Table S1. Table showing the GPCR crystal structures resolved between 2017 and 2021.

PDB ID	Date	Ligand Bound	Crystallisation Method	Resolution	Reference
5NX2	2017	Peptide 1	X-ray diffraction	3.7 Å	[1]
6KJV	2019	PF-0637222	X-ray diffraction	2.8 Å	[2]
6KK1	2019	PF-0637222	X-ray diffraction	2.8 Å	[2]
6GB1	2018	Peptide 11	X-ray diffraction	2.73 Å	[3]
6KK7	2019	PF-0637222	X-ray diffraction	3.1 Å	[2]
6LN2	2020	FAB7F38, PF-06372222	X-ray diffraction	3.2 Å	[4]
6ORV	2020	TT-OAD2	Electron microscopy	3.0 Å	[5]
6VCB	2020	LSN3160440	Electron microscopy	3.3 Å	[6]
6X18	2020	Glp-1	Electron microscopy	2.1 Å	[7]
6X19	2020	CHU-128	Electron microscopy	2.1 Å	[7]
6X1A	2020	PF-06882961	Electron microscopy	2.5 Å	[7]
6XOX	2020	LY3502970	Electron microscopy	3.1 Å	[8]
7C2E	2020	RGT1383	Electron microscopy	4.2 Å	[9]
7DUQ	2021	Compound 2	Electron microscopy	2.5 Å	[10]
7DUR	2021	Compound 2	Electron microscopy	3.3 Å	[10]
7E14	2021	Compound 2	Electron microscopy	2.9 Å	[10]
7EVM	2021	Compound 2	Electron microscopy	2.5 Å	[10]
7KI0	2021	Semaglutide	Electron microscopy	2.5 Å	[11]
7KI1	2021	Taspoglutide	Electron microscopy	2.5 Å	[11]
7LCI	2021	Pf-06882961	Electron microscopy	2.9 Å	[12]
7LCJ	2021	Pf-06882961	Electron microscopy	2.82 Å	[12]
7LCK	2021	Pf-06882961	Electron microscopy	3.24 Å	[12]
7RTB	2021	Peptide 19	Electron microscopy	2.14 Å	[13]

Table S2. The binding energy of the ligands upon docking onto the crystal structures studied.

Pose	Ligand	Structure	Binding Energy (Kcal/mol)
1	1	5VAI	−6.46
2	1	5VAI	−6.34
3	1	5VAI	−6.25
1	2	5VAI	−7.55
2	2	5VAI	−7.45
3	2	5VAI	−7.37
1	3	5VAI	−6.44
2	3	5VAI	−6.31
3	3	5VAI	−6.28
1	4	5VAI	−7.20
2	4	5VAI	−7.159
3	4	5VAI	−7.157
1	1	6B3J	−6.70
2	1	6B3J	−6.59
3	1	6B3J	−6.43
1	2	6B3J	−7.67
2	2	6B3J	−7.59
3	2	6B3J	−7.45
1	3	6B3J	−7.27
2	3	6B3J	−7.12
3	3	6B3J	−6.92
1	4	6B3J	−7.95
2	4	6B3J	−7.77
3	4	6B3J	−7.73
1	1	5VEW	−8.50
2	1	5VEW	−8.18
3	1	5VEW	−6.26

1	2	5VEW	−7.189
2	2	5VEW	−7.066
3	2	5VEW	−6.873
1	3	5VEW	−7.877
2	3	5VEW	−6.866
3	3	5VEW	−6.827
1	4	5VEW	−9.48
2	4	5VEW	−9.27
3	4	5VEW	−8.22

Table S3. Table showing amino acids present in the binding sites for compound **1** Pose 2.

S/N	5VAI	5VEW	6B3J
1	VAL 331	TYR 402	LEU 354
2	THR 355	SER 352	PHE 390
3	LEU 401	ASN 406	HIS 363
4	TYR 402	LEU 401	PHE 393
5	LEU 356	VAL 405	PRO 358
6	SER 352	LYS 351	MET 397
7	THR 353	ASN 407	
8	LEU 349	ARG 348	
9		LEU 349	
10		ILE 345	
11		GLU 408	
12		HIS 180	
13		ARG 176	

Table S4. Table showing amino acids present in the binding sites for compound **1** Pose 3.

