



Supplementary information, Fig. S7| The three human  $\beta$ ARs and three turkey  $\beta$ ARs have identical orthosteric pockets, and their different affinities to ligands correlate with different extracellular vestibule residues.

a, The turkey  $\beta_{3C}$ AR is similar to the human  $\beta_2$ AR. The  $K_i$  values of 46 different ligands to the human  $\beta_2$ AR are sorted ascendingly and set as X-axis values. The respective  $K_i$  values of the other five  $\beta$ ARs are set as Y-axis values. A linear regression analysis was performed. The turkey  $\beta_{3C}$ AR is most similar to the human  $\beta_2$ AR as the R square and slope values are close to 1. The  $K_i$  values of the ligands to the different  $\beta$ ARs are collected from previous publication<sup>22</sup>. b, The turkey  $\beta_{4C}$ AR is similar to the turkey  $\beta_1$ AR. The  $K_i$  values of 46 different ligands to the turkey  $\beta_1$ AR are sorted ascendingly and set as X-axis values. The respective  $K_i$  values of the other five  $\beta$ ARs are set as Y-axis values. A linear regression analysis was performed. The turkey  $\beta_{4C}$ AR is most similar to the turkey  $\beta_1$ AR as the R square and slope values are closer to 1 compared to other  $\beta$ ARs. c, The linear regression analysis of the  $K_i$  values of different ligands to the human  $\beta_1$ AR (X-axis) and the other five  $\beta$ ARs (Y-axis). No R-square values are above 0.9. d, The linear regression analysis of the  $K_i$  values of different ligands to the human

$\beta_3$ AR (X-axis) and the other five  $\beta$ ARs (Y-axis). No R-square values are above 0.9. e, The epinephrine binding pocket contains 11 residues, as represented by the  $\beta_2$ AR-epinephrine structure (PDB code: 4LDO). f, Sequence alignment suggests the three human  $\beta$ ARs and three turkey  $\beta$ ARs have identical orthosteric pockets.