s, 3H), 3.27 (dd, J = 13.9, 5.7 Hz, 1H), 3.10 (dd, J = 13.9, 6.2 Hz, 1H), 1.40 (s, 9H), 1.32 (d, J = 7.2 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 194.4, 172.6, 171.6, 162.5, 155.7, 150.8, 146.8, 140.6, 139.7, 134.1 (q, J C−F = 20.2 Hz), 133.0, 131.3, 125.1 (q, J C−F = 4.04 Hz), 124.5 (q, J C−F = 272.7 Hz), 123.2, 118.9, 111.5, 80.2, 53.1, 52.6, 50.2, 37.3, 28.3, 18.0. 19F NMR (376 MHz, CDCl3) δ -63.10. IR (cm⁻¹): 3304, 1742, 1711, 1666, 1428, 1324. HRMS (ESI) m/z: (M⁺) calcd for (C₃₁H₃₂F₃N₃O₇): 615.2192, found 615.2201.

Methyl (S)-2-[(S)-6-(((benzyloxy)carbonyl)amino)-2-((tert-butoxycarbonyl)amino) hexanamido]-3-[3-(4-methoxybenzoyl)-4-(pyridin-2-yl)oxy)phenyl]propanoate (3ka). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Lys(Cbz)-Tyr(OPy)-OMe (1k) (0.15 mmol, 95.1 mg) provided 65 mg (61% yield) of 3ka as a colorless oil. 1H NMR (400 MHz, CDCl3) δ 8.02 (dd, J = 5.1, 1.9 Hz, 1H), 7.75 (d, J = 8.9 Hz, 2H), 7.58 – 7.51 (m, 1H), 7.41 – 7.27 (m, 6H), 7.23 (d, J = 2.2 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 6.93 – 6.85 (m, 2H), 6.82 (d, J = 8.9 Hz, 2H), 6.64 (d, J = 8.2 Hz, 1H), 5.39 (d, J = 8.0 Hz, 1H), 5.14 (s, 1H), 5.10 (s, 2H), 4.97 – 4.86 (m, 1H), 4.18 – 4.04 (m, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.31 – 3.01 (m, 4H), 2.19 (s, 1H), 1.82 (d, J = 11.1 Hz, 1H), 1.64 – 1.47 (m, 2H), 1.43 (s, 9H), 1.39 – 1.30 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 193.8, 172.0, 171.7, 163.7, 162.9, 156.7, 155.9, 150.4, 147.0, 139.6, 136.7, 132.7, 132.5, 130.9, 130.1, 128.6, 128.2, 128.1, 122.9, 118.7, 113.5, 111.7, 80.1, 66.7, 55.6, 54.4, 53.1, 52.6, 40.4, 37.2, 31.7, 29.4, 28.4, 22.5. IR (cm⁻¹): 3322, 2935, 1702, 1657, 1595, 1508, 1427, 1242, 1166, 729. HRMS (ESI) m/z: (M⁺) calcd for (C₄₂H₄₈N₄O₁₀): 768.3370, found 768.3398.
Methyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-isoleucyl-L-leucinate (3la). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Tyr(OPy)-Ile-Leu-OMe (1l) (0.15 mmol, 89.8 mg) provided 70 mg (62% yield) (85:15 ratio) of 3la/3'la. The characterization of the major mono-functionalized peptide 3la is provided. Colorless oil. \( ^1 \)H NMR (400 MHz, CDCl₃) \( \delta \) 8.01 (dd, \( J = 5.0, 1.9 \) Hz, 1H), 7.76 (dd, \( J = 8.8 \) Hz, 2H), 7.54 (dd, \( J = 8.7, 7.2, 2.0 \) Hz, 1H), 7.42 – 7.32 (m, 2H), 7.18 (d, \( J = 8.2 \) Hz, 1H), 6.89 (dd, \( J = 7.2, 4.9 \) Hz, 2H), 6.86 – 6.79 (m, 2H), 6.66 (d, \( J = 8.3 \) Hz, 1H), 5.26 (d, \( J = 7.7 \) Hz, 1H), 4.63 – 4.51 (m, 1H), 4.48 – 4.38 (m, 1H), 4.39 – 4.29 (m, 1H), 3.84 (s, 3H), 3.72 (s, 3H), 3.19 (dd, \( J = 14.2, 5.4 \) Hz, 1H), 3.08 (dd, \( J = 14.2, 7.9 \) Hz, 1H), 2.42 (s, 1H), 1.96 – 1.84 (m, 1H), 1.73 – 1.46 (m, 4H), 1.40 (s, 9H), 1.00 – 0.84 (m, 12H). \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta \) 193.6, 173.1, 171.2, 170.8, 163.6, 163.0, 155.7, 150.4, 147.0, 139.5, 133.2, 132.6, 132.6, 132.5, 130.9, 130.2, 122.9, 118.6, 113.4, 111.7, 80.5, 57.9, 55.7, 55.5, 52.3, 50.9, 41.2, 37.4, 37.0, 28.3, 24.9, 22.8, 22.0, 15.4, 11.4. IR (cm\(^{-1}\)): 3270, 2960, 1641, 1597, 1427, 1253, 1167. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{40}\)H\(_{52}\)N\(_4\)O\(_9\)): 732.3734, found 732.3769.

