

Opioid activity profiles of oversimplified peptides lacking in the protonable *N*-terminus

Supporting Information

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Table S1. Non-obvious ROESY cross-peaks observed for **4**.^a

Cross peak ^b	Intensity ^c	Cross peak ^b	Intensity ^c
PheNH-TrpNH	w	PheNH-CONH ₂ (dw)	m
PheNH-PheArH	m	PheNH-TrpH α	s
PheNH-PheH α	m	PheNH-IndH2	w
TrpNH-TrpH α	m	TrpNH-IndH4	w
CONH ₂ (dw)-PheH α	m	TrpNH-IndH2	w
PheArH-PheH β (dw)	vs	IndH4-TrpH α	m
PheArH-PheH α	m	PheArH-PheH β (up)	s
IndH2-TrpH α	m	IndH2-TrpH β	w
TrpH α -TrpH β (up)	m	TrpH α -TrpH β (dw)	m
PheH α -PheH β (up)	m	PheH α -PheH β (dw)	m

^a Stereochemistry has been omitted; ^b up = upfield, dw = downfield; ^c vs = very strong, s = strong, m = medium, w = weak.

Table S2. Non-obvious ROESY cross-peaks observed for **5**.^a

Cross peak ^b	Intensity ^c	Cross peak ^b	Intensity ^c
PheNH-TrpNH	w	PheNH-GlyNH	s
PheNH-PheArH	m	PheNH-TrpH α	vs
PheNH-PheH α	m	TrpNH-IndH2	w
TrpNH-TrpH α	s	GlyNH-CONH ₂ (dw)	w
GlyNH-PheH α	s	GlyNH-GlyH α (dw)	vs
GlyNH-GlyH α (up)	vs	IndH4-TrpH α	m
PheArH-PheH β (dw)	vs	PheArH-PheH β (up)	vs
PheArH-PheH α	m	IndH2-TrpH β	w
IndH2-TrpH α	m	TrpH α -TrpH β (dw)	m
TrpH α -TrpH β (up)	m	PheH α -PheH β (dw)	m
PheH α -PheH β (up)	m		

^a Stereochemistry has been omitted; ^b up = upfield, dw = downfield; ^c vs = very strong, s = strong, m = medium, w = weak.

Analytical characterization of compounds **4-12**.

(4) IR (nujol) ν : 3410, 3319, 3292, 3199, 1670, 1612, 1548, 1461, 1377; $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.79 (s, 3H, CH_3), 2.78-2.84 (m, 3H, PheH β +TrpH β), 2.98 (dd, $J=4.0, 13.6$ Hz, 1H, TrpH β), 4.41 (m, 1H, PheH α), 4.45 (m, 1H, TrpH α), 6.70 (s, 1H, CONH_2), 6.90 (s, 1H, TrpH $_2$), 6.95 (t, $J=7.2$ Hz, 1H, TrpH $_5$), 7.02 (s, $J=7.6$ Hz, 1H, TrpH $_6$), 7.08-7.13 (m, 6H, PheArH+ CONH_2), 7.28 (d, $J=8.0$ Hz, 1H, TrpH $_7$), 7.48 (d, $J=7.6$ Hz, 1H, TrpH $_4$), 7.75 (d, $J=5.6$ Hz, 1H, TrpNH), 7.89 (d, $J=8.0$ Hz, 1H, PheNH), 10.75 (s, 1H, TrpH $_1$); $^{13}\text{C-NMR}$ (DMSO- d_6) δ : 22.9, 28.0, 54.3, 54.4, 110.5, 111.8, 118.7, 119.0, 121.4, 124.1, 126.7, 127.7, 128.5, 130.0, 136.6, 138.7, 170.1, 172.3, 173.6. Elem. Anal. for $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_3$, calcd: C 67.33, H 6.16, N 14.28; found: C 67.29, H 6.17, N 14.30.

(5) IR (nujol) ν : 3408, 3271, 1695, 1645, 1541, 1457, 1377 cm^{-1} ; $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.80 (s, 3H, CH_3), 2.82 (dd, $J=9.2, 14.1$ Hz, 1H, PheH β), 2.93 (dd, $J=7.2, 14.4$ Hz, 1H, TrpH β), 3.06 (dd, $J=5.7, 14.7$ Hz, 2H, TrpH β +PheH β), 3.44 (dd, $J=5.4, 16.8$ Hz, 1H, GlyH α), 3.73 (dd, $J=6.6, 16.8$ Hz, 1H, GlyH α), 4.36 (m, 1H, PheH α), 4.48 (q, $J=7.2$ Hz, 1H, TrpH α), 6.54 (s, 1H, CONH_2), 6.79 (s, 1H, CONH_2), 6.93 (t, $J=7.2$ Hz, 1H, TrpH $_5$), 6.98 (s, 1H, TrpH $_2$), 7.02 (t, $J=7.2$ Hz, 1H, TrpH $_6$), 7.06 (d, $J=7.8$ Hz, 2H, PheArH $_{2,6}$), 7.09-7.17 (m, 3H, PheArH $_{3-5}$), 7.27 (d, $J=8.4$ Hz, 1H, TrpH $_7$), 7.40 (dd, $J=5.4, 6.6$ Hz, 1H, GlyNH), 7.47 (d, $J=8.4$ Hz, 1H, TrpH $_4$), 7.65 (d, $J=7.2$ Hz, 1H, TrpNH), 7.89 (d, $J=7.8$ Hz, 1H, PheNH), 10.32 (s, 1H, TrpH $_1$); $^{13}\text{C-NMR}$ (DMSO- d_6) δ : 23.0, 28.1, 37.7, 42.6, 54.4, 54.8, 110.5, 111.8, 118.8, 119.0, 121.4, 124.2, 126.8, 127.8, 128.6, 129.8, 136.6, 138.5, 170.1, 171.4, 171.9, 172.7; Elem. Anal. for $\text{C}_{24}\text{H}_{27}\text{N}_5\text{O}_4$, calcd: C 64.13, H 6.05, N 15.58; found: C 64.11, H 6.05, N 15.60.

