SUPPORTING INFORMATION

Synthesis of mixed MOR/KOR efficacy cyclic opioid peptide analogs with antinociceptive activity after systemic administration

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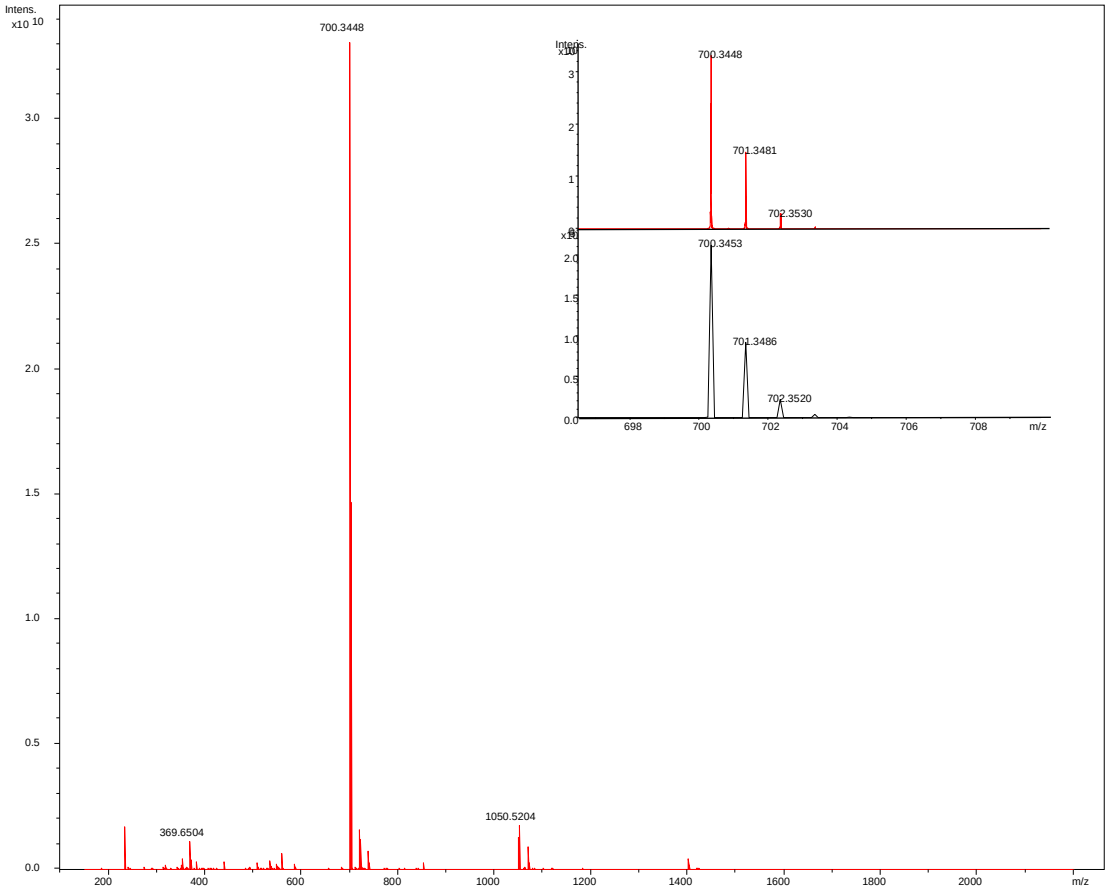

Figure S1. High resolution MS spectrum of peptide Tyr-c(D-Lys-Phe-Phe-Asp)-NH_2 (analog **1**). In inset, fragment of the experimental spectrum is compared with the simulated isotopic profile calculated for the expected molecular formula of protonated species (bottom panel).

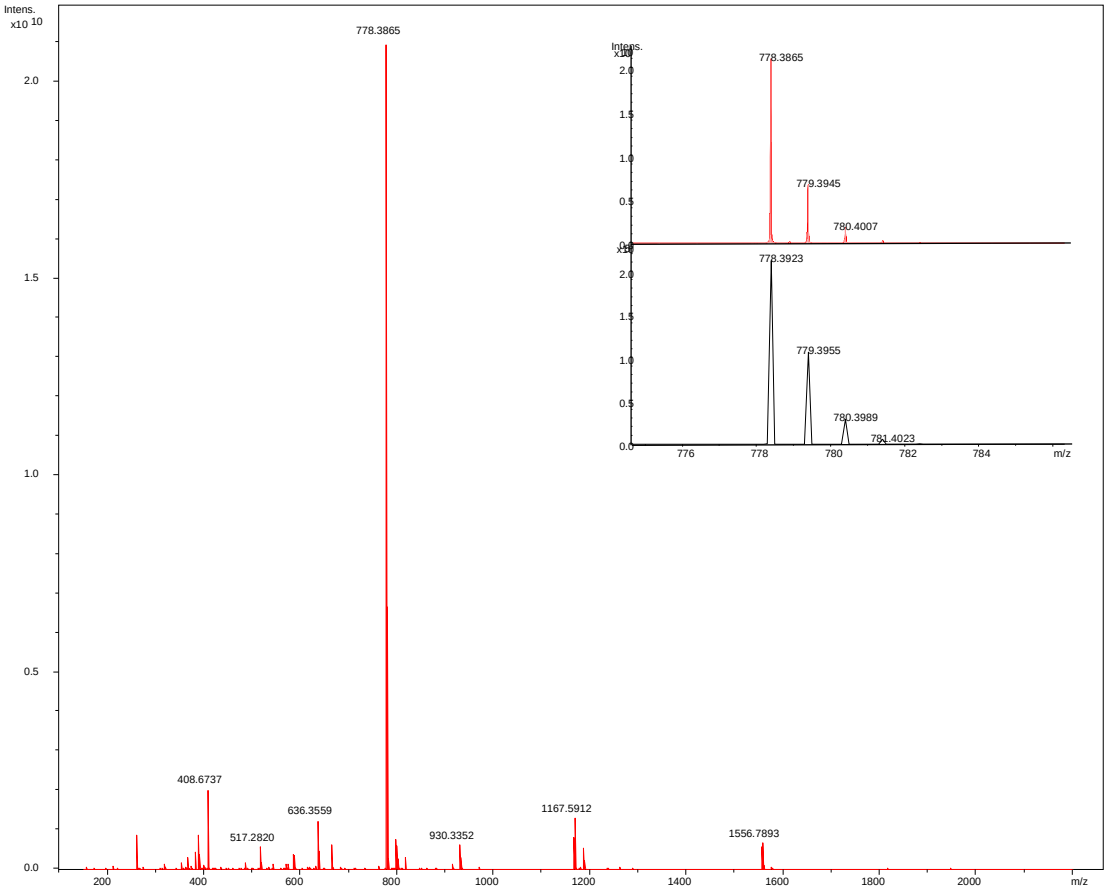

Figure S2. High resolution MS spectrum of peptide Dmt-c(D-Lys-D-1-Nal-Phe-Asp)-NH_2 (analog **2**). In inset, fragment of the experimental spectrum is compared with the simulated isotopic profile calculated for the expected molecular formula of protonated species (bottom panel).

