Cell-Permeable and Plasma-Stable Peptidomimetic Inhibitors of the Postsynaptic Density-95/N-Methyl-\(\text{-}\)D-Aspartate Receptor Interaction.

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1. Experimental of Alcohol Intermediates

**General procedure for reductions of carboxylic acids with LiAlH₄**

A 0.1 M solution of the acid (1.0 equiv) was prepared in freshly distilled THF under N₂ atmosphere and cooled to 0 °C. LiAlH₄, 1M in THF (3 equiv) was slowly added to the stirring solution subsequently allowing the mixture to heat to room temperature before refluxing for 3 h. The hot solution was then cooled to 0 °C and carefully quenched by addition of H₂O followed by dilution with EtOAc and 4 M HCl. The organic phase was separated and extracted twice with sat. NaHCO₃. After drying over MgSO₄ the combined organic phases were concentrated in vacuo resulting in the crude alcohol derivative.

**2-(Norborn-2-yl)-ethanol.** Following general procedure for reduction of carboxylic acids, norboranylacetic acid (0.94 mL, 6.48 mmol) was dissolved in freshly distillled THF (50 mL) and reacted with LiAlH₄ (19.45 mL, 19.45 mmol). After quenching with 10 mL of H₂O, which resulted in precipitation, the mixture was diluted with EtOAc (150 mL) and subsequently acidified by addition of 4 M HCl (50 mL) dissolving the precipitate. The organic phase was separated, and the organic layer washed with sat. NaHCO₃ (2×150 mL), dried over MgSO₄ and concentrated in vacuo resulting in a crude oil. The oil was subsequently purified by bulb-to-bulb distillation under reduced pressure (400 Pa, air bath at 150 °C) affording the known alcohol as a clear oil. Yield: 0.89 g (98%); ¹H NMR (CDCl₃) δ (ppm): 0.98-1.20 (m, 4H), 1.24-1.63 (m, 7H), 1.74-1.82 (m, 1H), 1.92-1.94 (m, 1H), 2.15-2.22 (m, 1H), 3.55-3.65 (m, 2H); GC-MS: EI m/z (%), 122 (6, M⁺-H₂O), 95 (43), 93 (50), 79 (52), 67 (100), 55 (40).

**Cycloheptylmethanol.** Following general procedure for reduction of carboxylic acids, cycloheptanecarboxylic acid (0.97 mL, 7.03 mmol) was dissolved in freshly distillled THF (50 mL) and reacted with LiAlH₄ (21.1 mL, 21.1 mmol). After quenching with 10 mL of H₂O, which resulting in precipitation, the mixture was diluted with EtOAc (150 mL) and subsequently acidified by addition of 4 M HCl (50 mL) dissolving the precipitate. The organic phase was separated, and the organic layer washed with sat. NaHCO₃ (2×150 mL), dried over MgSO₄ and concentrated in vacuo resulting in a crude oil. The oil was subsequently purified by bulb-to-bulb distillation under reduced pressure (400 Pa, air bath at 150 °C) affording the known alcohol as a clear oil. Yield: 0.88 g (97%); ¹H NMR (CDCl₃) δ (ppm): 1.08-1.23 (m, 2H), 1.31-1.72 (m, 13H), 2.48 (s, 1H), 3.56-3.63 (t, 2H, J = 6.9 Hz); GC-MS: EI m/z (%), 124 (1, M⁺-H₂O), 109 (4), 96 (62), 81 (40), 67 (52), 55 (100).

**2-Cycloheptylethanol.** Following general procedure for reduction of carboxylic acids, 2-cycloheptylacetic acid (1.00 g, 6.40 mmol) was dissolved in freshly distillled THF (50 mL) and reacted with LiAlH₄ (19.2 mL, 19.2 mmol). After quenching with 10 mL of H₂O, which resulting in
precipitation, the mixture was diluted with EtOAc (150 mL) and subsequently acidified by addition of 4 M HCl (50 mL) dissolving the precipitate. The organic phase was separated, and the organic layer washed with sat. NaHCO$_3$ (2×150 mL), dried over MgSO$_4$ and concentrated in vacuo resulting in a crude oil. The oil was subsequently purified by bulb-to-bulb distillation under reduced pressure (400 Pa, air bath at 150 °C) affording the known alcohol$^4$ as a clear oil. Yield: 0.89 g (98%); $^1$H NMR (CDCl$_3$) $\delta$ (ppm): 1.10-1.24 (m, 2H), 1.36-1.84 (m, 11H), 3.36-3.43 (d, 2H, $J = 5.9$ Hz); GC-MS: EI m/z (%), 110 (1, M$^+$-H$_2$O), 97 (25), 82 (20), 97 (16), 55 (100).

