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 #.

GLP-1R:TT-OAD2 (TM) Residues	Contacts occupancy (% frames)	GLP-1R:GLP-1 (TM) Residues	Contacts occupancy (% frames)
*K197$^{2.67}$	100.0	*R299^{ECL2}	302.9
A200$^{2.70}$	100.0	L388$^{7.43}$	288.0
Y220^{ECL1}	100.0	L201$^{2.71}$	273.2
*F230$^{3.33}$	99.9	L384$^{7.39}$	266.2
*M204$^{2.74}$	99.8	Y205^{ECL1}	261.3
*W297^{ECL2}	99.8	L142$^{1.37}$	222.5
W203$^{2.73}$	99.7	L141$^{1.36}$	196.2
C226$^{3.29}$	99.7	*Y145$^{1.40}$	193.2
*M233$^{3.36}$	99.5	F381$^{7.36}$	187.4
V229$^{3.32}$	99.2	R190$^{2.60}$	151.1
L201$^{2.71}$	98.9	*K197$^{2.67}$	140.8
L217^{ECL1}	98.1	*M233$^{3.36}$	139.1
I196$^{2.66}$	88.6	E387$^{7.42}$	132.1
*Y145$^{1.40}$	68.9	*Y148$^{1.43}$	131.2
Q221^{ECL1}	67.4	H212^{ECL1}	124.1
A199$^{2.69}$	52.4	Q213^{ECL1}	111.8
Q234$^{3.37}$	48.6	E364$^{6.53}$	103.7
D198$^{2.68}$	44.4	T391$^{7.46}$	101.3
T29^{ECD}	43.9	W214^{ECL1}	93.2

*Y148$^{1.43}$	43.4	V237$^{3.40}$	89.6
*V194$^{2.64}$	42.6	*F230$^{3.33}$	87.3
S31^{ECD}	41.5	*T298^{ECL2}	86.6
C296^{ECL2}	40.3	*V194$^{2.64}$	81.0
W33^{ECD}	38.7	Y241$^{3.44}$	80.3
A28^{ECD}	36.4	W306$^{5.36}$	76.6
L32^{ECD}	25.1	R376^{ECL3}	69.1
T149$^{1.44}$	23.6	*#W297^{ECL2}	67.0
*R299^{ECL2}	22.0	F367$^{6.56}$	62.6
*T298^{ECL2}	20.1	R310$^{5.40}$	59.6
		F385$^{7.40}$	57.0
		I313$^{5.43}$	56.7
		*M204^{ECL1}	52.7

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.

GLP-1R residues involved in intramolecular hydrogen bonds		GLP-1R:TT-OAD2:Gs	GLP-1R:GLP-1:Gs	GLP-1R:GLP-1:Gs / GLP-1R:TT-OAD2:Gs Δ occupancy $_a$
R40^{ECD}	D215^{ECL1}	38.2	68.6	30.4
R176$^{2.46}$	E408^{H8}	35.7		-35.7
R176$^{2.46}$	E247$^{3.50}$	46.7	97.9	51.2
N182$^{2.52}$	W274$^{4.50}$	73	81.4	8.4
R190$^{2.60}$	E364$^{6.53}$	4	5	1
R190$^{2.60}$	Y241$^{3.44}$	13.9	14.2	0.3
R190$^{2.60}$	N240$^{3.43}$	78,2	93.1	14.9
D198$^{2.68}$	K202^{ECL1}	60.2	18.8	-41.4
D198$^{2.68}$	Y145$^{1.40}$	74	59.2	-14.8
D198$^{2.68}$	K197$^{2.67}$	0.2	59.6	59.4
R227$^{3.30}$	D222^{ECL1}	4.1		-4.1
R227$^{3.30}$	D293^{ECL2}	63.5	31.9	-31.6
R227$^{3.30}$	S223^{ECL1}		37	37
N240$^{3.43}$	S186$^{2.56}$	54.9	69.1	14.2
E247$^{3.50}$	Y402$^{7.47}$	60.4	77.6	17.2
D293^{ECL2}	K288$^{4.64}$	23.4	4.9	-18.5
D293^{ECL2}	Y220^{ECL1}		13.6	13.6
E294^{ECL2}	S301^{ECL2}	0.8		-0.8
E294^{ECL2}	T298^{ECL2}	11.1		-11
E294^{ECL2}	K288$^{4.64}$	42.5	39	-3.5
R299^{ECL2}	E34^{ECD}	56.5	0.1	-56.4
R299^{ECL2}	E294^{ECL2}	26.5		-26.5
R299^{ECL2}	D293^{ECL2}	17.8		-17.8
R299^{ECL2}	N300^{ECL2}	16.2		-16.2

R299^{ECL2}	E373^{ECL3}		19.6	19.6
N300^{ECL2}	E292$^{4.68}$	13.9		-13.9
R310$^{5.40}$	E364$^{6.53}$	31.4	3.3	-28.1
R310$^{5.40}$	D372^{ECL3}		29,6	29.6
D344$^{6.33}$	K346$^{6.35}$	48.9	11,2	-37.7
H363$^{6.52}$	T391$^{7.46}$	38.5	0,5	-38
E364$^{6.53}$	Y241$^{3.44}$	48.6	59,6	11
D372^{ECL3}	K383$^{7.38}$	23.2	0,6	-22.6
R376^{ECL3}	D372^{ECL3}		21,2	21.2
R376^{ECL3}	E373^{ECL3}	13.4	42,7	29.3
R380$^{7.35}$	D372^{ECL3}	60.7	1	-59.7
R380$^{7.35}$	E387$^{7.42}$	2.4	44,7	42.3
E387$^{7.42}$	K383$^{7.38}$	62.6	2.2	-60.4