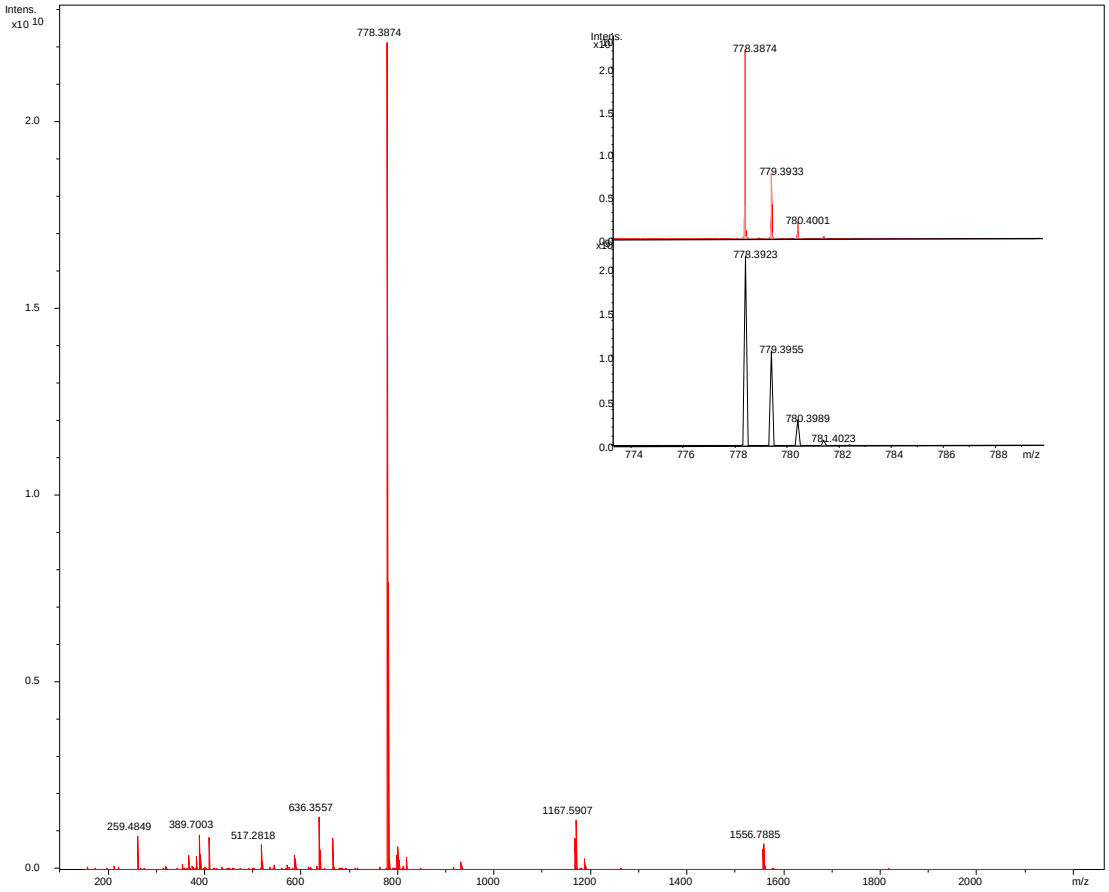

Figure S3. High resolution MS spectrum of peptide Dmt-c(D-Lys-D-2-Nal-Phe-Asp)-NH_2 (analog **3**). In inset, fragment of the experimental spectrum is compared with the simulated isotopic profile calculated for the expected molecular formula of protonated species (bottom panel).

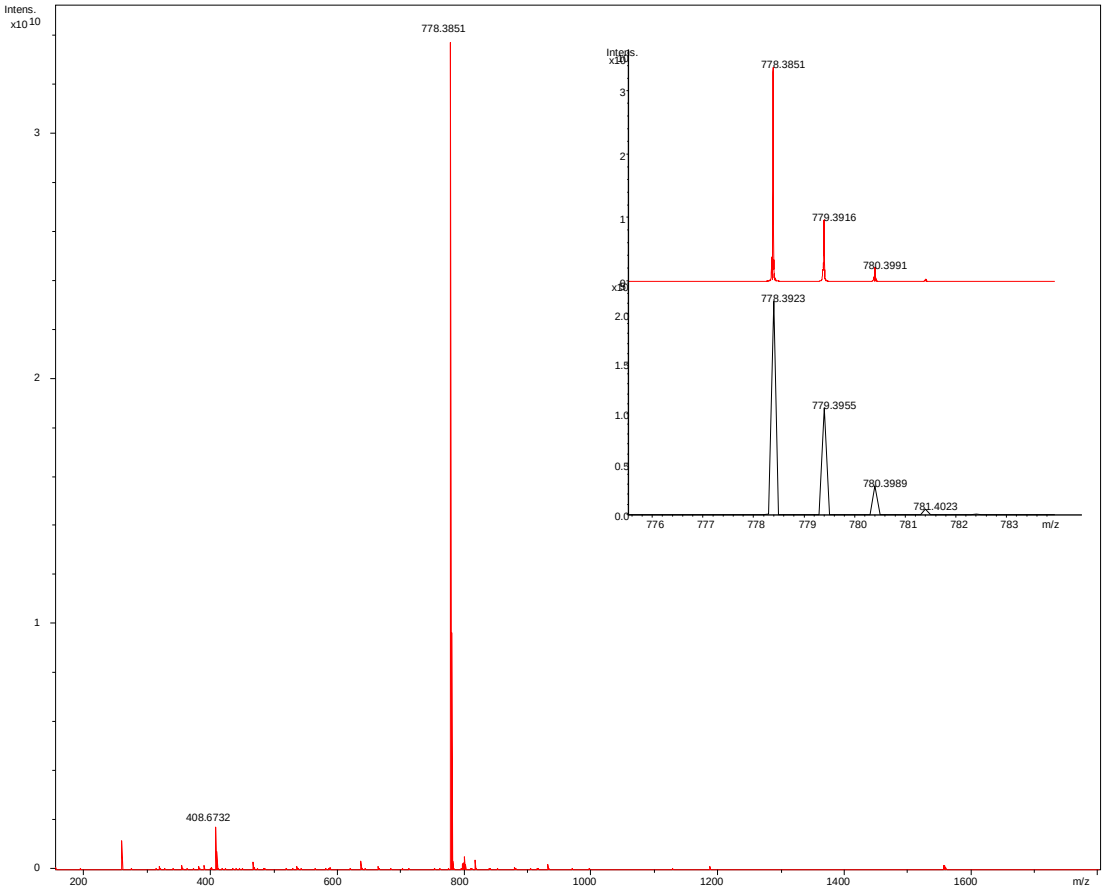

Figure S4. High resolution MS spectrum of peptide Dmt-c(D-Lys-Phe-D-1-Nal-Asp)-NH_2 (analog **4**). In inset, fragment of the experimental spectrum is compared with the simulated isotopic profile calculated for the expected molecular formula of protonated species (bottom panel).