2-(Pyren-1-yl)ethanol. Following general procedure for reduction of carboxylic acids, 1-pyreneacetic acid (1.00 g, 3.84 mmol) was dissolved in freshly distilled THF (50 mL) and reacted with LiAlH$_4$ (11.53 mL, 11.53 mmol). After quenching with 10 mL of H$_2$O, which resulting in precipitation, the mixture was diluted with EtOAc (150 mL) and subsequently acidified by addition of 4 M HCl (50 mL) dissolving the precipitate. The organic phase was separated, and the organic layer washed with sat. NaHCO$_3$ (2×150 mL), dried over MgSO$_4$ and concentrated in vacuo resulting in a crude solid. The solid was subsequently purified by flash chromatography (silica, heptane to EtOAc) affording the known alcohol$^5$ as a yellowish solid. Yield: 0.57 g (60%); $^1$H NMR (CDCl$_3$) $\delta$ (ppm): 3.57-3.65 (t, 2H, $J = 6.7$ Hz), 4.05-4.12 (t, 2H, $J = 6.7$ Hz), 7.86-7.90 (d, 1H, $J = 7.9$ Hz), 7.96-8.20 (m, 7H), 8.25-8.30 (d, 1H, $J = 9.2$ Hz); ESI$^+$ MS: m/z 247.00 [M+H]$^+$; ESI ELSD: 100 %

3-(2,3,4-Trifluorophenyl)propanol. Following previously published methods,$^6$ 3-(2,3,4-trifluorophenyl)propionic acid (3.06 g, 15.00 mmol) dissolved in distilled THF under N$_2$ atmosphere and cooled to 0 °C. BH$_3$, 1 M complex in THF (45.0 mL, 45.0 mmol) was slowly added to the stirring solution subsequently allowing the mixture to heat to room temperature before refluxing for 3 h. The hot solution was then cooled to 0 °C and carefully quenched by addition of 4 M HCl (50 mL). MeOH (50 mL) was added and the mixture was left to stir for 12 h at room temperature. The mixture was then diluted with EtOAc and the organic layer isolated and washed with sat. Na$_2$CO$_3$ (3×50 mL). The organic layer was then dried over Na$_2$SO$_4$ and concentrated in vacuo resulting in a crude oil. The oil was subsequently purified by bulb-to-bulb distillation under reduced pressure (80 Pa, air bath at 150 °C) affording the final product as a clear oil. Yield: 2.70 g (95%); $^1$H NMR (CDCl$_3$) $\delta$ (ppm): 1.77-1.88 (p, 2H, $J = 7.3$ Hz), 2.65-2.73 (t, 2H, $J = 7.3$ Hz), 2.90 (s, 1H), 3.59-3.66 (t, 2H, $J = 7.3$), 6.77-6.91 (m, 2H); GC-MS: EI m/z (%), 188 (2) 172 (70, M$^+$-H$_2$O), 153 (30), 145 (100), 132 (13), 119 (22).

2-(Anthracen-9-yl)acetonitrile. Following previously published methods,$^7$ NaCN (0.27 g, 5.50 mmol) was suspended in DMF (20 mL) and 9-(chloromethyl)anthracene (1.13 g, 5.00 mmol) was added to the
slurry leaving it to stir for 12 h. The mixture was then poured into 3 M NaOH (50 mL) and brine (10 mL) and the mixture extracted with Et₂O (3×50 mL). The combined organic phases were dried over Na₂SO₄ affording a crude oil. The oil was purified by flash chromatography (silica, heptane to EtOAc) affording the known cyano derivative₈ as yellow crystals. Yield: 2.03 g (93%); ¹H NMR (CDCl₃) δ (ppm): 4.60 (s, 2H), 7.49-7.56 (m, 2H), 7.60-7.67 (m, 2H), 8.03-8.08 (m, 2H), 8.13-8.19 (m, 2H), 8.51 (s, 1H).