S/N	5VAI	5VEW	6B3J
1	LEU 401	SER 389	LEU 359
2	PHE 393	PHE 390	LEU 401
3	GLN 394	GLN 394	ASN 406
4	PHE 390	MET 397	TYR 402
5	MET 397	LEU 396	LEU 356
6	PRO 358	LEU 359	
7	ILE 357	PHE 393	
8	THR 355		
9	LEU 354		
10	LYS 351		

Table S5. Table showing amino acids present in the binding sites for compound **2** Pose 2.

S/N	5VAI	5VEW	6B3J
1	PHE 324	THR 355	LEU 354
2	PHE 321	PRO 358	ILE 357
3	VAL 365	PHE 324	ILE 366
4	ILE 357	LEU 354	PRO 358
5	PHE 390	ILE 328	PHE 390
6	HIS 363	VAL 331	
7	GLU 387		
8	ILE 366		
9	ILE 325		

Table S6. Table showing amino acids present in the binding sites for compound **2** Pose 3.

S/N	5VAI	5VEW	6B3J
1	LEU 401	LEU 359	MET 397
2	LEU 354	THR 355	HIS 363
3	HIS 363	LEU 354	PHE 390
4	PHE 390	VAL 331	PRO 358
5		PHE 347	VAL 405
6		PHE 324	LEU 401
7		PRO 358	ILE 357
8			LEU 354

Table S7. Table showing amino acids present in the binding sites for compound **3** Pose 2.

S/N	5VAI	5VEW	6B3J
1	SER 352	ARG 348	LEU 356
2	VAL 331	LEU 349	LEU 359
3	LEU 356	LYS 351	GLU 408
4		LEU 401	VAL 405
5		VAL 405	LEU 401
6			TYR 402

Table S8. Table showing amino acids present in the binding sites for compound **3** Pose 3.

S/N	5VAI	5VEW	6B3J
1	ARG 176	ILE 345	MET 397
2	HIS 180	VAL 405	PRO 358
3	TYR 402	LYS 351	PHE 390
4	SER 352	LEU 401	PHE 393
5	THR 353	SER 352	PHE 385
6		ARG 348	
7		ASN 406	

Table S9. Table showing amino acids present in the binding sites for compound **4** Pose 2.

S/N	5VAI	5VEW	6B3J
1	PHE 324	HIS 363	LYS 351
2	PHE 321	LEU 359	ILE 357
3	VAL 365	THR 391	VAL 405
4	ILE 357	GLN 394	THR 355
5	PHE 390	LEU 360	MET 397
6	ILE 325	MET 397	LEU 401
7		LEU 396	PRO 358
8		PHE 393	HIS 363
9		ILE 400	PHE 390

Table S10. Table showing amino acids present in the binding sites for compound **4** Pose 3.

S/N	5VAI	5VEW	6B3J
1	LEU 251	LYS 351	ILE 357
2	LEU 356	LEU 401	LYS 351
3	THR 355	VAL 405	THR 355
4	LYS 351	ARG 348	LEU 354
5		LEU 349	LEU 401
6			MET 397
7			PRO 358
8			HIS 363
			PHE 390