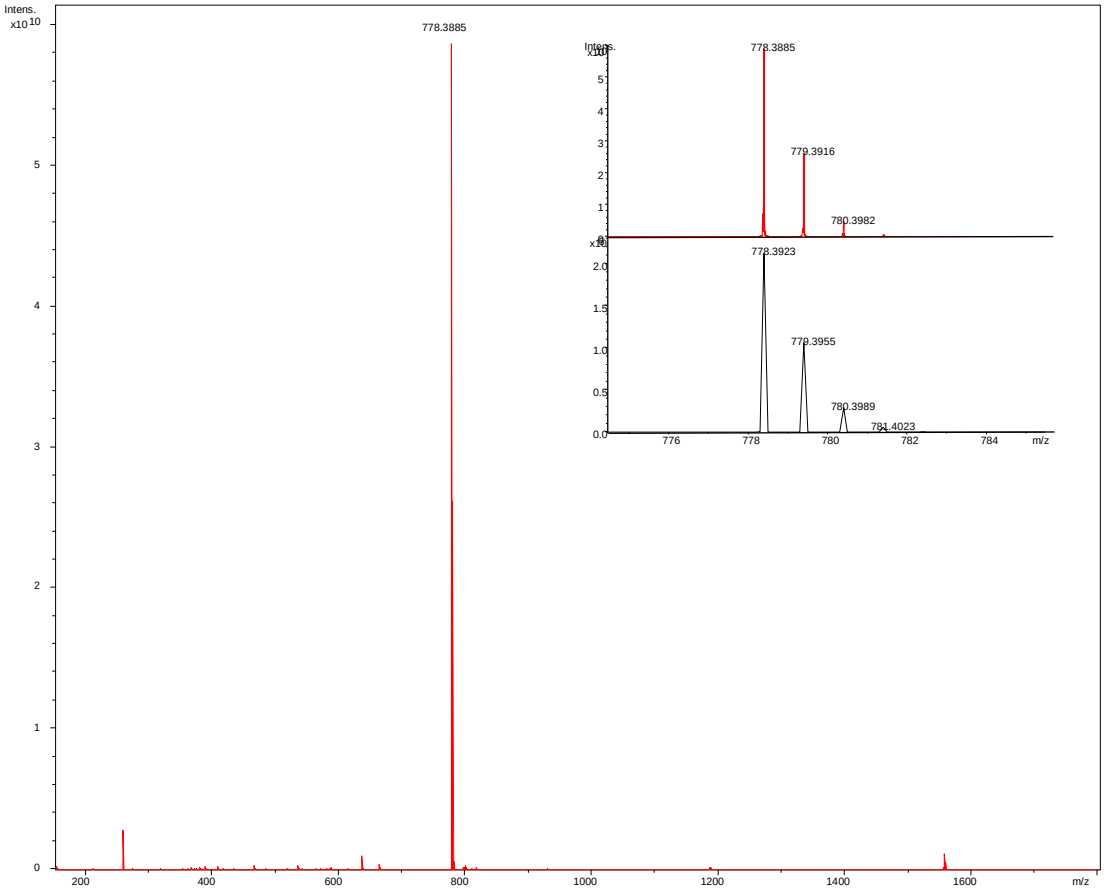

Figure S5. High resolution MS spectrum of peptide Dmt-c(D-Lys-Phe-D-2-Nal-Asp)-NH_2 (analog **5**). In inset, fragment of the experimental spectrum is compared with the simulated isotopic profile calculated for the expected molecular formula of protonated species (bottom panel).

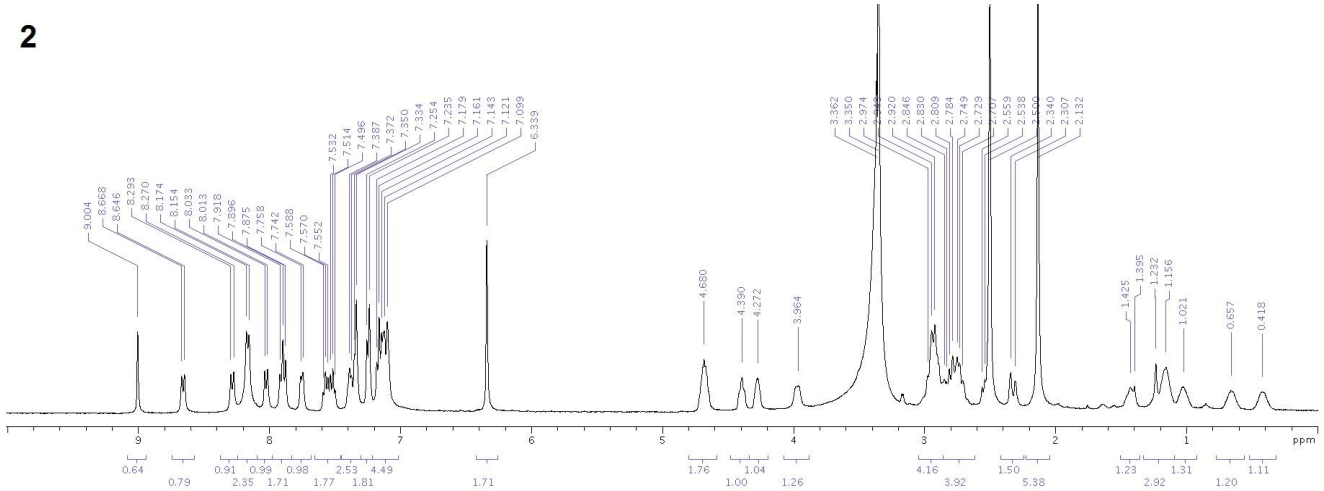

Figure S6. ^{1}H NMR (400 MHz, 8:2 DMSO-d_6/H_2O) for analog **2**.

