Data Fig. 4) suggest that cyclic peptide-based antagonists probably bind elsewhere, for example, in the orthosteric peptide-binding site. The C5aR1–NDT9513727 structure provides an example of an extra-helical binding site within the lipid bilayer that can be targeted to negatively modulate receptor activity (whether this binding site is ubiquitous or of functional relevance across GPCRs remains to be determined), building a more complete picture of the means by which GPCR activity can be controlled allosterically.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

Received 9 June; accepted 7 November 2017.

1. Woodruff, T. M., Nandakumar, K. S. & Tedesco, F. Inhibiting the C5-C5a receptor axis. *Mol. Immunol.* **48,** 1631–1642 (2011).
2. Klos, A., Wende, E., Wareham, K. J. & Monk, P. N. International Union of Basic and Clinical Pharmacology. Complement peptide C5a, C4a, and C3a receptors. *Pharmacol. Rev.* **65,** 500–543 (2013).
3. Landlinger, C. *et al.* Active immunization against complement factor C5a: a new therapeutic approach for Alzheimer's disease. *J. Neuroinflammation* **12,** 150 (2015).
4. Hutchison, A. J. & Krause, J. E. The discovery of small molecule C5a antagonists. *Annu. Rep. Med. Chem.* **39,** 139–147 (2004).
5. Sumichika, H. *et al.* Identification of a potent and orally active non-peptide C5a receptor antagonist. *J. Biol. Chem.* **277,** 49403–49407 (2002).
6. Brodbeck, R. M. *et al.* Identification and characterization of NDT 9513727 [*N*,*N*-bis(1,3-benzodioxol-5-ylmethyl)-1-butyl-2,4-diphenyl-1*H*-imidazole-5-methanamine], a novel, orally bioavailable C5a receptor inverse agonist. *J. Pharmacol. Exp. Ther.* **327,** 898–909 (2008).
7. Serrano-Vega, M. J., Magnani, F., Shibata, Y. & Tate, C. G. Conformational thermostabilization of the β1-adrenergic receptor in a detergent-resistant form. *Proc. Natl Acad. Sci. USA* **105,** 877–882 (2008).
8. Robertson, N. *et al.* The properties of thermostabilised G protein-coupled receptors (StaRs) and their use in drug discovery. *Neuropharmacology* **60,** 36–44 (2011).
9. Oswald, C. *et al.* Intracellular allosteric antagonism of the CCR9 receptor. *Nature* **540,** 462–465 (2016).
10. White, J. F. *et al.* Structure of the agonist-bound neurotensin receptor. *Nature* **490,** 508–513 (2012).
11. Zhang, D. *et al.* Two disparate ligand-binding sites in the human $P2Y_1$ receptor. *Nature* **520,** 317–321 (2015).
12. Cheng, R. K. Y. *et al.* Structural insight into allosteric modulation of protease-activated receptor 2. *Nature* **545,** 112–115 (2017).
13. Jazayeri, A. *et al.* Extra-helical binding site of a glucagon receptor antagonist. *Nature* **533,** 274–277 (2016).
14. Lu, J. *et al.* Structural basis for the cooperative allosteric activation of the free fatty acid receptor GPR40. *Nat. Struct. Mol. Biol.* **24,** 570–577 (2017).
15. Waters, S. M. *et al.* Molecular characterization of the gerbil C5a receptor and identification of a transmembrane domain V amino acid that is crucial for small molecule antagonist interaction. *J. Biol. Chem.* **280,** 40617–40623 (2005).
16. Rasmussen, S. G. *et al.* Crystal structure of the β_2 adrenergic receptor–Gs protein complex. *Nature* **477,** 549–555 (2011).
17. Rasmussen, S. G. *et al.* Structure of a nanobody-stabilized active state of the β_2 adrenoceptor. *Nature* **469,** 175–180 (2011).
18. Tehan, B. G., Bortolato, A., Blaney, F. E., Weir, M. P. & Mason, J. S. Unifying family A GPCR theories of activation. *Pharmacol. Ther.* **143,** 51–60 (2014).
19. Floyd, D. H. *et al.* C5a receptor oligomerization. II. Fluorescence resonance energy transfer studies of a human G protein-coupled receptor expressed in yeast. *J. Biol. Chem.* **278,** 35354–35361 (2003).
20. Klco, J. M., Lassere, T. B. & Baranski, T. J. C5a receptor oligomerization. I. Disulfide trapping reveals oligomers and potential contact surfaces in a G protein-coupled receptor. *J. Biol. Chem.* **278,** 35345–35353 (2003).
21. Rabiet, M. J., Huet, E. & Boulay, F. Complement component 5a receptor oligomerization and homologous receptor down-regulation. *J. Biol. Chem.* **283,** 31038–31046 (2008).
22. Cherezov, V. *et al.* High-resolution crystal structure of an engineered human β_2-adrenergic G protein-coupled receptor. *Science* **318,** 1258–1265 (2007).
23. Hebert, T. E. *et al.* A peptide derived from a β_2-adrenergic receptor transmembrane domain inhibits both receptor dimerization and activation. *J. Biol. Chem.* **271,** 16384–16392 (1996).
24. Wu, B. *et al.* Structures of the CXCR4 chemokine GPCR with small-molecule and cyclic peptide antagonists. *Science* **330,** 1066–1071 (2010).
25. Manglik, A. *et al.* Crystal structure of the μ-opioid receptor bound to a morphinan antagonist. *Nature* **485,** 321–326 (2012).
26. Wu, H. *et al.* Structure of the human κ-opioid receptor in complex with JDTic. *Nature* **485,** 327–332 (2012).
27. Wang, C. *et al.* Structure of the human smoothened receptor bound to an antitumour agent. *Nature* **497,** 338–343 (2013).
28. Higginbottom, A. *et al.* Comparative agonist/antagonist responses in mutant human C5a receptors define the ligand binding site. *J. Biol. Chem.* **280,** 17831–17840 (2005).

Supplementary Information is available in the online version of the paper.

Acknowledgements We thank R. Owen, J. Waterman and D. Axford for technical support. We thank C. G. Tate and other colleagues at Heptares Therapeutics for suggestions and comments.

Author Contributions N.R. carried out the conformational thermostabilization of the receptor, performed LCP crystallization, designed crystal optimization, devised functional mutations and characterized the binding site mutants. M.R. characterized truncation constructs and established procedures for, and carried out expression and purification of the final construct, collected and processed X-ray diffraction data, solved and refined the structure. A.S.D. established the platform/protocols for LCP crystallization, harvested crystals, collected and processed X-ray diffraction data, solved and refined the structure and devised functional mutations alongside N.R. J.B. carried out the pharmacology. J.C. sourced and characterized the radioligand. G.B. performed molecular dynamics simulations. Project management was carried out by A.J., M.K., R.C. and F.H.M. The manuscript was prepared by A.S.D., N.R. and F.H.M.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare competing financial interests: details are available in the online version of the paper. Readers are welcome to comment on the online version of the paper. Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations. Correspondence and requests for materials should be addressed to F.H.M. (fiona.marshall@heptares.com).

Reviewer Information *Nature* thanks A. Christopoulos, I. Kufareva and the other anonymous reviewer(s) for their contribution to the peer review of this work.