Table S6: ***Comparison of the receptor–ligand contacts in complexes of MC4R with the agonists NDP-α-MSH and setmelanotide as well as the antagonist SHU9119.*** Interactions of all relevant amino acids of the MC4R the calcium ion (Ca^{2+}) and water molecules within the ligand binding pocket towards the binding peptides NDP-α-MSH, setmelanotide and SHU9119 were summarized based on the Tables S2-4. Amino acids were abbreviated as one letter code, capital numbers display the position within the receptor or peptide (in the pdb file), and superscripted numbering refers to the conserved *HxRW* motif of the binding peptides. D-Nal corresponds to (2R)-2-amino-3-(naphthalene-2-YL)propanoic acid abbreviated as 4J2 in the protein database (PDB ID: 6w25). D-phenylalanine, D-alanine and norleucine are abridged as three letter code Dpn, Dal and Nle, respectively.

MC4R	**NDP-α-MSH** (agonist); (PDB ID: 7PIV, this study)	**Setmelanotide** (agonist); (PDB ID: 7PIU, this study)	**SHU9119** (antagonist); (PDB ID: 6w25)
F51	$H6^{0}$	$H4^{0}$	-
N97 (L97 - antagonized structure)	-	-	$Dnal4^{1}$
E100	$Nle4^{-2}$, $E5^{-1}$	A: $Dpn5^{1}$ B: $Dal3^{-1}$	$H3^{0}$, $Dnal4^{1}$, $D2^{-1}$
T101	$H6^{0}$	$H4^{0}$	$H3^{0}$
V103	-	-	$Nle1^{-2}$
I104	$Nle4^{-2}$	$Dal3^{-1}$	$Nle1^{-2}$, $D2^{-1}$, $H3^{0}$
T118	-	-	$Nle1^{-2}$
D122	$Nle4^{-2}$	$R1^{-3}$, $R6^{2}$	$Nle1^{-2}$, $D2^{-1}$, $R5^{2}$
N123	-	$R6^{2}$	$R5^{2}$
D126	$Dpn7^{1}$, $R8^{2}$	$Dpn5^{1}$, $Arg6^{2}$	$Dnal4^{1}$, $Arg5^{2}$
I129	$Dpn7^{1}$	$Dpn5^{1}$	$Dnal4^{1}$
C130	-	-	$Dnal4^{1}$
L133*	-	$Dpn5^{1}$	$Dnal4^{1}$
I185*	$R8^{2}$	-	$Dnal4^{1}$, $R5^{2}$
S188	$R8^{2}$, $W9^{3}$	$R6^{2}$, $W7^{3}$	$R5^{2}$, $W6^{3}$
V193	$W9^{3}$	-	-
I194	$W9^{3}$	$W7^{3}$	$W6^{3}$
L197	$W9^{3}$	$W7^{3}$	$Dnal4^{1}$, $W6^{3}$
F261	-	$Dpn5^{1}$	$Dnal4^{1}$
H264	$W9^{3}$, $G10^{4}$	$W7^{3}$, $C8^{4}$	$W6^{3}$, $K7^{4}$, $NH_2 8^{5}$
L265	-	-	$W6^{3}$
Y268	$W9^{3}$, $K11^{5}$, $P12^{6}$	$W7^{3}$	$W6^{3}$, $K7^{4}$
M281	-	-	$NH_2 8^{5}$
F284	$H6^{0}$, $R8^{2}$, $G10^{4}$	$H4^{0}$, $R6^{2}$, $C8^{4}$	$H3^{0}$, $R5^{2}$, $K7^{4}$
N285	-	$H4^{0}$	-
L288	$H6^{0}$, $Dpn7^{1}$	$H4^{0}$	$H3^{0}$, $Dnal4^{1}$
Ca^{2+}	MC4R: E100, D122, D126; Ligand: $E5^{-1}$, $Dpn7^{1}$	MC4R: E100, D122, D126; Ligand: $Dpn5^{1}$	MC4R: E100, D122, D126; Ligand: $D2^{-1}$, $Dnal4^{1}$
water 30	-	$Dal3^{-1}$, $H4^{0}$, $C8^{4}$, Q43, F284, N285	-
water 43	$Nle4^{-2}$	-	-

water 63	-	$R1^{-3}$, $R6^{2}$	-
water 101	-	-	$D2^{-1}$, $H3^{0}$, $K7^{4}$,
water 102	-	-	$R5^{2}$, $W6^{3}$, Y268, water 103, water 104
water 103	-	-	$W6^{3}$, $K7^{4}$, Y268, water102, water 105
water 104	-	-	$Dnal4^{-1}$, $R5^{2}$, $W6^{3}$, $K7^{4}$, water 102, water 105
water 105	-	-	$D2^{-1}$, $K7^{4}$, water 103, water 104