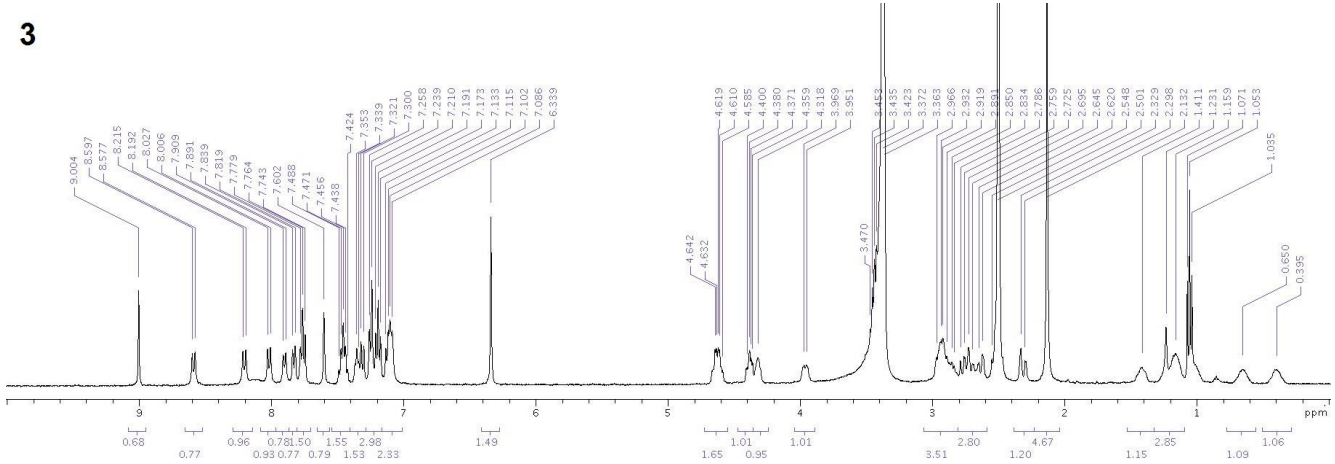

Figure S7. ^{1}H NMR (400 MHz, 8:2 DMSO-d_6/H_2O) for analog **3.**

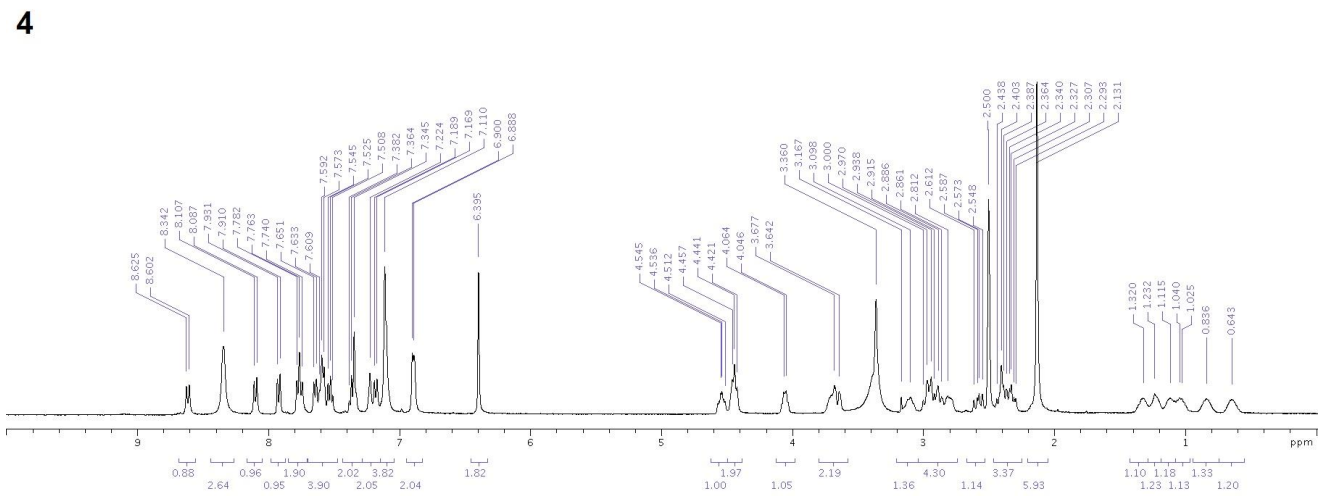

Figure S8. ^{1}H NMR (400 MHz, 8:2 DMSO-d_6/H_2O) for analog **4.**

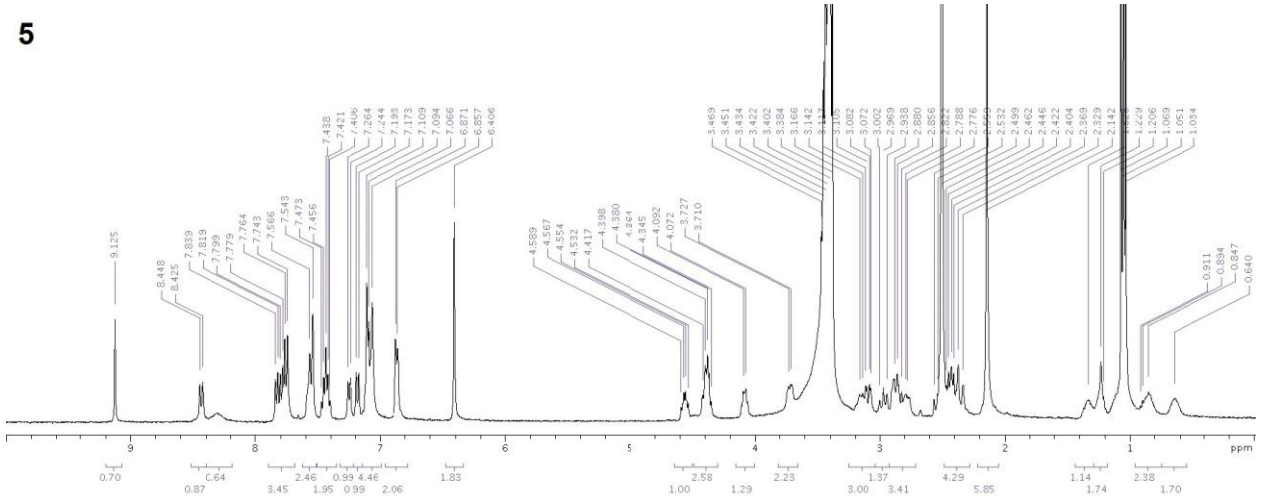

Figure S9. ^{1}H NMR (400 MHz, 8:2 DMSO-d_6/H_2O) for analog **5.**

Table S1. Non-obvious ROESY cross peaks[a] of **2**[b] in DMSO-d_6/H_2O (8:2)

Cross-peak	intensity	Cross-peak	intensity	Cross-peak	intensity
PheNH-PheHβ$_{2.8}$	vs	LysNH-LysHγ$_{0.4}$	s	$CONH_{2\ 7.1}$-AspHα	m
PheNH-PheHβ$_{2.9}$	m	LysNH-LysHγ$_{0.6}$	m	$CONH_{2\ 7.0}$-PheHα	w
PheNH-PheHα	m	LysNH-LysHβ$_{1.2}$	m	NalHα-NalHβ$_{2.8}$	vs
PheNH-NalHα	vs	LysNH-LysHβ$_{1.4}$	w	NalHα-NalHβ$_{2.5}$	vs
PheNH-PheArH	m	LysNH-DmtMe	m	PheHα-PheHβ$_{2.9}$	vs
PheNH-LysNH	w	LysNH-DmtHα	m	PheHα-PheHβ$_{2.8}$	vs
PheNH-NalH$_{2,3}$	w	LysNH-DmtHβ$_{2.8}$	w	PheHα-DmtHα	w
PheNH-AspNH	m	LysNH-AspHα	w	PheHα-NalHα	w
PheNH-NalNH	w	LysNH-NalHα	m	PheHα-AspHα	m
PheNH-NalH$_8$	m	NalH$_7$-LysHα	w	AspHα-AspHβ$_{2.4}$	vs
NalNH-LysHβ$_{1.4}$	vs	LysNHε-LysHγ$_{0.4}$	w	AspHα-AspHβ$_{2.5}$	s
NalNH-NalHβ$_{2.8}$	vs	LysNHε-LysHγ$_{0.6}$	m	AspHα-PheHβ$_{2.8}$	w
NalNH-NalHβ$_{2.9}$	w	LysNHε-LysHδ$_{1.0}$	m	AspHα-PheHβ$_{2.5}$	w
NalNH-LysHα	vs	LysNHε-LysHδ$_{1.2}$	s	AspHα-PheHα	m
NalNH-NalHα	m	LysNHε-AspHβ$_{2.3}$	vs	LysHα-LysHγ$_{0.4}$	w
NalNH-NalH$_{2,3}$	m	LysNHε-AspHβ$_{2.5}$	vs	LysHα-LysHγ$_{0.6}$	m
NalNH-LysNH	w	LysNHε-LysHε$_{2.9}$	vs	LysHα-LysHβ$_{1.2}$	vs
NalNH-AspNH	m	LysNHε- LysHε$_{3.0}$	vs	LysHα-LysHβ$_{1.4}$	vs
DmtNH-DmtMe	w	LysNHε-AspHα	s	LysHα-DmtMe	m
DmtNH-DmtHβ$_{2.8}$	vs	NalH$_{2,3}$-NalHβ$_{2.8}$	vs	LysHα-DmtHβα	w
DmtNH-DmtHβ$_{2.9}$	vs	NalH$_{2,3}$-NalHβ$_{2.5}$	m	DmtHα-DmtMe	s
DmtNH-DmtHα	m	NalH$_{2,3}$-NalHα	s	DmtHα-DmtHβ$_{2.7}$	s
DmtNH-DmtArH	w	NalH$_{2,3}$-LysHα	w	DmtHα-DmtHβ$_{2.9}$	m
NalH$_8$-NalHα	vs	PheArH-PheHβ$_{2.9}$	vs	LysHε$_{3.0}$-LysHγ$_{0.4}$	w
AspNH-AspHβ$_{2.4}$	w	PheArH-PheHβ$_{2.8}$	vs	LysHε$_{3.0}$-LysHγ$_{0.6}$	w
AspNH-AspHβ$_{2.6}$	s	PheArH-AspHα	w	LysHε$_{3.0}$-LysHδ$_{1.2}$	vs
AspNH-PheHβ$_{2.8}$	w	PheArH-LysHα	w	LysHε$_{3.0}$-LysHδ$_{1.4}$	m
AspNH-PheHβ$_{2.9}$	m	PheArH-PheHα	s	LysHε$_{3.0}$-DmtMe	m
AspNH-AspHα	m	$CONH_{2\ 7.1}$-AspHβ$_{2.4}$	m	LysHε$_{2.8}$-LysHγ$_{0.4}$	m
AspNH-PheHα	vs	$CONH_{2\ 7.1}$-AspHβ$_{2.5}$	w	LysHε$_{2.8}$-LysHγ$_{0.6}$	w
AspNH-DmtArH	w	$CONH_{2\ 7.1}$-AspHα	vs	LysHε$_{2.8}$-LysHδ$_{1.2}$	m
AspNH-$CONH_2$	m	$CONH_{2\ 7.0}$-AspHβ$_{2.4}$	w	LysHε$_{2.8}$-LysHδ$_{1.4}$	s
AspNH-LysHε	w	$CONH_{2\ 7.0}$-AspHβ$_{2.5}$	w		

