Table S1: ***Data collection, processing, and refinement statistics***

	NDP-α-MSH-MC4R-G_sαβγ-Nb35 complex PDB entry 7PIV EMDB entry EMD-13454	**Setmelanotide-MC4R-G_sαβγ-Nb35 complex** PDB entry 7PIU EMDB entry EMD-13453
Magnification	96000	
Voltage (kV)	300	
Electron exposure (e^-/ Å^2)	40	
Defocus range (μm)	-0.8 / -2.0	
Pixel size (Å)	0.832	
Symmetry imposed	*C1*	
Micrographs used (total)	5403 (5618)	6979 (7583)
Initial particle image (no.)	2746119	4330500
Final particle images (no.)	221682	370621
Map resolution (Å)	2.86	2.58
FSC threshold	0.143	0.143
Refinement		
Initial model used (PDB entries)	6W25 / 3SN6	NDP-MC4R-G_sαβγ-Nb35
Model resolution (Å)	2.88	2.60
Model resolution range (Å)	233 – 2.88	233 – 2.60
Map sharpening B factor (Å^2)	-99	-36
Model composition		
Total atoms	7814	7788
Water	115	88
Protein atoms	7696	7696
B-factors (Å^2)		
Overall	69.37	48.11
R.m.s. deviations bond length (Å)	0.013	0.013
R.m.s. deviations bond angle (°)	1.705	1.707
Validation		
Molprobity score	1.54	1.42
Clash score	3.53	3.39
Poor rotamers (%)	0.86	0.97
Ramachandran plot		
Favoured (%)	94.09	95.77
Allowed (%)	5.70	4.13
Disallowed (%)	0.21	0.11