2-(Anthracen-9-yl)ethanol. Following previously published methods,⁹, ¹⁰ 2-(anthracen-9-yl)acetonitrile (1.09 g, 5.00 mmol) was dissolved in toluene under N₂ atmosphere and cooled to 0 °C. DIBAL-H, 1 M in THF (7.50 mL, 7.50 mmol) was added slowly to the solution subsequently allowing it to heat to room temperature and leaving it to stir for 2 h. The mixture was then carefully poured into cold 10% HCl (100 mL) and left to stir for 1 h. This mixture was then extracted with heptane/EtOAc (2:1) (3×100 mL) and the combined organic phases dried over Na₂SO₄ and concentrated in vacuo resulting in a brown oil. The oil was dissolved in DCM (10 mL) and MeOH (20 mL) and cooled to 0 °C. NaBH₄ (0.24 g, 6.0 mmol) was added portion-wise affording a bright orange solution which was left to stir for 1 h at 0 °C. The mixture was then allowed to heat to room temperature stirring at this temp for another hour. The reaction was quenched by addition of 10% HCl (100 mL) and extracted with Heptane/EtOAc (2:1) (1×100 mL) then DCM (2×100 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo affording a crude orange oil. The oil was purified by flash chromatography (silica, heptane to EtOAc) giving the known alcohol¹¹ as an orange solid. Yield: 0.49 g (44%); ¹H NMR (CDCl₃) δ (ppm): 3.91-3.98 (m, 2H), 3.91-3.98 (m, 2H), 4.07-4.13 (m, 2H), 7.44-7.56 (m, 4H), 7.99-8.03 (m, 2H), 8.29-8.35 (m, 2H), 8.38 (s, 1H). GC-MS: EI m/z (%), 222 (21, M), 202 (5) 198 (17), 181 (100), 153 (57), 141 (90).

Diethyl 2-(naphthalen-2-ylmethyl)malonate. EtONa (0.68 g, 10.0 mmol) and diehtylmalonate (1.82 mL, 12.0 mmol) were dissolved in abs. EtOH (20 mL) and 2-naphthylbromide (2.21 g, 10.00 mmol) was added to the stirring solution. The mixture was heated to reflux and left to stir for 3 h. After cooling to room temperature the mixture was then poured into brine (150 mL) and extracted with EtOAc (3×150 mL). The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo to afford a crude oil. The oil was purified by flash chromatography (silica, heptane to EtOAc) giving the known diester¹² (2.11 g, 7.03 mmol) as a colorless oil. Yield: 2.11 g (70 %); GC-MS: EI m/z (%), 300 (36, M⁺) 226 (83), 198 (17), 181 (100), 153 (57), 141 (90).
Ethyl 3-(naphthalen-2-yl)propanoate. Following previously published methods,\textsuperscript{13} diethyl 2-(naphthalen-2-ylmethyl)malonate (2.11 g, 7.03 mmol) was dissolved in DMSO (3 mL) and NaCl (0.49 g, 8.44 mmol) and H\textsubscript{2}O (0.25 mL, 14.06 mmol) were added. The mixture was heated to 130 °C and left to stir for 72 h. After cooling to room temperature brine (10 mL) was added and the mixture was extracted with EtOAc (3×10 mL). The combined organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo} giving a crude oil. The oil was purified by flash chromatography (silica, heptane to EtOAc) giving the known monoester\textsuperscript{14} as a colorless oil. Yield: 0.86 g (54%); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) (ppm): 1.27-1.33 (t, 3H, \(J = 7.1 \text{ Hz}\)), 2.74-2.80 (t, 2H, \(J = 7.8 \text{ Hz}\)), 3.15-3.25 (t, 2H, \(J = 7.8 \text{ Hz}\)), 4.16-4.24 (q, 2H, \(J = 7.1 \text{ Hz}\)), 7.36-7.41 (dd, 1H, \(J = 1.8 \text{ Hz} \text{ and } 8.6 \text{ Hz}\)), 7.44-7.54 (m, 2H), 7.69 (bs, 1H), 7.79-7.87 (m, 3H); GC-MS: EI m/z (%), 228 (53, M\textsuperscript{+}), 183 (12), 154 (100), 141 (82), 115 (21), 77 (27).