[a] vs = very strong, s = strong, m = medium, w = weak; [b] stereochemistry has been omitted

Table S2. Non-obvious ROESY cross peaks[a] of **3**[b] in DMSO-d_6/H_2O (8:2)

Cross-peak	intensity	Cross-peak	intensity	Cross-peak	intensity
DmtOH-LysH$\gamma_{0.4}$	w	LysNH-DmtHα	vs	PheHα-PheH$\beta_{2.9}$	s
DmtOH-LysH$\delta_{1.0}$	w	LysNH-LysHα	m	AspHα-AspH$\beta_{2.3}$	s/vs
DmtOH-LysH$\beta_{1.4}$	w/m	LysNH-LysNHε	w	AspHα-AspHβ	m
DmtOH-LysHα	w	NalH$_1$-NalH$\beta_{2.5}$	vs	AspHα-LysH$\varepsilon_{2.8}$	w
PheNH-NalH$\beta_{2.5}$	w/m	NalH$_1$-NalH$\beta_{2.6}$	vs	LysHα-LysH$\gamma_{0.4}$	w
PheNH-NalH$\beta_{2.6}$	m	NalH$_1$-NalHα	vs	LysHα-LysH$\gamma_{0.7}$	m
PheNH-PheH$\beta_{2.7}$	vs	LysNHε-LysH$\gamma_{0.4}$	w	LysHα-LysH$\beta_{1.2}$	vs
PheNH-PheH$\beta_{2.9}$	w	LysNHε-LysH$\gamma_{0.7}$	w	LysHα-LysH$\beta_{1.4}$	vs
PheNH-DmtHα	w	LysNHε-LysH$\delta_{1.2}$	m/w	LysHα-DmtMe	w/m
PheNH-LysHα	w	LysNHε-AspH$\beta_{2.3}$	s	LysHα-DmtH$\beta_{2.7}$	w
PheNH-PheHα	m	LysNHε-AspH$\beta_{2.5}$	vs	DmtHα-LysH$\gamma_{0.4}$	w
PheNH-NalHα	vs	LysNHε-LysHε	vs	DmtHα-LysH$\beta_{1.4}$	w
PheNH-PheArH	m/s	LysNHε-AspHα	m	DmtHα-DmtMe	vs
NalNH-LysH$\gamma_{0.4}$	w	NalH$_3$-NalH$\beta_{2.5}$	s	DmtHα-DmtH$\beta_{2.7}$	s/vs
NalNH-LysH$\beta_{1.4}$	vs	NalH$_3$-NalH$\beta_{2.6}$	m/s	DmtHα-DmtH$\beta_{2.9}$	m/w
NalNH-NalH$\beta_{2.5}$	vs	NalH$_3$-NalHα	s	DmtH$\beta_{2.5}$-DmtMe	vs
NalNH-NalH$\beta_{2.5}$	vs	PheArH$_{2,6}$-PheH$\beta_{2.7}$	vs	LysH$\varepsilon_{2.9}$-LysH$\delta_{1.0}$	s
NalNH-NalH$\beta_{2.6}$	w	PheArH$_{2,6}$-PheH$\beta_{2.9}$	vs	LysH$\varepsilon_{2.9}$-LysH$\delta_{1.1}$	s
NalNH-LysHα	vs	PheArH$_{2,6}$-PheHα	s/vs	LysH$\varepsilon_{2.9}$-LysH$\beta_{1.4}$	m/w
NalNH-NalHα	m	PheArH$_2$-NalH$\beta_{2.5}$	w	LysH$\varepsilon_{2.8}$-LysH$\gamma_{0.4}$	m
NalNH-NalH$_3$	m	PheArH$_2$-NalH$\beta_{2.6}$	w/m	LysH$\varepsilon_{2.8}$-LysH$\delta_{1.0}$	m
NalNH-NalH$_1$	w	PheArH$_{3\text{-}5}$-PheH$\beta_{2.7}$	m	LysH$\varepsilon_{2.8}$-LysH$\delta_{1.1}$	m
AspNH-LysH$\gamma_{0.4}$	w	PheArH$_{3\text{-}5}$-PheH$\beta_{2.9}$	m	LysHε-LysH$\beta_{1.4}$	m/w
AspNH-LysH$\delta_{1.0}$	w	CONH$_2$-AspH$\beta_{2.3}$	w	DmtH$\beta_{2.7}$-DmtMe	s
AspNH-AspH$\beta_{2.5}$	vs	CONH$_2$-AspH$\beta_{2.5}$	w	DmtMe-LysH$\gamma_{0.4}$	m
AspNH-AspHα	m	CONH$_2$-PheH$\beta_{2.7}$	w	DmtMe-LysH$\delta_{1.1}$	s
AspNH-PheHα	vs	CONH$_2$-LysH$\varepsilon_{2.9}$	w	DmtMe-LysH$\beta_{1.4}$	w
AspNH-PheArH	vs	CONH$_2$-AspHα	vs	LysH$\beta_{1.4}$-LysH$\gamma_{0.4}$	w
AspNH-CONH$_{2\ 7.2}$	m/w	NalHα-LysH$\beta_{1.4}$	w	LysH$\beta_{1.4}$-LysH$\gamma_{0.7}$	m/s
AspNH-LysNHε	m	NalHα-DmtMe	w	LysH$\beta_{1.4}$-LysH$\delta_{1.0}$	w
LysNH-LysH$\gamma_{0.4}$	s	NalHα-NalH$\beta_{2.5}$	m	LysH$\beta_{1.1}$-LysH$\gamma_{0.4}$	s
LysNH-LysH$\gamma_{0.7}$	w	NalHα-NalH$\beta_{2.6}$	m/s	LysH$\beta_{1.1}$-LysH$\gamma_{0.7}$	m
LysNH-LysH$\delta_{1.2}$	w	PheHα-NalH$\beta_{2.5}$	m	LysH$\delta_{1.0}$-LysH$\gamma_{0.4}$	m/s
LysNH-LysH$\beta_{1.4}$	w	PheHα-NalH$\beta_{2.6}$	m	LysH$\delta_{1.0}$-LysH$\gamma_{0.7}$	m
LysNH-DmtMe	w	PheHα-PheH$\beta_{2.7}$	s		

[a] vs = very strong, s = strong, m = medium, w = weak; [b] stereochemistry has been omitted