Methyl [(S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanamido)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-leucinate (3ma). Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.30 mmol, 36.7 µL) and Boc-Phe-Tyr(OPy)-Leu-OMe (1m) (0.10 mmol, 63.0 mg)
provided 44 mg (57% yield) of 3ma as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.96 (dd, $J = 5.1$, 1.9 Hz, 1H), 7.74 (d, $J = 8.8$ Hz, 2H), 7.52 (ddd, $J = 8.5$, 7.2, 2.0 Hz, 1H), 7.32 (dd, $J = 8.3$, 2.3 Hz, 1H), 7.26 (d, $J = 1.8$ Hz, 2H), 7.23 – 7.11 (m, 5H), 6.87 (dd, $J = 6.6$, 5.0 Hz, 1H), 6.81 (d, $J = 8.9$ Hz, 2H), 6.62 (d, $J = 8.3$ Hz, 2H), 6.47 (d, $J = 6.9$ Hz, 1H), 5.14 (d, $J = 7.2$ Hz, 1H), 4.74 – 4.63 (m, 1H), 4.56 – 4.46 (m, 1H), 4.34 (q, $J = 7.0$ Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.19 – 3.02 (m, 3H), 3.00 – 2.89 (m, 1H), 1.64 – 1.46 (m, 3H), 1.34 (s, 9H), 0.89 (d, $J = 5.7$ Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 193.5, 172.8, 171.4, 170.1, 163.7, 163.0, 155.8, 150.2, 146.7, 139.8, 136.6, 133.2, 132.9, 132.8, 132.5, 131.0, 130.2, 129.4, 128.8, 127.1, 123.0, 118.6, 113.5, 111.8, 80.5, 56.2, 55.6, 53.9, 52.4, 51.1, 41.2, 37.9, 37.1, 28.3, 24.8, 22.9, 22.0. IR (cm$^{-1}$): 3295, 2959, 1646, 1597, 1428, 1254, 1168. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{43}$H$_{50}$N$_4$O$_9$): 766.3578, found 766.3611.

Methyl [(S)-2-((S)-5-amino-2-((tert-butoxycarbonyl)amino)-5-oxopentanamido)-3-(4-(pyridin-2-yloxy)-3-(4-(trifluoromethyl)benzoyl)phenyl)propanoyl]-L-leucinate (3nh). Following the general procedure in toluene as solvent, using commercially available 4-trifluoromethylbenzaldehyde (0.45 mmol, 61 µL) and Boc-Gln-Tyr(OPy)-Leu-OMe (1n) (0.15 mmol, 92 mg) provided 50 mg and 12 mg of 3nh and 3’nh, respectively, 48% yield (8:2 ratio). The characterization of the major monofunctionalized peptide 3nh is provided. Column chromatography (EtOAc). Yellow solid. Mp 142-143 ºC. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.97 (dd, $J = 5.1$, 1.8 Hz, 1H), 7.79 (d, $J = 8.1$ Hz, 2H), 7.63 – 7.39 (m, 6H), 7.17 (d, $J = 8.4$ Hz, 1H), 7.02 (t, $J = 6.3$ Hz, 1H), 6.91 (dd, $J = 7.1$, 5.1 Hz, 1H), 6.73 (s, 1H), 6.55 (d, $J = 8.3$ Hz, 1H), 6.05 (s, 1H), 5.98 (d, $J = 6.6$ Hz, 1H), 4.88 (td, $J = 8.1$, 5.7 Hz, 1H), 4.57 – 4.45 (m, 1H), 4.14 (d, $J = 7.4$ Hz, 1H), 3.67 (s, 3H), 3.28 (dd, $J = 14.5$, 5.5 Hz, 1H), 3.10 (dd, $J = 14.4$, 7.9 Hz, 1H), 2.48 – 2.18 (m, 3H), 2.11 (dt, $J = 15.6$, 6.2 Hz, 1H), 2.03 – 1.99 (m, 2H), 1.68 – 1.48 (m, 3H), 1.39 (s, 9H), 0.88 (q, $J = 2.9$ Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 193.6, 175.5, 173.2, 172.2, 170.5, 161.7, 156.2, 147.9, 145.8, 140.0, 139.9, 134.5, 134.1, 134.0, 133.1, 129.9,
128.0, 125.2 (q, $J_{CF} = 3.03$ Hz), 123.5 (q, $J_{CF} = 273.7$ Hz), 119.1, 110.7, 80.4, 54.2, 54.0, 52.4, 51.2, 41.1, 36.9, 31.4, 29.8, 28.4, 28.0, 26.5, 24.9, 22.8, 21.9. $^{19}$F NMR (376 MHz, CDCl₃) $\delta$ -63.16. IR (cm⁻¹): 3304, 1742, 1666, 1639, 1594, 1428. HRMS (ESI) m/z: (M⁺) calcd for (C₃⁹H₄₆F₃N₅O₉): 785.3248, found 785.3251.