3-(Naphthalen-2-yl)propan-1-ol. Following previously published methods,\textsuperscript{15} ethyl 3-(naphthalen-2-yl)propanoate (0.64 g, 2.80 mmol) was dissolved in THF (1.1 mL) and toluene (1.0 mL) under N\textsubscript{2} atmosphere and LiBH\textsubscript{4}, 2 M in THF (0.90 mL, 1.80 mmol) was added slowly to the stirring solution. The mixture was then heated to 100 °C and left to stir for 2 h. After cooling to room temperature the reaction mixture was quenched by addition of 10% HCl (10 mL) and extracted with Et\textsubscript{2}O (3×10 mL). The combined organic phases were washed with H\textsubscript{2}O (10 mL) and brine (10 mL) and subsequently dried over Na\textsubscript{2}SO\textsubscript{4} before concentrating \textit{in vacuo} affording a crude semi crystalline oil. The material was purified by flash chromatography (silica, heptane to EtOAc) giving the known alcohol\textsuperscript{16} as a white solid. Yield: 0.43 g (82 %); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) (ppm): 1.94-2.06 (p, 2H, \(J = 7.1 \text{ Hz}\)), 2.85-2.93 (t, 2H, \(J = 7.1 \text{ Hz}\)), 3.68-3.76 (m, 2H), 7.32-7.49 (m, 3H), 7.62-7.65 (bs, 1H)7.74-7.84 (m, 3H); GC-MS: EI m/z (%), 186 (22, M\textsuperscript{+}), 165 (34), 154 (51), 142 (100), 128 (36), 115 (67).

Diethyl 2-(anthracen-9-ylmethyl)malonate. EtONa (0.23 g, 3.40 mmol) and diethylmalonate (0.62 mL, 4.08 mmol) were dissolved in abs. EtOH (7 mL) and 9-(chloromethyl)anthracene (0.77 g, 3.40 mmol) was added to the stirring solution. The mixture was heated to reflux and left to stir for 3 h. After cooling to room temperature the mixture was then poured into brine (100 mL) and extracted with EtOAc (3×100 mL). The combined organic phases were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo} to afford a crude orange oil. The oil was purified by flash chromatography (silica, heptane to EtOAc) giving the known diester\textsuperscript{17} as an orange oil. Yield: 0.91 g (76 %); GC-MS: EI m/z (%), 350 (16, M\textsuperscript{+}), 274 (1), 231 (6), 203 (27), 191 (100).
Ethyl 3-(anthracen-9-yl)propanoate. Following previously published methods,\textsuperscript{13} diethyl 2-(anthracen-9-ylmethyl)malonate (2.68 g, 7.64 mmol) was dissolved in DMSO (3.5 mL) and NaCl (0.54 g, 9.16 mmol) and H\textsubscript{2}O (0.28 mL, 15.27 mmol) were added. The mixture was heated to 130 °C and left to stir for 72 h. After cooling to room temperature brine (25 mL) was added and the mixture was extracted with EtOAc (3×25 mL). The combined organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo giving a crude solid. The solid was purified by flash chromatography (silica, heptane to EtOAc) giving the known monoester\textsuperscript{17} as an orange solid. Yield: 1.04 g (49%); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \( \delta \) (ppm): 1.28-1.34 (t, 3H, \( J = 7.1 \) Hz), 2.78-2.85 (t, 2H, \( J = 8.3 \) Hz), 3.96-4.04 (t, 2H, \( J = 8.3 \) Hz), 4.20-4.28 (q, 2H, \( J = 7.1 \) Hz), 7.45-7.59 (m, 4H), 7.98-8.04 (m, 2H), 8.26-8.37 (m, 3H); GC-MS: EI m/z (%), 278 (28, M\textsuperscript{+}), 249 (1), 233 (3), 215 (1) 203 (30), 191 (100).