(6) $^1\text{H-NMR}$ (400MHz, DMSO- d_6) δ : 1.78 (s, 3H, CH_3), 2.84 (dd, $J=9.4, 13.6$ Hz, 1H, PheH β), 2.88 (dd, $J=6.0, 13.2$ Hz, 1H, TrpH β), 3.03 (dd, $J=5.6, 13.2$ Hz, 1H, TrpH β), 3.10 (dd, $J=4.4, 13.6$ Hz, 1H, PheH β), 3.47 (dd, $J=5.0, 16.8$ Hz, 1H, GlyH α), 3.72 (dd, $J=6.2, 16.8$ Hz, 1H, GlyH α), 4.40 (q, $J=5.2$ Hz, 1H, PheH α), 4.48 (q, $J=6.0$ Hz, 1H, TrpH α), 6.90-6.95 (m, 3H, TrpH $_{5,6}$ + CONH_2), 7.00 (m, 2H, TrpH $_2$ + CONH_2), 7.12-7.18 (m, 5H, PheArH), 7.27 (d, $J=7.6$ Hz, 1H, TrpH $_7$), 7.50 (d, $J=8.0$ Hz, 1H, TrpH $_4$), 7.74 (t, $J=5.0$ Hz, 1H, GlyNH), 7.91 (d, $J=7.2$ Hz, 1H, TrpNH), 8.05 (d, $J=7.2$ Hz, 1H, PheNH), 10.54 (s, 1H, TrpH $_1$); $^{13}\text{C-NMR}$ δ : 23.0, 28.1, 37.7, 42.6, 54.4, 54.8, 110.5, 111.8, 118.8, 119.0, 121.4, 124.2, 126.8, 127.8, 128.6, 129.8, 136.6, 138.5, 170.1, 171.4, 171.9, 172.7; Elem. Anal. for $\text{C}_{24}\text{H}_{27}\text{N}_5\text{O}_4$, calcd: C 64.13, H 6.05, N 15.58; found: C 64.15, H 6.06, N 15.56.

(7) $^1\text{H-NMR}$ (400MHz, DMSO- d_6) (two sets of signals) δ : 1.81 (s, 3H, CH_3), 2.70 (m, 1H, HisH β), 2.87 (dd, $J=6.4, 15.2$ Hz, 1H, PheH β), 2.92-3.06 (m, 2H, PheH β +HisH β), 4.44 (m, 1H, HisH α), 4.53 (m, 1H, PheH α), 6.97+7.24 (s, 1H, HisArH), 7.17-7.27 (m, 6H, PheArH+ CONH_2), 7.45+7.51 (s, 1H, CONH_2), 7.96+8.17 (d, $J=8.0$ Hz, 1H, PheNH),

8.07+8.09 (d, J=8.2 Hz, 1H, HisNH), 8.86+8.89 (s, 1H, HisArH). Elem. Anal. for C₁₇H₂₁N₅O₃, calcd: C 59.46, H 6.16, N 20.40; found: C 59.43, H 6.17, N 20.39.

(8) ¹H-NMR (400MHz, DMSO-d₆) δ (two sets of signals) δ: 1.80 (s, 3H, CH₃), 2.72 (m, 1H, HisHβ), 2.85 (m, 1H, PheHβ), 2.91-3.08 (m, 2H, PheHβ+HisHβ), 3.50 (m, 1H, GlyHα), 3.80 (m, 1H, GlyHα), 4.43 (m, 1H, HisHα), 4.56 (m, 1H, PheHα), 6.97+7.24 (s, 1H, HisArH), 7.18-7.29 (m, 6H, PheArH+CONH₂), 7.43+7.50 (s, 1H, CONH₂), 7.84 (t, J=5.8 Hz, 1H, GlyNH), 0.00+8.18 (d, J=8.0 Hz, 1H, PheNH), 8.07+8.10 (d, J=8.2 Hz, 1H, HisNH), 8.87+8.90 (s, 1H, HisArH). Elem. Anal. for C₁₉H₂₄N₆O₄, calcd: C 56.99, H 6.04, N 20.99; found: C 57.02, H 6.03, N 21.01.