Table S3. Non-obvious ROESY cross peaks of **4**[b] in DMSO-d_6/H_2O (8:2)

Cross-peak	intensity	Cross-peak	intensity	Cross-peak	intensity
NalNH-PheH$\beta_{2.3}$	m	LysNHε-LysH$\beta_{1.0}$	w	DmtArH-LysH$\gamma_{0.6}$	w
NalNH-PheH$\beta_{2.4}$	w	LysNHε-LysH$\delta_{1.1}$	s	DmtArH-LysH$\beta_{1.0}$	w
NalNH-NalH$\beta_{3.0}$	vs	LysNHε-LysH$\delta_{1.2}$	w	DmtArH-LysH$\delta_{1.2}$	w
NalNH- NalH$\beta_{3.6}$	w	LysNHε-PheH$\beta_{2.3}$	w	DmtArH-LysH$\delta_{1.4}$	m
NalNH-LysHα	w	LysNHε-AspH$\beta_{2.4}$	m	DmtArH-LysH$\beta_{1.5}$	w
NalNH-PheHα	vs	LysNHε-AspH$\beta_{2.4}$	vs	DmtArH-LysH$\varepsilon_{2.7}$	w
NalNH-NalHα	s	LysNHε-LysH$\varepsilon_{2.8}$	s	DmtArH-LysH$\varepsilon_{3.2}$	w
NalNH-PheArH	w	LysNHε-LysH$\varepsilon_{3.2}$	s	DmtArH-LysHα	w
NalNH-PheNH	w	LysNHε-LysHα	w	NalHα-LysHα	w
NalNH-$NalH_2$	m	LysNHε-DmtHα	w	NalHα-NalH$\beta_{3.6}$	s
NalNH-AspNH	s	$NalH_{2,3}$-PheH$\beta_{2.3}$	w	NalHα-NalH$\beta_{2.9}$	s
DmtNH-DmtMe	m	$NalH_{2,3}$-NalH$\beta_{3.0}$	vs	NalHα-PheH$\beta_{2.3}$	w
DmtNH-DmtH$\beta_{2.5}$	s	$NalH_{2,3}$-NalH$\beta_{3.6}$	m	PheHα-LysHα	w
DmtNH-DmtH$\beta_{3.0}$	m	$NalH_{2,3}$-NalHα	m	PheHα-PheH$\beta_{2.4}$	s
DmtNH-DmtHα	vs	$CONH_{2\ 7.2}$-AspHα	vs	PheHα-PheH$\beta_{2.3}$	s
$NalH_8$-NalH$\beta_{3.0}$	vs	$CONH_{2\ 7.2}$-AspH$\beta_{2.6}$	m	AspHα-AspH$\beta_{2.4}$	s
$NalH_8$-NalH$\beta_{3.6}$	vs	$CONH_{2\ 7.2}$-AspH$\beta_{2.4}$	w	AspHα-AspH$\beta_{2.6}$	m
$NalH_8$-NalHα	vs	$CONH_{2\ 7.2}$-NalH$\beta_{3.0}$	w	LysHα-DmtHα	w
LysNH-LysH$\gamma_{0.6}$	vs	PheNH-LysH$\gamma_{0.6}$	w	LysHα-DmtHβ	w
LysNH-LysH$\gamma_{0.8}$	m	PheNH-LysH$\gamma_{0.8}$	m	LysHα-DmtHMe	s
LysNH-LysH$\beta_{1.0}$	s	PheNH-LysH$\beta_{1.0}$	s	LysHα-LysH$\beta_{1.3}$	vs
LysNH-LysH$\beta_{1.3}$	s	PheNH-LysH$\beta_{1.3}$	w	LysHα-LysH$\delta_{1.1}$	m
LysNH-DmtMe	m	PheNH-PheH$\beta_{2.4}$	s	LysHα-LysH$\beta_{1.0}$	vs
LysNH-DmtH$\beta_{3.0}$	w	PheNH-PheH$\beta_{2.31}$	s	LysHα-LysH$\delta_{0.5}$	m
LysNH-DmtHα	vs	PheNH-DmtHα	w	LysHα-LysH$\delta_{0.6}$	m
LysNH-LysHα	m/s	PheNH-LysHα	m	DmtHα-DmtHβ	vs
LysNH-PheNH	m	PheNH-PheHα	m	DmtHα-DmtMe	s
AspNH-AspH$\beta_{2.4}$	m	PheNH-NalHα	w	LysH$\varepsilon_{3.2}$-LysH$\delta_{1.2}$	vs
AspNH-AspH$\beta_{2.6}$	vs	$CONH_{2\ 7.1}$-AspHα	w	LysH$\varepsilon_{3.2}$-LysH$\delta_{1.1}$	s
AspNH-NalH$\beta_{3.0}$	w	$PheArH_{6,9}$-PheH$\beta_{2.44}$	vs	LysH$\varepsilon_{3.2}$-LysH$\beta_{1.0}$	m
AspNH-NalH$\beta_{3.6}$	m	$PheArH_{6,9}$-PheH$\beta_{2.31}$	vs	LysH$\varepsilon_{3.2}$-LysH$\gamma_{0.6}$	s
AspNH-AspHα	m	$PheArH_{6,9}$-NalH$\beta_{3.0}$	w	LysH$\varepsilon_{3.2}$-LysH$\gamma_{0.8}$	m
AspNH-NalHα	s	$PheArH_{6,9}$-LysHα	w	LysH$\varepsilon_{2.6}$-LysH$\delta_{1.2}$	vs
LysNHε-LysH$\gamma_{0.6}$	m	$PheArH_{6,9}$-PheHα	s	LysH$\varepsilon_{2.6}$-LysH$\delta_{1.2}$	vs
LysNHε-LysH$\gamma_{0.8}$	m	$PheArH_{6,9}$-NalHα	w		

[a] vs = very strong, s = strong, m = medium, w = weak; [b] stereochemistry has been omitted

Table S4. Non-obvious ROESY cross peaks[a] of **5**[b] in DMSO-d_6/H_2O (8:2)