3-(Anthracen-9-yl)propan-1-ol. Following previously published methods,\textsuperscript{15} ethyl 3-(naphthalen-2-yl)propanoate (0.81 g, 2.91 mmol) was dissolved in THF (1.1 mL) and toluene (1.0 mL) under N\textsubscript{2} atmosphere and LiBH\textsubscript{4}, 2 M in THF (0.90 mL, 1.80 mmol) was added slowly to the stirring solution. The mixture was then heated to 100 °C and left to stir for 2 h. After cooling to room temperature the reaction mixture was quenched by addition of 10% HCl (10 mL) and extracted with Et\textsubscript{2}O (3×10 mL). The combined organic phases were washed with H\textsubscript{2}O (10 mL) and brine (10 mL) and subsequently dried over Na\textsubscript{2}SO\textsubscript{4} before concentrating in vacuo affording a crude solid. The material was purified by flash chromatography (silica, heptane to EtOAc) giving the known alcohol\textsuperscript{17} as a yellowish solid. Yield: 0.54 g (78 %); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \( \delta \) (ppm): 2.05-2.16 (m, 2H), 3.71-3.78 (t, 2H, \( J = 7.9 \) Hz), 3.80-3.87 (m, 2H), 7.42-7.54 (m, 4H), 7.98-8.03 (m, 2H), 8.28-8.36 (m, 3H); GC-MS: EI m/z (%), 250 (4), 236 (37, M\textsuperscript{+}), 218 (5), 203 (16), 191 (100), 179 (14).
2. Experimental of New N-Alkylated ETAV Compounds

N-(Adamantan-1-yl)ethyl-ETAV (19)
Following the general procedures for solid phase peptides synthesis and terminal N-alkylation in a 0.25 mmol scale and subsequent HPLC purification, 19 was isolated as a white solid. Yield: 8 mg (6%); \textsuperscript{1}H NMR (MeOH-d4) \(\delta\) (ppm): 0.98 (d, 6H, \(J = 6.8\) Hz), 1.24 (d, 3H, \(J = 6.5\) Hz), 1.39 (d, 3H, \(J = 7.1\) Hz), 1.43-1.52 (m, 2H), 1.53-1.58 (m, 6H), 1.62-1.82 (m, 7H), 1.93-2.02 (m, 3H), 2.05-2.24 (m, 3H), 2.50-2.57 (t, 2H, \(J = 7.1\) Hz), 2.91-3.01 (m, 2H), 3.96 (t, 1H, \(J = 6.4\) Hz), 4.12-4.22 (m, 1H), 4.29 (d, 1H, 5.7 Hz), 4.41-4.50 (m, 2H); ESI\textsuperscript{+} MS: m/z 581.40 [M+H]\textsuperscript{+}; ESI ELSD: 100 \%; HRMS (ES+) calcd for C\textsubscript{29}H\textsubscript{49}N\textsubscript{4}O\textsubscript{8} [M + H]\textsuperscript{+} m/e 581.3550, found m/e 581.3551.

N-(Norborn-2-yl)methyl-ETAV (20)
Following the general procedures for solid phase peptides synthesis in a 0.25 mmol scale, terminal N-alkylation was achieved through an alternative procedure\textsuperscript{18} using ADDP (5 equiv) and Bu\textsubscript{3}P (5 equiv) instead of DIAD and Ph\textsubscript{3}P, respectively. Following HPLC purification, peptide 20 was isolated as a white solid. Yield: 15 mg (11%); \textsuperscript{1}H NMR (MeOH-d4) \(\delta\) (ppm): 0.74-0.86 (m, 1H), 0.98 (d, 6H, \(J = 6.7\) Hz), 1.06-1.66 (m, 7H), 1.23 (d, 3H, \(J = 6.5\) Hz), 1.39 (d, 3H, \(J = 6.8\) Hz), 1.76-1.95 (m, 1H), 2.10-2.38 (m, 5H), 2.57 (t, 2H, \(J = 7.0\)), 2.83-3.12 (m, 2H), 3.94-4.03 (m, 1H), 4.11-4.19 (m, 1H), 4.27-4.33 (m, 1H), 4.41-4.51 (m, 2H); ESI\textsuperscript{+} MS: m/z 527.20 [M+H]\textsuperscript{+}; ESI ELSD: 100 \%; HRMS (ES+) calcd for C\textsubscript{25}H\textsubscript{43}N\textsubscript{4}O\textsubscript{8} [M + H]\textsuperscript{+} m/e 527.3081, found m/e 527.3093.

