## **Supporting information**

## Synthesis and pharmacological evaluation of hybrids targeting opioid and neurokinin receptors

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## **Table S1.** Physicochemical characterization of hybrids 2-7.

No.	Sequence			m/z	m/z
		Molecular	Molecular	calcul. for	found for
		Formula	Weight	[M+2H] <sup>2+</sup>	[M+2H] <sup>2+</sup>
2	H-Tyr-[D-Lys-Phe-Phe-Asp]-Asn-D-Trp-Phe-D-Trp-Leu-Nle-NH2	C84H102N16O14	1559.8075	780.3953	780.3904
3	H-Tyr-[D-Lys-Phe-Phe-Asp]-D-Trp-Phe-D-Trp-Leu-Nle-NH <sub>2</sub>	C80H96N14O12	1445.7048	723.3739	723.3701
4	H-Tyr-[D-Lys-Phe-Phe-Asp]-Gln-Phe-Phe-Gly-Leu-Met-NH <sub>2</sub>	C73H94N14O14S	1423.6779	712.3470	712.3422
5	H-Tyr-[D-Lys-Phe-Phe-Asp]-Phe-Phe-Gly-Leu-Met-NH <sub>2</sub>	$C_{68}H_{86}N_{12}O_{12}S$	1295.5486	648.3177	648.3129
6	H-Tyr-[D-Lys-Phe-Phe-Asp]-Phe-Gly-Leu-Met-NH <sub>2</sub>	C59H77N11O11S	1148.3748	574.7835	574.7780
7	H-Tyr-[D-Lys-Phe-Phe-Asp]-Gly-Leu-Met-NH <sub>2</sub>	$C_{50}H_{68}N_{10}O_{10}S$	1001.2009	501.2493	501.2438



**Figure S1.** High resolution MS spectrum of peptide H-Tyr-(D-Lys-Phe-Phe-Asp)-Asn-D-Trp-Phe-D-Trp-Leu-Nle-NH<sub>2</sub> (analog 2). In inset, fragment of the experimental spectrum is compared with the simulated isotopic profile calculated for the expected molecular formula of protonated species  $[M+2H]^{2+}$  (bottom panel).



**Figure S2.** High resolution MS spectrum of peptide H-Tyr-(D-Lys-Phe-Phe-Asp)-D-Trp-Phe-D-Trp-Leu-Nle-NH<sub>2</sub> (analog 3). In inset, fragment of the experimental spectrum is compared with the simulated isotopic profile calculated for the expected molecular formula of protonated species  $[M+2H]^{2+}$  (bottom panel).



**Figure S3.** High resolution MS spectrum of peptide H-Tyr-(D-Lys-Phe-Phe-Asp)-Gln-Phe-Gly-Leu-Met-NH<sub>2</sub> (analog 4). In inset, fragment of the experimental spectrum is compared with the simulated isotopic profile calculated for the expected molecular formula of protonated species  $[M+2H]^{2+}$  (bottom panel).



**Figure S4.** High resolution MS spectrum of peptide H-Tyr-(D-Lys-Phe-Phe-Asp)-Phe-Phe-Gly-Leu-Met-NH<sub>2</sub> (analog 5). In inset, fragment of the experimental spectrum is compared with the simulated isotopic profile calculated for the expected molecular formula of protonated species  $[M+2H]^{2+}$  (bottom panel).



**Figure S5.** High resolution MS spectrum of peptide H-Tyr-(D-Lys-Phe-Asp)-Phe-Gly-Leu-Met-NH<sub>2</sub> (analog 6). In inset, fragment of the experimental spectrum is compared with the simulated isotopic profile calculated for the expected molecular formula of protonated species  $[M+2H]^{2+}$  (bottom panel).



**Figure S6.** High resolution MS spectrum of peptide H-Tyr-(D-Lys-Phe-Phe-Asp)-Gly-Leu-Met-NH<sub>2</sub> (analog 7). In inset, fragment of the experimental spectrum is compared with the simulated isotopic profile calculated for the expected molecular formula of protonated species  $[M+2H]^{2+}$  (bottom panel).







Figure S7. Concentration response curves of EM-2 (1) and analogs 2-7 in calcium mobilization experiments.