Cross-peak	intensity	Cross-peak	intensity	Cross-peak	intensity
DmtOH-LysHδ	w	AspNH-AspHα	m	AspHα-NalHβ$_{3.1}$	w
DmtOH-DmtHα	w	AspNH-NalHα	m	AspHα-LysHε$_{3.2}$	m
NalNH-PheHβ	m	PheNH-LysHβ$_{1.0}$	w	PheHα-PheHβ	vs
NalNH-NalHβ$_{2.8}$	vs	PheNH-PheHα	w	LysHα-LysHγ$_{0.6}$	w
NalNH-NalHβ$_{3.1}$	w	PheNH-PheHα	m	LysHα-LysHγ$_{0.9}$	w
NalNH-PheHα	vs	NalH$_3$-PheHβ	w	LysHα-LysHβ$_{1.0}$	s
NalNH-NalHα	s	NalH$_3$-NalHβ$_{2.8}$	s	LysHα-LysHδ$_{1.1}$	m
NalNH-PheArH	w	NalH$_3$-NalHβ$_{3.1}$	s	LysHα-LysHδ$_{1.3}$	w
NalNH-NalH$_3$	w	NalH$_3$-NalHα	s	LysHα-LysHβ$_{1.4}$	s
NalNH-NalH$_1$	vs	NalH$_3$-PheHα	w	DmtHα-DmtMe	s
LysNH-LysHγ$_{0.6}$	vs	PheArH-NalHβ$_{3.1}$	w	DmtHα-DmtHβ$_{2.9}$	m
LysNH-LysHγ$_{0.9}$	w	CONH$_2$-LysHδ	w	DmtHα-DmtHβ$_{3.0}$	m
LysNH-LysHβ$_{1.0}$	s	CONH$_2$-AspHβ$_{2.3}$	s	LysHε$_{3.2}$-LysHγ$_{0.6}$	w
LysNH-LysHβ$_{1.4}$	m	CONH$_2$-AspHβ$_{2.5}$	m	LysHε$_{3.2}$-LysHγ$_{0.9}$	w
LysNH-DmtMe	w	CONH$_2$-LysHε$_{3.2}$	w	LysHε$_{3.2}$-LysHβ$_{1.0}$	m
LysNH-DmtHα	vs	CONH$_2$-AspHα	s	LysHε$_{3.2}$-LysHδ$_{1.1}$	s
LysNH-LysHα	m	PheArH$_{2,6}$-PheHα	s	LysHε$_{3.2}$-LysHδ$_{1.3}$	s
LysNH-PheNH	m	PheArH$_{2,6}$-AspHβ$_{2.3}$	m	LysHε$_{3.2}$-AspHβ$_{2.8}$	w
LysNHε-LysHγ$_{0.6}$	w	DmtArH-LysHγ$_{0.6}$	w	LysHε$_{2.8}$-LysHδ$_{1.1}$	s
LysNHε-LysHγ$_{0.9}$	w	DmtArH-LysHβ$_{1.0}$	m	LysHε$_{2.8}$-LysHδ$_{1.3}$	s
LysNHε-LysHδ$_{1.1}$	vs	DmtArH-LysHδ$_{1.1}$	m	AspHβ$_{2.5}$-LysHγ$_{0.6}$	m
LysNHε-AspHβ$_{2.3}$	s	DmtArH-LysHβ$_{1.4}$	w	AspHβ$_{2.3}$-LysHγ$_{0.9}$	w
LysNHε-AspHβ$_{2.5}$	s	NalHα-NalHβ$_{2.8}$	s	AspHβ$_{2.3}$-LysHδ$_{1.1}$	w
LysNHε-LysHε$_{2.8}$	s	NalHα-NalHβ$_{3.1}$	vs	LysHβ$_{1.3}$-LysHγ$_{0.6}$	w
LysNHε-LysHε$_{3.2}$	m	NalHα-AspHβ$_{2.3}$	w	LysHβ$_{1.3}$-LysHγ$_{0.9}$	s
AspNH-AspHβ$_{2.3}$	m	NalHα-PheHα	w	LysHδ$_{1.3}$-LysHγ$_{0.6}$	s
AspNH-AspHβ$_{2.5}$	s	AspHα-AspHβ$_{2.3}$	vs	LysHδ$_{1.1}$-LysHγ$_{0.6}$	m
AspNH-NalHβ$_{2.8}$	m	AspHα-AspHβ$_{2.5}$	m	LysHδ$_{1.1}$-LysHγ$_{0.9}$	m
AspNH-NalHβ$_{3.1}$	m	AspHα-NalHβ$_{2.9}$	w	LysHβ$_{1.0}$-LysHγ$_{0.6}$	m

[a] vs = very strong, s = strong, m = medium, w = weak; [b] stereochemistry has been omitted

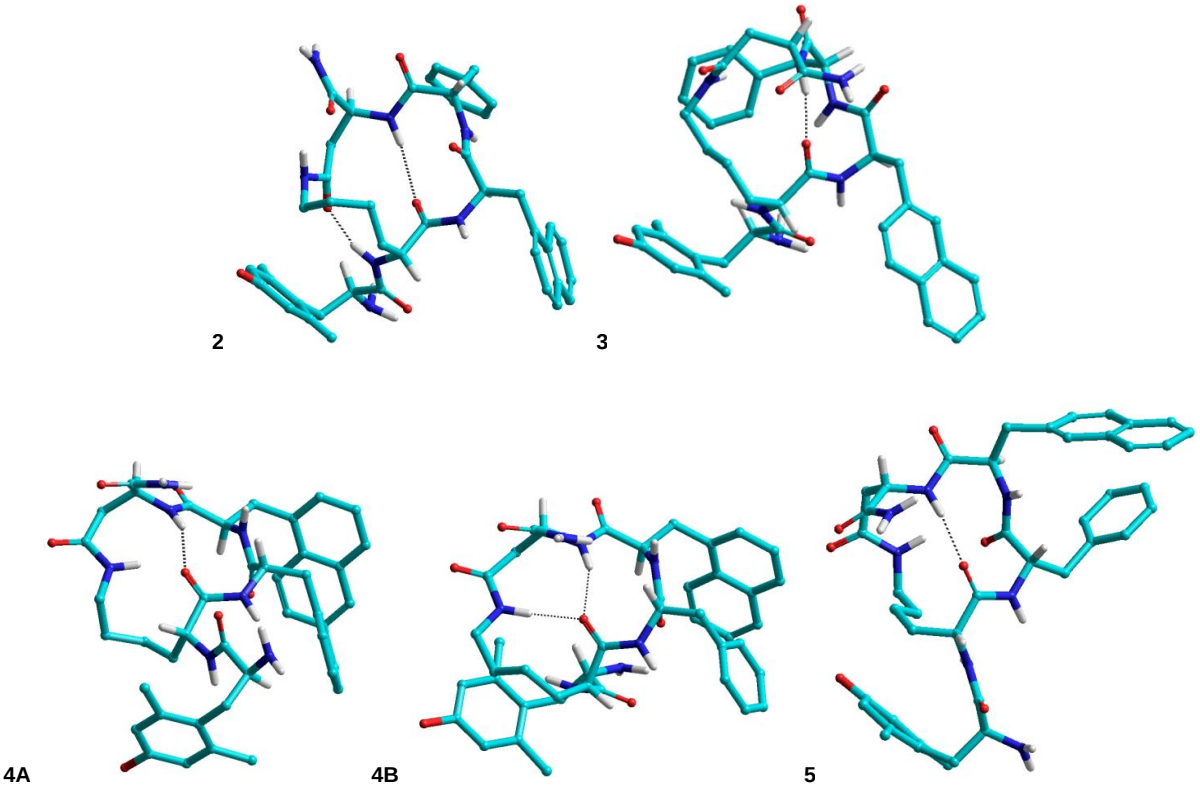

Figure S10. Representative lowest energy structures of **2-5**, calculated by ROESY-restrained MD in a 30x30x30 Å box of standard TIP3P water molecules. Only amide and α-protons are shown.