N-(Norborn-2-yl)ethyl-ETAV (21)
Following the general procedures for solid phase peptides synthesis and terminal N-alkylation in a 0.25 mmol scale and subsequent HPLC purification, peptide 21 was isolated as a white solid. Yield: 21 mg (16%); \textsuperscript{1}H NMR (MeOH-d4) \(\delta\) (ppm): 0.98 (d, 6H, \(J = 6.7\) Hz), 1.02-1.29 (m, 4H), 1.23 (d, 3H, \(J = 6.4\)), 1.31-1.58 (m, 6H), 1.39 (d, 3H, \(J = 7.1\) Hz), 1.62-1.77 (m, 1H), 1.96-2.26 (m, 5 H), 2.54 (t, 2H, \(J = 7.1\) Hz), 2.82-3.01 (m, 2H), 3.95-4.02 (m, 1H), 4.10-4.20 (m, 1H), 4.27-4.32 (m, 1H), 4.42-4.51 (m, 1H), 4.41-4.51 (m, 2H); ESI\textsuperscript{+} MS: m/z 541.30 [M+H]\textsuperscript{+}; ESI ELSD: 99 \%; HRMS (ES+) calcd for C\textsubscript{26}H\textsubscript{45}N\textsubscript{4}O\textsubscript{8} [M + H]\textsuperscript{+} m/e 541.3237, found m/e 541.3236.

N-Cycloheptylmethyl-ETAV (22)
Following the general procedures for solid phase peptides synthesis and terminal N-alkylation in a 0.25 mmol scale and subsequent HPLC purification, peptide 22 was isolated as a white solid. Yield: 14 mg (11%); \textsuperscript{1}H NMR (MeOH-d4) \(\delta\) (ppm): 0.98 (d, 6H, \(J = 6.9\) Hz), 1.23 (d, 3H, \(J = 6.2\) Hz), 1.27-1.36 (m, 2H), 1.39 (d, 3H, \(J = 6.9\) Hz), 1.43-1.97 (m, 11H), 2.08-2.24 (m, 3H), 2.58 (t, 2H, \(J = 6.9\) Hz), 2.71-2.80 (m, 1H), 2.84-2.92 (m, 1H), 3.96 (t, 1H, \(J = 6.6\) Hz), 4.10-4.20 (m, 1H), 4.27-4.33 (m, 1H), 4.42-4.51 (m, 2H); ESI\textsuperscript{+} MS: m/z 529.30 [M+H]\textsuperscript{+}; ESI ELSD: 100 \%; HRMS (ES+) calcd for C\textsubscript{25}H\textsubscript{45}N\textsubscript{4}O\textsubscript{8} [M + H]\textsuperscript{+} m/e 529.3237, found m/e 529.3219.

N-Cycloheptyl-ETAV (23)
Following the general procedures for solid phase peptides synthesis and terminal N-alkylation in a 0.25 mmol scale and subsequent HPLC purification (as stated above), peptide 23 was isolated as a white solid. Yield: 25 mg (18%); \textsuperscript{1}H NMR (MeOH-d4) \(\delta\) (ppm): 0.98 (d, 6H, \(J = 6.9\) Hz), 1.18-1.32 (m, 2H), 1.23 (d, 3H, \(J = 6.4\) Hz), 1.39 (d, 3H, \(J = 6.9\) ), 1.42-1.79 (m, 13H), 2.07-2.24 (m, 3H), 2.54 (t, 2H, \(J = 7.1\) Hz), 2.86-3.07 (m, 2H), 4.00 (t, 1H, \(J = 6.7\) Hz), 4.11-4.20 (m, 1H), 4.27-4.32 (m, 1H), 4.43-4.51 (m, 2H); ESI\textsuperscript{+} MS: m/z 543.40 [M+H]\textsuperscript{+}; ESI ELSD: 100 \%; HRMS (ES+) calcd for C\textsubscript{26}H\textsubscript{47}N\textsubscript{4}O\textsubscript{8} [M + H]\textsuperscript{+} m/e 543.3394, found m/e 543.3420.
**N-(2,3,4-Trifluorophenyl)ethyl-ETAV (24)**

Following the general procedures for solid phase peptides synthesis and terminal N-alkylation in a 0.25 mmol scale and subsequent HPLC purification, peptide 24 was isolated as a white solid. Yield: 23 mg (16%); $^1$H NMR (MeOH-d4) $\delta$ (ppm): 0.97 (d, 6H, $J = 7.1$ Hz), 1.22 (d, 3H, $J = 6.5$ Hz), 1.39 (d, 3H, $J = 7.1$ Hz), 2.07-2.26 (m, 3H), 2.56 (t, 2H, $J = 7.4$ Hz), 3.02-3.14 (m, 2H), 3.14-3.28 (m, 2H), 4.05 (t, 1H, $J = 6.5$ Hz), 4.08-4.18 (m, 1H), 4.26-4.32 (m, 1H), 4.39-4.51 (m, 2H), 7.05-7.15 (m, 2H); ESI$^+$ MS: m/z 577.20 [M+H]$^+$; ESI ELSD: 95%; HRMS (ES+) calcd for C$_{25}$H$_{36}$N$_4$O$_8$F$_3$ [M + H]$^+$ m/e 577.2485, found m/e 577.2466.

