Extended Data Table 1. GLP-1R – TT-OAD2 and GLP-1R - GLP-1 contacts during MD simulations performed on the GLP-1R:TT-OAD2:Gs and GLP-1R:GLP-1:Gs complexes. Contacts involving the GLP-1R transmembrane (TM) domain are determined as the sum of the occupancy (reported as % of frames) of all the contacts involving each residue. Values higher than 100% indicate residues able to interact with more than one peptide side chain. A contact was considered productive if the distance between the residue and the ligand was less than 3.5 Å. Data are summarised in Figure 4C**.** TT-OAD2 mainly interacted with TM2, ECL1, and TM3. Interactions with TM1 and ECL2 were present but not persistent (with the exception of $W297^{ECL2}$). The N-terminal helix of the extracellular domain (ECD) was engaged in (many) transient interactions. GLP-1, overall, interacted with a different set of residues and was able to further involve TM5, TM6, and TM7. TT-OAD2 and GLP-1 common contact residues (indicated with *) were located at TM1, TM2, and ECL2. Ligand contacts formed via interaction with the receptor backbone rather than a side chain interaction are indicated by $^{\#}$.

Extended Data Table 2. Main GLP-1R - GLP-1R intramolecular hydrogen bonds during MD simulation. Data expressed as the occupancy (% of frames) in which the interactions were present in the GLP-1R:TT-OAD2:Gs and GLP-1R:GLP-1:Gs complexes. Differences between GLP-1R:GLP-1:Gs and GLP-1R:TT-OAD2:Gs are reported in the right column; green indicates more contacts in GLP-1 vs TT-OAD2 and red more contacts in TT-OAD2 vs GLP-1. Grey cells indicate that hydrogen bonds were not present.