**Dimethyl [(S)-2-((tert-butoxycarbonyl)amino)-3-(3-(4-methoxybenzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl]-L-leucyl-L-phenylalanyl-L-glutamate (3oa).** Following the general procedure, using commercially available 4-methoxybenzaldehyde (0.45 mmol, 55.1 µL) and Boc-Tyr(OPy)-Leu-Phe-Glu(OMe)-OMe (1o) (0.10 mmol, 77.5 mg) provided 60 mg (64% yield) (8:2 ratio) of 3oa/3’oa. The characterization of the major mono-functionalized peptide 3oa is provided. Colorless oil. $^1$H NMR (400 MHz, CDCl₃) $\delta$ 8.02 (dd, $J = 5.0, 1.9$ Hz, 1H), 7.76 (d, $J = 8.8$ Hz, 2H), 7.62 – 7.54 (m, 1H), 7.38 (dd, $J = 8.2, 2.3$ Hz, 1H), 7.35 (d, $J = 2.1$ Hz, 1H), 7.29 – 7.14 (m, 6H), 7.06 – 6.96 (m, 1H), 6.92 (dd, $J = 7.1, 4.6$ Hz, 2H), 6.84 (d, $J = 8.9$ Hz, 2H), 6.69 (dd, $J = 13.2, 7.5$ Hz, 2H), 5.20 (d, $J = 6.5$ Hz, 1H), 4.85 – 4.72 (m, 1H), 4.61 – 4.52 (m, 1H), 4.40 – 4.26 (m, 2H), 3.85 (s, 3H), 3.72 (s, 3H), 3.63 (s, 3H), 3.27 (dd, $J = 14.3, 5.7$ Hz, 1H), 3.14 (dd, $J = 14.3, 5.5$ Hz, 1H), 3.08 – 2.93 (m, 2H), 2.43 – 2.30 (m, 2H), 2.26 – 2.13 (m, 1H), 2.06 – 1.95 (m, 1H), 1.62 – 1.43 (m, 3H), 1.41 (s, 9H), 0.85 (dd, $J = 12.6, 5.6$ Hz, 6H). $^{13}$C NMR (101 MHz, CDCl₃) $\delta$ 193.5, 173.3, 172.0, 171.7, 171.6, 169.9, 163.7, 162.8, 156.2, 150.4, 146.6, 139.9, 136.9, 132.8, 132.6, 132.5, 130.8, 130.1, 129.2, 128.7, 128.6, 126.9, 123.0, 118.7, 113.5, 111.9, 81.0, 56.1, 55.6, 54.0, 52.8, 52.6, 51.9, 51.8, 40.6, 37.5, 36.8, 30.1, 28.3, 27.2, 24.7, 22.9, 21.9. IR (cm⁻¹): 3376, 2969, 1739, 1638, 1428, 1255, 1215, 1168. HRMS (ESI) m/z: (M⁺) calcd for (C₄₀H₅₀N₅O₁₂): 909.4160, found 909.4187.
Methyl \( [(S)-2-((\text{tert}-\text{butoxycarbonyl})\text{amino})-3-(4-(\text{pyridin-2-yloxy})-3-(4-(\text{trifluoromethyl})\text{benzoyl})\text{phenyl})\text{propanoyl})-L-\text{prolyl}-L-\text{phenylalanyl}-L-\text{phenylalaninate} \ (3\text{ph}) \). Following the general procedure in toluene as solvent, using commercially available 4-trifluoromethylbenzaldehyde (0.45 mmol, 61 µL) and Boc-Tyr(OPy)-Pro-Phe-Phe-OMe \( (1p) \) (0.15 mmol, 114 mg) provided 67 mg and 21 mg of 3ph and 3’ph, respectively, 61% yield (8:2 ratio). The characterization of the major monofunctionalized peptide 3ph is provided. Column chromatography (EtOAc/hexanes, 8:2). Yellow solid. Mp 97-98 ºC. \(^1\text{H} \) NMR (500 MHz, DMSO-\( d_6 \) at 80 ºC) \( \delta \) 8.01 – 7.91 (m, 2H), 7.82 (d, \( J = 8.1 \) Hz, 2H), 7.71 (d, \( J = 8.2 \) Hz, 2H), 7.68 – 7.44 (m, 3H), 7.36 – 7.10 (m, 10H), 6.98 (dd, \( J = 7.1, 4.9 \) Hz, 1H), 6.61 (d, \( J = 8.4 \) Hz, 1H), 4.63 – 4.43 (m, 3H), 4.46 – 4.24 (m, 1H), 3.57 (s, 3H), 3.14 – 2.77 (m, 9H), 1.97 – 1.74 (m, 3H), 1.32 (s, 9H). \(^{13}\text{C} \) NMR (126 MHz, DMSO-\( d_6 \) at 80 ºC) 193.1, 170.9, 170.5, 170.2, 169.8, 161.9, 154.5, 