**N-(2,3,4-Trifluorophenyl)propyl-ETAV (25)**

Following the general procedures for solid phase peptides synthesis and terminal N-alkylation in a 0.25 mmol scale and subsequent HPLC purification, peptide 25 was isolated as a white solid. Yield: 23 mg (16%); $^1$H NMR (MeOH-d4) $\delta$ (ppm): 0.98 (d, 6H, $J = 7.1$ Hz), 1.20 (d, 3H, $J = 6.3$ Hz), 1.39 (d, 3H, $J = 7.1$ Hz), 2.01 (p, 2H, $J = 7.5$ Hz), 2.08-2.26 (m, 3H), 2.54 (t, 2H, $J = 7.4$ Hz), 2.78 (t, 2H, $J = 7.5$), 2.90-3.09 (m, 2H), 4.01 (t, 1H, $J = 6.8$ Hz), 4.10-4.19 (m, 1H), 4.27-4.33 (m, 1H), 4.40-4.51 (m, 2H), 7.03-7.12 (m, 2H); ESI$^+$ MS: m/z 591.20 [M+H]$^+$; ESI ELSD: 100%; HRMS (ES+) calcd for C$_{26}$H$_{38}$N$_4$O$_8$F$_3$ [M + H]$^+$ m/e 591.2642, found m/e 591.2664.

**N-(Naphthalene-2-yl)propyl-ETAV (26)**

Following the general procedures for solid phase peptides synthesis in a 0.25 mmol scale, terminal N-alkylation was achieved according to the general procedure using 5 equiv of the alcohol. Following HPLC purification, peptide 26 was isolated as a white solid. Yield: 46 mg (31%); $^1$H NMR (MeOH-d4) $\delta$ (ppm): 0.97 (d, 6H, $J = 6.8$ Hz), 1.10 (d, 3H, $J = 6.3$ Hz), 1.38 (d, 3H, $J = 7.2$ Hz), 2.06-2.26 (m, 5H), 2.53 (t, 2H, $J = 7.1$ Hz), 2.89 (t, 2H, $J = 7.3$ Hz), 2.93-3.09 (m, 2H), 3.99-4.05 (m, 1H), 4.06-4.16 (m, 1H), 4.29 (d, 1H, $J = 5.58$ Hz), 4.39-4.50 (m, 2H), 7.33-7.38 (m, 1H), 7.38-7.48 (m, 2H), 7.66 (s, 1H), 7.75-7.83 (m, 3H); ESI$^+$ MS: m/z 587.30 [M+H]$^+$; ESI ELSD: 100%; HRMS (ES+) calcd for C$_{30}$H$_{43}$N$_4$O$_8$ [M + H]$^+$ m/e 587.3081, found m/e 587.3082.

**N-(Anthracene-9-yl)ethyl-ETAV (27)**

Following the general procedures for solid phase peptides synthesis in a 0.25 mmol scale, terminal N-alkylation was achieved according to the general procedure using 5 equiv of the alcohol. Following HPLC purification, peptide 27 was isolated as a white solid. Yield: 3 mg (2%); $^1$H NMR (MeOH-d4) $\delta$ (ppm): 0.97 (d, 6H, $J = 7.1$ Hz), 1.05 (d, 3H, $J = 6.4$ Hz), 1.39 (d, 3H, $J = 7.0$ Hz), 2.10-2.28 (m, 3H), 2.62 (t, 2H, $J = 7.1$ Hz), 3.19-3.27 (m, 2H), 4.02-4.11 (m, 4H), 4.28 (d, 1H, $J = 6.0$ Hz), 4.38-4.50 (m, 2H), 7.47-7.54 (m, 2H), 7.56-7.64 (m, 2H), 8.07 (d, 2H, $J = 7.9$ Hz), 8.30 (d, 2H, $J = 8.8$ Hz), 8.49 (s, 1H); ESI$^+$ MS: m/z 623.30 [M+H]$^+$; ESI ELSD: 96%; HRMS (ES+) calcd for C$_{33}$H$_{43}$N$_4$O$_8$ [M + H]$^+$ m/e 623.3081, found m/e 623.3081.