(9) ¹H-NMR (400MHz, DMSO-d₆) δ: 0.92 (m, 1H, LysHγ), 1.01 (m, 1H, LysHγ), 1.31-1.43 (m, 4H, LysHβ+LysHδ), 1.83 (s, 3H, CH₃), 2.60 (br.t, 2H, LysHε), 2.71 (dd, J=10.6, 13.7 Hz, 1H, PheHβ), 3.14 (dd, J=3.6, 13.7 Hz, 1H, PheHβ), 4.03 (q, J=6.8 Hz, 1H, LysHα), 4.42 (m, 1H, PheHα), 6.83 (s, 1H, CONH₂), 7.11-7.18 (m, 5H, PheArH), 7.31 (s, 1H, CONH₂), 7.86 (d, J=6.4 Hz, 1H, LysNH), 8.11 (d, J=8.4 Hz, 1H, PheNH). Elem. Anal. for C₁₇H₂₆N₄O₃, calcd: C 61.06, H 7.84, N, 16.75; found: C 61.02, H 7.79, N, 16.68.

(10) ¹H-NMR (400MHz, DMSO-d₆) δ: 0.93 (m, 1H, LysHγ), 0.99 (m, 1H, LysHγ), 1.25-1.42 (m, 4H, LysHβ+LysHδ), 1.83 (s, 3H, CH₃), 2.60 (br.t, 2H, LysHε), 2.77 (dd, J=11.2, 14.0 Hz, 1H, PheHβ), 3.16 (dd, J=3.8, 14.0 Hz, 1H, PheHβ), 3.50 (dd, J=5.0, 16.8 Hz, 1H, GlyHα), 3.68 (dd, J=5.6, 16.8 Hz, 1H, GlyHα), 4.07 (q, J=6.8 Hz, 1H, LysHα), 4.42 (m, 1H, PheHα), 6.88 (s, 1H, CONH₂), 6.96 (s, 1H, CONH₂), 7.10-7.16 (m, 5H, PheArH), 7.92 (d, J=6.4 Hz, 1H, LysNH), 8.12 (br.t, 1H, GlyNH), 8.28 (d, J=7.6 Hz, 1H, PheNH). Elem. Anal. for C₁₉H₂₉N₅O₄, calcd: C 58.29, H 7.47, N 17.89; found: C 58.33 H 7.43, N 17.92.

(11) ¹H-NMR (400MHz, DMSO-d₆) δ: 1.11 (m, 1H, ArgHγ), 1.21 (m, 1H, ArgHγ), 1.36 (m, 1H, ArgHβ), 1.41 (m, 1H, ArgHβ), 1.83 (s, 3H, CH₃), 2.74 (dd, J=10.6, 13.8 Hz, 1H, PheHβ), 2.82-2.96 (m, 2H, ArgHδ), 3.15 (dd, J=4.0, 13.8 Hz, 1H, PheHβ), 4.08 (q, J=6.4 Hz, 1H, ArgHα), 4.43 (m, 1H, PheHα), 6.93 (s, 1H, CONH₂), 6.97-7.22 (m, 9H, ArgHη+PheArH), 7.37 (s, 1H, CONH₂), 7.60 (t, J=4.8 Hz, 1H, ArgHε), 7.97 (d, J=6.4 Hz, 1H, ArgNH), 8.19 (d, J=8.8 Hz, 1H, PheNH). Elem. Anal. for C₁₇H₂₆N₆O₃, calcd: C 56.34, H, 7.23, N, 23.19; found: C 56.29, H, 7.19, N, 23.24.

(12) ¹H-NMR (400MHz, DMSO-d₆) δ: 1.08 (m, 1H, ArgHγ), 1.13 (m, 1H, ArgHγ), 1.30 (m, 1H, ArgHβ), 1.40 (m, 1H, ArgHβ), 1.84 (s, 3H, CH₃), 2.73 (dd, J=10.2, 14.0 Hz, 1H, PheHβ), 2.90-3.00 (m, 2H, ArgHδ), 3.11 (dd, J=4.0, 14.0 Hz, 1H, PheHβ), 3.62 (dd, J=5.6, 16.2 Hz, 1H, GlyHα), 3.69 (dd, J=6.0, 16.2 Hz, 1H, GlyHα), 4.14 (q, J=6.4 Hz, 1H, ArgHα), 4.50 (m, 1H, PheHα), 7.08 (s, 1H, CONH₂), 7.01-7.30 (m, 10H, ArgHη+PheArH+CONH₂), 7.51 (t, J=4.8 Hz, 1H, ArgNHε), 8.07 (d, J=6.4 Hz, 1H, ArgNH), 8.26 (t, J=5.8 Hz, 1H, GlyNH), 8.32 (d, J=8.8 Hz, 1H, PheNH). Elem. Anal. for C₁₉H₂₉N₇O₄, calcd: C 54.40, H 6.97, N 23.37; found: C 54.37, H 7.00, N 23.41.