149.5, 146.3, 140.3, 139.3, 137.2, 136.6, 134.1, 132.0 (q, \( J_{\text{C-F}} = 37.8 \) Hz), 130.4, 130.1, 129.3, 128.6, 128.6, 128.5, 128.4, 127.7, 127.5, 126.0, 125.6, 124.7 (q, \( J_{\text{C-F}} = 3.78 \) Hz), 124.7 (q, \( J_{\text{C-F}} = 273.4 \) Hz), 122.0, 118.5, 110.5, 77.9, 59.4, 53.2, 53.1, 53.0, 51.1, 37.0, 36.8, 36.6, 35.8, 28.0, 27.7, 23.9. \(^{19}\text{F} \) NMR (376 MHz, CDCl\(_3\)) \( \delta \) -63.14. IR (cm\(^{-1}\)): 3303, 1742, 1645, 1593, 1428, 1164. HRMS (ESI) \( m/z \): (M\(^+\)) \( \text{caldc} \) for \( \text{C}_{39}\text{H}_{52}\text{F}_{3}\text{N}_{5}\text{O}_{9} \): 935.3717, \( \text{found} \) 935.3725.
Methyl ((S)-2-((S)-1-((N^2,N^6)-bis(tert-butoxycarbonyl)-L-lysyl-L-isoleucyl)pyrrolidine-2-carboxamido)-3-(4-(pyridin-2-ylxy)-3-(4-(trifluoromethyl)benzoyl)phenyl)propanoyl)-L-isoleucyl-L-leucinate (3qh). Following the general procedure in toluene as solvent, using commercially available 4-trifluoromethylbenzaldehyde (0.45 mmol, 61 µL) and Boc-Lys(Boc)-Ile-Pro-Tyr(OPy)-Ile-Leu-OMe (1q) (0.15 mmol, 155 mg) provided 81.2 mg and 27.6 mg of 3qh and 3’qh, respectively, 58% yield (8:2 ratio). The characterization of the major mono-functionalized peptide 3qh is provided. Column chromatography (EtOAc/hexanes, 8:2). Yellow solid. Mp 107-108 °C. \(^1\)H NMR (500MHz, DMSO-\(\text{d}_6\)) \(\delta\) 8.30 (d, \(J = 7.3\) Hz, 1H), 7.99 – 7.90 (m, 2H), 7.69 – 7.60 (m, 2H), 7.54 (dd, \(J = 8.4, 2.2\) Hz, 1H), 7.47 (d, \(J = 2.2\) Hz, 1H), 7.14 (d, \(J = 8.3\) Hz, 1H), 6.99 (dd, \(J = 7.2, 5.0\) Hz, 1H), 6.87 (d, \(J = 8.5\) Hz, 1H), 6.72 (t, \(J = 5.6\) Hz, 1H), 6.61 (d, \(J = 8.3\) Hz, 1H), 4.59 (td, \(J = 8.3, 5.1\) Hz, 1H), 4.38 – 4.28 (m, 2H), 4.27 – 4.14 (m, 2H), 3.87 (q, \(J = 3.9\) Hz, 1H), 3.66 (d, \(J = 1.5\) Hz, 1H), 3.58 (s, 3H), 3.54 (t, \(J = 6.7\) Hz, 1H), 3.05 (dd, \(J = 14.0, 5.0\) Hz, 1H), 2.90 – 2.82 (m, 3H), 2.04 – 1.86 (m, 1H), 1.86 – 1.63 (m, 5H), 1.64 – 1.40 (m, 7H), 1.36 (s, 9H), 1.35 (s, 9H), 1.09 – 0.97 (m, 2H), 0.93 – 0.69 (m, 18H). \(^{13}\)C NMR (126 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 193.7, 172.7, 171.9, 171.3, 171.0, 170.4, 170.0, 162.2, 155.5, 155.3, 149.7, 146.7, 140.5, 140.0, 134.5, 133.9, 132.1 (q, \(J_{C,F} = 25.2\) Hz), 130.7, 130.6, 129.9, 125.2 (q, \(J_{C,F} = 3.8\) Hz), 123.7 (q, \(J_{C,F} = 273.4\) Hz), 122.5, 118.9, 110.8, 78.0, 77.3, 59.3, 56.4, 54.4, 54.2, 53.6, 51.7, 50.2, 47.1, 37.0, 36.6, 36.3, 31.5, 29.1, 29.0, 28.3, 28.1, 24.2, 24.2, 24.1, 24.0, 23.9, 22.8, 22.6, 21.3, 21.2, 15.0, 15.0, 10.9, 10.9, 10.6. \(^{19}\)F NMR (376 MHz, DMSO-\(\text{d}_6\)) \(\delta\) -63.4. IR (cm\(^{-1}\)): 3273, 1744, 1639, 1594, 1428, 1164. HRMS (ESI) m/z: (M\(^+\)) calcd for (C\(_{62}\)H\(_{87}\)F\(_3\)N\(_8\)O\(_{13}\)): 1208.6345, found 1208.6345.
Chemical Ligation (Table 4)

