



**Fig. S21: Cryo-EM map differences of the NDP- $\alpha$ -MSH-MC4R-Gs-Nb35 and setmelanotide-MC4R-Gs-Nb35 complexes at H158<sup>IL2</sup> in the IL2-Gs interface.**

(a) Close-up view shows for H158<sup>IL2</sup> a double conformation in the NDP- $\alpha$ -MSH-MC4R-Gs-Nb35 complex,

(b) but not for the setmelanotide-MC4R-Gs-Nb35 complex.

(c) Superimposition of both complexes underlines the structural differences between the two activated MC4R and point out that MC4R agonists effect the IL2 conformation. NDP- $\alpha$ -MSH-MC4R, the corresponding Gs-protein, setmelanotide-MC4R and its Gs-protein are colored orange, dark green, yellow and slate, respectively. Amino acids are visualized as sticks and the protein as ribbon. Cryo-EM maps are displayed as mesh and volume, contoured at 4  $\sigma$  level and colored corresponding to the displayed proteins.