**Supporting Information**

# Development of novel enkephalin analogues which have enhanced opioid activities at both μ and δ opioid receptors

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**Table 1.** Analytical Data of Opioid Ligands

| no | molecular formula | LowMS [a] | HRMS [b] | | HPLC ($t_R$, min) [c] | | | | TLC ($R_f$) [d] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | observed | observed | calcd. | (A) | purity (%) | (B) | purity (%) | (I) | (II) | (III) |
| **8** | $C_{23}H_{29}N_2O_3$ | 381.3 | 381.2184 | 381.2178 | 15.0 | 98 | 7.0 | 98 | 0.26 | 0.63 | 0.65 |
| **10** | $C_{36}H_{46}N_6O_5$ | 643.3 | 643.3613 | 643.3603 | 13.4 | 100 | 6.5 | 100 | 0.04 | 0.66 | 0.70 |
| **11** | $C_{46}H_{57}N_8O_7$ | 833.1 | 833.4390 | 833.4350 | 16.3 | 100 | 8.9 | 100 | 0.07 | 0.65 | 0.70 |
| **12** | $C_{40}H_{52}N_8O_7$ | 757.3 | 757.4039 | 757.4037 | 13.2 | 100 | 6.4 | 100 | 0.04 | 0.66 | 0.70 |
| **13** | $C_{28}H_{37}N_5O_5$ | 524.5 | 524.2873 | 524.2897 | 13.6 | 100 | 6.8 | 100 | 0.03 | 0.71 | 0.61 |
| **14** | $C_{37}H_{46}N_6O_6$ | 671.2 | 671.3579 | 671.3557 | 19.1 | 98 | 11.0 | 98 | 0.10 | 0.42 | 0.49 |
| **15** | $C_{30}H_{41}N_5O_5$ | 552.3 | 552.3165 | 552.3186 | 15.5 | 100 | 7.6 | 100 | 0.14 | 0.63 | 0.63 |
| **16** | $C_{39}H_{50}N_6O_6$ | 699.3 | 699.3852 | 699.3870 | 20.1 | 100 | 12.7 | 100 | 0.14 | 0.76 | 0.71 |
| **17** | $C_{41}H_{52}N_8O_8$ | 784.9 | 785.4011 | 785.3986 | 16.5 | 100 | 9.1 | 100 | 0.10 | 0.77 | 0.64 |

[a]$(M - TFA + H)^+$, ESI method [Finnigan, Thermoelectron, LCQ classic]. [b]$(M - TFA + H)^+$, FAB-MS (JEOL HX110 sector instrument) or MALDI-TOF. [c]Performed on a Hewlett Packard 1100 [C-18, Microsorb-MV[TM], 4.6 mm x 250 mm, 5 μm]. (A)10-90% of acetonitrile containing 0.1% TFA within 40 min and up to 100% within additional 5 min, 1 mL/min, (B) 25-65% of acetonitrile containing 0.1% TFA within 20 min and up to 100% within additional 5 min, 1 mL/min. [d](I) $CHCl_3$/MeOH/AcOH = 90:10:3, (II) EtOAc/BtOH/water/AcOH = 5:3:1:1, (III) BtOH/water/AcOH = 4:1:1.