Methyl \( \{(S)-2-((\text{tert-butoxycarbonyl})amino)-3-(3-(4-(\text{(S)-2-(\text{tert-butoxycarbonyl})amino)-3-((\text{(S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl})phenoxy)benzoyl)-4-(\text{pyridin-2-yloxy})phenyl)propanoyl\}-L-leucinate \) (3at).

Following the general procedure in toluene, using aldehyde 2t (0.45 mmol, 246 mg) and Boc-Tyr(OPy)-Leu-OMe (1a) (0.15 mmol, 73.0 mg) provided 92 mg (60% yield) of 3at as a colorless oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.99 (dd, \( J = 5.1, 1.9 \) Hz, 1H), 7.56 (ddd, \( J = 8.7, 7.4, 2.0 \) Hz, 1H), 7.47 – 7.38 (m, 3H), 7.30 – 7.23 (m, 4H), 7.22 – 6.99 (m, 7H), 6.95 – 6.81 (m, 3H), 6.67 (d, \( J = 8.3 \) Hz, 1H), 6.54 (s, 1H), 6.42 (d, \( J = 7.7 \) Hz, 1H), 5.17 (d, \( J = 8.3 \) Hz, 1H), 5.03 (t, \( J = 8.1 \) Hz, 1H), 4.90 – 4.77 (m, 1H), 4.60 (td, \( J = 8.5, 4.4 \) Hz, 1H), 4.48 – 4.25 (m, 2H), 3.70 (s, 6H), 3.21 – 2.91 (m, 6H), 1.69 – 1.52 (m, 3H), 1.43 (s, 9H), 1.40 (s, 9H), 0.98 – 0.87 (m, 6H). \(^1\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 194.1, 171.5, 171.3, 170.8, 170.7, 162.8, 156.9, 155.7, 155.4, 155.3, 155.2, 150.5, 146.9, 139.3, 139.1, 135.5, 133.2, 133.2, 131.0, 130.7, 129.3, 129.2, 129.1, 128.6, 128.5, 127.1, 127.1, 125.1, 123.1, 122.9, 119.6, 119.8, 115.8, 115.3, 80.3, 80.2, 55.6, 55.3, 53.2, 52.3, 50.7, 41.4, 37.9, 37.5, 37.1, 28.2, 24.6, 22.7, 21.8. IR (cm\(^{-1}\)): 3304, 2957, 1742, 1656, 1505, 1429, 1243, 1167, 732. HRMS (ESI) m/z: (M\(^+\)) \text{calcd} \text{ for (C}_{57}\text{H}_{67}\text{N}_{5}\text{O}_{13}): 1029.4735, \text{found} 1029.4761.
Methyl ([S]-2-((tert-butoxycarbonyl)amino)-3-(3-(4-((S)-2-((tert-butoxycarbonyl)amino)-3-((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl)phenoxy)benzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl-L-leucinate (3as). Following the general procedure in toluene, using aldehyde 2s (0.45 mmol, 224 mg) and Boc-Tyr(OPy)-Leu-OMe (1a) (0.15 mmol, 73.0 mg) provided 76 mg (52% yield) of 3as as a white solid.

Mp 109 - 110 °C. 1H NMR (400 MHz, CDCl3) δ 7.97 (d, J = 4.9 Hz, 1H), 7.55 (t, J = 7.9 Hz, 1H), 7.50 – 7.35 (m, 4H), 7.34 – 7.23 (m, 1H), 7.23 – 7.15 (m, 3H), 7.10 (d, J = 8.3 Hz, 1H), 6.87 (dd, J = 12.1, 7.3 Hz, 3H), 6.66 – 6.53 (m, 3H), 4.66 – 4.53 (m, 1H), 4.53 – 4.22 (m, 3H), 3.70 (s, 3H), 3.68 (s, 3H), 3.27 – 2.94 (m, 4H), 2.16 – 2.13 (m, 2H), 1.70 – 1.49 (m, 3H), 1.42 (s, 9H), 1.41 (s, 9H), 0.96 – 0.78 (m, 12H). 13C NMR (126 MHz, CDCl3) δ 194.2, 173.0, 171.9, 171.3, 170.9, 163.0, 157.1, 155.9, 155.5, 150.6, 147.0, 139.5, 139.3, 133.4, 131.9, 131.2, 130.8, 130.8, 129.5, 125.2, 123.2, 123.0, 119.7, 119.0, 119.0, 118.6, 111.5, 80.3, 57.3, 56.0, 55.3, 52.4, 52.2, 50.9, 41.5, 37.4, 31.3, 28.4, 28.3, 24.8, 22.9, 21.9, 18.9, 17.9. IR (cm⁻¹): 3305, 1741, 1654, 1580, 1241, 1607. HRMS (ESI) m/z: (M⁺) calcd for (C₅₃H₆₇N₅O₁₃): 981.4735, found 981.4735.