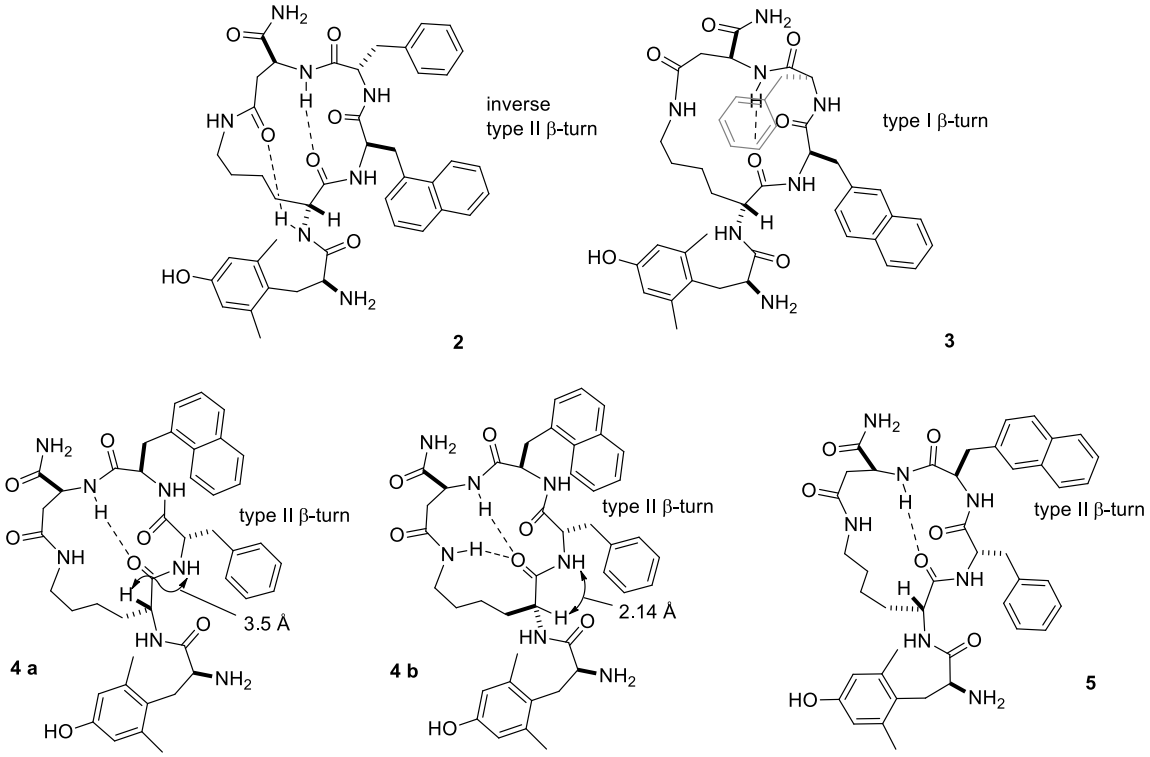

Figure S11. Sketches of the structures of **2-5** showing well-defined secondary structures, to be compared to Figure S1.

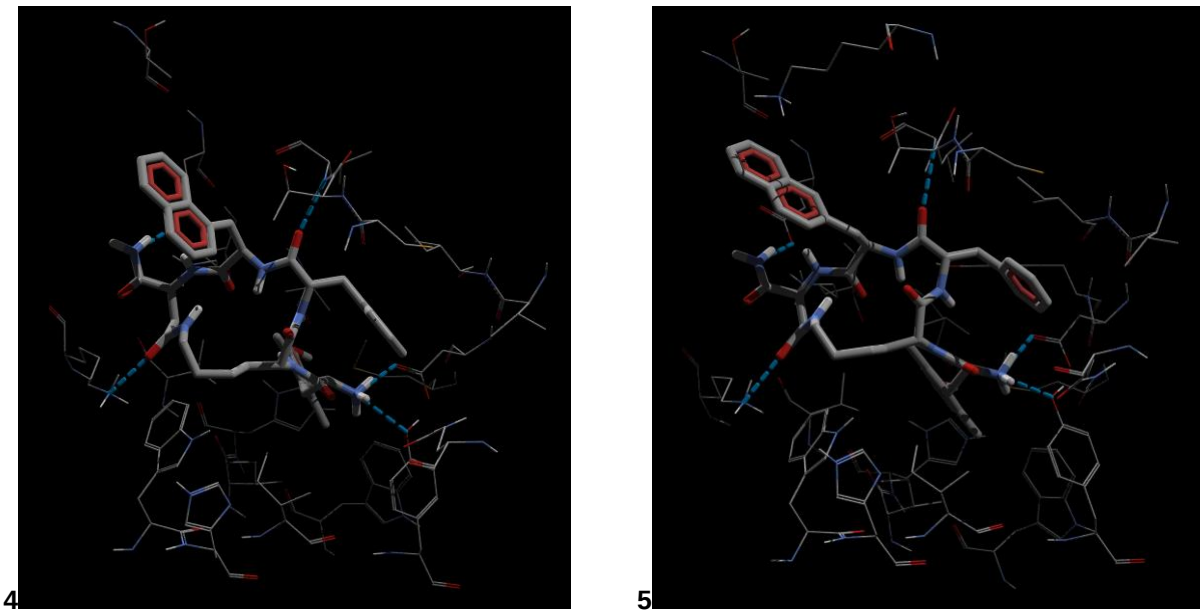

Figure S12. Schematic 3D diagrams of the interactions between analog **4** (A) and analog **5** (B) with hMOR. Residues belonging to the hMOR receptor are shown in wireframe, while the ligands are in stick. Hydrogen bonds are represented by dashed lines.

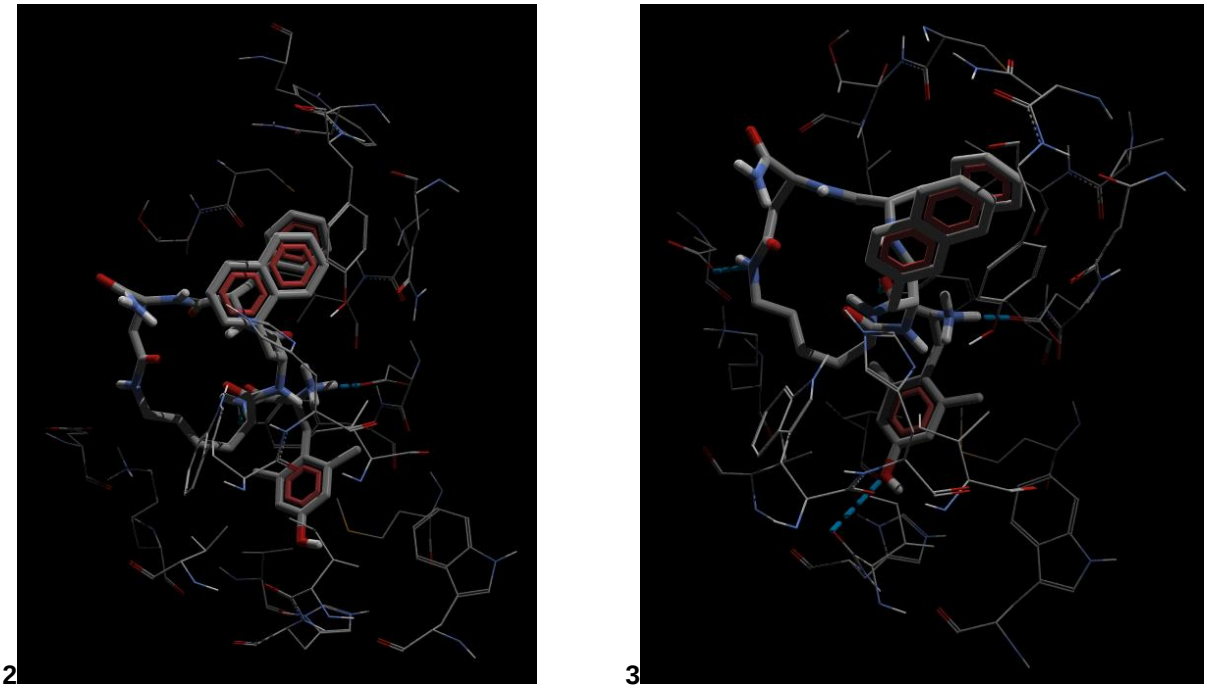

Figure S13. Schematic 3D diagrams of the interactions between analog **2** (A) and analog **3** (B) with hMOR. Residues belonging to the hMOR receptor are shown in wireframe, while the ligands are in stick. Hydrogen bonds are represented by dashed lines.