**Table 2.** $^{1}$H NMR Data of Opioid Ligands

| Compound | $^{1}$H NMR (DMSO-d$_6$) |
|---|---|
| **8** | 1.15-1.20 (m, 2H), 1.66 (d, $J$ = 11.4 Hz, 2H), 1.97-2.02 (m, 4H), 2.32 (t, $J$ = 6.9 Hz, 2H), 2.42 (t, $J$ = 8.1 Hz, 2H), 2.62 (t, $J$ = 7.8 Hz, 2H), 2.90 (d, $J$ = 11.4 Hz, 2H), 4.40 ( $J$ = 12 Hz, 1H), 7.14 (m, 3H), 7.21 (m, 4H), 7.42 (t, $J$ = 7.2 Hz, 1 H), 7.47 (t, $J$ = 7.5 Hz, 2H), 8.04 (s, 4H), 8.12-8.14 (m,3H), 8.19 (d, $J$ = 8.4 Hz, 1H), 8.48 (d, $J$ = 7.2 Hz, 1H) |
| **10** | 1.06 (t, $J$ = 6.6 Hz, 3H), 1.43-1.48 (m, 1H), 1.59-1.63 (m, 1H), 1.79(m, 1H), 1.92 (m, 1H), 2.77-3.03 (m, 8H), 3.24 (m, 2H), 3.52-3.56 (m, 2H), 3.62 (dd, $J_1$ = 15.6 Hz, $J_2$ = 4.2 Hz, 1H), 3.71-3.75 (m, 2H), 3.98 (d, $J$ = 4.8 Hz, 1H), 4.32 (dd, $J_1$ = 13.8 Hz, $J_2$ = 6.6 Hz, 1H), 4.46 (dd, $J_1$ = 15.0 Hz, $J_2$ = 7.8 Hz, 1H), 6.70 (d, $J$ = 8.4 Hz, 2H), 7.02 (d, $J$ = 8.4 Hz, 2H), 7.19 (d, $J$ = 6.6 Hz, 3H), 7.24-7.27 (m, 5H), 7.34 (t, $J$ = 7.5 Hz, 2H), 8.03 (d, $J$ = 7.8 Hz, 1H), 8.08 (brs, 2H), 8.19 (t, $J$ = 5.4 Hz, 2H), 8.52 (d, $J$ = 6.0 Hz, 1H), 9.32 (s, 1H) |
| **11** | 1.04 (d, $J$ = 7.8 Hz, 3H), 1.52 (q, $J$ = 12.0 Hz, 2H), 1.95 (d, $J$ = 12.6 Hz, 2H), 2.07 (t, $J$ = 7.2 Hz, 2H), 2.34-2.37 (m, 2H), 2.73(dd, $J_1$ = 13.5 Hz, $J_2$ = 9.9 Hz, 1H), 2.82-2.91 (m, 4H), 2.97 (dd, $J_1$ = 13.8 Hz, $J_2$ = 3.6 Hz, 2H), 3.10-3.16 (m, 2H), 3.20-3.23 (m, 2H), 3.55-3.59 (m, 1H), 3.71 (dd, $J_1$ = 16.8 Hz, $J_2$ = 5.4 Hz, 1H), 3.96 (m, 1H), 4.31 (m, 1H), 4.53-4.57 (m, 1H), 4.73 (m, 1H), 6.69 (d, $J$ = 8.4 Hz, 2H), 7.01 (d, $J$ = 7.8 Hz, 2H), 7.18-7.19 (m, 1H), 7.27 (m, 7H), 7.29 (d, $J$ = 7.8 Hz, 2H), 7.32 (t, $J$ = 7.2 Hz, 2H), 7.47 (t, $J$ = 7.2 Hz, 1H), 7.53 (t, $J$ = 7.5 Hz, 2H), 8.06 (m, 3H), 8.12 (t, $J$ = 5.7 Hz, 1H), 8.48 (d, $J$ = 7.2 Hz, 1H), 9.30 (brs, 1H), 9.79 (s, 1H), 10.00 (s, 1H) |
| **12** | 1.04 (d, $J$ = 7.8 Hz, 3H), 1.59 (dd, $J_1$ = 12.0 Hz, $J_2$ = 5.4 Hz, 2H), 1.96 (d, $J$ = 7.8 Hz, 2H), 2.33 (d, $J$ = 6.6 Hz, 2H), 2.37-2.39 (m, 4H), 2.60 (m, 1H), 2.76 (dd, $J_1$ = 15.6 Hz, $J_2$ = 10.2 Hz, 1H), 2.83 (dd, $J_1$ = 13.8 Hz, $J_2$ = 7.8 Hz, 1H), 2.88 (dd, $J_1$ = 13.8 Hz, $J_2$ = 6.6 Hz, 1H), 2.96-3.08 (m, 6H), 3.70 -3.75 (m, 2H), 3.95-3.98 (m, 2H), 4.32 (m, 1H), 4.56-4.60 (m, 1H), 6.69 (d, $J$ = 7.8 Hz, 2H), 7.01 (d, $J$ = 8.4 Hz, 2H), 7.18-7.20 (m, 1H), 7.24-7.27 (m, 7H), 7.35 (t, $J$ = 7.5 Hz, 2H), 7.99 (d, $J$ = 7.2 Hz, 1H), 8.04 (brs, 4H), 8.08 (d, $J$ = 9.0 Hz, 1H), 8.13 (t, $J$ = 5.4 Hz, 1H), 8.48 (d, $J$ = 7.8 Hz, 1H), 9.29 (s, 1H), 9.81 (s, 1H), 10.06 (s, 1H) |
| **13** | 0.87 (t, $J$ = 7.2 Hz, 3H), 0.97-1.14 (m, 5H), 1.76-1.82 (m, 4H), 2.60 (t, $J$ = 12.3 Hz, 1H), 2.81-2.89 (m, 2H), 3.05 (t, $J$ = 12.9 Hz, 1H), 3.77–3.96 (m, 4H), 4.34 (t, $J$ = 7.2 Hz, 2H), 4.66 (t, $J$ = 11.7 Hz, 1H) 6.68 (d, $J$ = 8.4 Hz, 2H), 7.00 (d, $J$ = 8.4 Hz, 2H), 7.18 (d, $J$ = 7.2 Hz, 2H), 7.39-7.46 (m, 3H), 8.0-8.05 (m, 3H), 8.44 (t, $J$ = 7.2 Hz, 1H), 9.61 (s, 1H) |
| **14** | 0.86 (t, $J$ = 7.8 Hz, 3H), 1.02 (dd, $J_1$ = 12.0 Hz, $J_2$ = 7.2 Hz, 3H), 1.53-1.80 (m, 4H), 2.68-2.98 (m, 6H), 3.57 (t, $J$ = 5.4 Hz, 2H), 3.66 (t, $J$ = 5.4 Hz, 2H), 3.79-3.89 (m, 1H), 3.98 (m, 1H), 4.28-4.33 (m, 2H), 4.54-4.62 (m, 1H), 4.83-4.91 (m, 1H) 6.70 (d, $J$ = 7.8 Hz, 2H), 6.96-7.23(m, 9H), 7.39-7.43 (m, 1H), 7.48-7.51 (m, 2H), 8.07-8.10 (m, 3H), 8.23 (t, $J$ = 5.7 Hz, 1H), 8.57 (d, $J$ = 7.8 Hz, 1H), 9.34 (s, 1H) |
| **15** | 0.82-0.88 (m, 6H), 0.93 (m, 1H), 1.10 (m, 1H), 1.75-1.81 (m, 4H), 2.15 (s, 6H), 2.19 (d, $J$ = 13.2 Hz, 1H), 2.59(t, $J$ = 6.3 Hz, 1H), 2.82 (dd, $J_1$ = 13.8 Hz, $J_2$ = 4.8 Hz, 1H), 2.97 (dd, $J_1$ = 15.0 Hz, $J_2$ = 2.4 Hz, 1H), 2.95-3.06 (m, 2H), 3.04 (t, $J$ = 12.6 Hz, 1H), 3.75-3.85 (m, 3H), 4.27 (m, 1H), 4.33 (d, $J$ = 12.6 Hz), 4.65 (t, $J$ = 11.7 Hz, 1H), 6.39 (s, 2H), 7.17 (d, $J$ = 7.2 Hz, 2H), 7.40-7.45 (m, 3H), 7.90 (t, $J$ = 5.4 Hz, 1 H), 7.99 (dd, $J_1$ = 11.4 Hz, $J_2$ = 3.0 Hz, 1H), 8.26 (s, 2H) |
| **16** | 0.68-1.05 (m, 9H), 1.48-1.80 (m, 4H), 2.12-2.16(m, 6H), 2.65-2.69(m, 1H), 2.81-2.84 (m, 3H), 2.89-3.01 (m, 2H), 3.49-3.66 (m, 2H), 3.73-3.87 (m, 2H), 4.21-4.32 (m, 2H), 4.61-4.87 (m, 1H), 4.79-4.89 (m, 1H) 6.40 (s, 2H), 6.94-6.98 (m, 3H), 7.09- |