Methyl ([S]-2-((tert-butoxycarbonyl)amino)-3-(3-(4-((S)-2-((tert-butoxycarbonyl)amino)-3-((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl)phenoxy)benzoyl)-4-(pyridin-2-yloxy)phenyl)propanoyl-L-leucinate (3as)
phenoxy)benzoyl)-4-(pyridin-2-yloxy)phenylpropanoyl]-L-valinate (3ct). Following the general procedure in toluene, using aldehyde 2t (0.45 mmol, 246 mg) and Boc-
Tyr(OPy)-Val-OMe (1c) (0.15 mmol, 71.0 mg) provided 89 mg (58% yield) of 3ct as a white solid. Mp 102 – 103 °C. 1H NMR (500 MHz, CDCl3) δ 7.98 (d, J = 4.9 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.51 – 7.37 (m, 4H), 7.32 – 6.99 (m, 11H), 6.86 (tt, J = 14.1, 7.1 Hz, 3H), 6.67 (t, J = 9.0 Hz, 2H), 6.45 (d, J = 7.6 Hz, 1H), 5.24 (d, J = 8.1 Hz, 1H), 5.05 (d, J = 9.1 Hz, 1H), 4.82 (dt, J = 20.2, 6.8 Hz, 1H), 4.60 – 4.20 (m, 3H), 3.69 (s, 6H), 3.20 – 2.94 (m, 6H), 2.25 – 2.09 (m, 3H), 1.42 (s, 9H), 1.41 (s, 9H), 1.35 – 1.22 (m, 1H), 0.89 (dd, J = 13.0, 6.8 Hz, 6H). 13C NMR (126 MHz, CDCl3) δ 194.5, 172.2, 171.9, 171.8, 171.3, 171.2, 163.2, 157.4, 156.1, 150.9, 147.2, 139.8, 139.6, 139.2, 136.0, 133.7, 133.6, 132.2, 132.1, 131.4, 131.1, 129.7, 129.6, 129.5, 129.0, 128.9, 127.5, 125.4, 123.5, 123.3, 119.9, 119.3, 118.7, 111.8, 80.7, 80.6, 57.6, 53.6, 53.5, 52.7, 52.5, 38.31, 38.2, 37.9, 37.4, 31.6, 28.6, 28.5, 19.2, 18.1. IR (cm⁻¹): 3306, 1740, 1655, 1580, 1427, 1240, 1160. HRMS (ESI) m/z: (M⁺) calcd for (C₅₆H₆₅N₅O₁₃): 1015.4579, found 1015.4579.

Methyl (S)-3-[3-(3-(4-(((S)-2-(((tert-butoxycarbonyl)amino)-3-(((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-oxopropyl)phenoxy)benzoyl)-4-(pyridin-2-yloxy)phenyl]-2-[((S)-2-((tert-butoxycarbonyl)amino)propanamido]propanoate (3jt). Following the general procedure in toluene, using aldehyde 2t (0.45 mmol, 246 mg) and Boc-Ala-Tyr(OPy)-OMe (1j) (0.15 mmol, 66.0 mg) provided 96 mg (65% yield) of 3jt as a white solid. Mp 93 – 94 °C. 1H NMR (500 MHz, CDCl3) δ 8.00 (d, J = 4.9 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.50 – 7.38 (m, 2H), 7.33 (d, J = 8.3 Hz, 1H), 7.31 – 7.20 (m, 5H), 7.20 – 6.95 (m, 6H), 6.91 (t, J = 6.1 Hz, 1H), 6.85 (d, J = 8.0 Hz, 3H), 6.64 (d, J = 8.2 Hz, 1H), 5.26 (s, 1H), 5.01 (s, 1H), 4.90 – 4.79 (m, 2H), 4.38 – 4.35 (m 2H), 3.73 (s, 3H), 3.69 (s, 3H), 3.25 (dd, J = 14.1, 5.8 Hz, 1H), 3.14 – 2.92 (m, 5H), 1.43 (s, 9H), 1.42 (s, 9H), 1.33 (d, J = 7.1 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 194.4, 172.6, 171.7, 171.6, 171.5, 171.0, 170.8, 162.8, 157.1, 155.9, 150.7, 147.0, 139.6, 139.3, 135.8,
Methyl \((\text{S})-2-((\text{tert}-\text{butoxycarbonyl})\text{amino})-3-(3-(3-(4-(\text{S})-2-((\text{tert}-\text{butoxycarbonyl})\text{amino})-3-((\text{(S)}-1-\text{methoxy}-1-\text{oxo}-3-\text{phenylpropan-2-yl})\text{amino})-3-\text{oxopropyl})\text{phenoxy})\text{benzoyl})-4-(\text{pyridin-2-ylxylo})\text{phenyl}\text{propanoyl})-\text{L-}\text{isoleucyl-L-leucinate}\) (3jt). Following the general procedure in toluene, using aldehyde 2t (0.45 mmol, 246 mg) and Boc-Ala-Tyr(OPy)-Ile-Leu-OMe (1l) (0.15 mmol, 90.0 mg) provided 106 mg (62% yield) of 3jt as a white solid. Mp 111 – 112 °C. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.97 (d, $J = 4.8$ Hz, 1H), 7.55 (t, $J = 7.9$ Hz, 1H), 7.51 – 7.35 (m, 4H), 7.33 – 7.19 (m, 5H), 7.17 – 7.01 (m, 6H), 6.87 (dd, $J = 21.2$, 7.0 Hz, 3H), 6.77 – 6.56 (m, 2H), 5.30 (t, $J = 9.3$ Hz, 1H), 5.19 – 5.05 (m, 1H), 4.86 – 4.81 (m, 1H), 4.59 – 4.55 (m, 1H), 4.54 – 4.38 (m, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.25 – 2.76 (m, 6H), 2.32 (s, 2H), 1.88 (s, 1H), 1.76 – 1.48 (m, 4H), 1.41 (s, 9H), 1.39 (s, 9H), 1.15 – 1.10 (m, 1H), 0.90 – 0.88 (m, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 194.0, 172.9, 171.7, 171.5, 171.1, 170.9, 170.7, 162.8, 162.7, 156.9, 155.7, 155.6, 155.5 155.2, 150.5, 150.4, 146.8, 146.8, 139.3, 139.1, 135.6, 135.5, 133.4, 133.2, 133.0, 131.9, 131.8, 131.0, 130.7, 129.3, 129.1, 129.0, 128.5, 128.4, 127.1, 127.0, 125.0, 123.1, 123.0, 122.9, 119.5, 118.8, 118.5, 111.3, 80.3, 80.1, 57.8, 55.5, 53.2, 53.1, 52.2, 52.1, 50.8, 41.0, 37.9, 37.6, 37.2, 28.9, 28.1, 24.7, 22.6, 21.8, 15.1, 11.2. IR (cm$^{-1}$): 3288, 1743, 1645, 1505, 1240, 1161. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{63}$H$_{78}$N$_6$O$_{14}$): 1142.5576, found 1142.5576.
Methyl (S)-3-[3-(3-(4-((S)-2-(((S)-2-(((S)-2-(tert-butoxycarbonyl)amino)-3-oxopropyl)phenoxy)benzoyl)-4-(pyridin-2-yloxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanamido)propanoate (3qt).

