



**Supplementary information, Fig. S5** Structural analysis of the ligand-binding pocket (LBP) of MC2R. **a.** Comparison of the LBP of MC2R, MC1R and MC4R. MC2R, MC1R and MC4R surfaces are colored with light pink, light green and light yellow, respectively, ACTH,  $\alpha$ -MSH (bound to MC1R) and  $\alpha$ -MSH (bound to MC4R) are shown as sphere colored with deep pink, forest green and orange, respectively. **b.** Electrostatic surface of MC2R (left) in comparison with MC1R (middle) and MC4R (right), two black circle areas indicate the positive charged bilateral parts. **c.** Electrostatic surface of ACTH (left) and MRAP1 (right) in different orientations. Deep blue represents positively charged and red represents negatively charged areas.