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|---|---|
| | 7.23 (m, 4H), 7.38-7.51 (m, 3H), 8.00-8.07 (m, 3H), 8.23 (d, $J$ = 10.8 Hz, 2H), 9.02 (s, 1H) |
| **17** | 0.87 (t, $J$ = 7.2 Hz, 3H), 0.96 (m, 1H), 1.04 (d, $J$ = 7.2 Hz, 3H), 1.11 (m, 1H), 1.74-1.81 (m, 4H), 2.26 (m, 2H), 2.45-2.56 (m, 3H), 2.75 (dd, $J_1$ = 13.8 Hz, $J_2$ = 10.2 Hz, 1H), 2.83 (dd, $J_1$ = 13.8 Hz, $J_2$ = 7.2 Hz, 1H), 2.89 (dd, $J_1$ = 13.8 Hz, $J_2$ = 6.6 Hz, 1H), 2.99 (dd, $J_1$ = 13.8 Hz, $J_2$ = 3.0 Hz, 1H), 3.05 (t, $J$ = 12.9 Hz, 1H), 3.57 (dd, $J_1$ = 16.8 Hz, $J_2$ = 5.4 Hz, 1H), 3.70 (dd, $J_1$ = 16.8 Hz, $J_2$ = 6.0 Hz, 1H), 3.86 (d, $J$= 12.6 Hz, 1H), 3.96-3.98 (m, 1H), 3.96 (q, $J$ = 6 Hz, 1H), 4.31 (m, 1H), 4.38 (d, $J$ = 12 Hz, 1H), 4.54-4.58 (m, 1H), 4.65 (m, 1H) 6.69 (d, $J$ = 6.6 Hz, 2H), 7.01 (d, $J$ = 6.6 Hz, 2H), 7.19 (d, $J$ = 6.0 Hz, 3H), 7.23 (m, 4H), 7.39-7.44 (m, 3H), 8.02-8.04 (m, 3H), 8.13 (t, $J$ = 5.4 Hz, 1H), 8.50 (d, $J$ = 7.2 Hz, 1H), 9.30 (s, 1H), 9.77 (s, 1H), 10.02 (s, 1H) |