Following the general procedure in toluene, using aldehyde 2t (0.45 mmol, 246 mg) and Boc-Lys(Boc)-Ile-Pro-Tyr(OPy)-Ile-Leu-OMe (1q) (0.15 mmol, 155.0 mg) provided 79 mg (33% yield) of 3qt as a white solid. Mp 68 – 70 °C. 1H NMR (500 MHz, DMSO-d6 at 80 ºC) δ 8.18 – 7.89 (m, 4H), 7.68 (t, J = 7.7 Hz, 3H), 7.57 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 7.5 Hz, 5H), 7.33 – 7.07 (m, 11H), 7.00 (t, J = 6.3 Hz, 1H), 6.91 – 6.79 (m, 2H), 6.64 (d, J = 8.3 Hz, 1H), 6.51 (s, 1H), 6.29 (s, 1H), 4.61 (dt, J = 14.4, 6.9 Hz, 2H), 4.43 – 4.21 (m, 6H), 3.91 (d, J = 7.1 Hz, 1H), 3.73 – 3.65 (m, 1H), 3.64 (d, J = 1.8 Hz, 2H), 3.60 (d, J = 2.2 Hz, 5H), 3.52 (s, 1H), 3.14 (dd, J = 14.5, 5.1 Hz, 2H), 3.01 – 2.59 (m, 7H), 2.05 – 1.72 (m, 8H), 1.38 (s, 27H), 1.15 – 1.07 (m, 3H), 0.90 – 0.78 (m, 21H). 13C NMR (126 MHz, DMSO-d6 at 80 ºC) δ 193.2, 172.0, 171.4, 171.1, 171.0, 170.9, 170.8, 170.3, 169.8, 169.8, 162.0, 156.5, 155.1, 154.7, 154.3, 154.2, 149.3, 146.4, 139.3, 138.8, 136.6, 133.9, 133.0, 132.5, 130.9, 130.3, 129.7, 129.3, 128.6, 128.5, 127.7, 126.0, 124.1, 122.2, 121.6, 118.4, 117.9, 117.8, 117.7, 110.6, 77.9, 77.8, 76.9, 59.2, 56.4, 54.4, 54.2, 54.0, 53.3, 53.0, 52.9, 51.2, 51.2, 51.0, 50.0, 46.6, 36.7, 36.6, 36.2, 36.0, 31.1, 28.8, 28.3, 27.9, 27.7, 27.7, 23.8, 23.8, 23.6, 22.3, 22.1, 21.0, 14.8, 14.7, 10.5, 10.1. IR (cm⁻¹): 3304, 1743, 1647, 1390, 1241, 1162. HRMS (ESI) m/z: (M⁺) calcd for (C₈₅H₁₁₆N₁₀O₉): 1580.8418, found 1580.8418.
5.-Ni-Catalyzed Reductive Cleavage