**N-(Anthracene-9-yl)propyl-ETAV (28)**

Following the general procedures for solid phase peptides synthesis in a 0.25 mmol scale, terminal N-alkylation was achieved according to the general procedure using 5 equiv of the alcohol. Following HPLC purification, peptide 28 was isolated as a white solid. Yield: 36 mg (23%); $^1$H NMR (MeOH-d4) $\delta$ (ppm): 0.97 (d, 6H, $J = 6.9$ Hz), 1.14 (d, 3H, $J = 6.9$ Hz), 1.38 (d, 3H, $J = 6.9$ Hz), 2.01-2.27 (m, 5H), 2.53 (t, 2H, $J = 7.3$ Hz), 3.13-3.24 (m, 2H), 3.73-3.81 (m, 2H), 3.90-3.96 (m, 1H), 4.08-4.17 (m, 1H), 4.26-4.32 (m, 1H), 4.35-4.48 (m, 2H), 7.43-7.58 (m, 4H), 8.04 (d, 2H, $J = 8.3$ Hz), 8.30 (d, 2H, $J = 8.3$ Hz), 8.41 (s, 1H); ESI$^+$ MS: m/z 637.30 [M+H]$^+$; ESI ELSD: 99%; HRMS (ES+) calcd for C$_{34}$H$_{45}$N$_4$O$_8$ [M + H]$^+$ m/e 637.3237, found m/e 637.3239.

**N-(Pyrene-1-yl)ethyl-ETAV (29)**
Following the general procedures for solid phase peptides synthesis and terminal N-alkylation in a 0.25 mmol scale and subsequent HPLC purification, peptide 29 was isolated as a white solid. Yield: 10 mg (6%); \(^1\)H NMR (DMSO-d6) \(\delta\) (ppm): 1.00 (d, 6H, \(J = 6.6\) Hz), 1.10 (d, 3H, \(J = 6.6\) Hz), 1.33 (d, 3H, \(J = 7.4\) Hz), 1.90-2.38 (m, 4H), 2.52 (t, 2H, \(J = 8.0\) Hz), 3.74-3.84 (m, 1H), 3.97-4.08 (m, 1H), 4.16-4.23 (m, 1H), 4.23-4.31 (bs, 1H), 4.40-4.57 (m, 2H), 5.02-5.07 (m, 1H) 7.94-8.29 (m, 6H), 8.29-8.54 (m, 5H), 8.84 (d, 1H, \(J = 8.7\) Hz), 9.13-9.31 (bs, 1H), 9.35-9.50 (bs, 1H); ESI\(^+\) MS: m/z 647.30 [M+H]\(^+\); ESI ELSD: 96%; HRMS (ES+) calcd for C\(_{35}\)H\(_{43}\)N\(_4\)O\(_8\) [M + H]\(^+\) m/e 647.3081, found m/e 647.3073.

\(-\)(Pyrene-1-yl)butyl-ETAV (30)
Following the general procedures for solid phase peptides synthesis and terminal N-alkylation in a 0.25 mmol scale and subsequent HPLC purification, peptide 30 was isolated as a white solid. Yield: 26 mg (15%); \(^1\)H NMR (DMSO-d6) \(\delta\) (ppm): 0.87 (d, 6H, \(J = 6.7\) Hz), 1.08 (d, 3H, \(J = 6.0\) Hz), 1.21 (d, 3H, \(J = 7.3\) Hz), 1.64-1.94 (m, 6H), 1.94-2.09 (m, 2H), 2.35 (t, 2H, \(J = 7.6\) Hz), 2.73-3.00 (m, 2H), 3.92-4.03 (m, 2H), 4.07-4.13 (m, 1H), 4.29-4.36 (m, 1H), 4.37-4.45 (m, 1H), 4.96-5.05 (bs, 1H), 7.91-8.15 (m, 6H), 8.15-8.37 (m, 5H), 8.70 (d, 1H, \(J = 7.9\) Hz), 8.73-8.87 (bs, 1H); ESI\(^+\) MS: m/z 675.40 [M+H]\(^+\); ESI ELSD: 100%; HRMS (ES+) calcd for C\(_{37}\)H\(_{47}\)N\(_4\)O\(_8\) [M + H]\(^+\) m/e 675.3394, found m/e 675.3373.
3. References