References

1. Jazayeri, A.; Rappas, M.; Brown, A.J.H.; Kean, J.; Errey, J.C.; Robertson, N.J.; Fiez-Vandal, C.; Andrews, S.P.; Congreve, M.; Bortolato, A.; et al. Crystal structure of the GLP-1 receptor bound to a peptide agonist. *Nature* **2017**, *546*, 254–258, doi:10.1038/nature22800.
2. Xu, Y.; Wang, Y.; Liu, K.; Peng, Y.; Yao, D.; Tao, H.; Liu, H.; Song, G. Mutagenesis facilitated crystallization of GLP-1R. *IUCrJ* **2019**, *6*, 996–1006.
3. Evers, A.; Bossart, M.; Pfeiffer-Marek, S.; Elvert, R.; Schreuder, H.; Kurz, M.; Stengelin, S.; Lorenz, M.; Herling, A.; Konkar, A.; et al. Dual Glucagon-like Peptide 1 (GLP-1)/Glucagon Receptor Agonists Specifically Optimized for Multidose Formulations. *J. Med. Chem.* **2018**, *61*, 5580–5593, doi:10.1021/acs.jmedchem.8b00292.
4. Wu, F.; Yang, L.; Hang, K.; Laursen, M.; Wu, L.; Han, G.W.; Ren, Q.; Roed, N.K.; Lin, G.; Hanson, M.A.; et al. Full-length human GLP-1 receptor structure without orthosteric ligands. *Nat. Commun.* **2020**, *11*, 1272, doi:10.1038/s41467-020-14934-5.
5. Zhao, P.; Liang, Y.-L.; Belousoff, M.J.; Deganutti, G.; Fletcher, M.M.; Willard, F.S.; Bell, M.G.; Christe, M.E.; Sloop, K.W.; Inoue, A.; et al. Activation of the GLP-1 receptor by a non-peptidic agonist. *Nature* **2020**, *577*, 432–436, doi:10.1038/s41586-019-1902-z.
6. Bueno, A.B.; Sun, B.; Willard, F.S.; Feng, D.; Ho, J.D.; Wainscott, D.B.; Showalter, A.D.; Vieth, M.; Chen, Q.; Stutsman, C.; et al. Structural insights into probe-dependent positive allosterism of the GLP-1 receptor. *Nat. Chem. Biol.* **2020**, *16*, 1105–1110, doi:10.1038/s41589-020-0589-7.
7. Zhang, X.; Belousoff, M.J.; Zhao, P.; Kooistra, A.J.; Truong, T.T.; Ang, S.Y.; Underwood, C.R.; Egebjerg, T.; Šenel, P.; Stewart, G.D.; et al. Differential GLP-1R Binding and Activation by Peptide and Non-peptide Agonists. *Mol. Cell* **2020**, *80*, 485–500, doi:10.1016/j.molcel.2020.09.020.
8. Kawai, T.; Sun, B.; Yoshino, H.; Feng, D.; Suzuki, Y.; Fukazawa, M.; Nagao, S.; Wainscott, D.B.; Showalter, A.D.; Droz, B.A.; et al. Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist. *PNAS* **2020**, *117*, 29959, doi:10.1073/pnas.2014879117.
9. Ma, H.; Huang, W.; Wang, X.; Zhao, L.; Jiang, Y.; Liu, F.; Guo, W.; Sun, X.; Zhong, W.; Yuan, D.; et al. Structural insights into the activation of GLP-1R by a small molecule agonist. *Cell Res.* **2020**, *30*, 1140–1142, doi:10.1038/s41422-020-0384-8.
10. Cong, Z.; Chen, L.-N.; Ma, H.; Zhou, Q.; Zou, X.; Ye, C.; Dai, A.; Liu, Q.; Huang, W.; Sun, X.; et al. Molecular insights into ago-allosteric modulation of the human glucagon-like peptide-1 receptor. *Nat. Commun.* **2021**, *12*, 3763, doi:10.1038/s41467-021-24058-z.
11. Zhang, X.; Belousoff, M.J.; Liang, Y.-L.; Danev, R.; Sexton, P.M.; Wootten, D. Structure and dynamics of semaglutide- and taspoglutide-bound GLP-1R-Gs complexes. *Cell Rep.* **2021**, *36*, doi:10.1016/j.celrep.2021.109374.
12. Zhang, X.; Johnson, R.M.; Drulyte, I.; Yu, L.; Kotecha, A.; Danev, R.; Wootten, D.; Sexton, P.M.; Belousoff, M.J. Evolving cryo-EM structural approaches for GPCR drug discovery. *Structure* **2021**, *29*, 963–974, doi:10.1016/j.str.2021.04.008.
13. Johnson, R.M.; Zhang, X.; Piper, S.J.; Nettleton, T.J.; Vandekolk, T.H.; Langmead, C.J.; Danev, R.; Sexton, P.M.; Wootten, D. Cryo-EM structure of the dual incretin receptor agonist, peptide-19, in complex with the glucagon-like peptide-1 receptor. *Biochem. Biophys. Commun.* **2021**, *578*, 84–90, doi:https://doi.org/10.1016/j.bbrc.2021.09.016.