**General Procedure:** A reaction tube containing a stirring bar was charged with peptide 3′ih (0.25 mmol, 204 mg), NiCl$_2$·DME (10 mol %, 5.5 mg), PCy$_3$·HBF$_4$ (20 mol %, 18 mg), B$_2$(nep)$_2$ (0.50 mmol, 113 mg) and K$_3$PO$_4$ (0.27 mmol, 175 mg). The reaction tube was then evacuated and back-filled with dry argon (this sequence was repeated up to three times). Then, dry 1,2-dimethoxyethane (1 mL) was added by syringe under argon atmosphere. The reaction tube was next warmed up to 100 ºC in a heating block and stirred for 16 hours. The mixture was then allowed to warm to room temperature, filtered off through a pad of celite and evaporated under vacuum. The resulting crude was then purified by column chromatography (EtOAc/hexanes, 4:6) to afford 75.2 mg (42% yield) of 4.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.04 (d, $J$ = 1.7 Hz, 1H), 7.99 – 7.88 (m, 4H), 7.78 (t, $J$ = 8.5 Hz, 3H), 5.26 (d, $J$ = 8.6 Hz, 1H), 4.75 (dd, $J$ = 8.6, 6.1 Hz, 1H), 4.52 (dd, $J$ = 8.6, 3.7 Hz, 1H), 3.78 – 3.41 (m, 4H), 3.30 (dd, $J$ = 13.8, 6.4 Hz, 1H), 3.05 (dd, $J$ = 13.9, 6.1 Hz, 1H), 2.17 (dd, $J$ = 8.5, 4.9 Hz, 1H), 2.05 – 1.86 (m, 3H), 1.34 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 193.5, 172.1, 169.8, 161.6, 155.2, 147.8, 145.9, 140.2, 139.4, 134.4, 134.0, 133.7 (q, $J$$_{C-F}$ = 25.2 Hz), 129.9, 129.8, 127.6, 125.0 (q, $J$$_{C-F}$ = 4.0 Hz), 123.7 (q, $J$$_{C-F}$ = 273.7 Hz), 118.8, 110.5, 80.0, 58.9, 52.6, 52.1, 47.1, 37.5, 29.0, 28.3, 24.9. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -63.06. IR (cm$^{-1}$): 1744, 1709, 1645, 1322, 1010. HRMS (ESI) m/z: (M$^+$) calcd for (C$_{36}$H$_{34}$F$_6$N$_2$O$_7$): 720.2270, found 720.2271.

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6.- $^1$H NMR and $^{13}$C NMR Spectra

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

13C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, MeOH-$d_4$)

$^{13}$C NMR (101 MHz, MeOH-$d_4$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^{1}H$ NMR (400 MHz, CDCl$_3$)

$^{13}C$ NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

13C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, MeOH-$d_4$)

$^{13}$C NMR (101 MHz, MeOH-$d_4$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, DMSO-$d_6$ at 80 °C)

$^{13}$C NMR (126 MHz, DMSO-$d_6$ at 80 °C)
$^1$H NMR (500 MHz, DMSO-$d_6$ at 80 °C)

$^{13}$C NMR (126 MHz, DMSO-$d_6$)

S72
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

\[
\text{(2s)}
\]

$^{13}$C NMR (126 MHz, CDCl$_3$)

\[
\text{(2s)}
\]
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
\(^1\)H NMR (400 MHz, CDCl\(_3\))

\(^{13}\)C NMR (101 MHz, CDCl\(_3\))
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
\[^1\text{H} \text{NMR (400 MHz, CDCl}_3\text{)}\]

\[^{13}\text{C} \text{NMR (101 MHz, CDCl}_3\text{)}\]
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)

S103
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

![NMR spectrum of compound (3ma)](image)

$^{13}$C NMR (101 MHz, CDCl$_3$)

![NMR spectrum of compound (3ma)](image)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
\(^1\)H NMR (500 MHz, DMSO-\(d_6\) at 80 ºC)

\(^{13}\)C NMR (126 MHz, DMSO-\(d_6\) at 80 ºC)
$^1$H NMR (500 MHz, DMSO-$d_6$ at 80 °C)

$^{13}$C NMR (126 MHz, DMSO-$d_6$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (126 MHz, CDCl$_3$)
\[^1\text{H} \text{NMR (500 MHz, DMSO-}d_6 \text{ at 80 °C)}\]

\[^{13}\text{C} \text{NMR (126 MHz, DMSO-}d_6 \text{ at 80 °C)}\]
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (101 MHz, CDCl$_3$)
6. $^{19}$F NMR Spectra

$^{19}$F NMR (376 MHz, CDCl$_3$)

$^{19}$F NMR (376 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)

(3as)

(3eh)

S118
$^{19}$F NMR (376 MHz, CDCl$_3$)

![Diagram of compound (3fh)](image)

$^{19}$F NMR (376 MHz, CDCl$_3$)

![Diagram of compound (3'lh)](image)

S119
$^{19}$F NMR (376 MHz, CDCl$_3$)

![NMR Spectrum of (3jh)]

$^{19}$F NMR (376 MHz, CDCl$_3$)

![NMR Spectrum of (3nh)]

S120
$^{19}$F NMR (376 MHz, CDCl$_3$)

$^{19}$F NMR (376 MHz, DMSO-$d_6$)
$^{19}$F NMR (376 MHz, CDCl$_3$)